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The College on Problems of Drug Dependence, Inc.

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Editor:

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INTRODUCTION OF THE NATHAN B. EDDY MEMORIAL AWARD

M.W. Adler

Temple University, Philadelphia, PA

Two years ago, at the CPDD meeting in Nashville, I sat in the front row in the audience and listened as Dr. Bill Dewey said a whole bunch of great things about me when he introduced me as the winner of the Nathan B. Eddy Award. That was the proudest moment of my professional life, although it was sometimes difficult to believe that it was me that Bill was talking about. Well, now it's my turn to say some wonderful things about the person about to be presented with the 1999 Eddy Award.

As I'm sure you all know, the winner is Dr. Mary Jeanne Kreek. Mary Jeanne, I don't want you to become overly troubled by this, but do you realize that you are the last person that will ever receive the Eddy Award in this century? Actually, I think that's very appropriate because you are truly an outstanding and unique individual.

For those who may not know you very well, I would like to provide a brief history of your professional life. Dr. Kreek graduated from Woodrow Wilson High School in Washington, D.C. and then attended Wellesley College where she received honors in chemistry and biology. She went to Columbia for her M.D. where she won an award for her research. Her internship and residency at Cornell University-New York Hospital Medical Center included internal medicine, gastroenterology, and neuroendocrinology. She also did a research rotation at the Rockefeller Institute in 1964 with Dr. Vincent Dole, a former winner of the Eddy Award. Working with Dr. Dole and Dr. Marie Nyswander, who received the Eddy Award with Dr. Dole, Dr. Kreek was part of the team that performed the initial studies of the use of methadone in the chronic management of heroin addiction. There is no need to tell this audience of the importance of this work in the treatment of addiction. As important as were her efforts as part of that group, Dr. Kreek's career really went uphill after that.

Dr. Kreek joined the Rockefeller as Associate Physician in 1967, and rose to the rank of Professor and Head of the Laboratory of the Biology of Addictive Diseases and Senior Physician at the Rockefeller University Hospital. That was in 1994. Dr. Kreek was the first woman to become a Head of Laboratory at the Rockefeller. Glass ceilings are just another temporary slowdown for Dr. Kreek. I should also mention that Dr. Kreek is the Director of a P50 Center from the National Institute on Drug Abuse titled "Treatment of Addictions-Biological Correlates" and she has been the recipient of a NIDA Senior Research Scientist Award since 1978.

When I was preparing these comments, I tried to determine which of Dr. Kreek's many, many contributions to research I would mention. She has long espoused the view that addictions are diseases of the brain with associated behaviors, she provided evidence that methadone maintenance therapy provides stability for the neuroendocrine system, she developed new analytical techniques for pharmacokinetic studies of opioids, and she provided strong support for the hypothesis that genetic factors play a major role in addiction but that early developmental and environmental factors are also important. In addition, she has provided strong evidence that the endogenous opioid system exerts its effects via interactions with other neuropeptide and neurotransmitter systems (a belief that she and I have shared for many years), she was among the first to demonstrate opioid interactions with disease states, and she helped provide data supporting a link between prevalence of HIV-I and parenteral drug abuse. In the past 10 years, Dr. Kreek has not only continued her work with opioids, but has made numerous contributions to our knowledge about cocaine. For example, she developed the "binge" model for studying cocaine effects and has demonstrated that cocaine can alter mu and kappa opioid receptor densities and 5HT1a serotonergic receptors. In collaboration with a group in Japan, she used PET scans to study cocaine and its effects on D1 and D2 receptor binding.

Finally, with regard to Mary Jeanne's research, I want to draw your attention to her studies with opioids and the immune system, studies that are near and dear to me and my group at Temple University. She is one of the leaders in the very rapidly developing field of the relationships between drugs of abuse, addiction, and the immune system. The reasons for the markedly increased incidence and severity of a number of diseases in drug abusers are not well understood at this time. However, it is almost certain that the differences are not due solely

to lifestyle or contaminated needles. Rather, it appears that various abused drugs, including the opioids, have a profound effect on the immune system and may act as cofactors in such diseases as HIV and opportunistic infections such as hepatitis B and C, and tuberculosis.

At this point, I might just add that Dr. Kreek has published over 300 papers, that she has collaborated with many laboratories throughout the world, and that she is one of the best examples that I know of a scientist who truly goes from genetic and molecular approaches to studies in humans and then back again. I could then sit down and all of you would fully understand why Dr. Kreek is so richly deserving of the Eddy Award and marvel about how much she has accomplished. But I'm not going to do that. Rather, I will take just a couple of more minutes to tell you of some of the things that Mary Jeanne does in her spare time:

1) CPDD - Dr. Kreek has played a vital role in the evolution of the CPDD into a membership society. She has served the CPDD as a member of the Board of Directors, as Chairman (President) for two years, as Chairman of the Scientific Program Committee for 5 years, and as a member of the Long-Range Planning Committee for two years. She is also responsible for beginning the CPDD Travel Awards Program and many of you in this audience have that program to thank for your involvement with CPDD.

2) Federal Government - Dr. Kreek has served on numerous governmental committees. Of particular note is her service on various FDA Advisory Committees, on the Search Committee for the Director of NIDA, on several study sections at NIH and NIDA, on the NIDA National Advisory Council, and most recently, on the Peer Review Oversight Group (PROG) at NIH.

3) International Groups - Dr. Kreek has been involved with several WHO committees, and with several NIH and State Department missions. She is an extremely articulate spokesperson. Mary Jeanne has participated in 3 Central European/USA meetings and one to China, and her contributions invariably represent one of the highlights of each meeting.

I apologize for taking so long, but I'm going to take one more minute from Dr. Kreek's time to relate my favorite Mary Jeanne story. When a team from NIDA site-visited her for her Center grant renewal a couple of years ago, Mary Jeanne handed us a schedule that had her talking for 45 minutes. I was asked to tell her that she only had 20 minutes. I thought that she might be upset, but she just looked and me and the rest of the committee and said "Don't worry about it, 20 minutes is fine, I'll just talk faster."

When I stood here two years to accept the Eddy Award, I looked at the audience and saw my wife, my two children, and my two grandchildren. Their support was a vital element in any success that I achieved and I was thrilled to see how proud they were that day. Well, now I look into the audience and I see Mary Jeanne's husband Bob, her son Robert, and her daughter Esperance and I see that same pride. So to the three of you, I want to say that you certainly have a right to be proud. Without any further ado, it is my great pleasure to introduce to you the winner of the 1999 Nathan B. Eddy Award for Research in the field of drug abuse - the irrepressible and dynamic Dr. Mary Jeanne Kreek.

NATHAN B. EDDY MEMORIAL AWARD LECTURE

M.J. Kreek

The Rockefeller University, New York, NY

OPIATES, OPIOIDS, SNP'S AND THE ADDICTIONS

I am deeply honored to receive the Nathan B. Eddy Memorial Award for Lifetime Excellence in Drug Abuse Research from the College on Problems of Drug Dependence. I wish to thank so many people here: the President, Billy Martin; all the other officers and the Board of Directors of CPDD; Marty Adler, the Executive Officer of CPDD and a scientific colleague; his wonderful wife, Toby; Ellen Geller who has been so supportive of all our work in this organization; the Awards Committee, all those who supported this nomination; and all of CPDD. I am very moved and honored by this award.

I would like to recognize the incredible input of my late parents. My mother used to teach me, "Do whatever you do with excellence, if possible," and my father simply would say "Do anything you want to do - you can do it!" I would also like to acknowledge my own wonderful family who have given endearing support and loyalty: my husband for almost 30 years, Bob, my son, Robert, who is now a lawyer in New York and my daughter, Esperance, who is going into her senior year at Yale majoring in molecular and neurobiology, an unusual field to choose! I would also like to recognize my entire laboratory - past, present and future - and all of you who are my adopted laboratory children whom I did not really mentor, but whom I pretend like I did, and that is, all of the Travel Awardees of CPDD.

I also need to acknowledge those who taught me science. The late Frederic Bartter at the NIH, an endocrinologist who taught me to respect clinical research and related laboratory research; Donald Tapley at Columbia P & S who taught me bench work in metabolism, and the importance of hormones in anything we studied; Marvin Schleisenger and Graham Jeffries at Cornell - New York Hospital who taught me hepatology and gastroenterology, both clinically and at the bench; and Vincent Dole at Rockefeller who taught me how to approach a brand new problem (about which both he and I knew nothing, but we both were mentored by the late Marie Nyswander).

I also want to acknowledge the very early supporters of our work, specifically those who supported our addictive disease research in the 1960s - Eric Simon, Jack Fishman and Enoch Gordis, while he was doing his work at the Rockefeller University. When I was first introduced to CPDD, it was the mid-1970s and those who welcomed me initially were Marty Adler, Beny Primm, Louis Harris, Bill Dewey and Joe Brady, and those who welcomed me to INRC were Eddie Way and the late Hans Kosterlitz. Four people were very supportive of the initiation of my work at Rockefeller, and they were intriguingly the discoverer of DNA's role in genetics, Maclyn McCarty, two Noble Laureate chemists, Bruce Merrifield and the late Stanford Moore, and the theoretical physicist, Abraham Pais - none of whom had any involvement in research related to drugs of abuse, and who never brought ideology to our work, but only appreciated the science and the need for that science.

I also want to acknowledge many from NIDA, specifically, my first grants management person, Monique Braude, who told me I had to go to CPDD and I had to go to INRC. She was right. Next, Jack Blaine and the late Pierre Renault, who were my early grants management people, and Joe Frascella and Harold Gordon who have subsequently taken over some of those roles, along with Steve Zukin; and the three most recent Directors or Acting Directors of NIDA, Bob Schuster and his entire team, Dick Millstein and his entire team, and Alan Leshner and his entire team. NIDA has been my major source of funding since 1975, with continuous support with many grants over many years, and providing us with great appreciation of both the work that our group does, but also, the mutual excitement in sharing with us our own science. And then, I would like to acknowledge our six presidents of the Rockefeller University who, in my research lifetime, have supported, or at least allowed us to continue, over many years, our research, and especially, the two most recent Presidents, Torsten Wiesel, our new President Emeritus, and our new President, Arnold Levine, who have been enormously supportive of our endeavors.

I present a picture of my family, taken when I first got involved in CPDD. You can see the thrill and expectation going up and down that flume ride and getting wet, and a lot of challenges going around comers. Esperance and Robert were a bit smaller then and my hair was a slightly different color, but in fact, the thrill of starting involvement deeply in CPDD began around 1982 when I was elected to go on the then-Executive Committee (now Board of Directors).

One of my activities on the Board was to ask if we could get a history of the early days because I did not know it well and I suspected that others also did not. A wonderful history of CPDD, which I recommend to you all, was written by Everette May and Art Jacobson, and published in 1989 in our *Drug and Alcohol Dependence* journal. In the preface, there is a statement which, in fact, I always have to refresh in my own memory, that CPDD has its origins in the committee which was chaired by the son of the founder of our University, John D. Rockefeller, Jr., in 1913. Rockefeller said that it was essential to create a committee on drug addiction in New York. Later, in fact, Nathan B. Eddy was commissioned to do a major report for that committee.

I became chairman (now called President) of CPDD in 1985 (through 1987) and I looked forward to working with Joe Cochin, the Executive Secretary (now Officer). A tragedy occurred; Joe passed away at the very beginning of my office. It was a difficult time from many standpoints, emotionally and administratively, but because of this wonderful crew of people who pulled together, including one who was in the year to emerge as the new Executive Officer, Marty Adler, we had a very successful year. With Ted Cicero and with Marty, we plotted from that moment onward to create a membership organization, and with Bill Dewey and others, we planned to both broaden and deepen the scientific basis of the scientific programs, and with the help of Lou Harris, we were able to do so in a wonderful way. It was from Lou Harris that I learned how to run a scientific program (which I did as Scientific Program Chairman from 1990-1995). Beny Primm, Joe Brady, Ray Houde, the late Keith Killam and many others were part of our wonderful Board at that time and they are treasured friends of mine, as is everyone in this organization.

As you already heard from Marty Adler, the one thing about CPDD that I think I am personally most proud of is the Travel Awards Program which I decided, in 1983, should exist. The entire Board accepted this concept. The first awards were created in 1984. You know who you are (and you cannot read it on the slide), but these are all the Travel Awardees from 1984 up through last year, and the track record of this group is absolutely outstanding, better than the track record from any follow-up study of any group of young professionals of which I am aware.

This is my laboratory, a picture taken after a stressful occasion two years ago, of my laboratory and also many other members of my Center. That day, our part (of a major site visit) was at an end, and we all got outside and said “We’ll get a picture now.” This is a listing of my current Center and Laboratory. I want to highlight three people on and off this list, two of whom are in this room, Dr. Ann Ho who joined our group in late 1964, Dr. Joyce Lowinson who is here and joined the original team later in the 1960s and Dr. Elizabeth Khuri who joined our group in late 1969. We have had long-staying power with many of our collaborators!

I. EARLY TREATMENT RESEARCH: DEVELOPMENT OF METHADONE MAINTENANCE TREATMENT AND RELATED STUDIES OF MECHANISMS AND PHYSIOLOGICAL EFFECTS OF OPIOIDS

My laboratory research in the addictive diseases began in 1964, (really, the autumn of 1963). The first epic was early treatment research that spanned late 1963 to 1978, but also, goes on right to this day. The initial research, which we engaged in, was work that was precipitated by Vincent Dole working with the late Lewis Thomas on a Health Research Council of the City of New York subcommittee. Dole and Thomas recognized heroin addiction as the leading medical and public health problem that was not being well addressed clinically and scientifically, and also, with so few research teams involved in related laboratory research, with the exception of USPHS facility at Lexington, and a few other groups, and thus, the urgent need for scientific input into this area specifically.

At that time, Dole decided to change his own Laboratory at the Rockefeller University to the studies of addictive diseases. He approached the President of Rockefeller University (the late Detlov Bronk) and asked if he could

have two first year Medical Residents to come and do research at the Rockefeller University. With Bronk's approval, Dole came over to Cornell University - New York Hospital. There was no research elective for clinical Residents at Rockefeller at that time. The Chairman of Medicine (the late Hugh Luckey) thought this was a great idea, but could spare only one person, not two as requested. Dole interviewed all eighteen of the First Year Residents in Internal Medicine ("PGY2"), two were chosen by Dole, and the Chairman of Medicine chose me, (and yes, ladies in the audience, it was reverse discrimination because I was the only woman in sight in that hospital at that time).

Our initial, newly coalesced team (Professor V.P. Dole, joined by the late Marie Nyswander, a psychiatrist, and myself) hypothesized in 1963, when we were planning the work which we initiated in early 1964, that heroin addiction is a disease - a metabolic disease of the brain - with resultant behaviors and continued self-administration despite negative consequences to self and others, and that heroin addiction is not simply a criminal behavior, antisocial personality or some other personality disorder (Dole *et al.* 1966a). We based this primarily on the many published reports as well as other available information on the lack of success of drug-free, abstinence-based approaches, even when excellent behavior modification or psychiatric care was applied.

Dole and I were novices in this field. Marie Nyswander had worked for many years at Lexington and Bellevue and she sent us out to the streets and to the "detoxification" centers to interview heroin addicts. Our first diagram (published in 1966) is one depicting the life of the heroin addict, characterized by multiple daily self-administrations of the short-acting opiate, heroin, first to gain a "high," or euphoria, but in time, simply to prevent the withdrawal symptoms (with the development of tolerance and physical dependence (Dole *et al.* 1966ab). We wanted to develop a pharmacotherapy to be used in combination with behavioral therapy and counseling, a pharmacotherapy which would prevent the signs and symptoms of opiate withdrawal (or the abstinence syndrome), would reduce drug "craving," and one which would normalize any physiological functions that might be disrupted by the chronic use of heroin. We also wanted to target the treatment agent to a specific site of action; a specific receptor or a physiologic system affected or altered by chronic use of the drug of abuse (Table 1) (Kreek 1991a, 1992a). We wanted to utilize a medication that would be orally effective, have a slow on-set of action, long duration of action, and slow offset of action.

We selected methadone, a synthetic opioid, for the initial studies, which had been studied and modestly used for the relief of pain, and which had been found to have similar properties to morphine in pain relief, but also found, when given in multiple doses to naive subjects, to result in respiratory depression. These latter findings suggested that methadone may, in fact, have, in part, some long-acting effects. Methadone had also been used at Lexington and a few other centers including Bellevue, for the short-term detoxification of heroin addiction, administered in multiple doses each day (since it was not recognized in these tolerant and dependent persons to be long-acting), and for 7 to 14 days only, not in a long-term maintenance mode. Marie Nyswander had worked as a psychiatrist at Bellevue and I had rotated through the "detoxification unit" as a medical student from Columbia P & S; both of us had observed that methadone, even when it was not administered in its prescribed four doses a day, would, in fact, continue to prevent signs and symptoms of opiate withdrawal or abstinence, again suggesting its long-acting properties.

We therefore decided to study methadone, and found, indeed, that methadone was orally effective, that it had a very desirable, slow onset of action, preventing any reinforcing effects which are coupled with a rapid rise of plasma levels of a drug and rapid onset rate at brain sites of action. The duration of action of methadone was clinically observed by our team to be quite long, in fact, in preventing withdrawal symptoms, but also, in preventing "drug hunger" and "drug craving," for a 24 hour dosing interval, which was a very exciting, additional finding (Dole *et al.* 1966ab). We also learned that if methadone was given at a dose that was less than the degree of tolerance which had been developed by that individual, at any point in the dose escalation and stabilization, there was no euphoria, no "high," and no narcotic-like effects, and if excessive doses were given, sleepiness would be the major side effect seen (Table 2).

Our first studies were all performed in 1964 at the Rockefeller Hospital, and reported by Dr. Dole in 1966 at the "Old Turks" meeting, the Association of American Physicians, as well as published that same year (Dole *et al.* 1966ab). We knew by clinical observations of our patients in a clinical research setting that methadone could be given orally, and one time only each day, and would both prevent all signs and symptoms of opiate withdrawal,

or abstinence, and also prevent drug craving, thus allowing patients to start to think about getting an education or job counseling and re-establishing family and other social ties.

Also in 1964, we conducted a sequence of double-blinded, random-order, Latin-square design studies in which each day we superimposed one additional entity, heroin, other short-acting opiates including morphine and hydrocodone, as well as methadone itself, or saline, in one intravenous dose per day against a background of a chronic daily dose of oral methadone. We had found that the adequate dose of methadone for most patients then, in 1964, was 80 to 120mg a day. Therefore, we performed the "blockade," or cross-tolerance studies, against a daily oral dose of 100mg. When a single dose of the short-acting opiate was administered (against the background of daily methadone treatment), we found, when the code was broken, there was no "high," no euphoria, or other opiate-like effects, and also no deleterious or adverse effects (Dole *et al.* 1966ab; Kreek 1991a, 1992a). Thus, through the mechanisms of tolerance and cross-tolerance, protection against any adverse effect of any super-imposed short-acting opiate was provided, but also excitingly, no positive reinforcement from a potentially "priming" dose was perceived. Thus one could have not only a pharmacotherapy which prevents "drug hunger," along with withdrawal, but also which allows "de-conditioning" or "extinction."

We did not have any gas liquid chromatography or radioimmunoassay techniques yet. These studies were performed many, many years ago (1964) in ancient history with respect to sensitive analytical chemistry! Thus, we relied on clinical observations for both pharmacodynamics and pharmacokinetics. However, by 1972-1973 we would have gas liquid chromatography (GLC) techniques. Charles Inturrissi at Cornell (then, working solely independently, and now, also through my Center) and my own group each developed a sensitive and specific GLC method for measuring quantitatively levels of methadone, as well as heroin and morphine, in plasma (Inturrisi and Verebey 1972; Kreek 1973a). We found that when a patient takes the 100mg dose of methadone each day, there is, as we had seen clinically, a slow rise of plasma levels coupled with a slow onset of action, a protracted duration of action, associated with sustained plasma levels, with a minimal peak effect coupled with plasma levels, that was barely a doubling of the nadir, and sustained steady state plasma levels over a 24 hour dosing interval (Inturrisi and Verebey 1972; Kreek 1973a). In further studies it was learned that heroin itself in humans has a half-life of three minutes; the half-life of the first metabolite, 6-acetyl-morphine, is thirty minutes; and the major metabolite, morphine, has a half-life of four to six hours. In contrast, racemic methadone, as given in treatment, has a half-life of around twenty-four hours (Table 3).

My laboratory, in conjunction with the group of Klein, formerly at Argonne National Laboratories, using stable isotope techniques with selective labeling of the two separate enantiomers of methadone, conducted studies in methadone maintained subjects, and found that the inactive (+)(S) enantiomer has a half-life of around 16 hours and the active (-)(R) enantiomer, a half-life of 48 hours (Table 3) (Hachey *et al.* 1976, 1977; Kreek *et al.* 1979; Nakamura *et al.* 1982).

The "on-off" effects of heroin disrupt behaviors, physiology, receptor function, and we now know, also gene expression. In sharp contrast, the steady-state perfusion of a long-acting opioid, such as methadone (or more recently, LAAM or the combination treatment of buprenorphine-naloxone) allows normalization of behaviors, physiology, and receptor mediated events as well as levels of gene expression (Table 4).

In 1983, two years after the first identification of the AIDS disease, working in collaboration with the Center for Disease Control, we used the first, second, and finally, third and reliable assay for detecting antibodies to HIV-1. In those studies, we used bloods which we had taken prospectively from those coming in for neurobiological and treatment research from 1969 onward (Des Jarlais *et al.* 1984; Novick *et al.* 1986ab). What we learned was that there was no HIV-1 positivity from 1969-1977, but in the New York City catchment area we were studying, HIV-1 antibodies began to appear in parenteral drug abusers in 1978, and by 1981-82, over 50% of untreated heroin addicts were HIV-1 positive - an astonishing finding! These studies were conducted in my laboratory in 1983-1984. Des Jarlais, connected to our Center, has continued to conduct similar studies, and has found that since 1992, with the help of AIDS risk reduction education and practical efforts, the prevalence of HIV-1 infection has dropped below 50% in the parenteral drug abusing population not in treatment. (Des Jarlais *et al.* 1989).

At the same time that we conducted that initial AIDS study in untreated heroin addicts in 1983-1984, we were able to look at a cohort of heroin addicts who had entered, and remained in, an effective methadone maintenance treatment program prior to the epidemic hitting New York City in 1978. We found that only 9% were anti-HIV-1 positive in 1984, as contrasted with 50-60% of untreated heroin addicts who were HIV-1 positive at that time (Table 5) (Des Jarlais *et al.* 1984; Novick *et al.* 1986a). We reported this immediately in the CDC Weekly, since a rigorous scientific or clinical peer reviewed journal publication could have taken over a year to get the information out (Des Jarlais *et al.* 1984; Novick *et al.* 1986a). The World Health Organization also published an article two years later (Novick *et al.* 1986b). However, when I went to WHO in the summer of 1984 with this information, the official response was, "We don't have any heroin addiction in Europe. It is only a problem in the U.S.". I replied, "I do not think that it is true because we have collaborations going on in many countries, including right here in Switzerland, in France, as well as in Denmark, and we know that you in Europe (like us) have hepatitis B, spread by unsterile needles, because of heroin addiction" (Des Jarlais *et al.* 1984; Novick *et al.* 1986ab). Two years later, with the widespread recognition of parenteral drug abuse as the second, or even first, risk factor for HIV-1 infection (in Europe, as well as in the U.S.A.), I was called back to the WHO and asked to repeat my findings, and I did so, and of course, we all know what happened next, with the acceptance and proliferation of pharmacotherapy for heroin addicts.

My laboratory and many others very early on were concerned about co-morbidity and concomitant medical diseases in the heroin addicted population. In addition to HIV-1, which had been first reported in 1981, we had identified that hepatitis B markers (indicating prior or active infection) were present in over 90% of untreated heroin addicts from our prospective studies begun in 1964 up through 1985 (Borg *et al.* 1999; Kreek 1973b. 1978; Kreek *et al.* 1972, 1990a; Novick *et al.* 1981, 1985, 1988). As soon as hepatitis C virus was identified and markers available, we were again able to go back to prospectively banked sera and now know that from at least 1978 onward, hepatitis C affected over 80% untreated addicts (Novick *et al.* 1997). The prevalence of all three of these viruses are now being reduced, at least in the New York City area, as a result of AIDS risk reduction education, as well as enhanced intervention and treatment efforts (Borg *et al.* 1999). Depression, phobic disorders, anti-social personality and general anxiety disorders, our laboratory and many other groups in this country and elsewhere have found to be very prevalent in heroin addicted populations (Mason *et al.* 1998).

There are now 179,000 persons in the U.S. in methadone maintenance treatment. Volunteer retention in treatment for one year or more is 60 to 85%, and the prevalence of continuing illicit use of heroin drops to below 5 to 20% (Table 6). Methadone (as well as LAAM and buprenorphine-naloxone) prevents withdrawal symptoms, prevents drug hunger, and blocks euphoric effects of superimposed short-acting opiates, and is medically safe as we showed in the 1964 studies, and many others at Yale, University of Pennsylvania, and elsewhere have replicated the findings since (Dole *et al.* 1966ab; Kreek 1978, 1991a, 1992a; Novick *et al.* 1993). Also, chronic methadone pharmacotherapy allows normalization of heroin-disrupted physiology (Cushman and Kreek 1974ab; Kreek 1972, 1973bc, 1978, 1991a, 1992a; Kreek and Hartman 1982; Kreek *et al.* 1981, 1983a, 1984a). The mechanism of action of methadone is by its long-acting pharmacokinetic properties in humans providing steady state levels of opioid effects at specific opioid receptor sites, which we now know is the mu opioid receptor.

In 1997, Harold Varmus and Alan Leshner, Director for the National Institute of Health and Director of the National Institute of Drug Abuse, convened the National Consensus Conference at the NIH, on "Effective Medical Treatment of Opiate Addiction." At that conference, after two days of presentations, the jury concluded unequivocally that pharmacotherapy, primarily utilizing methadone (or else alternatively, LAAM or in the future, buprenorphine-naloxone), needed to be much more widely used in treatment of heroin addiction. Medicalization also was recognized to be essential, requiring dramatic changes of Federal regulations governing treatment (Rettig and Yarmolinsky 1995). This consensus report was released very recently, both in JAMA and directly from the NIH (*JAMA* 1998).

II. HYPOTHESES ON VULNERABILITY TO DEVELOP AND MOLECULAR NEUROBIOLOGICAL BASIS OF ADDICTIONS: ROLE OF THE ENDOGENOUS OPIOID SYSTEM

The second epic of our work could be said to have started in 1967 when we developed two sets of hypotheses about the vulnerability to develop and the molecular neurobiological basis of addictions, and the related role of the endogenous opioid system. At that time, we hypothesized that three different domains of factors could be involved in the addictions. As you see these now, it is history, because there is ample evidence from many laboratories, including our own, that each of these domains indeed plays a role in each major addiction. What we hypothesized is that there could be 1) genetic factors, probably involving multiple alleles of multiple genes, acting in concert, to increase or decrease the vulnerability to develop addiction, once self-exposed to the drug of abuse; 2) secondly, we hypothesized that drugs of abuse might alter physiology, with or without a genetic or early environmentally-induced vulnerability, and that these alterations in physiology might be persistent or permanent; 3) and thirdly, we hypothesized that there would be multiple host-response factors in exposure to drugs of abuse, including altered physiological and pathological states, as well as psychological states, the role of conditioning and learning, "set and setting," and a variety of other developmental and environmental factors (Bond *et al.* 1998; Dole *et al.* 1966ab; Kreek 1972, 1973bc, 1987ab, 1991a, 1992a, 1996a).

We also hypothesized that atypical responsivity to stress and stressors may contribute to the acquisition and persistence of and relapse to self-administration to drugs of abuse and addictions, and that such atypical stress responsivity in some individuals may precede the use of addictive drugs, with genetic, environmental and direct drug-effects, each contributing to this altered stress responsivity (Bond *et al.* 1998; Culpepper-Morgan and Kreek 1997; Cushman and Kreek 1974b; Kreek 1972, 1973bc, 1987ab, 1992a, 1996a; Kreek and Hartman 1982; Kreek *et al.* 1981, 1983a, 1984a; Schluger *et al.* 1998a). We also hypothesized that the endogenous opioid system, (which was already conceptualized by Dole, and by Martin and Collier, who had always talked about specific opioid receptors from 1963 onward, but which were not unequivocally delineated until later) playing a central role in the addictions (Kreek 1992a, 1996ab; Kreek and Hartman 1982; Kreek *et al.* 1981, 1983a, 1984a; 4,26-29,33,38 In 1973, Snyder, Simon, and Terenius demonstrated that opioid receptors do exist, and with use of increasingly selective chemical ligands, the three types of opioid and receptors were defined that were later, in 1992 onward, cloned - the mu, delta and kappa opioid receptors. Three classes of endogenous opioids (the enkephalins, dynorphins and beta-endorphin from proopiomelanocortin) have been defined, each with a single gene yielding a single large peptide, which is in turn processed to several biologically active peptides. A new fourth class of endogenous opioids (the endomorphins) has been characterized, but their parent peptide has not been identified and the gene encoding these peptides not yet cloned.

Heroin acts primarily on the endogenous opioid system, but also affects other systems, including the dopaminergic system, through inhibition of the normal GABAergic inhibitory control, primarily in the ventral tegmental area. Cocaine acts primarily on the presynaptic reuptake transporter of dopamine, as well as at the reuptake transporters of serotonin and norepinephrine, but we hypothesized and now many groups, including ours, have shown that cocaine also affects the endogenous opioid system. Alcohol affects both the dopaminergic and opioid systems, as well as the serotonergic, noradrenergic, GABAergic, and excitatory amino acid neurotransmitter systems. There are similarities and there are also differences in each of these drug actions. Dopaminergic neurons in the substantia nigra which projects to the caudate putamen regions of the striatum, or the nigrostriatal system, and a second mesolimbic-mesocortical dopaminergic system, which has dopaminergic neurons in the ventral tegmental area projects to, with dopamine release, in the nucleus accumbens, as well as in the amygdala and in the anterior cingulate and in some other regions, are impacted upon by drugs of abuse and play a role in their effects. A third dopaminergic system is the tuberoinfindibular dopaminergic system, which also is affected. In each case, we have hypothesized and have documented that there may be linkages with the endogenous opioid system, and these linkages may, in fact, both contribute to the development, continuation of and relapse to addiction and drug use.

In the early work of our NIH-NIDA Center, we modified existing solution hybridization mRNAse protection assay techniques to be more sensitive and more quantitative, by using larger riboprobes and by using a more stable internal standard that is not affected by aging or drugs of abuse. By bringing the tools of analytical chemistry and by using both sense and anti-sense probes to construct calibration curves, after establishing the

major hybridized species on gels, we use TCA precipitation and quantitation of hybridization products for better throughput, a methological approach worked on by Inturrisi, Branch, Robertson, Spangler, LaForge and Yuferov and others in our Center (Branch *et al.* 1992; Pham *et al.* 1998; Spangler *et al.* 1993a, 1996a). We then went back to re-map the brain with respect to precise levels of opioid peptide and receptor gene expression, expressed in picograms/per microgram or molar equivalent of mRNA, for genes of interest compared to an internal standard. In work done by Spangler, Yuferov, LaForge, Unterwald, Branch, Zhou and others, we found that proenkephalin and prodynorphin and mu, kappa and delta opioid receptor (and also, orphan opioid-like receptors) gene expression is abundant in these very areas of abundant dopaminergic terminals from both the nigrostriatal and mesolimbic-mesocorticol dopaminergic systems, the caudate putamen, nucleus accumbens, amygdala and anterior cingulate (Branch *et al.* 1992; LaForge *et al.* 1995, 1997; Peluso *et al.* 1998; Pham *et al.* 1998; Spangler *et al.* 1993a, 1995; 1996ab, 1997a; Yuferov *et al.* 1996, 1999).

Recently, Wang and Spangler and colleagues in our group have shown that subacute intermittent morphine increases preprodynorphin and kappa opioid receptor mRNA levels in rat brain significantly (Wang *et al.* 1999). In other related work, Zhou and colleagues in our group has found that intermittent short-acting morphine administration also alters gene expression (mRNA levels) of important peptides and steroids of the stress responsive axis (Zhou *et al.* 1999a).

III. ROLE OF ATYPICAL RESPONSIVITY TO STRESSORS IN THE DEVELOPMENT OF, PERSISTENCE OF AND RELAPSE TO ADDICTIVE AGENTS: THE RELATED ROLE OF THE ENDOGENOUS OPIOID SYSTEM

The next epic of our work could also be said to have begun in 1967, with first reports in 1972 and 1973 and continuing in the 1980s using new, improved analytical techniques then available and right through the present day, including *in vivo* studies in humans and in animal models (Culpepper-Morgan and Kreek 1997; Cushman and Kreek 1974b; Kennedy *et al.* 1990; Kosten *et al.* 1986ab, 1987, 1992; Kreek 1972, 1973bc, 1978, 1992a, 1996b; Kreek and Hartman 1982; Kreek *et al.* 1981, 1983a, 1984ab; Rosen *et al.* 1995, 1996; Samyai *et al.* 1998ab; Spangler *et al.* 1997b; Zhou *et al.* 1996abc, 1999b). We conducted studies directly asking the question of the potential role of atypical responsivity to stressors in the development, persistence and relapse to addictions and the involvement of the endogenous opioid system. One aspect of the stress responsive axis (but only one part) a part which we can study in humans is the hypothalamic-pituitary-adrenal axis, with CRF released from the hypothalamus acting to drive the production and release of proopiomelanacortin peptides (POMC), beta-endorphin and adrenocorticotropin (ACTH) with the ACTH acting at the adrenal cortex to enhance release of cortisol, which then acts with negative feedback modulation at both the hypothalamus and the anterior-pituitary. We hypothesized (and there were various early findings that supported this hypothesis), that the endogenous opioids might also tonically modulate, through chronic inhibition, this stress responsive HPA axis, both at the hypothalamic and anterior pituitary sites of action.

In our early clinical research, started in 1964 with our prospective studies and then intensified from 1967 onward, we found that in humans, short-acting opiates, such as heroin both on an acute and on chronic basis, suppress the HPA axis in humans (whereas in contrast, short-acting opiates activate this axis acutely in rodents) Krreek 1972, 1973bcd, 1975, 1978, 1979, 1983, 1992a, 1996b; Stimmel and Kreek 1975ab). Methadone maintenance allows normalization of that HPA axis, with normal levels and normal circadian rhythm of the hormones of that axis (Cushman and Kreek 1974b, Kreek 1972, 1973bcd, 1975, 1978, 1992a, 1996b; Kreek *et al.* 1981, 1983a, 1984a; Zhou *et al.* 1996c). In contrast, opiate withdrawal is occurring three to six times each day in active heroin addicts, and is characterized by activation of the HPA axis (Cushman and Kreek 1974b; Kreek 1992a, 1996b; Stimmel and Kreek 1975ab). In more recent studies by Kennedy, in my laboratory, as well as other studies in collaboration with Kosten and colleagues, and most recently, in studies by Culpepper-Morgan, we have found that opiate withdrawal is, in fact, preceded by activation of the HPA axis (Culpepper-Morgan and Kreek 1997; Kennedy *et al.* 1990; Rosen *et al.* 1995, 1996). The signs and symptoms of objective withdrawal are actually preceded by elevation of hormones of this axis, which then may contribute to the abstinence syndrome. Our group and others also have shown that opioid antagonists, both in healthy subjects, as well as those with addictive disease, activate this axis, as does cocaine, and the acute and chronic administration of alcohol, in humans, and animal models (Albeck *et al.* 1989; Chou *et al.* 1993; Culpepper-Morgan *et al.* 1992; Farren *et al.* 1999; Hahn *et al.* 1983; Hartman *et al.* 1983; Kosten *et al.* 1986ab; Kreek 1975, 1981a, 1984b,

1986; 1987a, 1990a, 1992b, 1996cd; 1997a; Kreek and Culpepper-Morgan 1991; Kreek and Koob 1998; Kreek *et al.* 1983bc; Ragavan *et al.* 1983; Rosen *et al.* 1995, 1996; Schluger *et al.* 1998a; Spangler *et al.* 1997b; Unterwald *et al.* 1994a, 1997; Zhou *et al.* 1996ab). Zhou and Unterwald, in our group, have shown that methadone, which has a half-life of 60 minutes in a mouse and 90 minutes in a rat, thus needing to be administered by pump to achieve steady state, when thus administered, results in no disruption of stress responsive gene expression or of hormone levels, in sharp contrast to intermittent morphine (Burnstein *et al.* 1980; Kreek 1981b, Unterwald *et al.* 1995; Zhou *et al.* 1996c).

There are three opioid antagonists which can be introduced in clinical research studies: naloxone, naltrexone, and more recently, nalmefene. These have different pharmacokinetic profiles, as well as metabolic profiles. Naloxone has minimal systemic bioavailability after oral administration; early findings in our group from studies of a methadone-naloxone oral combination led to the recognition of the ability to combine naloxone with buprenorphine for a combination product to prevent a potential parenteral abuse liability of buprenorphine. We actually reported in 1973 on an orally administered naloxone-methadone combination, but which was not needed in therapeutics because methadone has a very limited parenteral abuse liability (Kreek 1973). The half-life of naloxone is one to two hours in humans and less than 2% systemic bioavailability after oral administration (Albeck *et al.* 1989; Chou *et al.* 1993; Culpepper-Morgan *et al.* 1992, 1995; Farren *et al.* 1999; Hahn *et al.* 1983; Kreek *et al.* 1983bc, Rosen *et al.* 1995, 1996; Schluger *et al.* 1998a). Naltrexone has greater systemic bioavailability (20% to 30%) because of rapid plasma production and tissue binding and a half-life of 5 to 6 hours in humans (Farren *et al.* 1999; King *et al.* 1997; Kosten *et al.* 1986, 1987, 1992; Kreek 1975, 1983, 1996d; Kreek *et al.* 1984b; Schluger *et al.* 1998a; Unterwald *et al.* 1997). Nalmefene has even greater systemic bioavailability (over 70%) after oral administration, with a half-life of 8 to 9 hours (Chou *et al.* 1993; Schluger *et al.* 1998a). Two of these antagonists, naloxone and naimefene, are cleared by glucuronidation; the third, naltrexone, by oxidative metabolism. Using human brain membranes, it has been recently shown by Emerson that, similar to findings in rodent membranes, naloxone, nalmefene, and naltrexone act primarily at mu opioid receptors; however, different from the rodents, both nalmefene and naltrexone have appreciable action, with high affinity, at kappa opioid receptors, whereas naloxone does not; and all three have very limited binding on action at the delta opioid receptors (Emerson *et al.* 1994).

Recently, Schluger in our group took advantage of this difference in opioid receptor afftnities and compared the effects of intravenously administered naloxone and nalmefene in healthy human volunteers (Schluger *et al.* 1998a). He has found that both high (10 mg) and very high (30mg) of naloxone significantly activate POMC peptides as measured here by plasma ACTH levels, as well as peripherally, cortisol levels. Nalmefene at high (10 mg) and very high (30mg) doses delivered intravenously had a highly significantly, greater activation of POMC peptides, as well as cortisol, than did naloxone, also administered at maximally effective doses, suggesting that the tonic inhibition at hypothalamic-pituitary sites is both by kappa - directed dynorphin opioid peptides, as well as mu opioid receptor directed endogenous opioids, probably primarily beta endorphin and met-enkephalin-arg-phe. These studies have shown that not only do the glucocorticoids (cortisol in man and corticosterone in rat and mouse), but also endogenous opioids of both mu and kappa receptor directed types play a role in the normal tonic regulation of the HPA axis.

Metyrapone is a compound which blocks the 11-beta-hydroxylation, the last step of cortisol synthesis, and in humans, more dramatically so than in rodent model, thus, abruptly, significantly reducing even basal levels of the glucocorticoid (in humans), cortisol. We started using this compound in 1967 studies using an older protocol of multiple oral doses of metyrapone, with measuring the three day, 24 hour urinary excretion of the precursors of cortisol as the end point (Cushman and Kreek 1974; Kreek 1972, 1973bc, 1978). More recently, we have conducted studies using a single dose of metyrapone and measuring directly the neuropeptides ACTH and beta-endorphin in peripheral blood (Kennedy *et al.* 1990; Kreek 1992a; 1996ab; Kreek *et al.* 1984a; Schluger *et al.* 1998b). When metyrapone is given, there is a sudden drop in cortisol levels, leaving only the endogenous opioids to tonically inhibit release of CRF and in turn, the POMC peptides, beta-endorphin and ACTH from the anterior pituitary. We have shown in our earlier studies, and redocumented in our more recent studies using the single dose test in heroin addicts, that there is a hypo-responsivity to this chemically induced stress (Cushman and Kreek 1974b; Kreek 1972, 1973bc, 1992c). In methadone maintained, former heroin addicts there is euresponsivity (Cushman and Kreek 1974b; Kreek 1972, 1973bc, 1992a; Kreek *et al.* 1984a). In drug-free former opiate dependent persons, who are not receiving any kind of medication and not using any illicit drugs,

we found in the mid-80's, provocatively, a hyper-responsivity to this chemically-induced stressor (Kreek *et al.* 1984a). Very recently, we have found a similar hyper-responsivity in recently abstinent cocaine addicts (Schluger *et al.* 1998b). These two findings suggest a relatively inadequate endogenous opioid tone in both abstinent former heroin addicts not receiving opioid agonist pharmacotherapy, and in recently abstinent cocaine addicts, leading to an inability to counter-regulate by the opioids in the HP part of the HPA axis.

Methadone maintenance treatment, we have found, allows normalization of stress responsivity in the HPA axis, the POMC peptides, as well as cortisol and circadian rhythm thereof, and in animal models also of that part of stress responsivity other than the HPA axis, that is, in the amygdala and the prefrontal cortex, as well as other regions (Kreek 1992, 1996abc, 1997b; Kreek and Koob 1998; Zhou *et al.* 1996c).

Also, not to be discussed today, our group and others have found normalization of reproductive biology. Along with the groups of Mendelson and Cicero and others, we have found that the disruption by short-acting opiates such as heroin, becomes normal during extended methadone maintenance treatment (Cushman and Kreek 1974a; Kreek 1978, 1983).

Also, not to be discussed further today, but mentioned by Dr. Adler, we have found that natural killer cell activity, which is profoundly altered (reduced) in active heroin addicts, becomes normal in steady dose methadone maintained patients. We have gone on to show at the bench, as many other groups now have, the impact of endogenous versus exogenous opiates, especially the on-off effects of short-acting exogenous opiates and also of alcohol on specific parameters of immune function either *in vivo* or *in vitro* (Bodner *et al.* 1998; Kreek 1990bcd, 1991b; Novick and Kreek 1992; Novick *et al.* 1989, 1991; Ochshorn-Adelson *et al.* 1990, 1994ab).

IV. MOLECULAR NEUROBIOLOGICAL BASIS OF COCAINE ABUSE AND ADDICTION

The fourth epic of our work began in 1986 after I made the determination, based on our clinical findings, that so many heroin addicts at that time had co-dependency with cocaine. The cocaine epidemic had soared from 1970 to 1985. In 1985, "crack' or "free base" cocaine surfaced in New York, and the numbers of those abusing and addicted to cocaine increased even further. We found large numbers of persons who started with cocaine addiction turned to opiate addiction, with opiate use as self-medication for some of the side effects of cocaine, and many cocaine abusers or addicts developing opiate addiction. By the mid-80s over 70% of all heroin addicts entering methadone maintenance, or other pharmacotherapy treatments, were in fact co-dependent with cocaine (Borg *et al.* 1999; Kreek 1987a). Dopamine, and also serotonin and norepinephrine, are involved in primary action of cocaine, with cocaine's action to block all three neurotransmitter transporters, causing enhancement in monoamine neurotransmitters in the perisynaptic region, with resultant enhanced activation of D1, D2 and D3-5 dopamine receptors when they are present in a specific brain region. An opposing effect on the adenylyl cyclase and other single transduction mechanisms, is found because these different dopamine receptors may differentially increase or decrease adrenal cyclase (Unterwald *et al.* 1996).

In our laboratory, we developed, in the rat, a "binge" pattern model of cocaine abuse, since this is the pattern most commonly used by human abusers and addicts of cocaine. In this particular model, three doses of cocaine are administered one hour apart, and then no other cocaine for the remainder of the 24 hours (Branch *et al.* 1992; Unterwald *et al.* 1992). Using the technique of microdialysis in freely moving animals, Maisonneuve in our group has determined that the levels of dopamine after one day of "binge" pattern cocaine (Maisonneuve and Kreek 1994). We found, as many previous investigators had found, there is a prompt rise of dopamine levels in extracellular fluid after each one of the three doses of cocaine, with levels of dopamine becoming escalated in parallel with levels of cocaine in those brain regions which we measured, both in the caudate putamen, as well as the brain region which has been linked with the reinforcing effects of drugs of abuse, the nucleus accumbens (Maisonneuve and Kreek 1994). However, after 14 days of "binge" pattern cocaine administration, we found three very intriguing things (Maisonneuve *et al.* 1995). First, the extracellular levels of dopamine at baseline were significantly lower than in animals who had received cocaine on a chronic basis. Secondly, after each dose of cocaine, the actual extracellular levels of dopamine that were achieved were less than after the first exposure to cocaine. Thirdly, the amplitude of rise in extracellular dopamine levels was just as great as after the first day of "binge" doses of cocaine. It is intriguing to think that these lower levels of dopamine after chronic use, at both

basal time points and after cocaine administration, may contribute to what the addict tells us, the need to take increasing amounts of cocaine to attempt to achieve a "high" or euphoria, and that the first "high" was greater than all subsequent "highs."

Ho and Unterwald conducted parallel locomotor activity studies in the rat model of "binge" pattern cocaine administration, with all studies conducted in home cage, in a stress-minimized environment to minimize novelty and cueing effects (Unterwald *et al.* 1994b). We found that acutely, every dose of cocaine activates levels of locomotor activity, and chronically, even with regular daily administration of this "binge," irregular pattern of administration, sensitization clearly had occurred (Unterwald *et al.* 1994b). Quinones-Jenab in our group has recently shown that female rats respond even more rigorously and with a more disruptive, almost sensitized-type pattern, than do male rats following acute "binge" pattern cocaine administration and has shown in further studies that this happens primarily during the estrous phase of the menstrual cycle (Quinones-Jenab *et al.* 1999). Thus, in these and other studies in female rats, there is evidence that this interaction of the estrogen hormones plays a role in response to cocaine (Quinones-Jenab *et al.* 1997). Ho and Schlussman are getting increasingly involved in studies in transgenic and "knock-out" mice models (Schlussman *et al.* 1998). They have studied the 129 strain mice that contributes most of the embryonic stem cells used in the constructs for transgenic mice, and their response to "binge" pattern cocaine (Schlussman *et al.* 1998). Very little locomotor response for cocaine is observed in the 129-J strain of mice studied as contrasted to C57BL/6J strain often used as breeding pairs which showed a very dramatic response to cocaine again, with all studies conducted in home cage.

We were able early on to conduct the first studies in living rats using selective radiolabeled ligands both for the D1 and D2 dopamine receptors using positron emission tomography (PET) technology modified for selective ligand studies on rats (Kreuter *et al.* 1998; Maggos *et al.* 1998; Tsukada *et al.* 1996; Unterwald *et al.* 1997). We took our scientists to Japan to work with the group at Hamamatsu who developed a PET machine with around 2 mm resolution, thus allowing quantitation in the rat striatum taken as a whole. Maggos, Schlussman, Kreuter and Tsukada and others working on this project found that acute or subacute cocaine administration does not alter either D1 or D2 dopamine receptors (Tsukada *et al.* 1996). After seven days of "binge" pattern cocaine, there is also a significant lowering or reduction in binding at D1 sites which persists at 14 days; and after 14 days of "binge" pattern administration, there is also a significant reduction at D2 sites (Tsukada *et al.* 1996). The D2 receptors have been shown by Volkow to be reduced in human cocaine addicts during early and protracted abstinence (Volkow *et al.* 1993). Studies are yet to be performed in D1 dopamine receptors in human cocaine addicts. In a sequence of two more sets of studies, we went back to Japan with our neuroscientists and asked the question "How long does it take to recover?" In fact, with respect to both the D1 dopamine site and the D2 dopamine sites, Maggos, Kreuter and Schlussman found that it takes longer to recover than to cause the problem of dopamine receptor "down regulation," with no recovery at either D1 or D2 dopamine receptor at one day; after ten days the D1 dopamine receptor sites recover back to normal binding, and after 21 days recovery to normal binding potential at the D2 sites occurs (Maggos *et al.* 1998; Kreuter *et al.* 1998).

Perret and Schluger in our group have shown that chronic "binge" pattern cocaine administration causes significant alterations in 5HTIA serotonergic receptors, specifically in the dentate gyrus and in the ventral medial hypothalamus, now linked with depression (Perret *et al.* 1998).

Unterwald in 1992 first reported that cocaine, administered in a "binge" pattern for over 14 days significantly increases mu opioid receptor density; specifically, chronic cocaine administration alters mu opioid receptor expression in regions of the dopaminergic terminals in the caudate putamen, the nucleus accumbens, the amygdala and the anterior cingulate (Unterwald *et al.* 1992). Importantly, Zubieta, Gorelick, Frost and colleagues at Hopkins in studies a few years later showed that in recently abstinent human cocaine addicts, there is a similar increase in human mu opioid receptor density in several specific regions of the brain as measured by PET, again, those with the mesolimbic-mesocorticol dopaminergic system terminals (Zubieta *et al.* 1996). Yuferov in our group very recently, along with the group of Cox, has reported that acute "binge" pattern cocaine causes increases in mu opioid receptor mRNA levels and again in the nucleus accumbens, the amygdala and the prefrontal cortex, the areas seen, again and again, to be involved in many of these responses to cocaine (Azaryan *et al.* 1996ab; Yuferov *et al.* 1999).

Unterwald went on to show that chronic "binge" pattern cocaine administration causes increases in kappa opioid receptor density and again, in the dopaminergic terminal fields - the caudate putamen, nucleus accumbens, and also anterior cingulate, where the dopaminergic terminals exists.

At this meeting several years ago, Zhou reported and continues to build upon the findings that "binge" pattern cocaine administration causes changes in gene expression (of quantitative mRNA levels) of CRF, with significant increases on the first day, but intriguingly, after 14 days, an actual reduction of gene expression of CRF (Zhou *et al.* 1996). Like many groups, he found that acutely and subacutely cocaine enhances ACTH levels and corticosterone levels, but intriguingly, after chronic cocaine administration, he discovered that although ACTH and corticosterone levels are still elevated, they are significantly less elevated than after acute and subacute administration, making it very clear that tolerance occurs with respect to the chronic "binge" pattern administration effects on activating the stress responsive axis, a finding recently confirmed in humans by the Mendelson-Mello group (Mendelson *et al.* 1998; Zhou *et al.* 1996). Spangler, Zhou and Schlussman also found that either D1 or D2 dopamine receptor selective antagonists would block the cocaine activation of the HPA axis hormones (Spangler *et al.* 1997b). Very recently, in collaboration with Greengard's group at Rockefeller using the DARPP32 "knock-out" mouse model (DARPP32 being a signal transduction pathway primarily for D1 type dopamine receptors, but also D2) we find an attenuation of both ACTH and corticosterone elevations following "binge" pattern cocaine administration in the DARPP32 deleted mice (Zhou *et al.* 1999b).

At this CPDD meeting in 1992, Spangler, using the "binge" pattern cocaine administration model, and McGinty using the self-administration model, in rats both reported that chronic cocaine significantly enhances preprodynorphin gene expression in the caudate putamen (Daunais and McGinty 1995; Spangler *et al.* 1993ab). Spangler has gone on to show that both acute, subacute and chronic intermittent "binge" pattern cocaine administration causes significant increases in preprodynorphin gene expression (mRNA levels) and thus, this is a persistent effort (Spangler *et al.* 1996b, 1997a). Spangler has gone on to show that in the substantia nigra, the brain region which would be expected to get the greatest load of dynorphin peptides from the enhancement of dynorphin gene expression in the striatum, through the striatonigral pathway, one sees a significant reduction in kappa opioid receptor gene expression (Spangler *et al.* 1996a). Thus, a negative feedback mode, regulated by dynorphin acting at kappa opioid receptors exists, initially caused by cocaine-induced activation of D1 dopamine receptors. Thus, increased dynorphin gene expression during cocaine administration results in a full counter-regulatory mechanism (involving also adenylyl cyclase mediated signal transduction) (Claye *et al.* 1996). Spangler and Maggos have gone on to show that D1, but not D2 dopamine antagonist will block the cocaine-induced increase in dynorphin mRNA levels, with no effect on dopamine transporter (DAT) mRNA levels (Maggos *et al.* 1997; Spangler *et al.* 1996b).

Building on the earlier work of Spanagel and Shippenberg; studying the effects of synthetic kappa opioid receptor ligands, and Claye in our group has found that the natural opioid, dynorphin A_{1-17}, directed at kappa opioid receptors when instilled into the nucleus accumbens, using techniques of microdialysis, causes a significant reduction in basal dopamine levels in freely moving rats (Claye *et al.* 1997).

The hypothalamic-prolactin axis in humans is a promptly accessible window into dopaminergic tone, specifically the dopaminergic tone in the tuberoinfindibular dopaminergic system. In humans, dopamine essentially exclusively controls through tonic inhibition, the release of prolactin by the pituitary lactotopes. We hypothesized, based on our very early work, that kappa as well as mu opioid receptor ligands may regulate this system. We had found that during chronic methadone maintenance treatment, in fact, the prolactin release enhancing effect of the long-acting synthetic opioid, though levels not into the abnormal range, is the one mu opioid receptor effect to which tolerance does not develop (Kreek 1978). Therefore, we hypothesized that dynorphin A_{1-13}, a shortened version of dynorphin A_{1-17}, but a natural sequence, by acting directly or indirectly to lower dopaminergic tone, might cause an elevation of serum prolactin levels (King *et al.* 1999; Kreek *et al.* 1994, 1999). Using matrix assisted laser-desorption-mass spectrometry, in collaboration with the Rockefeller laboratory of Chait, we have developed a technology for measuring the kinetics of dynorphin and dynorphin analogs and found that dynorphin $A_{1-13}$is is probably transformed in humans more rapidly than dynorphin A_{1-17} but nevertheless, has substantial biological activity (Chou *et al.* 1994, 1996; Kreek *et al.* 1999; Yu *et al.* 1996ab). We then went on to study healthy volunteers with no history of drug abuse or addiction. When dynorphin A_{1-3}, at low dose or high dose, is given intravenously, there is a prompt rise in serum prolactin levels,

which then returns to baseline within 90 minutes (Kreek *et al.* 1999). We also found that this is a mu, but also a kappa opioid receptor-mediated event, since naloxone will attenuate this prolactin release effected by dynorphin, but nalmefene, an opioid antagonist that has both mu and kappa opioid receptor directed action, has an even greater attenuation effect (Kreek *et al.* 1999).

Butelman in our group, working in the female rhesus monkey, also has shown that natural dynorphin A_{1-17} causes rapid rise in prolactin, whereas the major biotransformation product of dynorphin in man and in monkey, dynorphin A_{2-17}, a non-opioid peptide, has no effect on prolactin release (Butelman *et al.* 1999c). Thus, dopaminergic tone in the tuberoinfindibular system is reduced by the natural peptide dynorphin action at kappa opioid receptors. Also, dopaminergic tone reduction, as evidenced by elevations in serum prolactin levels as observed after administration of the commonly studied synthetic kappa agonists, has been observed after administration of Eisai-2078 a peptide that has primarily kappa opioid activity. We suggest that this synthetic peptide, which passes the blood brain barrier, could be a prototype for a therapeutic agent to modulate dopaminergic tone to deter stimulant abuse, and also possibly to manage heroin addiction and chronic pain (Butelman *et al.* 1999bc; Portenoy *et al.* 1999; Specker *et al.* 1998; Yu *et al.* 1997ab).

V. HUMAN MOLECULAR GENETICS AND THE ADDICTIONS: POSSIBLE ROLE OF ALLELIC VARIANTS IN INDIVIDUAL DIFFERENCES IN RESPONSES RELATED TO OPIOIDS

The last epic of our work began in 1994 when we began to ask the question of the role of human molecular genetics in the addictions, and the role of any observed polymorphisms in response to drugs of abuse. We have hypothesized that single nucleotide polymorphisms (SNP's) might exist which, with or without consequences, can serve as markers for the genetic basis of the addictions, and which, if present in coding regions, might result in amino acid residue changes which, in turn, could result in changes in receptor function. We have now found, in studies done in collaboration over the last five years with the group of Lei Yu, then at Indiana University, and now at Cincinnati University, five different single nucleotide polymorphisms within the coding region of the human mu opioid receptor gene (Bond *et al.* 1998). Three of these result in amino acid changes; two of these which result in amino acid changes are very high allelic frequency of 10.5 and 6.6% respectively (Bond *et al.* 1998). We have gone on to examine possible allele associations of these, with the collaboration of Ott and Leal at the Rockefeller University, both statistical geneticists. There were significant differences of each of these alleles across ethnicities. For the C17T variant, we are close ($p=0.054$), but without finding a significant relationship between the presence of the C17T allele and the presence of opioid dependency (Bond *et al.* 1998). However, with the A118G, there was no significant relationship with opioid dependency. We have gone on to study possible binding and functional alterations of the most frequent of these, the A118G allelic variant (Bond *et al.* 1998). These studies were conducted in collaboration with Yu's group. We have found that, whereas most synthetic and natural opioids bind normally to the A118G variant, beta-endorphin has a three-fold shift showing three-fold increase in binding activity at the A118G variant than at the prototype mu opioid receptor (Bond *et al.* 1998). When signal transduction, specifically the G-protein coupled inwardly rectifying potassium currents was studied in appropriate cellular constructs, again most ligands were normal, when the A118G variant was compared with the prototype allele, but after binding of beta-endorphin at the A118G variant allele, there was a leftward shift, with three-fold increased activation as contrasted to binding to the prototype mu receptor (Bond *et al.* 1998).

Possible functional differences of mu opioid receptor and other receptors and ligands might explain, in part, the physiological and functional differences in human responses to a drug of abuse, or pain medications (pharmacogenomics) as well as to each of our own endogenous opioids ("physiogenomics"). We therefore have extended these studies, and to enhance through-put identification of known SNP variants, we have formed a collaboration with the laboratory of Mirzabekhov at the Department of Energy in Argonne National Laboratories. My group, including LaForge, Yuferov and Spangler working there, as well as in our own laboratories, have created our own custom gel pad single nucleotide polymorphism microarrays, or as I call it, our "SNP chip." We have put on the gel pad microarray the two most common allelic variants identified so far, the change of prototype mu receptor nucleotides of A to G at the 118 position and the change of C to T at the 17 position. We can easily identify "wild-type" or prototypic homozygotes, heterozygotes with one copy of the atypical variant, and variant homozygotes. With the augmented capacity provided by our custom SNP chip

technology, we plan to study much further this mu opioid receptor gene and its variants, as well as many other genes.

It is intriguing and provocative to us that, to date, the medications which have been successful in the management of over 20 to 25% of those with heroin addiction and also alcoholism are those directed at the mu opioid receptor (Kreek 1996cd). For heroin addiction, all effective agents are long-acting opioid agonists or partial agonists, methadone, LAAM and buprenorphine (in combination with naloxone). For alcoholism effective treatments, most are opioid antagonists, naltrexone and nalmefene. It is also enormously provocative that studies both in methadone maintained patients, and more recently, studies using buprenorphine or buprenorphine-naloxone combination, it has been found in populations where co-dependency with cocaine is very high (70 to 90%), after one year stabilization of methadone treatment, the prevalence of continued cocaine dependence drops precipitously down to 20 - 30%, when effective counseling, access to medical and psychiatric care, along with appropriate doses of methadone or buprenorphine-naloxone are used (Borg *et al.* 1999; Kreek 1996c). However, it is also provocative to think that these medications directed at mu or mu-kappa receptor may play a part in stabilizing the endogenous opioid system in cocaine dependent persons. It may also offer us a blueprint for further pharmacological approaches to treatment of specific addictions.

I could get only two family members in the flume ride last month [May 1999]. Here, you see this one with Esperance, exuberant and happy, and you see me, poised and excited, about to face the new ups and downs, the splashes, the unexpected, the thrill of getting this Eddy Award today, and the challenges with what I see as my next 25 years in the molecular, neurobiological, genetic and behavioral research in the addictive diseases. I thank you all.

ACKNOWLEDGEMENTS: I would acknowledge our funding support from the NIH: DA-P50-05130, DA-K05-00049, DA-09444, M01-RR00102, and NYS:OASAS.

Goals and Rationale for Specific Pharmacotherapy for an Addiction

1. Prevent withdrawal symptoms
2. Reduce drug craving
3. Normalize any physiological functions disrupted by drug use
4. Target-treatment agent to specific site of action, receptor, or physiological system affected or deranged by drug of abuse

MJ Kreek, MD., 1994 (from Kreek, MJ; Addictive States (CP O'Brien and JH Jaffe, eds), Raven Press Ltd., New York, 1992)

Heroin versus Methadone*

	Heroin	Methadone
Route of administration	intravenous	oral
Onset of action	immediate	30 min
Duration of action	3-6 hrs	24-36 hrs
Euphoria	first 1-2 hrs	none
Withdrawal symptoms	after 3-4 hrs	after 24 hrs

*effects of high dosages in tolerant individuals

Kreek, 1976

Opioid Agonists

Compound	Systemic Bioavailability After Oral Administration	Apparent Plasma Terminal Half-life ($t_{½}$ Beta)	Major Route of Biotrans-formation
Heroin	Limited (<30%)	3 m (30 m for active 6-acetyl-morphine metabolite) (4-6 h for active morphine metabolite)	Successive Deacetylation and morphine glucuronidation
Methadone	Essentially Complete (>70%)	24 h (48 h for active 1-enantiomer)	N-demethylation

Kreek et al., 73,76,77,79,82; Inturrisi 1984

“On-Off” versus “Steady-State”

Disruption versus Normalization

- behaviors
- physiology
- receptor-mediated events
- levels of gene expression

Kreek, 1996

Prevalence of HIV (AIDS Virus) Infection in Intravenous Drug Users

New York City - 1984 Study

50-60% Untreated, street heroin addicts:
Positive for HIV antibody

9% Methadone maintained since < 1978 (beginning of AIDS) epidemic):
less than 10% positive for HIV antibody

Des Jarllais, Kreek et al., Morbidity and Mortality Weekly Report, 33: 377-379, 1984

Opiate Addiction Treatment Outcome*

Methadone Maintenance	60-80%
Naltrexone Maintenance	10-20%
"Drug Free" (non-pharmacotherapeutic)	5-30%
LAAM Maintenance	to be determined (early data like methadone)
Buprenorphine-Naloxone Maintenance	to be determined
Short-term Detoxification (any mode)	5-20%

*One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates.

Laboratory of the Biology of **Addictive Diseases and NIH-NIDA Research Center** The Rockefeller University — 1999

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SYMPOSIUM I

RECENT ADVANCES IN INHALANT ABUSE

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Although inhalant abuse is now recognized as a world-wide problem, relatively little is known about the mechanisms of action by which these substances produce their effects. Surveys of drug use show that a significant percentage of the population has used volatile solvents for their intoxicating properties. In the 1993 High School Survey, it was found that about 17% of adolescents in the US have sniffed inhalants at least once in their lives, and 2.5% of the sample of high school seniors had used inhalants within the past 30 days (Edwards and Oetting, NIDA Research Monograph 148, 1995). Inhalants are, after tobacco and alcohol, the major drug problem in Mexico. Volatile solvents are the substances most commonly abused by children and adolescents. The problem is more prevalent in street children. In a recent study, 11, 172 street children were identified, 75% between 12-17 years of age. The prevalence of lifetime use in this group was 27% and 22% reported daily use. Among high school students, inhalants are the substance of choice after tobacco and alcohol. In total, 4% reported lifetime use of these substances (Medina and Berenzon, NIDA Research Monograph 148, 1995).

After a brief introduction by Dr. Robert Balster, Dr. Maria Elena Medina-Mora and Dr. James Anthony presented recent information on the epidemiology of inhalant abuse in Latin America and the U.S., respectively. Dr. Silvia Cruz described the latest findings on the effects of volatile solvents on ligand-gated ion channels. Dr. Fernandez-Guardiola presented the results of his ongoing research on the effects of abused solvents on the patterns of sleep of solvent abusers. Short abstracts and/or lists of relevant readings for the presentations follow.

INHALANT ABUSE IN LATIN AMERICA

M.E. Medina-Mora and C. Fleiz

Mexican Institute on Psychiatry, Mexico

This work reviews current research on the epidemiology of inhalant abuse in the Latin America Region based on general surveys and studies taken among special groups. Comparisons are difficult to make because different definitions are used in different surveys and the substances used in each country are frequently not specified. The practice of inhalation is quite prevalent in the region. According to recent household surveys, rates of "ever inhaled' are 4.2% for the population 12 to I7 years in Colombia (Ospina 1996); 3.7% for the group between 12 and 19 in Peru (Ferrando 1990); 1.2 % for that between 12 and 18 in Chile (Fuentealba 1996); and 0.6% in Mexico (SSA 1998). Rates reported in the region are lower than those found in the United States (7.2%, SAMHSA 1997). In Mexico, thinner is the substance of preference (56% among males, 42% among females) among children and adolescents that earn their living, and it is followed by glue (40% and 44%, respectively); gasoline is reported by less than 5% of the users. In Mexico City, street children prefer toluene to glue because they consider it to be less damaging and to cause a less severe hangover. In Brazil, "lanca-perfume" (spray), "cola" glue, "cheirinho de lolo", ether, chlorophorm, benzene and hexane have been reported by street children (Murad 1983). In Peru, glue, gasoline, thinner, sprays, paint, poppers, deodorants and volatile anesthetics are used (Ferrando 1990). The studies reviewed suggest that there are 3 different typologies of abusers: i) Children and adolescents whose main abused drugs are inhalants being daily use the most common pattern; ii) multiple drug users that tried inhalants often as the first drug of abuse, the majority being experiments at the time of the study; iii) adults that continue to inhale. In the first two groups, solvents are abandoned as users mature and turn into marihuana, cocaine or alcohol. In the third group inhalant abusers show more deterioration and usually inhale when other substances are not available; this group includes imprisoned addicts or persons exposed at work. Minors used solvents for reasons conditioned by their poverty. Many children inhale toluene before going to sleep in order to avoid feeling cold while they sleep on the floor or while hungry, bored, sad, or fearful of

street. Some minors pretend to be able to control their "trip", while others loose control. While intoxicated, children might get confused and drink the solvent. Craving for the drug is often observed. Patterns of use may shift between daily use to complete abstinence. Although inhalant abuse is a prevalent problem in the region, linked to poverty and young age, there are many gaps in knowledge, weak definitions and many confounding factors that make it difficult to draw conclusions. Moreover, few studies have addressed consequences and long-term effects. There is an urgent need for more research and to integrate basic, clinical and social sciences.

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EPIDEMIOLOGICAL EVIDENCE AND ISSUES IN RESEARCH ON INHALANTS

***J.C. Anthony* — ABSTRACT UNAVAILABLE**

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NEURONAL BASES OF SOLVENT ABUSE

S.L. Cruz[1], R.L. Balster[2], and J.J. Woodward

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Organic solvents are the least studied drugs of abuse. These substances differ from other abused drugs in several ways: they are cheap, legal and easily available. A strong body of behavioral evidence indicates that solvents are Central Nervous System (CNS) depressants. This paper reviews recent evidence supporting the hypothesis that abused solvents, like other CNS depressants, inhibit NMDA receptors. In a first approach, we studied the effects of toluene on NMDA recombinant receptors expressed in Xenopus laevis oocytes. Toluene inhibited NMDA-induced currents in a dose-dependent fashion. This inhibition was rapid, almost complete (90 %) and reversible. It was also voltage-independent and non-competitive. Receptor subtype sensitivity was observed for the inhibitory effects of toluene, being the NR1/2B combination the most sensitive of all (IC_{50} = 0.17 ± 0.2 mM as compared with 1.4 ± 0.17 and 2.13 ± 0.27 for NR1/2A and NR1/2C, respectively; Cruz *et al.* 1998). Similar studies with benzene, m-xylene, ethylbenzene and propylbenzene revealed that non-competitive NMDA-inhibition may be a common mechanism of action for alkylbenzenes and, to a lesser extent, for 1,1,1-tricloroethane or TCE. All these drugs dose-dependently inhibited NMDA-induced currents in the submillimolar range. The same order of sensitivity for their inhibitory effects was observed for receptor subtypes being the

NR1/2B combination more sensitive than NR1/2A (Cruz *et al.,* 1998). In a second study we tested the hypothesis that toluene acted as an NMDA antagonist *in vivo*. For this purpose we studied the effects of toluene on NMDA-induced convulsions in male albino mice. Animals were injected with NMDA (120 mg/kg i.p.) immediately before placing them in a static exposure chamber to inhale different concentrations of toluene during 30 min. The results were compared with a control group injected with the same dose of NMDA. Toluene dose-dependently decreased the latency to the appearance of convulsions as well as their magnitude, Taken together, these results strongly suggest that NMDA inhibition is a common mechanism of action of abused solvents.

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EEG PATTERNS OF SLEEP AND REACTION TIME PRODUCED BY REPEATED USE OF ORGANIC SOLVENTS: A POLYSOMNOGRAPHIC AND SPECTRAL (3D) STUDY IN YOUNG INHALANT ABUSERS

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In a previous work we reported experimental results in cats showing the inducement of 3 Hz spike and wave EEG patterns in the cingulate gyrus, amygdala and cerebral cortex, by repeated dosages of the industrial solvents toluene and benzene. The animals displayed ataxia, head nodding, bilateral contraction of facial musculature and blinking. Toluene induced electrographic and behavioral changes similar to "Petit Mal" and benzene induced, in addition, changes similar to complex partial seizures in humans, followed by tonic-clonic seizures of "Grand Mal" epilepsy (Contreras *et al.* 1979). Although the amount of solvent to which we exposed our animals was quit high, the exposure lasted only few minutes. In humans, inhalation lasts often several hours. We now report on the results of all-night sleep studies in young addicts (24 subjects, 21.5 years in average, nine of them less than 18 years, 5 females and 19 males). Volunteers were detected by the "Ama la Vida" Foundation which is a Mexican center against addictions. For the aims of this study, subjects were submitted to two night sleep recordings after a previous habituation night in the same room and bed. The polysomnogram was normal in 5 subjects (20.8%); insomnia alone was evident in 4 (16.6%); motor activity with myoclonus and insomnia was displayed by 13 (54.2%) and seizures (3 per sec spikes and waves, "Petit Mal") and partial complex seizures (PCS) in 2 subjects (8.3%). One of the subjects with PCS was a 31-year-old male and had a 19-year history of solvent addiction. The Petit Mal repetitive seizure was displayed by a 19-year-old female with a 1-year history of solvent abuse and other drugs including cocaine. Both sleep patterns and reaction time (RT) of addicts were compared with the same measures obtained from young non-addicts of similar ages that constitutes the control group. Total sleep time was 464.4 ± 24.5 in the control versus 440.2 ± 53.8 in addicts Wakefulness and delta sleep time was increased in the addicts' group but stage II and REM sleep diminished significantly. All these polysomnographic sleep changes were also analyzed in time evolution by the spectral 3D graphic with the capacity to evaluate non-stationary rhythms like sleep spindles at 14-16 Hz. A noticeable alteration of sleep and RT was evident in the addicts' group where RT average was of 419.9 ± 114.7 msec as compared with 277.6 ± 94.2 msec in the control group.

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SYMPOSIUM II

THE INTERSECTION OF DRUG TREATMENT AND THE CRIMINAL JUSTICE SYSTEM

M.Y. Iguchi and H. Kleber, Chairpersons*

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SUBSTANCE ABUSE AND AMERICA'S PRISON POPULATION: AN OVERVIEW

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Substance abuse and addiction have had an enormous impact on the nation's prison and jail systems. At the end of 1997 there were more than 1.8 million adults behind bars, up from 500,000 in 1980 (Gilliard, 1999). The cost of building and operating these prisons and jails grew from $7 billion in 1980 to $38 billion in 1996. This trend reflects increasing numbers of drug arrests and convictions, harsher sentencing practices, and high recidivism rates for drug-involved offenders. African American and Hispanic substance abusers have been particularly affected. An estimated 80% of inmates violated drug or alcohol laws, were high when they committed their crime, committed their crime to get money to buy drugs, or had a history of substance abuse (Belenko and Peugh, 1998). Most of these inmates have other issues that complicate their treatment, including mental and physical health problems (including high risk for HIV), and lack of education and job skills. Yet there is a large gap in service delivery: only about 18% of inmates in need of treatment receive such services, and most of this is short-term and non-intensive (Belenko and Peugh, 1998; Camp and Camp, 1997). Based on expected success rates (Andrews *et al.,* 1990; Inciardi *et al.,* 1994; Lipton, 1995; Wexler *et al.,* 1999), investing in long-term prison and jail treatment, education and training, and aftercare will pay substantial economic and social dividends for society (Belenko and Peugh, 1999; Rydell *et al.,* 1996. In addition to expanding treatment and related service access for inmates, this paper also recommends increased use of treatment diversion for nonviolent substance-involved offenders, revisions of mandatory sentencing laws to allow more sentencing discretion for judges and use of treatment as an incentive for early release, improved and expanded assessment of offenders.

WHAT IS A DRUG COURT?

S. Turner

RAND Criminal Justice Program

Drug courts have become one of the fastest growing interventions for dealing with drug involved criminal offenders. The first Drug Court was established in 1989 in Miami, Florida (Goldkamp and Weiland 1993). Since that time over 300 courts have been planned or become operational. Most programs are aimed at reducing offender recidivism, reducing substance abuse, and enhancing offender rehabilitation. Although there is no single drug court model, key components generally include judicial supervision of community-based treatment, early identification and referral of eligible cases, regular hearings the Drug Court judge, and use of graduated sanctions and rewards and mandatory drug testing (Belenko 1998). Drug Court programs represent a form of "therapeutic jurisprudence" (Hora *et al.* 1999) and offer a distinctly different approach from that of traditional criminal justice processing. Despite their popularity, conclusive evidence on the effectiveness of drug courts is

relatively scarce. Most studies to date have been process evaluations; more research needs to be conducted on the long term effectiveness and costs of this promising intervention.

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THE EFFECTIVENESS OF IN-PRISON TREATMENT

***D. Lipton* -- ABSTRACT UNAVAILABLE**

National Development and Research Institutes, New York, NY

TRANSITIONAL AND AFTERCARE TREATMENT FOR DRUG-INVOLVED PRISON RELEASEES

J.A. Inciardi

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A multistage therapeutic community treatment system has been instituted in the Delaware correctional system, and its effectiveness has captured the attention of the National Institutes of Health, the Department of Justice, members of Congress, and the White House. Treatment occurs in a three-stage system, with each phase corresponding to the client's changing correctional status -- incarceration, work release, and parole. In this presentation, 18 and 42 month follow-up data are analyzed for those who completed treatment (with and without aftercare) and for treatment dropouts. These groups are compared with a "no-treatment" comparison group. At 18 and 42 months, significantly greater proportions of those completing treatment with aftercare were both arrest free and drug free. The results support the effectiveness of a multistage therapeutic community model for drug-involved offenders, and stress the importance of aftercare as a component of treatment.

DISCUSSANT

C. Visher

National Institute of Justice, Washington, DC

The National Institute of Justice (NIJ) is the research arm of the U.S. Department of Justice. Created in 1968, NIJ supports research, evaluation, and demonstrations to prevent and reduce crime and improve justice. NIJ's portfolio includes both basic and applied social science research, forensic science, and technology development. NIJ's research on drug use and crime includes studies on justice system responses to drug-involved offenders, including drug courts and in-prison treatment programs, links between drug use and criminal behavior, prevention programs, and a nationwide data collection program on drug use among persons arrested and held at local booking facilities. Funding opportunities are announced on the NIJ website: www.ojp.usdoj.gov/nij. Several drug-related requests for proposals are likely to be announced in FY 2000.

SYMPOSIUM VI

NEW APPROACHES TO NON-ADDICTIVE ANALGESICS

W.K. Schmidt,[1] and Frank Porreca, Chairpersons

D.L. DeHaven-Hudkins,[2] H.O. Petit,[3] R.W. McNutt,[3] K.-J. Chang[3] and C. Wright[4]

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Fundamental changes in our understanding of the neurobiology of pain and addiction have presented new opportunities to develop high-efficacy analgesic drugs which lack the addictive potential of morphine. This symposium was designed to highlight several opioid and non-opioid approaches to non-addictive drugs which are in varying stages of clinical and preclinical development. Speakers were asked to address the pharmacological and biochemical principles underlying the development of each class of drug and include information on the abuse liability and clinical efficacy where available.

Dr. Andrew Brugger (G. D. Searle & Co.) began the symposium with a discussion of the development of both first and second generation COX-2 inhibitors as alternatives to aspirin-like drugs for the treatment of inflammation and pain. Dr. Diane DeHaven-Hudkins (Adolor) reviewed the role of peripheral mu opioid receptors in inflammatory pain and discussed the development of ADL 2-1294 as a peripheral anti-hyperalgesic agent. Dr. William Schmidt (NorthStar) reviewed the development of kappa opioid analgesics as alternatives to morphine for moderate-severe post-operative and cancer pain or as peripherally-selective drugs for the treatment of visceral pain. Dr. Kwen-Jan Chang (Delta Pharmaceuticals) reviewed the analgesic potential and addictive liability of dual-acting mu and delta opioid compounds. Dr. Todd Vanderah (Univ. Arizona) discussed the development of compounds which modify opioid tolerance or dependence while enhancing the analgesic activity of morphine-like drugs. Dr. Harlan Shannon (Eli Lilly & Co.) reviewed the development of novel muscarinic cholinergic approaches to developing drugs to treat moderate-severe pain. And finally, Dr. Curtis Wright (Purdue Frederick) offered his personal evaluation of whether we have actually made any progress in developing non-addicting analgesic drugs.

Brugger: COX-2 inhibitors. Celecoxib is the first selective COX-2 inhibitor approved for use in man. In phase III orthopedic surgery clinical trials, celecoxib demonstrated similar onset, peak analgesic activity, and duration of action as a commercial opioid-APAP preparation (hydrocodone 10 mg + acetaminophen 1000 mg). As this study continued with additional dosing q 8 hr on days 2-5, celecoxib was rated as having better analgesic activity than the commercial opioid-APAP preparation. Valdecoxib (oral use) and parecoxib (water soluble prodrug of valdecoxib for parenteral use) are second-generation COX-2 inhibitors which are currently in phase III clinical trials. Intravenous parecoxib is as active as i.v. ketorolac in the Hargreaves inflammatory pain model in rats. In a comparison of analgesic activity following 3rd molar extraction surgery in man, 50 mg i.v. parecoxib produced analgesic activity similar to 30 mg i.v. ketorolac with a similar 20 min onset time for both drugs. The average time to redosing was 8-10 hours for parexocib and 8 hr for ketorolac. These data demonstrate that selective COX-2 inhibitors produce oral and parenteral analgesic activity similar to opioid-APAP and high-efficacy NSAID products, respectively.

DeHaven-Hudkins: Peripheral mu opioids as anti-hyperalgesic agents. ADL 2-1294 (loperamide) is a μ-selective peripheral opioid agonist currently under development as a topical antihyperalgesic agent for the treatment of acute cutaneous pain or itch. Although μ-selective compounds such as morphine and fentanyl are efficacious in rodent experimental models of inflammatory pain and in man when administered locally, these and other centrally acting opioid analgesics possess undesirable side effects that limit their use as peripherally selective antihyperalgesics. Due to its inability to cross the blood-brain barrier, ADL 2-1294 does not produce sedation or respiratory depression and its unique physicochemical properties of lipophilicity and lack of distribution from the site of administration make ADL 2-1294 an ideal agent for use as a peripheral antihyperalgesic to alleviate inflammatory pain at the site of injury following local administration.

ADL 2-1294 exhibits an affinity of 3 nM for the cloned human μ opioid receptor, and the agonist-induced stimulation of [^{35}S]GTPγs binding produced by ADL 2-1294 is competitively antagonized by naloxone. The antihyperalgesia resulting from administration of ADL 2-1294 is not associated with its systemic circulation, since ADL 2-1294 must be administered directly to the site of inflammation in order to produce antihyperalgesia. In rat models of inflammatory pain, locally administered ADL 2-1294 dose-dependently inhibits the hyperalgesia that results from injection of kaolin-carrageenan into the knee joint, injection of formalin or Freund's complete adjuvant into the paw, or that which results from an abrasive tape stripping injury to the paw. The observed antihyperalgesia is antagonized by naloxone. Injection into the contralateral paw or knee joint fails to produce antinociception. When applied topically to the inflamed paw, cream and gel formulations of ADL 2-1294 also produce antihyperalgesia in the Freund's model. ADL 2-1294 exhibits antipruritic activity in the mouse as evidenced by inhibition of scratching behavior induced by injection of the mast cell releasing agent, compound 48/80.

ADL 2-1294 exhibits greater potency than morphine when administered locally, is efficacious only when administered at the site of inflammation or injury, and the observed antihyperalgesia is not mediated centrally or systemically. ADL 2-1294 has potential therapeutic utility as a peripherally selective opiate antihyperalgesic agent that lacks many of the side effects associated with administration of centrally acting opiates.

Schmidt: Central and peripheral kappa agonist analgesics. Enadoline (CI-977) is a highly selective non-peptide kappa agonist analgesic which produces strong analgesic activity in animal models of nociceptive pain, inflammatory/hyperalgesic pain, and neuropathic pain. It produces sedation but little or no respiratory depression within its analgesic dose range in animals. However, phase I clinical studies showed that enadoline produced dysphoria and psychotomimetic activity in normal volunteers similar to the adverse CNS effects observed following single dose administration of spiradoline, nalorphine, ketocyclazocine, MR2034, and other structurally diverse kappa agonist analgesics in normal volunteers. Analgesic doses of enadoline (25 to 40 μg, i.m.) produced similarly adverse CNS side effects following 3rd molar extraction surgery or gynecologic surgery in phase 11 clinical studies in man.

However, as reported at last year's CPDD conference by Walsh and colleagues from the Johns Hopkins Behavioral Pharmacology Research Unit, enadoline produced surprisingly fewer adverse CNS side effects in a group of 9 opioid-experienced adult volunteers who met DSM-IV criteria for opioid abuse or opioid dependence, Volunteers in this study reported using heroin twice or three times per week but they were not physically dependent on opioid drugs. Using standard Addiction Research Center (ARC) perception scales, these opioid-experienced volunteers showed minimal or no CNS effects of any type following 20 or 40 μg doses of enadoline. At 80 μg, enadoline produced threshold significance on the "feel any drug" and "bad effects" scales, but it was still inactive on the "perception detachment" subscale. It produced frank hallucinations only at a 160 μg dose in a smaller group of these volunteers. This 3x-4x shift toward lower adverse CNS side effects in opioid-experienced individuals may be particularly important for the future use of centrally-acting kappa agonist analgesics in patients with cancer pain who have become tolerant to the analgesic effects of morphine-like mu agonist analgesics. Preclinical studies demonstrate that kappa agonist analgesics retain full analgesic potency in morphine-tolerant animals and that there is no cross-tolerance between mu and kappa agonist compounds. These observations need to be replicated in real patients with chronic pain who have become tolerant to the effects of morphine-like drugs.

Other strategies for limiting the adverse CNS effects of kappa agonist compounds have been to administer the compounds locally into inflamed peripheral tissues where they may activate peripheral opioid receptors, or to add "peripheralization" components to the chemical structure which prevent easy transport of the molecule through the blood-brain barrier. Asimadoline and ICI-204,448 are prototype peripheral kappa agonist analgesics which produce potent antinociceptive activity vs. inflammatory pain (tactile hyperalgesia following carrageenan paw edema), tactile allodynia (formalin test), visceral chemical pain (phenylquinone writhing test), and visceral distention pain in rats or mice. Recent studies in rats showed that twice daily administration of asimadoline in the rat adjuvant arthritic model reduces pain scores and attenuates joint damage over a 21-day period. Asimadoline is reported to be in phase II clinical studies in man; no human data have been published to date.

Other kappa agonist analgesics reported to be in clinical development include TRK-820 (phase II clinical studies), niravoline (phase II clinical studies for aquaresis), and ADL 10-0101 (peripherally-selective; phase I clinical studies). Kappa agonist compounds which have been discontinued following phase I or phase II clinical trials include apadoline, enadoline, spiradoline, E-2078, and ZT-52656A.

These data demonstrate that (a) special populations including cancer pain patients should be used to study centrally-acting kappa agonist analgesics; (b) local administration or peripheralization approaches may be useful for reducing adverse CNS effects while retaining good levels of activity vs. inflammatory or visceral pain; and (c) kappa agonist compounds should be evaluated for activity in non-analgesic models (e.g. aquaresis) where it may be possible to use doses that do not approach the threshold for adverse CNS side effects.

Pettit, McNutt, and Chang: The development of mixed delta and mu agonist compounds as analgesics. Respiratory depression limits the amount of mu opiate receptor analgesics prescribed to patients, and thus limits the clinical treatment of severe pain. In animal models, delta receptor agonists selectively inhibit the respiratory depression (RD), but not antinociception, induced by mu opiate agonists. The selective neuromodulatory effects of a delta agonist could be used to provide a novel treatment for severe pain. Furthermore, an agonist at both delta and mu receptors may thereby produce strong antinociception with reduced RD. This presentation described the discovery and development of DPI-3290, a potent agonist at both delta and mu opiate receptors.

DPI-3290 produces antinociceptive effects with significantly reduced levels of RD in animal models. The hypothesis that a single chemical entity with selectivity at both delta and mu opiate receptors can produce high levels of analgesia with minimal levels of RD has recently been tested in a human clinical trial. Results indicate that DPI-3290 produces analgesia in humans that is believed to be strong enough to treat severe surgical pain. Unlike results obtained with the mu agonist fentanyl, DPI-3290 can produce strong analgesia at doses that do not produce RD. DPI-3290 will, however, produce some RD effects, but only at doses that are high enough to be used following cardiac surgery. Interestingly, DPI-3290 also appears to have a significantly reduced tendency to produce the nausea and emesis/vomiting that typically occurs following treatment with the strong analgesics that are currently used in the clinic.

A clinical need exists for a pharmacological treatment that can be used to relieve severe symptoms of pain without producing RD. We report that the selective neuromodulatory effects of a delta agonist may provide the breakthrough that is needed to adequately treat patients with severe pain.

Vanderah: Agents which enhance opiate action or retard tolerance/dependence. Following L5/L6 ligation of the sciatic nerve (Chung neuropathic pain model), rats develop tactile allodynia and thermal hyperalgesia which are resistant to intrathecal (ith.) morphine in the tail-flick (TF) analgesic model. Intrathecal DAMGO retains full efficacy but has a significant right-ward shift in its dose response curve in the Chung model, showing that DAMGO has lower analgesic potency in this model vs. intact rats. Since the TF test involves activation of pain fibers projecting to the sacral cord which are not physically damaged in the Chung model, these data suggest that L5/L6 ligation produces segmental changes to spinal cord function which may involve neurohumural changes in opioid receptor function. Further evaluation has demonstrated increased levels of dynorphin and Dyn 2-17 in the rostra] lumbar and sacral cord following L5/L6 ligation. Based on studies of dynorphin and dynorphin-related peptides, these data suggest that dynorphin and/or Dyn 2-17 may be responsible for tactile allodynia in this model through an activation of spinal cord NMDA receptors. I.th. administration of dynorphin or Dyn 2-17 in intact rats produces thermal hyperalgesia and tactile allodynia which are reversed by administration of MK801 (NMDA receptor antagonist) or Dyn A(1-17) antiserum; naloxone is inactive. MK801 and dynorphin antiserum also restore the full analgesic activity of i.th. morphine in the Chung model.

Chronic (1x/day) intrathecal administration of DAMGO in intact rats also causes an increase in spinal cord dynorphin and a loss of analgesic efficacy. Continuous infusion of i.th. DAMGO via osmotic minipumps results in thermal and tactile allodynia on days 5-6 similar to the thermal and tactile allodynia produced in the Chung model. Administration of dynorphin antiserum restores the full analgesic potency of DAMGO in this model. These data suggest that adaptive neurohumoral changes occurring following L5/L6 ligation or chronic i.th. administration of morphine or a mu opioid peptide are mediated by NMDA receptor activation and not by changes in the inherent functionality of opioid receptors.

Shannon: The role of the muscarinic cholinergic analgesic system in pain and analgesia. Vedaclidine (LY297802 / NNC 11-1053 / butylthio[2.2.2]) is a novel muscarinic receptor ligand which produces analgesia similar in magnitude to that produced by NSAIDs and opioids. Moreover, vedaclidine produces analgesia at doses which do not produce parasympathomimetic effects. Vedaclidine is efficacious in a variety of diverse pain models, ranging from acute to persistent pain models. Moreover, vedaclidine does not appear to produce the most serious side-effects of either NSAIDs (GI ulceration) or opioids (constipation and tolerance), as well as being synergistic with NSAIDs. Thus, vedaclidine may have therapeutic utility in the treatment of pain as an alternative to NSAIDs and opioids, and, in addition, vedaclidine may have clinical utility in a broader range of pain states than either NSAIDs or opioids.

Wright: The Search for the Non-Addicting Opioid Analgesic; "Hope or Hype." The search for non-addicting opioids has consumed the attention of researchers and commercial developers of pharmaceuticals since the latter part of the 19th century. Post Civil War morphine addiction led to the development of semi-synthetic opioids (such as heroin), which in turn drove development of the synthetic opioids of the mid-20th century. The search culminated in the partial and mixed agonist opioids, such as butorphanol and buprenophine, which have markedly less abuse potential than morphine or heroin. Unfortunately, the goal of reduced risk of opiate dependence in clinical analgesia has not been reached. This is due, in part, to a problem with numbers.

Most physicians agree that iatrogenic addiction is an uncommon event in the clinical management of acute pain states, with an incidence of perhaps 1:10,000 patients treated. Being so uncommon, it is assumed to represent a negligible risk. This is a grave error. Iatrogenic addiction ceases to be a rare and negligible problem as soon as the size of the acute opioid analgesic market is taken into account. There are about 130 million prescriptions written for oral medications containing oxycodone, hydrocodone, hydromorphone and propoxyphene every year. If even 1 in ten thousand patients (1/10,000) a year develops de-novo addiction as the result of such treatment, this means 13,000 new addicts each year. Since the duration of addiction, especially to pharmaceuticals, may be as long as 10 years, an incidence rate of 13,000 will predict a prevalence of 130,000 addicts in the population.

Acute exposure to opioids carries a very low risk, but is so common an event that it poses a significant public health problem.

The street value (the amount a stranger in a bar will pay for a tablet) of diverted opioids is substantial, ranging from $1 up to $20 per tablet (prices vary depending on strength, desirability, and the current supply). Given that the cost of most common opioid analgesics is less than $0.50 a tablet, there is substantial profit in diversion and resale, at all levels (manufacturer, wholesaler, retail pharmacy, physician and patient). After alcohol, tobacco, inhalants and cannabis (the classic portal agents), oral dosage forms of pharmaceuticals are the most common agents for drug experimentation. They are attractive because they are easily identified, assumed safe (FDA approved!), and readily obtained in the illicit market.

Diverted pharmaceuticals with high abuse potential are an important source of "gateway" drugs for opioid experimentation and abuse and may contribute significantly to opioid addiction.

The current addict population is divided into two groups. By far the larger is the group that has entered into illicit trafficking in opioids, and is using a mixture of heroin, cocaine, and other illicit and diverted pharmaceuticals to maintain their habit. There is another population, less well understood, who are not connected with illicit sources of supply, but who are soliciting physicians for their drugs and use diverted drugs as their primary source of supply.

Diversion of pharmaceuticals by addicts regardless of reason has direct adverse effects on the population at large, patients in pain, and the health care system as a whole and is to be avoided.

The author suggests that there are substantial benefits for the culture in the development of less abusable analgesics for mild to moderate pain, in developing strategies to control diversion of opioids in Schedules III, IV & V, and in improving methods for the diagnosis and management of so-called "medical" addicts dependent on prescription drugs.

SYMPOSIUM VII

TAKING IT TO THE STREETS: CONTINGENCY MANAGEMENT FOR REAL-LIFE DRUG ABUSE TREATMENT

L. Amass and M. Y. Iguchi, Chairpersons

Despite a wealth of research demonstrating the efficacy and acceptability of contingency management interventions for reducing drug use, community providers have been slow to adopt these procedures. This symposium showcased innovative and cost-effective contingency management interventions for reducing drug use amongst substance abusers, including dually-diagnosed and homeless populations. Moreover, techniques for transferring and facilitating the use of contingency management for real-life drug abuse treatment were demonstrated.

CONTINGENT MANAGEMENT OF DISABILITY BENEFITS IMPROVES SUBSTANCE ABUSE IN THE SEVERELY MENTALLY ILL

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About half of persons with severe mental illnesses such as schizophrenia experience periods of substance abuse or dependence, often leading to significant personal, social, legal, and health services costs. This project contingently rewarded better case manager weekly ratings of substance use, treatment attendance and responsible money management with a small weekly (cash vs. voucher) study participation reward paradigm and a monthly paradigm which adjusted the form (cash vs. voucher) and frequency (weekly to daily) of disbursement of social security disability benefits. Subjects = 41 were 83% male, diagnoses in addition to substance abuse/dependence were schizophrenia 59%, schizoaffective 20%, bipolar 7%, and recurrent major depression 12%. All were on social security disability for major mental illness and used the mental health agency as their representative payee. After three months of baseline observation, subjects were randomized to either contingent or non-contingent management of the reward systems above and followed for six months. A “clean” week required that both a weekly case manager rating, as well as a blinded weekly research urine done on Monday, were clean. Using intent to treat methods, at the end of six months, the contingent cohort (n=18) demonstrated a greater percentage of weeks clean of alcohol ($p<.008$), as well as alcohol and drugs ($p<.045$). They also demonstrated better money management ($p<.001$). This is a preliminary analysis, with data from six subjects yet to be completed and analyzed, and likely represents a conservative evaluation of the power of this intervention. Other psychiatric, social, and services data will be analyzed and presented in the future.

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LOW COST, COMMUNITY-BASED CONTINGENCY MANAGEMENT TREATMENT FOR COCAINE DEPENDENCE

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A variable-ratio schedule of reinforcement may be efficacious in retaining substance abusers in treatment and reducing substance use. In one study, alcohol-dependent outpatients were randomly assigned to receive standard treatment (ST) at a VA treatment program or ST+ contingency-management (CM), in which subjects earned the opportunity to win prizes for submitting negative breathalyzer samples and completing steps toward treatment goals. Throughout an 8-week period, 84% of CM subjects were retained in treatment compared to 22% in ST ($p<.001$). By the end of the treatment period, 69% of those receiving CM had not experienced a lapse to alcohol use, but only 39% of those receiving ST were abstinent ($p<.05$). In addition, illicit drug use decreased from baseline levels only in the CM group ($p<.05$). A second, ongoing study is evaluating whether this system is

efficacious for cocaine-dependent outpatients and whether even lower-cost prizes improve outcomes. Thus far, 32 cocaine-dependent outpatients have been randomly assigned to ST, ST+CM with an expected probability of winning $80 in prizes, or ST+CM with an expected probability of winning $240 in prizes. Among ST subjects, 0% were retained for 12 weeks, compared with 17% in the $80 CM condition, and 33% in the $240 CM condition. Only 14% of ST subjects achieved >1 month of continuous cocaine abstinence, compared with 25% and 53% of subjects in the two CM conditions. Although magnitude of reinforcement is an important variable, these results support the efficacy of this variable-ratio CM procedure in community-based treatment programs.

CONTINGENCY MANAGEMENT IN EFFECTIVE TREATMENT FOR DUALLY DIAGNOSED, COCAINE ABUSING HOMELESS PERSONS

J.B. Milby, J.E. Schumacher, C. McNamara, D. Wallace*, and S. Usdan

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Homeless persons are vulnerable to substance abuse, preventable disease, progressive morbidity, and premature death. Substance abuse is often a homelessness precursor. This randomized controlled study compared behavioral day treatment with contingency management (DT), to day treatment with abstinence contingent housing, work and housing access during aftercare (DT+). Homeless persons, n=141 meeting DSM III-R criteria for Substance Use Disorder, Cocaine Abuse or Dependence, and/or one or more SCL-90-R scales >70, included: 72% males; 83% African American; 17% European American; average age 37.7 years, were participants. They were randomly assigned and assessed by blind interviewers at 0, 2, 6, and 12 months. Both involved daily psycho- educational groups, individual counseling, goals in five domains of dysfunction, transportation, lunch, a voucher system and naturally available contingencies, to reinforce participation in non-drug related social/recreational activities. DT+ showed greater reductions in drug abuse, homelessness, and unemployment and had 9.10 (SD=6.89) average consecutive weeks abstinence vs. DT with 3.99 weeks (SD=4.17) at 6 months (p=0.0008). Results replicate earlier work demonstrating day treatment, adapted for homeless substance abusers, can be effective. The study did not evaluate effects of non-manipulated contingency management, but investigators believe it contributed to outcomes. Findings support the hypothesis that effective interventions for homelessness must be combined with effective substance abuse treatment to optimize outcomes.

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TRANSPORTING CONTINGENCY MANAGEMENT THERAPIES TO THE COMMUNITY

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Voucher-based reinforcement therapies are an excellent contingency-management approach. There are several benefits of voucher programs, including their acceptability by patients, compatibility with pharmacotherapy, enhancement of treatment retention and ability to reinforce sustained drug abstinence. However, these therapies are also associated with issues that impact the broadscale dissemination of this treatment approach into community treatment. One issue is cost. In most settings, patients do have to pay for at least some portion of their treatment and we do not know what types of results we will obtain when voucher programs are used with populations of clients who also have to pay for the treatment services they are being provided. If we examine further the cost of providing voucher therapy, these programs typically cost between $5-8 per day per patient. This price for a treatment with potentially large benefits is relatively small in comparison to the large cost associated with either no treatment or a treatment that lacks efficacy. Unfortunately, despite this small cost, federal and/or state funding for substance abuse treatment is unlikely to be increased to support voucher programs. We have established some strategies to facilitate the use of voucher-based technologies by community providers. Our strategies focus on adapting the technology to the existing program structure and identifying existing sources of revenue or resources that can be harnessed and used to reinforcement target behavior. We have explored using fees paid by the clients (i.e., no third-party fees) and getting goods and services donated

from the community. The fee rebate strategy utilizes a portion of the revenue generate by client fees to reinforce behavior change. Fees charged to patients are increased just slightly and a portion is set aside for rebates. We have demonstrated a positive, linear relationship between the percentage of the rebate earned and the probability the patient retrieves an envelope containing the rebate, suggesting that these fee rebates are positively reinforcing envelope retrievals. This procedure is a viable, cost-effective and easily managed contingency management strategy that could be easily integrated into any clinic that charges clients directly for services. Our community-sponsored voucher program allows patients to earn vouchers contingent on smoking abstinence. These vouchers are redeemable at an on-site exchange containing a variety of products donated by the local community. Such community sponsorship may offer another cost effective alternative for financing voucher programs for substance abuse treatment.

SELLING CONTINGENCY MANAGEMENT TO THE MASSES: TECHNOLOGY TRANSFER

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The transfer of knowledge and behavioral technologies from research to practice occurs infrequently. Researchers demonstrate efficacy but treatment agencies and practitioners rarely adopt the innovations. This may be due to: 1) Poor communication of results; 2) The studies lack relevance; 3) The interventions are too complicated; 4) There is resistance to change; and 5) There are insufficient $$ for innovation. This list is not exhaustive, but the challenges are clear. We address the above issues by designing interventions that: 1) cost little to implement; 2) include plain talk instructional sets; 3) build on the existing clinical behaviors of our target audience; and 4) create new income opportunities for the provider. Our strategy has been to shape provider acceptance of basic behavioral principles by demonstrating how contingency management can be effective in their everyday environments. We talk about emphasizing what people are doing right, about the need to create a reinforcing environment, and about helping our clients out of that downward spiral of repeated failure and frustration. Our evidence that this approach can be effective is largely anecdotal. For example, one counselor stated, “If I’d have known it was this easy to get clients to change and ‘open up,’ I’d have been paying them [with low $ value vouchers] out of my own pocket a long time ago.” Further, some clinics in New York have adopted our intervention as part of their standard treatment, and requests for information have been received from treatment agencies. One large caution; however, we must be careful that in our attempt to simplify and transfer our technologies, that the effective components will be preserved in real world settings.

DISCUSSANT

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Having an opportunity to act as Discussant in this symposium is an honor. The Chairs, Drs. Amass and Iguchi, and presenters, Drs. Milby, Petry, and Ries are to be commended on a stimulating and timely symposium. The challenges involved in efforts to disseminate contingency-management (CM) interventions to community drug abuse treatment settings are substantial. Dissemination of this approach is going to require dialogue and patience. Researchers and others involved with this treatment approach need to learn from each other. Notions that cost factors are the major obstacle to the dissemination of CM are too simplistic. I suspect that philosophical issues are as big or bigger obstacles to disseminating CM to community clinics as are cost factors. That is not to deny the significance of the cost issue, but to challenge notions that cost is THE major obstacle. The available evidence, including the impressive results of Dr. Petry in this symposium, suggests that outcomes vary as a positive function of the magnitude of the incentive. Advocates of CM should also be active and humble. With regard to being active, advocates of CM have to participate in the meetings and forums that community clinicians attend. Regarding humility, we should not promise more than CM can deliver. Further, our goals for dissemination should be broader than formal drug abuse treatment clinics. The work of Drs. Ries and Milby reported in this symposium illustrate some of the potential of implementing CM in these other agencies, but

more such work is needed. We should also acknowledge instances where CM has been or is currently being implemented in community settings, although without any explicit connection to the formal CM literature. For example, CM is an integral part of many of the Drug Courts that are increasing in number throughout the U.S. CM was also central to the U.S. military's intervention to decrease heroin use among soldiers in Vietnam. If random urinalysis monitoring revealed drug use, the soldier entered treatment, but that time was added to the soldier's tour of duty. Our esteemed colleague Jerome Jaffe was involved in the development and implementation of that intervention. We also should not underestimate the importance of small inroads. A worthwhile effort might be to survey agencies like those mentioned above to see where they feel CM might be applicable in their setting. Last, but certainly not least, there is the need for more good science. More and diverse trials of CM, like those described in this symposium, are needed. Good science has brought CM to this point and will be key to future success as well.

SYMPOSIUM VIII

PHARMACOLOGY AND CLINICAL POTENTIAL OF DELTA OPIOID AGONISTS

S.S. Negus and F. Porreca, Chairpersons

THE DELTA OPIOID RECEPTOR: STRUCTURE, SECOND MESSENGERS AND *IN VITRO* MEASURES OF LIGAND EFFICACY

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The delta opioid receptor is a member of the 7-transmembrane domain G protein coupled family of receptors. The receptor has close homology with the mu- and kappa-opioid receptors, particularly in the transmembrane domains, which make up the ligand binding pocket, and in the intracellular loops. Modeling and molecular biology studies (receptor chimeras and site directed mutagenesis) indicate that the third extracellular loop is particularly important in governing delta ligand selectivity.

Whereas the extracellular loops and transmembrane domains are important for ligand binding, it is the intracellular loops, which couple to inhibitory, heterotrimeric G proteins of the Gi/Go family. This leads to changes in intracellular proteins, including the inhibition of adenylyl cyclase. G protein activation is a very early event in the signal transduction cascade. Agonist occupation of the receptor causes the dissociation of GDP from the Go subunit and allows for the binding of GTP. This activation of G protein can be measured in membrane preparations using the stable, radiolabeled analog of GTP, [35S]GTPγS and provides for a measure of the potency and relative efficacy of opioids. Our studies in NG108-15 cells and in C6 cells expressing the delta opioid receptor show that delta ligand efficacy decreases in the order SNC80 = BW373U86 = DSLET > DPDPE = deltorphin II > etorphine > diprenorphine > SIOM = diprenorphine > naltrindole = buprenorphine. Thus buprenorphine, which binds to the delta receptor with high affinity, has no agonist efficacy in this system and acts as a pure antagonist. The putative delta1 antagonist BNTX (benzylidenenaltrexone) and putative delta2 antagonist NTB (naltriben) both shift agonist concentration-effect curves, providing no evidence for delta receptor subtypes in these cell systems. The relative efficacy of delta opioids to inhibit adenylyl cyclase, downstream of G protein activation, shows closer similarity between compounds, with the partial agonists SIOM and DPDPE giving maximal effects similar to that seen with the full agonist DSLET

The delta receptor expresses constitutive activity in that it can activate Gi/Go proteins, and stimulate the binding of [35S]GTPγS, even in the absence of agonist. In this regard, it appears different from the mu receptor. The peptide ICI 174864 has long been known to have inverse agonist activity and blocks this constitutive activation in a concentration-dependent manner. We have also identified NTB, BNTX and clocinnamox (the irreversible mu antagonist) as inverse agonists at the delta opioid receptor. Inverse agonism is a receptor phenomenon because it can be blocked by the neutral antagonist naltrindole. ICI 174864 and clocinnamox bind with highest affinity to a low agonist affinity state of the delta receptor, thereby promoting formation of a non-functional conformation of the receptor and so inhibiting the binding of [35S]GTPγS. In contrast BNTX and NTB have similar affinity for both high and low agonist affinity states. This suggests different mechanisms for constitutive activity. The in vivo consequences of this constitutive activity of the delta receptor are unknown.

SPINAL AND SUPRASPINAL DELTA OPIOID RECEPTORS IN PAIN

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Opioids are known to produce antinociception by hyperpolarization of neurons and resultant inhibition of transmitter release. The localization of opioid receptors on central terminals of primary afferent c-fibers and at post-synaptic pain transmission cells as well as in descending pain modulatory pathways provides anatomical support for mechanisms by which nociceptive signal transmission can be blocked. Opioid delta receptors are

localized appropriately in pain transmission cells, and opioid delta agonists are known to produce hyperpolarization of cells and to inhibit transmitter release from primary afferent fibers. While most clinically effective analgesic agents act at opioid mu receptors, the activation of these receptor sites is associated with undesirable side-effects including respiratory depression and constipation along with psychic effects which can lead to abuse. An important component of analgesic actions of opioid mu agonists is the supraspinal and spinal analgesic synergy that allows clinically important compounds such as morphine to be used at approximately 30-times lower doses than would otherwise be possible. It is believed that opioid delta receptor activation might elicit sufficient analgesia to be of clinical utility but without some of these undesirable side effects. However, in order for opioid delta agonists to achieve sufficient potency to be clinically useful, it seems likely that supraspinal and spinal antinociceptive synergy should occur. For these reasons, we investigated the antinociceptive actions of [D-Ala2, Glu4]deltorphin, a highly selective peptidic opioid delta agonist, following intrathecal (i.th.) administration or following microinjection into the medullary reticular formation (MRF) of the rat. Evaluation of the antinociceptive actions of [D-Ala2, Glu4]deltorphin revealed dose-related antinociceptive effects in both the 55°C hot-plate test and in the 2.5% formalin test when given at either site. Additionally, the antinociceptive actions of [D-Ala2, Glu4]deltorphin were antagonized by selective opioid delta antagonists such as 5N-naltrindole isothiocyanate (5N-NTII) but not by mu or kappa antagonists (i.e., ß-funaltrexamine or nor-binaltorphimine given at doses which were effective in antagonizing mu or kappa selective agonists). Microinjection of [D-Ala2, Glu4]deltorphin into the MRF effectively suppressed formalin-induced spinal expression of FOS, suggesting the presence of a descending pain modulatory pathway. Lesions of the dorsolateral funiculus blocked the inhibition of formalin-induced FOS expression in the spinal cord by MRF [D-Ala2, Glu4]deltorphin. Finally, MRF and i.th. co-administration of [D-Ala2, Glu4]deltorphin produced a highly significant synergistic antinociceptive effect in both the hot-plate and formalin-flinch assays. These findings suggest that systemically available opioid delta agonists should exhibit supraspinal-spinal synergy, adding confidence that molecules with this profile might achieve sufficient analgesic potency to be of clinical utility.

Recent studies with mice genetically engineered to prevent expression of the opioid mu receptor have suggested that the antinociceptive actions of opioid delta agonists are reduced or absent and that antinociceptive actions of opioid delta agonists may depend on circuitry involving mu opioid receptors. These conclusions were reached on the basis of antinociceptive actions of opioid delta agonists with moderate selectivity for the opioid delta receptor, such as [D-Pen2, D-Pen5]enkephalin (DPDPE). The antinociceptive actions of opioid delta agonists in the mu knock-out mice were studied using more highly selective opioid delta agonists including [D-Ala2, Glu4]deltorphin and SNC 80. Additionally, we examined the ability of these agonists to stimulate [35S]GTPγS binding in brain and spinal cord membranes from mu receptor knock-out or wild-type mice. In these studies, we found that the maximal stimulation of [35S]GTPγS binding by DPDPE was lower in mu knock-out brain or spinal cord membranes, compared with wild-type tissues. However, there was no change in [35S]GTPγS binding produced by [D-Ala2, Glu4]deltorphin in wild-type or mu receptor knock-out tissues. Similarly, administration of DPDPE by the intracerebroventricular or intrathecal route showed a decreased antinociceptive potency in suppression of the hot-water (55EC) tail-flick test in mu receptor knock-out mice, compared with the wild-type. However, no change in antinociceptive potency was seen between the two groups with [D-Ala2, Glu4]deltorphin or with subcutaneous administration of SNC 80. The data suggest that activation of mu opioid receptors is not critical for antinociceptive actions of opioid delta agonists when the agonists employed are sufficiently selective for the delta opioid receptor.

A major advance in the pharmacology of opioid delta receptors occurred with the discovery of BW 373U386, a moderately selective compound for the delta receptor but which was non-peptidic in structure. This compound was used as the basis for the development of SNC80, a highly selective non-peptidic delta agonist which demonstrated antinociceptive actions following systemic administration. While the antinociceptive actions of SNC80 have been significant following systemic administration, the potency of this compound has been somewhat disappointing compared to that seen with opioid mu agonists. Nevertheless, this molecule has provided a structural basis for the synthesis and exploration of opioid delta receptor pharmacology. New synthetic efforts may lead to fully bioavailable delta selective molecules, which may be tested in humans for their analgesic efficacy. Based on studies in animals which predict that (a) supraspinal and spinal antinociceptive synergy will occur with opioid delta agonists, (b) expression of opioid mu receptors is not critical for opioid delta agonist antinociception and (c) non-peptidic, systemically available and highly-selective

opioid delta agonists can be synthesized, it seems reasonable to suggest that the development of opioid delta agonists for therapy of human pain states can be achieved.

GENETIC DETERMINANTS OF THE BEHAVIORAL EFFECTS OF DELTA OPIOID AGONISTS IN MICE

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Previous antinociception studies in our laboratory demonstrated genotype-dependent receptor selectivity using the presumed μOR agonist morphine. Genotype-dependent agonist selectivity was confirmed using the mu opioid receptor agonist heroin in studies done in collaboration with Dr. Fujimoto. In these studies morphine or heroin produced analgesic effect through either the mu, delta or kappa receptor in a manner that was dependent upon the genotype of the subject. The purpose of the studies described in this presentation is to determine if a similar genotype-dependency for agonist receptor selectivity is present using delta opioid agonists.

Our first goal was to determine if the analgesic potency of the delta 1 receptor agonist DPDPE and the delta 2 receptor agonist Deltorphin II was under separate genetic control. Full dose-effect studies revealed significant genetic differences in the potency of both agonists. The method of genetic correlation was used to determine if sensitivity to these agonists was determined by the same or by similar genetically-mediated mechanisms. A significant Pearson's correlation coefficient between the ED50 values of DPDPE and DeltII across all eight genotypes suggest that similar genetically-determined intermediates control sensitivity to each drug. Further studies with the delta agonist BW373U86, however, suggest that this compound produces its analgesic effects through a distinct mechanism (as determined through a genetic correlation across ED50 values). Serendipitously, we also discovered that the volatile anesthetics, metofane and isoflurane, differentially antagonized the analgesic effects of DPDPE and DeltII and that this antagonism was genotype-dependent.

Our second goal was to use the antagonists naltrexone, NTI, NTB, 5'NTI and ßFNA to determine if agonist selectivity was again genotype-dependent using these two delta receptor agonists. The results suggest that, as with the mu opioid receptor agonists, the receptor subtype through which the delta receptor produces its effects is determined in part by the genotype of the subject. Further, more extensive pharmacological analysis was conducted in one of the more interesting genotypes. Through a series of studies, we determined that morphine (and heroin) act as clear delta 2 receptor agonists in the CXBH mice (NTB sensitive). Conversely, ßFNA will block the effects of DeltII in this genotype. We then looked at the reinforcing effects of morphine in these mice using an i.v. self-administration paradigm. Preliminary studies suggest that when these mice are pretreated with ßFNA prior to self-administration sessions, this mu opioid receptor antagonist will block the reinforcing effects of morphine. Thus, the pharmacological specificity of morphine appears to be genotype and phenotype (behavioral assay) dependent.

ANALGESIC AND OTHER BEHAVIORAL EFFECTS OF NON-PEPTIDIC DELTA AGONISTS IN PRIMATES

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The recent development of non-peptidic delta opioid agonists has made it possible to evaluate the analgesic and other behavioral effects of delta opioids in primates. In recent studies in our laboratory, we have evaluated the effects of the piperazinyl benzamide delta agonist SNC80 and a series of structurally-related compounds in rhesus monkeys.

The potential analgesic effects of SNC80 and related compounds were examined using two procedures, a warm-water tail-withdrawal assay of thermal nociception, and an assay of capsaicin-induced thermal hyperalgesia/allodynia. In the assay of thermal nociception, the monkey's tail is immersed in a container of water heated to various temperatures (42, 46, 50 and 54°C), and the latency to tail withdrawal from each temperature is recorded. SNC80 produced a dose-dependent antinociceptive effect in this procedure, although

the maximal effect SNC80 was smaller than the maximal effect of the high efficacy mu agonist fentanyl. The antinociceptive effects of SNC80 were surmountably antagonized by naltrindole, suggesting that they were delta-receptor mediated. In addition, BW373U86 failed to produce analgesic effects in this procedure and antagonized the effects of SNC80, suggesting that in monkeys, SNC80 may have higher efficacy at delta receptors than BW373U86. In the assay of capsaicin-induced hyperalgesia/allodynia, thermal hyperalgesia/allodynia is produced by s.c. injection of capsaicin into the tip of the monkey's tail prior to tail withdrawal measurements. SNC80 (1-10 mg/kg) administered before capsaicin produced a dose-dependent, naltrindole-reversible and complete blockade of capsaicin-induced hyperalgesia/allodynia. The other delta agonists SNC162 and SNC243A also produced maximal effects in this procedure, but neither SNC67 [the (-) enantiomer of SNC80] nor the NSAID ketorlac were effective. These results suggest that delta agonists may be more effective than clinically-available NSAIDS in producing analgesic effects under some conditions of hyperalgesia and allodynia.

Other studies have evaluated potential undesirable effects of SNC80. Because SNC80 and other piperazinyl benzamides have been reported to produce convulsant effects in mice, we evaluated the effects of SNC80 on EEG activity in rhesus monkeys. In ongoing studies, we found that SNC80 at doses up to 56 mg/kg did not produce EEG seizures or convulsions in monkeys. We also evaluated the respiratory effects and abuse-related effects of SNC80, because the use of clinically available mu opioid agonists is limited by respiratory depression and high abuse potential. SNC80 at doses up to 10 mg/kg did not produce respiratory depression in rhesus monkeys, whereas the mu agonist fentanyl produced profound respiratory depression. In studies to examine the potential abuse-related effects of SNC80, we found that SNC80 was not self-administered by monkeys under conditions in which cocaine was self-administered. In addition, SNC80 was found to produce delta receptor-mediated discriminative stimulus effects in monkeys, and other drugs of abuse (mu agonists, cocaine, ketamine) did not produce SNC80-like discriminative stimulus effects. Taken together, these findings suggest that delta agonists such as SNC80 may produce relatively mild side-effects in rhesus monkeys at doses that produce robust analgesic effects in the assay of chemically-induced hyperalgesia/allodynia.

POTENTIAL OF DELTA OPIOID AGONISTS AS THERAPEUTICS

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The advancement of peptide or non-peptide delta opioid agonists from the preclinical laboratory into clinical development should be accompanied by clear therapeutic goals if they are to compete with or replace existing mu opioid analgesics. At the minimum, these goals should include: (a) evidence for moderate-strong analgesic activity in multiple animal species; (b) a moderate-long duration of action for single doses in animals that is predictive of once or twice daily dosing in man; (c) no sedation within its analgesic dose range; (d) no respiratory depression and minimal adverse GI, CV, and renal effects; (e) no or minima1 drug dependence liability; (f) no or minimal aversive CNS activity at analgesic doses and no mood altering activity at higher doses; and (g) acceptable bioavailability for the possibility of oral dosing in man.

Early preclinical work with selective delta agonist peptides such as DPDPE and deltorphin II demonstrated considerable promise for the potential use of delta opioid agonists as analgesics in man (e.g. Krames *et al., 1986;* Porreca *et al.,* 1987; Jiang *et al.,* 1990). In particular, these studies raise the possibility of using delta opioid analgesics along with mu agonist analgesics in chronic pain conditions, such as cancer pain, to maintain better analgesic control, avoid significant tolerance development, and reduce some of the more problematic side effects of morphine-like drugs.

The possibility of moving delta opioid analgesics into man was increased with the discovery of several non-peptide piperazinyl benzamide delta agonists including BW373U86 and SNC80. However, as already reviewed by Dr. Negus, both of these compounds produced seizures in mice within their analgesic dose range, and BW373U86 produced seizures at lower than analgesic doses in monkeys (Comer *et al.* 1993, Dykstra *et al.* 1993; Negus et *al.* 1994). Newer non-peptide compounds are also in development (e.g. Liao *et al.* 1998). One of these compounds, DPI-3290 from Delta Pharmaceuticals, has undergone initial clinical evaluation in man. DPI-3290 is an N-Me-3'-fluorophenyl analog of BW373U86 with mixed mu-delta agonist activity, and it

produced an encouraging profile of analgesic effects with minimal side effects in Phase I clinical trials (see Symposium VI on "New Approaches to Non-Addictive Analgesics"). Most importantly, the compound did not produce seizures in preclinical safety evaluation studies. In addition to these non-peptide compounds, DPDPE, a metabolically stable cyclized peptide with moderately high selectivity for the delta receptor, is reportedly in advanced preclinical development with plans to evaluate it for analgesic activity following intrathecal infusion in man (V. Hruby, Univ. Arizona, personal communication).

It is unclear whether the early success of DPI-3290 is due to its mixed mu-delta agonist profile or whether it is due to other pharmacologic features which provide a greater safety margin (i.e. no seizures) and potentially stronger analgesic activity than BW373U86 and SNC80. This may become more apparent as other non-peptide and peptide delta agonist compounds are moved into clinical development. Other strategies that may prove useful in eliminating the seizure potential and increasing the analgesic potency of delta agonist compounds include: (a) evaluating single-enantiomer vs. racemic compounds; (b) evaluating whether the parent compound or a putative toxic metabolite may be responsible for adverse side effects, and determining whether animal studies are predictive of formation of this metabolite in man; (c) evaluating spinal drug delivery for patients with chronic intractable morphine-tolerant pain; (d) evaluating compounds with restricted access to the CNS for treatment of peripheral inflammatory pain or hyperalgesia; and (e) evaluating mixed-function compounds with delta agonist activity combined with analgesic or anti-seizure activity at non-opioid receptors. It will also be important to evaluate whether the newer delta agonist compounds retain the earlier promise of lower addiction and dependence liability vs. the potent mu agonist opioids that are in widespread use today.

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SYMPOSIUM XI

A STONE UNTURNED: THE PROMISE OF GABAERGIC MODULATION IN COCAINE DEPENDENCE TREATMENT

A.R. Childress[1] and D.C.S. Roberts[2], Chairpersons

Speakers: D.C.S. Roberts[2], S. Dewey[3], S. Shoptaw[4], and A.R. Childress[1]
Discussant: W. Ling[4]

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SYMPOSIUM SUMMARY

GABAergic agents are a relatively understudied, but potentially very promising, class of medications for cocaine dependence. Recently published data from Drs. Dave Roberts' and Steve Dewey's preclinical laboratories show that GABAergic agents (either GABA B agonists, or vigabatrin, an inhibitor of GABA transaminase) produce dramatic and specific reductions in cocaine self-administration. A likely mechanism is reduced synaptic dopamine (DA) in terminal mesolimbic regions, minimizing the effect of cocaine on DA reuptake inhibition. At least one clinical study (Drs. Shoptaw / Ling) has demonstrated potential clinical benefits of the prototypic GABA B agonist, baclofen, in cocaine users. Dr. Childress' laboratory has begun encouraging studies of these GABAergic agents in cue-induced cocaine craving, a phenomenon that may depend, in part, upon DA release.

As there is likely overlap in the reinforcement substrate for cocaine, other drugs of abuse, and natural rewards (e.g., food, sex), GABAergic agents may have broad therapeutic potential. The symposium speakers (see individual summaries, below) offered up-to-the-moment data on the preclinical and clinical promise of both new and prototypic GABAergic agents for cocaine dependence.

Following the individual presentations, Dr. **Walter Ling,** the symposium discussant, presented an historical and evolutionary context for these findings, emphasizing the critical importance of brain inhibitory systems in understanding brain-behavior relationships. Brain inhibitory systems may have particular relevance in the understanding of addiction, wherein behavioral inhibition/control often seems lost or diminished. At a fundamental level, where relapse is understood in terms of failed inhibition, GABAergics may be good candidate medications to support behavioral control/inhibitory functions -- which could in turn help prevent lapse/relapse to drug use. We have no medications which offer specific benefit for relapse prevention in cocaine dependence: GABAergic agents offer a new, and potentially very effective, approach to understanding the mechanisms of relapse and providing novel strategies at both the laboratory and clinical levels.

GABA B AGONISTS PRODUCE PROFOUND AND SPECIFIC REDUCTIONS IN RATS' SELF-ADMINISTRATION OF COCAINE (D.C.S. Roberts)

Recent behavioral and physiological data indicate that GABAergic drugs specifically attenuate cocaine reinforcement through a modulation of the mesolimbic dopamine system. Using three distinct self-administration procedures, we examined the effect of the GABAB agonist baclofen on cocaine- and food--reinforced responding. Despite the differences in demand characteristics between the schedules, the data consistently suggest that baclofen selectively reduces cocaine-reinforced responding.

Baclofen reduced intake of low (0.18 - 0.75 mg/kg/inj) but not high (1.5 mg/kg/inj) unit injection doses of cocaine on a FRL schedule. On a progressive ratio schedule, baclofen decreased cocaine-reinforced break points at doses that had only modest effects on food-reinforced responding. Cocaine self-administration was also examined using a discrete trials procedure. Limiting access to cocaine to 2 trials/hr produced a circadian pattern of cocaine self-administration. Baclofen suppressed cocaine self-administration during high intake periods at

doses that had no effect on food intake. The site of action of baclofen's suppression of cocaine self administration is likely within the ventral tegmental area (VTA). Intracerebral injections of baclofen (32, 56, 100 ng/side) into the VTA reduced cocaine- but not food-reinforced responding. Much higher doses were required to produce similar effects from injections into the nucleus accumbens or striatum.

In summary, cocaine self-administration is particularly sensitive to modulation by GABA B agonists: 1) at low unit injection doses, 2) when the response cost is high, or 3) when access to cocaine is limited. These results support the suggestion that GABAergic drugs represent a potentially useful strategy for the development of a pharmacological treatment for cocaine addiction.

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VIGABATRIN, AN INHIBITOR OF GABA TRANSAMINASE, ELIMINATES COCAINE SELF-ADMINISTRATION IN RATS, AND MAY BE EFFECTIVE IN HUMAN COCAINE DEPENDENCE (S. Dewey)

We have used vigabatrin (gvg; Sabril), a selective and irreversible inhibitor of GABA-transaminase, in an effort to develop a novel pharmacologic approach for the treatment of substance abuse. Vigabatrin is currently used for the treatment of partial complex seizures in both adults and pediatric patients. By taking advantage of the well known GABAergic inhibition of nucleus accumbens dopamine, we have demonstrated that vigabatrin-induced increases in extracellular and synaptic GABA concentrations are effective at blocking the dopaminergic response to cocaine, nicotine, methamphetamine and amphetamine, heroin and morphine, alcohol, and phencyclidine. These studies took unique advantage of different techniques designed to specifically measure these effects in both freely moving rodents (microdialysis) and adult female baboons (positron emission tomography) using either an acute or a chronic treatment regimen. In addition to these biochemical findings, we have extended our studies to include behavioral measures such as self-administration (using both a PR and an FR schedule), brain stimulation reward thresholds, conditioned place preference (both expression and acquisition), sensitization, and locomotor activity. Combined, we have demonstrated that vigabatrin is effective at dose-dependently blocking the biochemical effects of these drugs of abuse, as well as the behavioral consequences associated with these effects. This extensive preclinical data set strongly supports the development of clinical trials in substance abusers with vigabatrin.

ACKNOWLEDGEMENTS: Research supported by NIDA (NIH) and by DOE.

OUTCOMES WHEN USING THE GABA B AGONIST BACLOFEN IN HUMAN COCAINE USERS (S. Shoptaw)

Conceptual Rationale: No dopaminergic agents have consistently demonstrated efficacy as a pharmacotherapy for cocaine dependence. Thus our group has focused inquiry into medications that indirectly modulate the behavioral effects of cocaine. Preclinical data are accumulating to indicate that GABAergic medications may function by: (1) decreasing dopamine tone, thereby reducing cocaine reinforcing effects; and/or (2) dampen cocaine sensitization, thereby ameliorating cocaine craving.

Open Label Experience: Our initial experience with baclofen (20 mg t.i.d.) in an open label trial (n=10, in a group counseling model) suggested that baclofen is safe for use in cocaine outpatients. Side effects were in the mild range (nausea, nightmares, headache, sedation, and dizziness). Most patients continued cocaine use while on baclofen, but no adverse effects due to baclofen/cocaine interaction were noted. We concluded that 60 mg daily dose was feasible, and that baclofen was worth systematic evaluation as a potential cocaine pharmacotherapy.

Double-Blind Trial: In a placebo-controlled randomized trial of baclofen, we assigned 70 patients to receive 20 mg baclofen t.i.d.(n=35) or placebo (n=35) in the context of three times per week Matrix Model counseling. All

participants were cocaine-dependent (verified by SCID), with the average participant being a 35 year-old male (32% female) who graduated high school (12.8 years). Participants reported using cocaine for 10.8 years prior to admission and 13 days in the month prior. Urine results showed no statistically significant effects for baclofen over placebo using the following indices: treatment effectiveness score, joint probability index, percent negative urine samples, longest period of consecutive "clean" urine samples, and percent of subjects who achieved three consecutive weeks of abstinence during the trial, though all comparisons favored the baclofen group. Post hoc analyses showed that baclofen-treated subjects were more likely to abstain from cocaine use than placebo subjects between weeks 3 and 8 during the trial ($p<.01$). There were no differences between baclofen and placebo-treated subjects in frequency of reported adverse events, with the most commonly reported complaints being headaches, flu/colds, body aches/pain, and nausea. These results demonstrate the safety of baclofen as a cocaine medicine. They also imply that another trial using baclofen (perhaps at a higher dosage), or using other GABA agents is appropriate.

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GABAERGIC MODULATION OF CUE-INDUCED COCAINE CRAVING (A.R. Childress)

As preclinical data show that dopamine release can occur to signals for both natural and drug rewards, the ability of GABAergics to modulate endogenous dopamine release may offer a novel and potent intervention for cue-induced cocaine craving. To set the stage for testing this hypothesis, we have initiated work with GABAergics in three different contexts: *1) open label dose-finding in our clinic, 2) cue-reactivity screens in the laboratory, and 3) GABAergic pre-treatment prior to brain imaging of cue-induced craving.*

Clinical dose-finding: Dose finding with the GABA B agonist **baclofen** (n=13, 10 of whom received several doses of medication) indicated that cocaine patients may be very sensitive to the sedating effects of baclofen: the dose tolerated by cocaine patients without complaint (10-20 mg b.i.d.) was substantially less than the dose usually prescribed for muscle spasm (baclofen's common use) or for recent trials in depression. Dose-finding **with tiagabine** (n=6), a reuptake inhibitor of GABA, was generally well-tolerated in the 4-8mg daily range. One patient who was increased to 16mg daily complained of dizziness; this symptom remitted when the dose was reduced. *Cue-reactivity laboratory:* Two patients who had received a few days to several weeks of clinical baclofen (during dose-finding) were also tested in the cue reactivity laboratory. Both showed reductions in cue-induced cocaine high; one of these also showed a blunting of cue-induced cocaine craving. *PET imaging laboratory:* Two baclofen pre-treated cocaine patients have also been tested in the PET imaging laboratory, to see if the medication might prevent the limbic activation we have demonstrated in cocaine patients viewing videos which induce craving. Though image analysis is not yet complete for these pilot studies, preliminary examination suggests patients pre-treated with baclofen indeed did not exhibit the increases in amygdalar and anterior cingulate regional blood flow characteristic of cocaine patients in this craving-induction paradigm.

Though our GABAergic efforts are still in the pilot stage, we feel these preliminary data encourage larger, systematic studies of these agents in cocaine dependence treatment. GABAergics may be particularly well-suited to prevention of relapse, as it may be easier for their DA-modulatory actions to blunt the conditioned effects of cocaine cues (e.g., cue-induced appetitive "craving") than to over-ride the whopping direct effects of cocaine itself on endogenous dopamine. Since at this point we do not know which GABAergic mechanism - raising overall GABA levels [either by reuptake inhibition, or by inhibition of the catabolic enzyme] vs. direct agonism of GABA B receptors -- will be most effective, we will be testing the promise of differing GABAergics in a novel paradigm which will features presentation of cocaine cues just prior to a cocaine challenge ("cue + safety challenge"). This approach will allow us to evaluate each medication's impact on cocaine's direct, cue-conditioned, and drug-primed effects, guiding selection of the most promising GABAergics for full-scale clinical trials.

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SYMPOSIUM XII

BASIC AND CLINICAL PHARMACOLOGY OF SELECTIVE CANNABINOID RECEPTOR (CB1 AND CB2) ANTAGONISTS

S.J. Heishman[1] and B.R. Martin[3], Chairpersons

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RECENT ADVANCES IN CANNABINOID RECEPTORS

S. J. Heishman

Humans have used the Cannabis plant to make rope and clothing and for medicinal purposes for thousands of years. However, it wasn't until 1964 that Mechoulam and his colleagues isolated delta-9-THC from among the 60 other cannabinoids in the Cannabis plant and identified it as the compound responsible for the psychoactive effects of cannabis. In an effort to determine the mechanism of action of cannabinoids and to develop pharmacologically active compounds devoid of adverse side effects, several potent cannabinoid analogs were synthesized in the 1980's, including the Pfizer compound CP-55,940 and WIN 55,212 from Sterling Winthrop. The stereoselectivity of these compounds suggested that cannabinoids acted through a specific receptor. In 1988, using radiolabelled CP-55,940, Devane and his colleagues identified cannabinoid binding sites in rat brain. In the early 1990's, Herkenham and colleagues reported that these binding sites are concentrated in the basal ganglia, cerebellum, HC, and cortex. Definitive evidence for a cannabinoid receptor came in 1990 when the cannabinoid receptor was first cloned from rat brain and in 1991 when the human receptor was cloned. The CB1 receptor belongs to a family of G protein-coupled receptors and is located primarily in brain, but has also been described in the periphery. In 1993, the CB2 receptor was identified and cloned. It appears to be localized in the periphery. The discovery of cannabinoid receptors pointed to the possibility of an endogenous ligand. In 1992, Devane, Mechoulam and colleagues isolated anandamide, a derivative of arachidonic acid. Anandamide binds to cannabinoid receptors and produces pharmacological effects that are similar to delta-9-THC. The discoveries in 1994 of the CB1 receptor antagonist (SR141716) and in 1998 of the CB2 receptor antagonist (SR144528) have provided pharmacological tools with which we can begin to explore the physiological and behavioral functions of the cannabinoid neurochemical system.

CHARACTERIZATION AND LOCALIZATION OF CANNABINOID RECEPTORS

M. Herkenham

Brain localization studies using the radiolabeled high-affinity ligand [3H]CP55,940 have revealed a very high abundance of cannabinoid receptors in brain, as high as glutamate receptors. Receptors are densely localized to basal ganglia, cerebellum, hippocampus, and cortex, with low levels in diencephalon, brainstem, and spinal cord. Such localization of receptors can explain certain cannabinoid effects, such as motor (basal ganglia, cerebellum) and memory (hippocampus). Early studies showed that there was only one binding site, and structure-activity profiles indicated that this receptor mediated all known psychoactive effects of cannabinoid agonists (including marijuana). The invariance of cannabinoid receptor distribution across species is unusual and suggests conserved evolution of the receptor. This is supported by the recent discovery of cannabinoid receptors and the endogenous ligand in hydra. Receptor localization can be confirmed by mRNA localization done by in situ hybridization. These studies indicate that the brain form of the cannabinoid receptor is CB1 and the peripheral form is CB2. There is little to no CB2 in brain and limited presence of CB1 in the periphery. Peripheral distribution is highly localized to specific immune cell types and sparsely localized to other cell types. The most recent studies indicate that brain receptors are predominantly presynaptic (localized to axon terminals) in most

areas. Receptors in the basal ganglia circuits are on GABAergic projection neurons (dense in the terminal zones in the palladium and nigra) and not on dopaminergic nigrostriatal neurons. An implication for drug abuse research is that THC effects on dopamine release are indirect. In fact, in animals, moderate to high agonist (THC or CP55,940) doses are aversive and strongly activate the hypothalamic-pituitary-adrenal axis as do other stressors. Receptors in the hippocampus are densely localized to terminals of interneurons. Receptors in the cerebellum are localized to terminals of granule cells and to interneurons Receptors in the dorsal horn of the spinal cord are localized to terminals of primary afferent fibers. In situ hybridization and double-label studies show that the high-threshold nociceptive fibers carrying pain information comprise part, but not all, of the receptor-bearing inputs. The cannabinoid antagonist (SR141716) can be used to detect local endogenous cannabinoid activity. The antagonist has been shown to decrease dopaminergic activity and to improve short term memory. Therapeutic applications of cannabinoid agonists include nausea, hyperkinesia, chronic pain, and autoimmune disorders. The antagonist could be used to treat Parkinson's disease and memory disorders. Actions of cannabinoids that are not receptor-mediated suggest clinical utility as antioxidant or antistroke medications.

SR141716A: AN ANTAGONIST OR INVERSE AGONIST?

B.R. Martin

Although there is no doubt that SR141716A interacts with the CB1 receptor, there has been some question as to what consequences arise from this interaction. In their initial report, Rinaldi-Carmona *et al.* (1994) demonstrated that SR141716A was an effective cannabinoid antagonist. Later studies confirmed these observations by demonstrating that low doses of SR141716A antagonized the effects of Δ^9-THC in mice, Δ^9-THC drug discrimination in rats, and Δ^9-THC-induced overt behavioral changes in dogs. More importantly, these actions of SR141716A occurred at doses that produced no observable pharmacological effects. Therefore, this compound has specific cannabinoid antagonistic properties. Questions have arisen regarding possible inverse agonist properties of SR141716A, especially from *in vitro* studies. High doses of SR141716A produced motor stimulation that may represent inverse agonist effects. However, it failed to alter baseline sensitivity in the tail-flick assay or to produce hyperthermia, effects that would be expected if SR141716A were acting as an inverse agonist. Other laboratories have examined SR141716A in various pain models for possible hyperalgesic effects. SR141716A increased nociception in the formalin test and in the hotplate assay, but not in the paw pressure test and tail withdrawal assay. In an attempt to explore the possibility of SR141716A-induced hyperalgesia, we lowered the tail-flick intensity to optimize the system for hyperalgesic responsiveness and still failed to elicit an effect with SR141716A. We also examined SR141716A in the hot-plate set at various temperatures and under no conditions did we obtain consistent hyperalgesia. In conclusion, SR141716A appears to be able to produce hyperalgesia under selected conditions, but this property is not readily reproducible in all pain models. More importantly, any hyperalgesic effect of SR141716A would most likely be of insufficient intensity to contribute to its antagonistic properties. Other possible inverse-agonist effects of SR141716A have been noted in precipitated withdrawal studies in which SR141716A challenge to Δ^9-THC-treated mice and rats produced a distinct withdrawal syndrome. In some of these studies, administration of SR141716A alone produced some of these same withdrawal effects, albeit at low levels. These findings, along with some of the hyperalgesia reports raise the possibility that the endogenous cannabinoid, anandamide, may be exerting a tonic influence that is altered by the administration of SR171616A. Alternatively, SR141716A could be producing some of these effects as an inverse agonist. These two possibilities have yet to be resolved.

IN VITRO AND *IN VIVO* RESEARCH WITH SR144528, A SELECTIVE CB2 RECEPTOR ANTAGONIST

F. Barth and M. Rinaldi-Carmona

Delta-9-THC, the major psychoactive component of cannabis, and anandamide, the putative endogenous ligand for the cannabinoid receptor, mediate their cellular effects through specific G protein-coupled receptors designated CB1 and CB2. The CB1 receptor, cloned both in rat (1990) and human (1991) is found in brain, but

also in lower abundance in some peripheral tissues. In 1993, a peripheral-specific receptor, hCB2, was cloned from human promyelocytic cells HL60. It shares only 44% overall identity with hCB1. This subtype expressed in immune tissue, but not in the brain, may be involved in cannabinoid-mediated immune modulation. Although most cannabinoid ligands bind to CB1 and CB2 receptors with similar affinities, we developed a selective CB2 antagonist based on the diatylpyrazole structure of SR 141716, the first CB1 antagonist introduced in 1994. This presentation will focus on *in vitro* and *in vivo* pharmacology of this new compound, SR 144528, which behaves as a highly potent, selective and orally active antagonist for the peripheral cannabinoid receptor CB2. This compound displays nanomolar afftnity for the cloned human CB2 receptor and rodent immune tissue with the same potency (IC_{50} = 0.7 nM) and shows low affinity for the cloned human CB1 receptor and rodent brain tissue (IC_{50} = 500 nM) or for any of the over 70 receptors or ion channels investigated (IC_{50} > 1 μM). *In vitro,* SR 144528 antagonizes the inhibitory effects of the cannabinoid receptor agonist, CP 55940 (3 nM), on forskolin-induced cAMP production in cell lines permanently expressing the hCB2 receptor (EC_{50} = 10 nM), but not in cells expressing the hCB1 (EC50 > 1 μM). Furthermore, SR 144528 is able to selectively block the MAP kinase activity induced by 6 nM CP 55940 in cell lines expressing hCB2 (EC_{50} = 40 nM) but not in cells expressing hCB1 (EC_{50} = 1600 nM). In addition, SR 144528 is shown to antagonize the stimulating effects of 10 nM CP 55940 on human tonsillar B-cell activation evoked by cross-linking of Igs (EC_{50} = 20 nM). *In vivo,* after oral administration SR 144528 totally inhibits the *ex vivo* [^{3}H]-CP 55940 binding to mouse spleen (ED_{50} = 0.35 mg/kg) with a long duration of action. In contrast, it does not interact with the cannabinoid receptor expressed in the brain (CB1). It is expected that SR 144528 will provide a powerful tool to investigate the *in vivo* functions of the cannabinoid system in the immune response.

PHARMACOKINETIC PROFILE OF SR141716 IN HUMANS

M.A. Huestis

SR141716 is the first CB1 specific cannabinoid receptor antagonist. Studies were conducted to characterize the pharmacokinetics of single and multiple-dose oral administration of SR141716 in human research volunteers. SR141716 is highly lipophilic with a low clearance rate (8 L/hr), modest volume of distribution (1000 L), and a moderate rate of absorption. Due to these physicochemical factors, plasma elimination half-life is 3-5 days. Area under the curve (AUC) and C_{max} values increased in an approximate dose proportional manner up to 5-10 mg single doses. Above these doses, AUC and C_{max} increased, but in a less than dose proportional fashion. Another study examined the pharmacokinetic profile of repeated daily dosing of SR141716 for 21 consecutive days. Through plasma concentrations of SR141716 reached steady state within 2 weeks after initiation of daily dosing. Intra-subject variability was low, and overall variability was moderate. Systemic exposure, based on AUC and C_{max}, increased in a slightly less than dose proportional manner. Based on AUC, the extent of accumulation was 3-3.5 fold. Following administration of ^{14}C-SR141716, less than 3% of the radioactive dose was excreted in the urine, indicating that urinary excretion did not play a major role in the elimination of SR141716 metabolites. This suggests that metabolism and/or biliary excretion are major pathways of SR141716 clearance. *In vitro,* the hydrolysis of SR141716 to SR141715 (inactive metabolite) is the predominant metabolic pathway. *In vitro,* SR141716 did not induce or inhibit various human liver cytochrome P450 enzymes, suggesting that interactions between SR141716 and other drugs that are metabolized via cytochrome P450 enzymes are not likely to occur.

SYMPOSIUM XIII

ALLELIC POLYMORPHISM OF HUMAN OPIOID RECEPTORS: FUNCTIONAL STUDIES

K.S. LaForge and M.J. Kreek, Chairpersons

MU OPIOID RECEPTOR VARIANTS, SUBSTANCE ABUSE AND PAIN

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Human individuals and mouse strains differ from each other in levels of mu opiate receptor (MOR) expression, responses to painful stimuli, reward from opiate drugs and other responses to opiate drugs. Variation at the mu opiate receptor (MOR) gene locus is one of the best candidates for contributions to these individual and strain differences. Support for this idea comes from analyses of the human and murine MOR genes. Assessments of individual differences in human MOR expression add further support. Studies in mice, including quantitative trait locus (QTL), knockout transgenic, and strain comparison studies, also strongly support the possibility that allelic variants of the MOR gene would be strong candidates to contribute to individual differences in human nociception and opiate drug responses.

Recent data from transgenic mice provide important information about the role of MOR expression levels in mouse models of human pain and addiction. Morphine is not analgesic or rewarding in mice lacking mu receptors. Mouse strain comparisons have also revealed both reduced antinociceptive responses to morphine and lower levels of MOR expression in some mouse strains. QTL studies in mice have mapped a significant portion of the genetic variance in morphine preference, analgesic responses and receptor B_{max} values to the vicinity of the MOR locus. We have identified a novel polymorphism of the murine MOR gene candidate promoter/enhancer regions that displays striking correlations with both levels of MOR expression and the extent of morphine antinociception in the BxD recombinant inbred lines.

Humans differ in their responses to pain and in their vulnerability to addiction to opiate drugs. Twin studies document that individual differences in addiction vulnerabilities, and several types of pain, are likely to have substantial genetic determinants. Humans also differ from one another in mu receptor densities; binding and PET studies both suggest 30-50% ranges of human individual differences in mu receptor densities.

We have identified human genomic DNA that contains the entire MOR gene coding region and substantial 5' flanking sequence. Searches in our laboratory and others have failed to identify common variants in the human mu receptor protein coding sequence that dramatically change receptor function, although a modest alteration in affinity for the ß-endorphin has been noted by Yu and colleagues (see below). These data are in accord with studies that document no convincing individual differences in MOR affinities among humans. They also fit with the substantial MOR coding sequence conservation among species These observations suggest that genetic components which result in functionally-different MOR protein sequences may be unlikely to explain commonly-encountered individual differences, and contrast with the abundant data, noted above, documenting frequent individual differences in expression levels of the mu receptor.

We and others have also identified a number of interesting MOR gene polymorphic markers. We identified the first reported human polymorphism, a *Msp*I RFLP. We have used PCR to amplify and have sequenced DNA from more than 1 kb of DNA containing the -268/-793 region from 12 unrelated human individuals. We identified repetitive sequences in these regions that have not been polymorphic in initial screens. Two other types of sequence variation have also been identified. In addition, more than 20 single nucleotide polymorphisms (SNPs) have been found in these upstream sequences by other researchers.

Information about MOR gene polymorphisms that can predict the likelihood of levels of mu expression in an individual may allow opiate drug treatments to be individualized to better treat pain. Conceivably, this information could also help in anticipating addiction vulnerabilities (Uhl *et al.,* 1999).

REFERENCE: Uhl GR, Sora I, and Wang Z (1999) Proc Natl Acad Sci USA 96:7752-7755.

GENETIC CONTRIBUTIONS TO PROTECTION FROM, OR VULNERABILITY TO, ADDICTIVE DISEASES

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Evidence from both clinical and animal studies suggest that the mu opioid receptor (MOR) gene is a reasonable candidate for studying potential genetic contributions to differences in responses to opioids, as well as in vulnerability to opiate addiction. In collaboration with the group of Lei Yu, we studied the MOR gene in 113 former heroin addicts currently in methadone maintenance treatment, and 39 control subjects (Bond et al., 1998). By sequencing PCR-amplified genomic DNA, we identified five separate single nucleotide polymorphisms (SNPs) in the coding region of the gene. Two of these SNPs were common, with overall allelic frequencies of 10.5% and 6.7% for the A118G and C17T SNPs, respectively. Both of these common SNPs were found to vary significantly among the three main ethnic groups studied.

Allele frequency differences between opioid dependent and non-dependent groups were assessed using Chi-square tests, as well as the pooled Relative Risk and Mantel-Haensel Chi-square statistic for data stratified by ethnic group. With all ethnic groups combined, the C17T allele variant was present in a higher overall proportion of opioid dependent persons than controls at a borderline significance level (P=0.05 using either test). With all ethnic groups combined, we found no difference in allele frequencies for the A118G variant using either statistical test; however, this allele was present in a significantly higher proportion of opioid-dependent subjects compared to controls within the Hispanic study group (Yates corrected χ^2=8.22 [p=0.0041]). Although population admixture is a likely explanation for this finding, it also suggests the possibility that this allele might confer a relative protection against opioid dependence.

In collaboration with the group of Andrei Mirzabekov at Argonne National Laboratory, we have developed custom acrylamide gelpad oligonucleotide microchips for identification of specific SNPs of the MOR gene. This specific microchip technology was selected because of the ease of fabrication of microchips, which allows for ready customizability, the robust signal to noise ratio in detection, and the ability to re-use the microchips many times, which makes them relatively inexpensive.

These microchips consist of an array of 100 x 100 x 20 μ^3 acrylamide gelpads fixed to a microscope slide. "Base call sets" of "probe" oligonucleotides coupled to the gelpads were designed to query the A118G and C17T SNPs of the MOR gene by differential hybridization. Human DNA samples from our bank were sequenced to determine genotypes at nucleotide positions 118 and 17. Fluorescently labeled "target" material was prepared from this genomic DNA and hybridized to microchips. Measurement of hybridization levels was by fluorescence microscopy. The base substitution at the polymorphic sites was then determined by target hybridization to perfect duplex or single base mismatched oligonucleotides linked to specific gelpad positions. Fluorescence levels at gelpads with perfectly matched oligonucleotides were easily and reproducibly distinguishable from signal intensity at positions with single base mismatched oligonucleotides.

This method provides a highly reproducible alternative to DNA sequencing or other methods, and should enable inexpeniive and high-throughput analysis of MOR gene SNPs for genetic and genomic studies.

REFERENCE: Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Leal SM, Tischfield JA, Kreek MJ, Yu L (1998) Proc Natl Acad Sci USA 95:9608-9613.

DIFFERENCES IN CELLULAR FUNCTION OF ALLELIC VARIANTS OF THE HUMAN MU OPIOID RECEPTOR

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The most commonly used opioids, both in the clinical management of pain and in the setting of drug abuse and addiction and the treatment thereof, primarily activate the mu opioid receptor to mediate their physiological effects. In collaboration with the group of Mary Jeanne Kreek at The Rockefeller University, we have identified five different single nucleotide polymorphisms (SNPs) in the coding region of the mu opioid receptor (MOR) gene by sequencing DNA from former heroin addicts and control subjects. The most prevalent SNP identified is a substitution at position 118 (A118G) in the protein coding region, predicting an amino acid substitution (N40D) at a putative N-glycosylation site in the N-terminal region of the receptor. This amino acid position is predicted to be in the first extracellular domain of the receptor.

To study potential effects of this common amino acid substitution on the cellular functioning of the receptor, we expressed the prototype and variant forms in AV12 cells to study ligand binding, and in oocytes co-expressing G-protein activated inwardly rectifying K^+ (GIRK) channels, activation of which is an important cellular consequence of agonist binding to the receptor. The N40D variant and the prototype receptors had similar binding affinity for most opioid peptides and alkaloids tested, including Met- and Leu-enkephlin, endomorphin-1 and -2, DAMGO, dynorphin $A_{(1-17)}$, morphine, methadone, fentanyl and naloxone. However, we found a significant difference in the binding affinity of β-endorphin: compared to prototype receptor, the N40D variant binds β-endorphin approximately three times more tightly. Furthermore, the binding of β-endorphin to the N40D variant receptor displayed an approximately threefold greater activation of GIRK channels compared to β-endorphin binding to the prototype receptor. Other opioid agonists showed no significant difference in GIRK channel activation between the two receptor forms. These results suggest the A118G SNP in the receptor gene may result in changes in cellular function of the receptor. These potential functional differences of the allelic forms may have implications for normal physiology, therapeutics, and diseases including the addictive diseases (Bond *et al.,* 1998).

REFERENCE: Bond C, LaForge KS, Tian M, Melia D, Zhang S, Borg L, Gong J, Schluger J, Strong JA, Lea1 SM, Tischfield JA, Kreek MJ, Yu L (1998) Proc Natl Acad Sci USA 95:9608-9613.

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A SINGLE NUCLEOTIDE POLYMORPHIC MUTATION IN THE HUMAN MU OPIOID RECEPTOR SEVERELY IMPAIRS RECEPTOR SIGNALING

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Large-scale sequencing of the human mu opioid receptor (MOR) gene revealed polymorphic mutations (Hoehe), some of which occur within the coding region: N40D at a putative N-glycosylation site in the N-terminal domain, N152D in the third transmembrane domain, and R265H and S268P in the third intracellular loop. We investigated if these MOR variants exhibit altered functional properties when expressed in COS cells. The N152D receptor was found expressed at lower densities compared to wild-type and other mutants receptors. Affinities of the peptide agonist DAMGO, the peptide antagonist CTOP and the alkaloid antagonist diprenorphine were slightly increased at the R265H mutant receptor (3.7-, 1.9- and 2.5-fold, respectively), while binding affinity of the alkaloid agonist morphine was greater at most mutant receptors (2.6- to 4-fold).

Receptor signaling was measured by the agonist-induced [35S]GTPγS binding assay. Maximal DAMGO-promoted [35S]GTPγS binding was barely detectable at S268P (132% of basal level) compared to wild-type receptor (228% of basal level), demonstrating a dramatic impairement of agonist efficacy. Also, the EC50 value was increased two fold, indicating a concomitant decrease in agonist potency at this variant receptor. DAMGO responses of N40D and R265H mutants did not significantly differ from wild-type receptors and none of the mutations induced detectable constitutive activity. Our data, therefore, show that natural mutations of the mu receptor can modify receptor density or ligand binding. More importantly, the S268P MOR variant represents a loss of function mutant of the human mu-receptor that may have an effect on opioid-regulated behaviors or drug addiction *in vivo.*

ALLELIC VARIATION OF DELTA AND KAPPA OPIOID RECEPTORS AND ITS IMPLICATION FOR RECEPTOR FUNCTION

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There is a significant association between an allelic variation (C to T exchange in codon 307) of the delta opioid receptor gene with heroin addiction (Mayer *et al.* 1997). Our recent studies indicate that there is also an association of this allelic variation of the delta receptor with alcoholics with a family history of alcoholism. We found another allelic variation of the delta receptor gene (exchange of T to G in codon 27 results in an exchange of Phe to Cys; allele frequency T = 90%; G = 10%). This coding mutation has little effect, if any, on both binding and coupling of delta opioids and β-endorphin as measured in frog oocytes and in transfected HEK293 cells. We found no association of this polymorphism with heroin addiction.

We detected four silent variations in the kappa opioid receptor gene (exchange of G to T at nucleotide 36; C to T at nucleotide 459; AC to GC at nucleotide 843 and GC to CT at nucleotide 846). The allele frequencies of these polymorphisms are low (below 5%).

M. Hoehe and B. Wendel described in a PCT patent application (Publication WO 98133937) a large series of polymorphisms in the mu opioid receptor gene. One causes an exchange of the amino acid Ser to Pro at position 268. Since Ser 286 is a phophorylation side for CamKinase II, we mutated this site to Pro and Ala in the human and rat gene. After expression in frog oocytes and in HEK293 cells, a marked decrease in coupling efficiency and in agonist-induced desensitization was found.

Within the promoter region of the human prodynorphin gene, a 68 bp sequence was found which occurs as polymorphic element, either singularly, or as tandemly repeated element (either 2, 3, or 4 times). This 68 bp repeat element contains an AP1 factor binding site. Reporter gene assays provide evidence of allele dependent differences in promoter activities. However, prodynorphin allelic distributions were not significantly different in heroin addicts and control subjects.

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SYMPOSIUM XIV

DEVELOPMENTAL FOLLOW-UP OF PRENATAL DRUG EXPOSURE IN PRE-SCHOOL AND SCHOOL-AGED CHILDREN

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Developmental follow-up studies of infants and children exposed to illicit drugs in utero have been ongoing for many years, permitting discussion of outcomes from infancy to puberty. Across these studies, cohorts of children have been assessed at varying ages. Children in marijuana or opiate focused projects are older than those exposed to cocaine.

One major cohort study is the Maternal Lifestyle Study (MLS), a multi-site prospective study of neonatal events and long-term health and developmental outcomes relative to drug use during pregnancy (i.e., cocaine, opiates, or both). MLS sites are located in Detroit, Ml; Memphis, TN; Miami, FL; and Providence, RI. The long-term aspect of the MLS is in progress, and is currently designed to observe the children to age seven years. One analysis in the MLS focused on the association between prenatal exposure status and patterns of motor development over the first 18 months of life. Infants exposed (EXP) to cocaine/opiates (N=658) were studied relative to 730 infants in a comparison group (COMP), which was group matched for gestational age, race, and gender. Alcohol, marijuana, and tobacco exposure occurred in both groups. Measures were administered by masked certified examiners, and included: the NICHD Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (NNNS) at 1 mo corrected age; the Posture and Fine Motor Assessment of Infants (PFMAI) at 4 mo; the Bayley Psychomotor Index (PDI) at 12 mo; and the Peabody Motor Scales (PMS). Motor scores from each measure were converted to standard (Z) scores, scores for each infant were averaged, a slope of the four averaged Z scores was computed for each infant, and mean slopes for EXP and COMP were compared (t test). Regression analysis was performed adjusting for birth weight, exposure to alcohol, marijuana, tobacco, opiates, and social class (Hollingshead). Cluster analysis was used to identify subgroups of infants with specific patterns of motor development across the four motor exams. Complete motor data were available for 605 infants (263 EXP, 342 COMP). The mean PDI was 91, and the mean on the PMI was 95 for gross motor and 87 for fine motor, There was no significant difference between the mean slopes of the EXP and COMP infants by t test. Cluster analysis identified a group of infants (N=60) characterized by motor scores which were significantly below the means: 1.7 SD on the PDI, .66 SD on the PDI, and .49 SD on the PMS. EXP infants were more likely than COMP to show this pattern of low motor scores (60% vs 40%, Chi Square=7.47, $p<.03$). Regression analysis revealed that this effect was due to poly-substance abuse (alcohol, marijuana, tobacco, and opiates) rather than cocaine alone, and was independent of SES ($p<.05$). It was concluded that, although the trajectory of motor development is similar between EXP and COMP infants, there is a subgroup of poly-substance exposed infants with consistently poor motor function at 1, 12, and 18 mo. The finding that the mean motor score of both groups is below the norm, especially for fine motor at 18 mo, is consistent with other studies of children growing up in underprivileged environments. Continued follow up of this large cohort is providing data on a wide range of health and development outcomes.

Ongoing longitudinal research at Yale University is examining relationships among prenatal cocaine exposure, postnatal environmental instability, and the cognitive and social development of infants and children from birth through eight years of age. This research is being conducted in the context of four lines of evidence suggesting a plausible link between prenatal cocaine exposure and specific effects on mechanisms subserving arousal and attention regulation in infants and preschool children: (1) the association of prenatal cocaine exposure with alterations in monoaminergic system ontogeny with suggestive findings pointing to a functional decoupling of dopamine D1/D2 interaction, and an increase in D2 and norepinephrine activity, (2) neurobehavioral effects of

prenatal cocaine exposure in animals, including inhibited exploration and altered responses to stress, suggesting overarousal in the face of novel/stressful situations and disrupted attention and learning, (3) altered norepinephrine system functions in cocaine-exposed human infants and altered glucocorticoid response suggesting altered stress response systems, and (4) neurobehavioral findings in infants and preschool aged children suggestive of disrupted arousal regulation in the face of stress or novelty, increased distractibility, impulsivity, and consequent impaired attention to novel, structured tasks.

The developmental domains of particular focus in this research relate to the regulation of arousal and attention. The cohort under study involves 442 children (254 prenatally cocaine-exposed and 188 non-cocaine-exposed), who currently range in age from 3.5 to 7 years. Children are divided into three study groups: (1) those exposed to cocaine and other drugs including alcohol, tobacco, and/or marijuana, (2) those exposed to other drugs in varying combinations but not to cocaine, and (3) those exposed prenatally to no other drugs. Children are seen biyearly between 4 and 8 years with repeated assessments in the following domains: (1) arousal regulation operationalized behaviorally as state and emotional reactivity and neuropsychologically as the startle response and heart rate variability, (2) attention regulation operationalized as the ability to sustain attention, identify stimuli, and inhibit responses, (3) aspects of executive functioning (in particular, reflective of prefrontal cortex functioning), (4) cognitive function, (5) adaptive and maladaptive behavior, (6) school performance, (7) social adjustment, and (8) the incidence of childhood psychiatric disorders of attention, anxiety, and conduct. Analyses for a cross-sectional sample of the larger cohort involved measures at 4.5 and 5.5 years of age in the following four paradigms (1) delayed response, (2) Stroop task modified for preschool age children, (3) a continuous performance task, and (4) an auditory startle procedure. Across the four measures, children in the cocaine exposed group differed significantly from children in the other two groups. These differences may be characterized as increased emotional lability, impulsivity, perseveration, problems with attention shifting and inhibiting responses. For some of these behavioral differences, particularly the inhibition of salient responses, there was a relationship between amount of cocaine exposure prenatally and the degree of difficulty, with heavier exposure associated with more difficulty inhibiting salient responses. Findings such as these suggest a disruption for cocaine-exposed children in the interactive relationship between arousal regulation and prefrontal cortical functions as assessed by so-called executive function tasks. Early disruption of the developmental ontogeny of arousal regulatory capacities may possibly have effects that extend well into the school-aged years and alter the normal trajectory of cognitive and social-emotional development.

Topics such as attention, executive function, and prefrontal lobe functioning have also been of much interest in research on the development of children exposed prenatally to marijuana. For over 15 years, the Ottawa Prenatal Prospective Study (OPPS) has reported the neurobehavioral outcomes in the offspring of women who used marijuana and/or cigarettes during pregnancy. The subjects participating in the ongoing OPPS are primarily middle-class, low risk women who entered the study early in their pregnancy. Extensive demographic and lifestyle information was gathered several times during pregnancy, after the birth, and continue to be collected. A cohort of 190 children was selected. The children have been assessed repeatedly during the neonatal period, at least annually until the age of six and less frequently thereafter. The data gathered when these children are entering adolescence have recently been analyzed. The outcome measures include a variety of age appropriate standardized global measures as well as a large series of neuropsychological tests assessing discrete functioning within particular domains including language development, memory, visual/perceptual functioning, components of reading, sustained attention, and executive function. The latter is a multiple, non-unitary set of cognitive/behavioral processes critical in effortful, non-routine goal-oriented situations. Across all ages of assessment, a dose dependent association, that remains after controlling for potential confounds (including second hand smoke), has been noted between prenatal cigarette exposure and lower global IQ with tests of auditory/verbal functioning showing the maximum vulnerability. In contrast, global measures, particularly between the ages of one and three years, have not revealed an association with prenatal marijuana exposure. However, as the children became older, aspects of neuropsychological functioning that discriminated between marijuana and control children included increased behavior problems and decreased performance on visual perceptual tasks requiring integration of basic perceptual abilities, and aspects of attention. The nature and the timing of the appearance of these deficits is congruent with the notion of prenatal marijuana exposure affecting facets of executive functioning. Such an interpretation would be consistent with the extant literature with non-pregnant adult users suggesting that chronic marijuana use may impact upon aspects of prefrontal lobe functioning.

Long-term follow-up of children exposed to opiates in utero has been conducted at the University of Chicago. Thirty-six children whose mothers used opioid drugs, primarily methadone, during pregnancy and a comparison group of 41 children whose mothers did not abuse opioids or alcohol. The children have been followed longitudinally from the prenatal period. At age 9-11 years, relative to the comparison group, children exposed prenatally to opioids showed no deficits in general intelligence (assessed with the WISC-R), but did have difficulties on the Continuous Performance Test, suggestive of problems with regard to focusing attention and inhibiting motoric response. Boys with histories of prenatal exposure were particularly at risk for attention problems. Children exposed prenatally to opioids did not have more behavior problems (assessed with the Diagnostic Interview for Children and Adolescents) than other children during middle childhood. Children's behavior problems were, however, associated with the quality of parenting they received, and in particular with maternal responsiveness when the children were infants.

Knowledge about the development of children prenatally-exposed to illicit drugs is increasing and will continue to do so as the children in various cohorts age. Currently, federally-funded research studies of this type are being conducted in at least 14 U.S. cities. Investigators continue in their efforts to examine specific and subtle aspects of developmental functioning in a range of developmental domains, to identify level or severity of exposure, and to address the challenges presented by the many co-occurring factors which themselves may be responsible for variation in child outcomes (e.g., parenting practices, environmental conditions).

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SYMPOSIUM XV

EMERGING BIOLOGICAL TARGETS FOR THE TREATMENT OF NICOTINE DEPENDENCE

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Nicotine dependence remains one of the greatest health concerns facing the US. Despite the availability of pharmacological treatment, represented by several forms of nicotine replacement as well as the antidepressant bupropion (Zyban), smoking cessation represents a significant unmet medical need that could be further facilitated by effective pharmacotherapy. Recent advances in the understanding of neuronal nicotinic receptors have permitted unprecedented insight into the physiological and cellular mechanisms responsible for the reinforcing and subjective effects of nicotine. The purpose of this symposium was to highlight new biological targets that may be manipulated to alter smoking behavior and therefore serve as usefitl adjuncts in helping individuals to quit. Dr. Linda Dwoskin discussed her work concerning nicotinic receptor subtypes responsible for dopamine release in the CNS. Her data suggest that selective antagonists, particularly at the $\alpha3\beta2$ subtype, may be useful in altering the neurochemical effects of nicotine that are responsible for its dependence liability. Dr. Robert Mansbach presented his work on selective ligands at the $\alpha4\beta2$ subtype of the nicotine receptor. His data indicate that the behavioral and neurochemical effects of nicotine may be mediated by this subtype of the receptor, and that stimulation of $\alpha4\beta2$ receptors with partial agonists decreases the self-administration of nicotine in laboratory animals. Dr. Michael Bardo shared his recent work with nornicotine, a CNS metabolite of nicotine. His research demonstrates that nornicotine evokes dopamine in the nucleus accumbens, serves as a reinforcer, and diminishes nicotine self-administration in rats. Dr. Rachel Tyndale discussed the role of nicotine metabolism by cytochrome P450 isozymes and the potential of altered nicotine metabolism to decrease the probability of smoking behavior. Finally, Dr. John Hughes put the status of smoking cessation therapy into a broader context and assessed the potential value of alternative medical approaches to the disorder, as well as the kinds of clinical end-points that could drive future development of the field.

NOVEL SUBTYPE-SELECTIVE NICOTINIC RECEPTOR ANTAGONISTS BLOCK THE NEUROCHEMICAL EFFECTS OF NICOTINE (L.P. Dwoskin)

The present research focuses on the development of subtype-selective nicotinic receptor antagonists *via* facile pyridine-N alkylation of the nicotine (NIC) molecule to provide useful tools for elucidating structural and functional diversity of native nicotinic receptors in brain. A series of quaternary pyridine-N-n-alkyl nicotinium analogues (alkyl-substituents ranging from C_1 to C_{12}) were synthesized and tested for their ability to inhibit NIC-evoked [^{3}H]dopamine ([^{3}H]DA) release from [^{3}H]DA-preloaded striatal slices, to inhibit [^{3}H]NIC binding to rat striatal membranes and to inhibit NIC-evoked $^{86}Rb^+$ efflux from rat striatal synaptosomes. Increasing the alkyl chain length from C_1 to C_9 resulted in a direct correlation with potency to inhibit NIC-evoked [^{3}H]DA release, mediated by the purported $\alpha3\beta2$ receptor subtype. The C_{10} analogue, N-n-decylnicotinium iodide (NDNI), did not inhibit NIC-evoked [^{3}H]DA release. Schild analysis with the C_8 analogue, N-n-octylnicotinium iodide (NONI) indicated a competitive receptor interaction as well as the potential involvement of more than one subtype. Assays for [^{3}H]NIC binding to striatal membranes and $^{86}Rb^+$ efflux from striatal synaptosomes assessed interaction with the putative $\alpha4\beta2$ nicotinic subtype. [^{3}H]NIC binding was inhibited by all the analogues, however, no correlation was found between alkyl chain length and afftnity. Both NDNI and NONI competitively inhibited [^{3}H]NIC binding with Ki values of 60 nM and 20 μM, respectively. The lack of correlation between analogue-induced displacement of [^{3}H]NIC binding and inhibition of NIC-evoked [^{3}H]DA release, suggests that different nicotinic receptor subtypes are involved in these two assays. NONI was the most potent antagonist in the [^{3}H]DA release assay, which also completely inhibited evoked [^{3}H]DA overflow; whereas, NONI was the least potent inhibitor in the [^{3}H]NIC binding assay. A more than 100-fold greater concentration of NONI was required to displace [^{3}H]NIC

binding compared to inhibition of [^{3}H]DA release, suggesting a selective interaction with the nicotinic $\alpha3\beta2$ subtype. Furthermore, NDNI was most potent in the binding assay and was completely ineffective in inhibiting NIC-evoked [^{3}H]DA release, suggesting selectivity for the $\alpha3\beta2$ subtype. NDNI and NONI were also examined in the NIC-evoked $^{86}Rb^+$ efflux assay and Ki values were 30 pM and 85 nM, respectively. As in the [^{3}H]NIC binding assay, NDNI inhibited NIC-evoked $^{86}Rb^+$ efflux at concentrations 3-4 orders of magnitude higher than did NONI. Taken together, these results support a selective interaction for NDNI with $\alpha4\beta2$ nicotinic receptors, and for NONI with $\alpha3\beta2$ receptors. A second series of compounds was synthesized which lacked the N-methyl pyrrolidine ring (pyridinium series) and in which the N-alkyl substituent was varied from C_8 to C_{12}. These compounds were examined in the [^{3}H]DA release and [^{3}H]NIC binding assays. None of the compounds showed any improvement in binding affinity over NDNI. However, in the nicotine-evoked [^{3}H]DA release assay, two alkylpyridinium iodide analogues (N-n-decylpyridinium iodide[NDPI] and N-n-dodecylpyridinium iodide [NDDPI]) were more potent (IC50 = 110 and 90 nM, respectively) than NONI at the $\alpha3\beta2$ receptor subtype. NDDPI exhibited more than 3-orders of magnitude greater selectivity for the $\alpha3\beta2$ over the $\alpha4\beta2$ receptor subtype, and is currently the most selective $\alpha3\beta2$ antagonist in this novel structural class. These subtype-selective nicotinic receptor antagonists will undoubtedly be valuable tools for probing the consequences of activating different subtypes of the nicotinic receptor.

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PARTIAL AGONISTS AT THE $\alpha4\beta2$ NICOTINIC RECEPTOR MODIFY THE BEHAVIORAL AND NEUROCHEMICAL EFFECTS OF NICOTINE. (R.S. Mansbach)

Cytisine is a naturally occurring product of *Laburnum anagyroides* and other plant species which binds potently to nicotinic receptors in the central nervous system (IC50 ~ 0.5 nM). In vivo, cytisine produces effects which partially reproduce those of nicotine, and in vitro data suggest that this compound acts as a partial agonist at the $\alpha4\beta2$ receptor subtype (Papke and Heinemann, Mol. Pharmacol. 45:142-9, 1994). In the present study, effects of cytisine and several potent analogs were examined on dopamine turnover in the rat nucleus accumbens, a neurochemical index of nicotinic receptor stimulation, as well as in two behavioral models known to reflect the drug's psychoactive effects, nicotine discrimination and nicotine drug self-administration. Cytisine itself produced an increase in dopamine turnover that ranged from 30-50% of the response elicited by nicotine, and also attenuated the effect of nicotine on this measure. Several substituted cytisine derivatives with binding IC50s ranging from 0.2-15 nM produced similar effects, providing further evidence that these compounds act as partial agonists at central nicotinic receptors. In rats trained to discriminate injections of nicotine (0.4 mg/kg) from saline, cytisine produced a dose-dependent partial substitution (55%) for nicotine that was reversible by the noncompetitive nicotinic antagonist mecamylamine. Several cytisine derivatives also produced nicotine-like effects, with maximum substitution levels ranging from 40-95%. Three of these analogs, acetyl, chloro and bromo, were found to selectively decrease lever-pressing maintained by intravenous self-administration of nicotine in rats (30 µg/kg/infusion), as did pretreatment with nicotine itself. In rats trained to self-administer nicotine under a progressive ratio schedule, the nicotinic antagonists mecamylamine and erysodine decreased break-points, although nicotine and cytisine had no effect other than to lengthen latencies to break-point. Taken together, these data indicate that potent nicotinic ligands based on cytisine act as partial agonists in vivo at neuronal nicotinic receptors that are considered to mediate the subjective and reinforcing effects of nicotine. Such partial agonists may have therapeutic potential for the treatment of nicotine dependence.

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NORNICOTINE, A CNS METABOLITE OF NICOTINE, HAS NEUROCHEMICAL AND BEHAVIORAL EFFECTS SIMILAR TO NICOTINE (M.T. Bardo)

Nicotine is a tobacco alkaloid known to be important in the acquisition and maintenance of tobacco smoking. In addition to nicotine, however, recent evidence suggests that nornicotine may play a role in the dependence liability of tobacco use. Nornicotine is a major tobacco alkaloid and a metabolite in the periphery that has a plasma half-life of approximately 8 hours (Kyerematen *et al. Clin Pharmacol Ther* 48:641-651,1990). Importantly, substantial biotransformation of nornicotine from nicotine may occur locally in the brain (Crooks *et al. Drug Metab Dispos* 25:47-54, 1997). The purpose of our research was to determine if nornicotine has a reinforcing effect similar to nicotine. Rats were prepared with a chronic indwelling jugular catheter and then were allowed to self-administer intravenously either S(-)-nicotine or RS(±)-nornicotine using a two-lever operant procedure similar to that described previously (Corrigall and Coen *Psychopharmacology* 99:473-479, 1989). Rats self-administered nornicotine (0.075-0.6 mg/kg/infusion) in a dose-dependent manner significantly above saline control levels; however, responding for nornicotine was less avid than responding for nicotine. Extinction of responding was evident when saline was substituted for nornicotine, and responding was reinstated when nornicotine again was available. The rate of nornicotine self-administration did not differ significantly between rats tested with either 24 or 48 hr intersession intervals. In other experiments, we also found that nornicotine pretreatment (1-10 mg/kg, SC) dose-dependently decreased nicotine self-administration. Importantly, across repeated pretreatment sessions, nornicotine continued to decrease nicotine self-administration, but not food-maintained responding. These results indicate that nornicotine contributes to the dependence liability associated with tobacco use and that nornicotine may serve as a useful pharmacotherapy for smoking cessation.

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NICOTINE METABOLISM DEFECT REDUCES SMOKING (R.F Tyndale and E.M. Sellers)

In humans, approximately 70% of nicotine (NIC) is inactivated by CYP2A6. We have found that those with *CYP2A6* defective alleles have a decreased risk of becoming smokers (OR= 1.7, p=0.04 C.I. 1.02-2.94) and smoke less if dependent (19 vs. 23 cigarettes/day, p=0.02) *(Nature* 393: 750, 1998). We have since investigated if CYP2A6 inhibition could be used to imitate the defective NIC metabolism and decrease smoking behavior as a therapeutic. We identified tranylcypromine (TCP) and methoxsalen (MET) as potent CYP2A6 inhibitors. In dependent smokers MET, 30-50 mg orally 30 min prior to nicotine 31 µg/kg s.c. (≈1 cigarette x 3, hourly of NIC inhalation kinetics), increased the 8-hour mean plasma NIC by 49% ($p < 0.01$) compared to placebo (PLAC) strongly suggesting that oral CYP2A6 inhibitors could be useful in decreasing smoking by prolonging the half life of NIC. NIC oral bioavailability is low (approximately 25%) but higher doses cause intestinal distress prohibiting a NIC pill. In oral NIC (4 mg) studies, compared to PLAC, MET 10 and 30 mg and TCP 2.5 and 10 mg increased mean plasma NIC concentrations ($p < 0.01$) 72, 83, 43 and 65% respectively, as well as reducing subjects' self-rated current desire to smoke ($p < 0.05$). To test the effect on smoking, overnight NIC-abstinent dependent smokers (n=12) had one cigarette in the AM, and were then given MET 30 mg or PLAC with either NIC 4.0 mg or PLAC in a cross over counterbalanced order. After 60 min, subjects could smoke *ad libitum* for 90 min. Subjects receiving MET/oral NIC smoked less than PLAC/PLAC (e.g., 50% less increase in breath CO; 83% increase in latency to the 2nd cigarette, 24% decrease in the number of cigarettes and in the total number of puffs taken, all $p<0.05$). On several measures the rank order of response was MET/NIC > MET/PLAC > PLAC/NIC > PLAC/PLAC suggesting that MET alone (no oral NIC) also decreased smoking indices. In conclusion these studies support the original genetic findings and indicate that CYP2A6 inhibition alone, or combined with oral NIC, decreases smoking and therefore should have a role in tobacco smoking cessation, exposure reduction or relapse prevention strategies.

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SYMPOSIUM XVI

FROM CAFFEINE TO OPIATES: NOVEL INTERVENTIONS FOR SUBSTANCE USE IN PREGNANCY

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Substance use during pregnancy has been associated with a variety of adverse maternal and infant outcomes (Finnegan, 1989; Svikis and Huggins, 1996). Although much attention has focused on illicit drugs such as cocaine and heroin, adverse sequelae have also been documented for licit substances including alcohol, tobacco and caffeine (McCaul *et al.,* 1991). To meet the complex needs of this high-risk population of women and children, a variety of specialized treatment programs have been developed (e.g., Hailer *et al.,* 1993; Jansson *et al.,* 1996). Unfortunately, many pregnant women deny substance use problems and are unwilling to seek care in such programs because of social stigmatization (Svikis *et al.,* 1998). In addition, economic constraints within the expanding managed health care system in this country continue to reduce the number of such programs available to this high-risk population of women and their children. To meet the clinical needs of this patient population while also addressing cost-effectiveness of treatment services, a variety of innovative intervention strategies have been developed and evaluated for implementation in medical primary care settings as opposed to drug treatment programs. This symposium examined the effectiveness of four alternative intervention models for reducing both licit and illicit substance use during pregnancy. The interventions ranged from brief physician advice to intensive case management and outreach. All interventions shared in common, however, their application in a variety of medical care settings. The substances targeted by the interventions included both licit (e.g., caffeine, tobacco, alcohol) and illicit (e.g., cocaine, opiates) drugs.

Caffeine use in pregnancy has been associated with a variety of adverse sequelae. The extent to which practitioners counsel pregnant women to reduce or eliminate caffeine use during pregnancy remains variable and, at present, little is known about the impact of such advice on caffeine use among pregnant women. The present study examined: 1) patterns of caffeine use before and after women were counseled by their physician to eliminate caffeine use for the remainder of their pregnancy; and 2) the relationship between patient variables and degree of caffeine dependence and a woman's ability to eliminate or reduce caffeine use during pregnancy. Participants were pregnant women with mean age 32.0 years; 96% Caucasian; 100% married; and 73% employed full time. All participants (N=96) provided informed consent at first prenatal visit and completed an initial questionnaire documenting caffeine use (lifetime) and during the 3 months prior to pregnancy awareness. Upon completing the questionnaire, subjects were counseled by their obstetrician to eliminate caffeine use for the remainder of their pregnancy. Subjects then completed brief follow-up questionnaires at the next prenatal visit and at their 28th week visit. In addition to questionnaire data, 45 women participated in a personal interview to obtain more detailed data including a DSM-IV diagnosis of caffeine dependence. The interviews occurred between the first and second follow-up assessments. Based on questionnaire data, 92% of women reported pre-pregnancy caffeine use and over half (58%) of the subjects met DSM-IV criteria for Caffeine Dependence. Rates of caffeine abstinence varied over the course of pregnancy. At the first obstetrics visit, 38% of women had already eliminated caffeine from their diet. By the second prenatal visit, nearly half (48%) reported caffeine abstinence, but by an estimated gestational age of 28 weeks, only 40% of women were caffeine abstinent. These data suggest that many women spontaneously eliminate caffeine from their diet at the time of pregnancy awareness, but that physician advice was associated with additional short-term reductions in caffeine use. Additional data analyses are underway to examine the impact of caffeine dependence diagnosis and family history of alcohol abuse/dependence on patient ability to eliminate or reduce caffeine use during pregnancy.

Another problem facing pregnant women is smoking cessation. As many as 40% of pregnant smokers in the U.S. stop on their own before starting prenatal care. Only a small proportion of continuing smokers will stop sometime later in pregnancy (up to 8% for low SES and 15% for higher SES women). Spontaneous quitting is most likely among better

educated, lighter smokers having their first child, and least likely among Native American and Caucasian women of low SES. With brief intervention, the natural rate of smoking cessation can be increased modestly, nearly doubling the natural rate. Generically, brief intervention includes pregnancy-specific guidance materials followed by 3-10 minutes of brief counseling with a prepared health care provider. Positive effects of brief intervention include significant, validated reduction and cost savings of $3 for every $1 invested within 12 months of the intervention investment (based on the initial hospitalization of the infant) and long term abstinence by nearly 40% of women who stop successfully while they are pregnant. Broad scale dissemination of brief intervention strategies is currently under way. Brief intervention does little, however, to achieve cessation among heavier, more addicted smokers, and discussion of pharmacotherapy is ongoing. Development and testing of more intensive interventions to address stress, family conflict, and depression that decrease motivation and emotional resources for cessation also seems to be needed. More counseling alone has not been shown to bring about more quitting. An innovative intervention currently being tested focuses cessation efforts on fathers and other family members who influence the environment for the pregnant woman and who contribute to environmental tobacco smoke in the household.

A challenge for professionals is providing interventions for the highest risk mothers abusing alcohol and drugs during pregnancy. The Birth to 3 Program, begun in 1991, is a unique Seattle-based model of paraprofessional advocacy for high-risk women who abused alcohol and/or drugs during pregnancy. Five advocates worked with 65 women from the child's birth to the age of three, addressing complex social, behavioral, medical, and financial issues. Results of the 36-month exit interview indicated a statistically significant positive impact among intervention women compared with similarly recruited controls on a composite variable consisting of alcohol/drug treatment, abstinence from alcohol/drugs, family planning, child well-being, and connection to services. A 2 ½ yr, post-program follow-up was conducted with 47 women to determine if successful outcomes were maintained. The proportion abstinent from illicit drugs and not abusing alcohol, for a period of one year continued to increase after completion of the program from 38% to 46%; for 2 years, from 16% to 28%. While regular birth control use dropped slightly (76% to 70%), use of more reliable methods (Nor-plant, Depo Provera, tubal ligation) stayed virtually the same (47% to 45%) and subsequent births and pregnancies decreased (births: 27% to 11%; pregnancies: 51% to 36%). Following completion of the demonstration project, other sources of funding have permitted replication of the Birth to 3 program and these data reveal similar findings to the first study. In recent years, the program has focused on modifying community services to be more responsive to the needs of these high-risk mothers and their families (e.g., special focus on needs of Native American mothers, identification of and special programming for mothers who are themselves fetal alcohol affected). The Washington State Legislature recently funded over $3 million for the biennium to continue and expand the program to four sites (Seattle, Tacoma, Yakima and Spokane), with each site serving ninety women.

The prevalence of substance use remains high during pregnancy despite well-documented maternal and fetal risks. Substance abusing, pregnant, Medicaid-enrolled women were the focus of a study because of important health services issues specific to this population. Using a harm reduction approach, the Better Chance project introduced easily accessible, substance abuse support group services and comprehensive case management on-site into a hospital-based prenatal clinic. Twice weekly support group sessions were facilitated by an experienced substance abuse counselor and addressed drug education, strategies for reducing drug use, and peer support. The goal of case management services was to gain and maintain access to needed wrap-around services. Components included office visits, home visits, escort services and telephone calls. Subjects (N=156) were: cocaine or heroin dependent, recruited in the obstetrics clinic in their first or second trimester, not seeking or currently enrolled in substance abuse treatment, and Medicaid eligible through AFDC. Women were assigned to one of three groups: case management + support groups; support groups alone; or a standard care comparison sample. Data were collected at enrollment, delivery and 12-months post-delivery. Study participants had a mean age of 28.3 years, averaged 10.8 years of education, and were predominantly African-American (94%) and unemployed (82%). Women in the case management + support group participated in an average of 15.4 office visits and 15.7 telephone sessions; received an average of 7.4 referrals for wrap around services and 2.2 home visits. Women in case management attended an average of 7.0 support groups compared to 4.6 sessions for support group only women. Further, 69% of case management + support group subjects attended two or more support group sessions compared to 46% of support group only subjects ($p<.02$). Women in the two intervention conditions were significantly more likely to participate in drug treatment during the 30 days prior to delivery than women in the comparison group ($p<.005$). Women in case management + support group and support group only conditions kept more prenatal care visits (6.2 and 7.6, respectively) than women in the comparison group (3.1 visits) ($p<.05$). Overall, study findings show substance abusing women will access support groups and case management services in an obstetrics setting. In turn, these services increase engagement in prenatal care and drug

abuse treatment, and decrease frequency of prenatal drug use. Importantly, these case management + support group services resulted in improved birth outcomes. These findings highlight usefulness of providing interventions for substance abusing women in nontraditional settings.

The treatment of substance abuse problems in pregnant women is a complicated issue. Most of the focus has been on the children born to these women. There has been little research on the best treatments for pregnant drug abusing women, and the majority of reports in the literature have focused on opiate dependence. The symposium presented some important new observations about drugs other than opioids and on new and cost effective treatment approaches for these women. Future areas that need to be addressed are approaches to withdrawal of pregnant women from alcohol, caffeine, nicotine, sedative hypnotics and cocaine, drugs for which no maintenance therapies are currently available. These withdrawal techniques should take into consideration not only withdrawal symptoms of the pregnant women but the effects on the fetus. It may be worthwhile to consider the development of maintenance therapies for pregnant addicted women on drugs other than opioids so that the stress of withdrawal is not incurred by the fetus. If we are going to protect the offspring of these women, we must concentrate on the development of effective treatment programs that will 1) attract women into treatment; 2) maintain them in treatment until delivery; and 3) permit them to get excellent prenatal and postnatal care.

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REINFORCING EFFECTS OF MORPHINE IN FEMALE VS. MALE RATS

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Numerous investigations have demonstrated that morphine is a more potent or efficacious antinociceptive agent in male than in female rodents. In contrast, several self-administration studies indicate that morphine may produce greater reinforcing effects in females than in males. The purpose of the present study was to examine sex differences in morphine's reinforcing effects using a brain stimulation procedure. Adult Sprague-Dawley rats responded for electrical brain stimulation delivered to the medial forebrain bundle (MFB) under a VI 3-sec schedule, in consecutive 5-min periods in which stimulation was available at 60, 80 and 100 Hz. Morphine was injected s.c. twice daily at approximately 8 a.m. and 8 p.m., at doses of 0, 3, 10 and 20 mg/kg/injection during weeks 1, 2, 3 and 4 respectively; responding for MFB stimulation was examined 1, 2 and 3 hr after the morning injection each day. There were no sex differences in rate of responding for MFB stimulation under non-drug conditions (Week 1). Morphine's effects were dependent on pretreatment time, dose, day of testing, and sex of subject. Morphine produced response rate increases that were greater at 2-3 hr than at 1 hr post-injection; in fact, morphine decreased response rate dose-dependently at 1 hr post-injection. The 3.0 mg/kg dose produced similar effects in both sexes. The 10-20 mg/kg doses produced significantly greater response rate decreases in males than in females; this rate suppression diminished over successive days of testing. Conversely, the rate-increasing effects of 10-20 mg/kg were greater in females than in males, and tolerance did not develop to morphine's rate-increasing effects. These results suggest that morphine produces greater reinforcing effects in female than in male rats. However, morphine (10 mg/kg) also increased rate of non-reinforced responding (responding during timeouts) significantly more in females than in males, indicating that morphine may simply produce greater locomotor activation in females than in males.

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SEX DIFFERENCES IN THE REGULATION AND REINSTATEMENT OF COCAINE SELF-ADMINISTRATION

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The present experiments were designed to compare male and female rats on regulation of cocaine intake and reinstatement of extinguished cocaine-reinforced responding. Regulation of cocaine self-administration was investigated using a two-lever drug self-administration procedure that allowed subjects' access to ten doses of cocaine (0.0-2.4 mg/kg) during 5 h sessions. The correlation between interdose interval and proceeding dose size was determined daily for each subject as a measure of drug regulation. Reinstatement of responding was examined using a priming model in which lever-pressing for drug (2 h) was extinguished by replacing cocaine infusions (0.2 mg/kg) with saline infusions (5 h). Reinstatement of responding was then tested by administering one of several priming injections of cocaine (0, .32, 1.0, 3.2 mg/kg) during the extinction period. Results showed initially all rats precisely regulated their intake of cocaine as shown by a high correlation between the size of the previous dose and time until next dose. After responding stabilized, regulation was disrupted in female rats compared to males with the greatest disruption observed in females during the estrous phase. For both male and female rats, reinstatement of responding increased in a dose-dependent manner. Although there was no significant difference between male and female rats in total cocaine intake during hours 1 and 2, levels of reinstatement responding after the two highest cocaine priming injections were greater in female rats compared to males. These results suggest that there may be differences between males and females during the transitory periods of drug addiction (e.g. acquisition and relapse).

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NICOTINE SELF-ADMINISTRATION IN MALE AND FEMALE RATS UNDER FIXED AND PROGRESSIVE RATIO SCHEDULES OF REINFORCEMENT

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Both human experimental and clinical data suggest that males and females differ in their smoking behavior. This difference could reflect the effects of gender and/or ovarian hormones on the reinforcing efficacy of nicotine. Self-administration of other drugs (e.g., cocaine, alcohol) in laboratory animals is affected by both sex and ovarian hormones. However, while sex differences also exist for several behavioral and physiological effects of nicotine in rats, there are no published reports comparing male and female rats self-administering nicotine. We have now begun to compare male and female Sprague-Dawley rats in our intravenous self-administration paradigm. As has been previously reported only for males, females self-administered nicotine. Dose/response analyses indicate that the pattern of intake during both acquisition and maintenance on a fixed ratio schedule was similar for males and females. However, females reached higher break points on a progressive ratio schedule. Females also responded more on the inactive lever and during the timeout period. There was no effect of estrous cycle on either fixed or progressive ratio self-administration. The results presented will further our understanding of the reinforcing effects of nicotine in females as well as address the question of potential sex differences in nicotine-seeking behavior.

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THE INFLUENCE OF GENDER AND MENSTRUAL CYCLE PHASE ON THE BEHAVIORAL EFFECTS OF ALPRAZOLAM

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This study evaluated the effects of gender and menstrual cycle phase on the behavioral effects of alprazolam. Seven male and 6 female healthy adults, blind to the study drug, gave written consent and participated on three consecutive nights per week over eight consecutive weeks (i.e., across successive menstrual cycles). Menstrual cycle activity was monitored prior to the study, and study days for women were selected to coincide with four cycle phases (early follicular, late follicular, early luteal and late luteal). On test days, subjects consumed a standard meal at 5:30 p.m., received drug at 6:30, and completed 20-minute sessions consisting of computerized performance tasks and visual-analog (VAS) ratings of drug effect 0, 0.5, 1, 2, 3, 4 and 5 hours after drug administration, and upon waking the next morning. Each of 3 doses (0, 0.4 and 0.8 mg/70 kg) was administered orally 1 day each week in random order. Blood samples were collected prior to the first day of each week to monitor HPG hormone levels. Alprazolam altered task performance, including response rate during a psychomotor performance task, correct and incorrect response rates during a learning task, time estimation and performance accuracy during a delayed matching-to-sample task, as well as VAS ratings of 'Feel Drug,' 'Down' and 'Light-Headed.' The magnitude of drug effect on VAS ratings of 'Down' and 'Drug Effect' was greater in females than in males, while increases in time estimation were greater in males than in females. Interactions between the behavioral effects of alprazolam and phase of the menstrual cycle were also observed on learning task performance, with drug effects occurring more rapidly during the late follicular and early luteal phases and for an extended duration during the early follicular and late luteal phases. Residual next-day effects were obtained on several dimensions of task performance but not on ratings of drug effect. These results indicate that the behavioral effects of alprazolam on selected dimensions of performance and verbal reports of drug effect differ between males and females, and that alprazolam-induced impairment of acquisition varies across the menstrual cycle.

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THE CHINESE HERB, KUDZU, ALTERS ETHANOL EFFECTS IN MALE AND FEMALE SUBJECTS

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A number of Chinese herbs have been used over the centuries to treat alcohol-related problems. The finding that an extract of *Radix lobata* (kudzu) reduced ethanol drinking in rats and hamsters prompted us to conduct a safety and efficacy study in male and female volunteers. After providing informed consent, male and female moderate (15-30 drinks/week) or light (< 5 drinks/week) drinkers were given pre-packaged envelopes and instructed to take one packet of 15 capsules (each containing 1.0 g of crushed kudzu root or gelatin placebo) t.i.d. for two consecutive days. Riboflavin was added to the capsules to monitor compliance. On the third day, subjects came to the laboratory to participate in an ethanol challenge experiment during which subjective, physiologic and plasma ethanol levels were measured before and for 3 hours after drinking 0.7 g/kg of ethanol. The compliance/safety data indicate that subjects did take all of their doses, were unable to discriminate kudzu from placebo and experienced no side effects. Blood and urine laboratory assessments were unaffected by kudzu treatment. Kudzu pretreatment had no significant effect on plasma ethanol levels or on ethanol-induced changes in subjective mood in the moderate drinkers. In contrast, the effects of kudzu in light drinkers were much more profound. There were substantial reductions in a number of ethanol-induced mood effects including "High", "Drunk", "Alcohol Effects", "Dizzy" and the PCAG scale of the ARCI. However, plasma ethanol levels were either unchanged by kudzu or slightly increased. The mechanism by which kudzu alters ethanol-induced in toxication remains unknown. These results suggest that this non-toxic herb may be a useful adjunct in modulating alcohol intake in light drinkers, but that a more concentrated extract may be needed to modify the effects of ethanol in moderate or heavy drinkers. Such studies are currently underway in our laboratory.

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SEX DIFFERENCES IN PHYSIOLOGICAL RESPONSE TO COCAINE-RELATED CUES IN HUMAN LABORATORY

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We recently reported the effects of sex and the phase of the menstrual cycle in subjective response to cocaine in humans. In this study, we addressed whether there are sex differences in the physiological and subjective response to cocaine-related cues in laboratory conditions. The cues that subjects were exposed to were the observation of cocaine coils being loaded into the smoking device and the anticipation of cocaine delivery. Subjects were 46 male and 27 female cocaine users. In response to cocaine-related cues, heart rate and blood pressure increased from baseline. Men had significantly higher systolic ($p<0.01$) and diastolic blood pressure ($p<0.02$) response compared to women. For all three measures, when controlling for baseline measurements the level of cue-reactivity was found to be a significant positive predictor of postdose response ($p<0.01$ in all three cases). Examining only the postdose maximum response, a positive correlation was seen between cue-reactivity and postdose response for systolic and diastolic blood pressure ($p<0.01$ and $p<0.05$, respectively), while heart rate showed a borderline trend ($p=0.074$). The changes in systolic blood pressure in response to cocaine cues were positively related to the response "I desire cocaine" ($p<0.05$). These results suggest that there may be sex differences in physiological response to cocaine-related cues.

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BEHAVIORAL EFFECTS OF AMPHETAMINE: INFLUENCE OF GENDER AND MENSTRUAL CYCLE PHASE

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This study examined the effects of gender and menstrual cycle phase on the behavioral effects of d-amphetamine. Eight male and seven female healthy adults, blind to the study drug, gave written consent and participated on three consecutive nights per week over eight consecutive weeks (i.e., across successive menstrual cycles). Menstrual cycle activity was monitored prior to the study, and study days for women were selected to coincide with menstrual cycle phases. On test days, subjects consumed a standard meal at 5:30 p.m., received drug at 6:30, and completed 20-minute sessions consisting of computerized performance tasks and visual-analog (VAS) ratings of drug effect and blood pressure recordings 0, 0.5, 1, 2, 3, 4 and 5 hours after drug administration, and upon waking the next morning. Each of 3 doses (0, 5 and 10 mg/70 kg) was administered orally 1 day each week in random order. Blood samples were collected prior to the first day of each week to monitor HPG hormone levels. Amphetamine results were consistent with previous studies. Increased heart rate and blood pressure, increased ratings of 'Drug Effect,' 'Stimulated' and 'High,' decreased ratings of 'Hungry,' and enhanced performance on psychomotor, learning and memory tasks were observed. Gender differences in amphetamine effects were observed on VAS ratings 'Stimulated' and 'High,' with greater increases occurring in females than in males, and in learning task performance, with greater effects occurring in males than in females. No interactions between the behavioral effects of amphetamine and phase of the menstrual cycle were observed. No evidence of residual next-day effects was obtained on any measure. These results indicate that the behavioral effects of amphetamine on selected dimensions of performance, on verbal reports of drug effect, and on systolic blood pressure differ between males and females, and that the behavioral effects of amphetamine do not vary across the menstrual cycle.

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ORAL COMMUNICATIONS II

EFFECTS OF INTRAVENOUSLY ADMINISTERED DYNORPHIN A(1-17) IN RHESUS MONKEYS

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The effects dynorphin A(1-17) and its main non-opioid biotransformation fragment, dynorphin A(2-17), were compared in rhesus monkeys with those of the selective κ--opioid agonist, U69,593, in assays of operant behavior, thermal antinociception and prolactin release. Dynorphin A(1-17) (0.1-3.2 mg/kg, i.v.), and U69,593 (0.001-0.032 mg/kg, s.c.) decreased rates of schedule-controlled (fixed ratio 20) food-reinforced responding, whereas dynorphin A(2-17) (1-3.2 mg/kg, i.v.) was ineffective. Pretreatment with the opioid antagonist quadazocine (0.32 mg/kg, s.c.) revealed that the operant effects of dynorphin A(1-17) were not mediated by κ- or μ- opioid receptors. A different profile was observed in the warm water tail withdrawal assay of thermal antinociception, where both dynorphin A(1-17) and A(2-17) (0.032-3.2 mg/kg, i.v., n=4) were modestly effective in 50°C water, and both ineffective in 55°C water. By comparison, U69,593 (0.032-0.18 mg/kg, s.c.) was fully effective in 50°C water, and partially effective in 55°C. Kappa-opioid agonists increase serum levels of prolactin (PRL) in animals and humans. Dynorphin A(1-17) (ED_{50}= 0.0011 mg/kg, i.v.), similarly to U69,593 (ED_{50}=0.0030 mg/kg, i.v.) was very potent in increasing PRL levels in follicular phase female monkeys, whereas dynorphin A(2-17) (0.32 mg/kg, i.v.) was ineffective. The effects of dynorphin A(1-17) and U69,593 on PRL were both antagonized by quadazocine (0.32 mg/kg, s.c.) in a surmountable manner, consistent with opioid receptor mediation. The present studies show that prolactin levels are a sensitive quantitative endpoint to study the systemic effects of the endogenous opioid peptide, dynorphin A(1-17), in primates.

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2INTRACISTERNAL NOR-BINALTORPHIMINE DISTINGUISHES CENTRAL AND PERIPHERAL KAPPA OPIOID ANTINOCICEPTION IN RHESUS MONKEYS

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Nor-binaltorphimine (nor-BNI) produces a long-lasting antagonism against *kappa* opioid agonists across assays and species. The aim of this study was to establish the pharmacological basis of central *kappa* opioid receptor antagonism in non-human primates. Intracistemal (i.c.) administration of small doses of nor-BNI was evaluated against two putative *kappa* subtype agonists, U50,488 and bremazocine, in rhesus monkeys (n=7). Thermal antinociception was measured by a warm water (50°C) tail-withdrawal assay and sedation was evaluated by observers blind to treatments. Following i.c. pretreatment with 0.32 mg of nor-BNI, a 5- to 10-fold rightward shift of the U50,488 baseline dose-effect curve was observed in antinociception. In contrast, this dose of nor-BNI only produced an insignificant 2-fold shift against bremazocine. Pretreatment with a smaller dose (0.032 mg) of nor-BNI produced a 3-fold shift of U50,488, which lasted for 7 days; but there was no significant antagonism of bremazocine. This differential antagonism profile of i.c. nor-BNI was also similarly observed in sedation ratings. In addition, the centrally effective dose of nor-BNI (0.32 mg), when administered s.c. in the back, did not antagonize either U50,488 or bremazocine. After i.c. pretreatment with the same dose, nor-BNI also did not antagonize the peripheral antinociception of U50,488 against capsaicin-induced thermal hyperalgesia in the tail. These results indicate that i.c. nor-BNI produces central *kappa* opioid antagonism and is consistent with the notion of two functional *kappa* opioid subtypes in the CNS. Likewise, it provides a valuable pharmacological basis for characterizing both centrally vs. peripherally mediated effects of various *kappa* opioid agonists in non-human primates.

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SELECTIVE ATTENUATION OF THE ANTINOCICEPTIVE EFFECTS OF KAPPA (KAP) OPIOID AGONISTS BY PUTATIVE DOPAMINE (DA) D3 AGONISTS

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The present study evaluated the effects of the putative D3 agonists 7-OH-DPAT and PD128,907 as well as various DA agonists and antagonists on the antinociceptive effects of KAP opioids using a warm-water tail-withdrawal procedure in rats. The KAP1 agonists spiradoline (3.0-30 mg/kg) and U69,593 (1.0-30 mg/kg) produced dose related increases in antinociception with maximal effects obtained at 52°C water and near maximal effects obtained at 55°C water. The KAP2 agonist bremazocine (.01-3.0 mg/kg) produced antinociception with maximal effects obtained at 50ºC water and intermediate effects obtained at 52°C water. Pretreatment with 7-OH-DPAT (1.0 and 10 mg/kg) produced a dose-dependent attenuation of the antinociceptive effects of all the KAP agonists. For example, 10 mg/kg 7-OH-DPAT shifted the spiradoline, U69,593 and bremazocine dose-effect curves to the right by approximately 0.60, 1.8 and 1.66 log units, respectively. The D2/3 antagonist spiperone (0.1 and 1.0 mg/kg), the D2/3 agonist quinpirole (1.0-10 mg/kg), the D1 antagonist SCH23390 (0.1 and 1.0 mg/kg), the D1 agonist SKF38393 (1.0 and 10 mg/kg) and the indirect DA agonist cocaine (1.0-10 mg/kg) did not markedly alter the spiradoline dose-effect curve. Spiperone (1.0 and 2.0 mg/kg) dose-dependently reversed the effects of 7-OH-DPAT (10 mg/kg) on spiradoline (56 mg/kg) antinociception in a time-course procedure. In addition to 7-OH-DPAT, PD128,907 (0.05-5.0 mg/kg) dose-dependently attenuated the effects of spiradoline (30 mg/kg) antinociception in a time-course procedure. The present study demonstrated that putative D3 agonists attenuate the antinociceptive effects of spiradoline, U69,593 and bremazocine and this was independent of the KAP opioid's site of action (i.e., KAP1 vs. KAP2).

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THE *DELTA* OPIOID AGONIST SNC80 REVERSES CAPSAICIN-INDUCED THERMAL ALLODYNIA IN RHESUS MONKEYS

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The antinociceptive effects of SNC80 and other structurally related delta agonists were assessed in a model of capsaicin-induced allodynia and hyperalgesia in four rhesus monkeys. The shaved tail of each monkey was exposed to warm water (38, 42, 46 and 50ºC), and the latency to tail withdrawal from each temperature was recorded. The temperature that produced a 10-sec tail-withdrawal latency (T10) was interpolated from the temperature-effect curve, and the effect of drugs on the T10 value were assessed. Capsaicin (0.01-0.32 mg) injected into the tail of monkeys dose-dependently decreased the T10, indicating that capsaicin produced thermal allodynia/hyperalgesia. A dose of 0.1 mg of capsaicin decreased the T10 from 48.2° to 43.2° (a -5.0°C change) 15-min after injection. SNC80 (1.0-10.0 mg/kg s.c.) dose-dependently reversed the capsaicin-induced decrease in the T10, and a dose of 10.0 mg/kg of SNC80 fully reversed capsaicin-induced allodynia/hyperalgesia. The delta selective antagonist naltrindole (0.1-1.0 mg/kg) dose-dependently blocked the effects of SNC80, whereas a *mu* selective dose of the opioid antagonist quadazocine (0.1 mg/kg) did not. The delta selective agonists SNC162 (1.0-10.0 mg/kg) and SNC243A (1.0-10.0 mg/kg) also dose-dependently reversed capsaicin-induced allodynia/hyperalgesia. In contrast, the non-steroidal anti-inflammatory drug (NSAID) ketorolac (1.0-10.0 mg/kg) did not modify capsaicin-induced allodynia. These findings suggest that *delta* agonists have antinociceptive effects in primates under conditions of chemically-induced allodynia and hyperalgesia and might be effective under a broader range of conditions than clinically available NSAIDs.

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INTERACTIONS BETWEEN THE DELTA AGONIST, SNC 80, AND THE MU AGONISTS, MORPHINE, BUPRENORPHINE, AND BUTORPHANOL IN SQUIRREL MONKEYS

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Previous studies indicate that delta opioid agonists can potentiate the antinociceptive effects of mu opioid agonists under certain conditions. The present study evaluated this interaction with the selective delta agonist, SNC 80 [(+)4-[alphaR)-alpha-((2S,5R)-4-allyl-2,5,-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethyl-benzamide] and three mu opioid agonists, morphine, buprenorphine, and butorphanol. Antinociception was examined with the titration procedure in which squirrel monkeys control the intensity of a shock stimulus by responding on a lever. When given alone, SNC 80 (0.1-3.0 mg/kg) did not increase the intensity below which the monkeys maintained shock 50% of the time (median shock level, MSL) nor decrease rates of responding (RR). Both morphine (0.3-3.0 mg/kg) and buprenorphine (0.003-0.1 mg/kg) produced dose-dependent increases in MSL in all monkeys, and at the highest doses examined, decreased rates of responding. Butorphanol (0.3-13.0 mg/kg) only produced very small increases in MSL in selected monkeys. Dose-effect curves for these opioid agonists were not altered by pretreatment with a range of doses of SNC 80. These data suggest that the modulation of mu agonists by delta agonists depends on the delta agonist examined and/or the species investigated.

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MECHANISM BEHIND THE BELL-SHAPED DOSE-RESPONSE CURVE OF BUPRENORPHINE (BN) IN RATS: ANTAGONISM BY NORBUPRENORPHINE (NBN)

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In this study, we characterized plasma concentration-time and antinociception-time profiles of BN in rats and examined the role of NBN (the primary metabolite) in the bell-shaped dose-response curve of BN. The jugular vein of male Sprague-Dawley rats (200-250 g; n=6) was cannulated and BN (0.1, 0.3, 1, 3, 10 and 30 mg/kg) was given as an i.v. bolus. Antinociception was monitored by the warm water (52°C) tail dip test. Plasma levels of BN and NBN (measured by GC-MS) declined in a multiple exponential manner. Antinociception reached a first peak at 0.57 ± 0.27 hr, declined to a valley at 1.1 ± 0. 15 hr, reached a secondary peak at 1.4 ± 0.67 hr, and declined thereafter in a zero-order manner. Values for peak effect (E_{peak}) and area under the effect curve (AUEC) exhibited a bell-shaped relationship with dose BN; maximal values of 93.9 ± 1.8% and 204.7 ± 3.3% * hr occurred at 1 mg/kg of BN. Minimal values of 5.5 ± 0.64% and 36.1 ± 1.6% * hr occurred at 30 mg/kg of BN. Simultaneous administration of NBN (0.3 mg/kg) and BN (1 mg/kg) to rats yielded identical peak plasma levels of NBN to that found after 30 mg/kg of BN yet gave an E_{peak} of 34.3 ± 7.8% and AUEC of 48.4 ± 3.2% * hrs. These values were significantly lower ($p < 0.01$) than those obtained with 1 mg/kg of BN alone. Co-administration of NBN (1 mg/kg) and BN (1 mg/kg) gave an E_{peak} of 25.8 ± 3.0% and AUEC of 35.4 ± 10.9% * hr and a concentration-time profile similar to that after 30 mg/kg of BN. In a separate study, antinociception was not associated with 1 mg/kg of NBN. Overall, our results indicate that one mechanism behind the bell-shaped dose-response curve of BN is receptor antagonism by NBN (in a competitive or non-competitive manner).

SIGNAL TRANSDUCTION EFFICACY OF THE HIGHLY POTENT MU OPIOID AGONIST 14-METHOXYMETOPON

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In our search for a truly high-efficacy (i.e., tau > 100) mu opioid analgesic, we set out to determine the efficacy (tau) and apparent *in vivo* affinity (K_A) of the high-potency alkoxymorphinan 14-methoxymetopon in the mouse 50°C hot plate assay. 14-Methoxymetopon had been shown to be 313-fold more potent than morphine in the mouse 55°C hot plate assay and 99-fold more potent in the mouse acetic acid induced writhing test (Fuerst *et al.,* Eur. J. Pharmacol. 236:209-215, 1993). However, 14-methoxymetopon's efficacy proved to be only 1.5-fold higher than that of morphine (tau, 19 vs. 12). K_A values were 2,900 nmol/kg for 14-methoxymetopon and 46,000 nmol/kg for morphine (K_i for [^{3}H]DAMGO binding, 0.33 vs 3.4 nmol/l). The 24-fold higher potency of methoxymetopon (ED_{50}, 0.054 vs. 1.3 mg/kg) could be fully accounted for by its 16-fold higher in apparent *in vivo* affinity and its only 1.5-fold higher efficacy. Furthermore, the 10-fold higher affinity of 14-methoxymetopon for the mu opioid receptor - as previously determined in radioligand binding assays - was confirmed in the present behavioral tests.

PET IMAGING IN AWARE RHESUS MONKEYS DURING COCAINE SELF-ADMINISTRATION: DRUG-INDUCED CHANCES IN REGIONAL CEREBRAL BLOOD FLOW (rCBF)

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Positron emission tomography (PET) imaging techniques were used in awake rhesus monkeys during cocaine self-administration to investigate drug-induced functional changes in CNS activity. An effective restraint device was developed those attaches to a commercially available primate chair to facilitate immobilization, and subsequently attaches to the end of a scanning table to allow for proper orientation in the tomograph. Functional changes in regional cerebral blood flow (rCBF) were characterized with the positron-emitting tracer ^{15}O water following acute i.v. self-administration of cocaine (0.3 and 1.0 mg/kg total dose) during 15-min behavioral sessions. Regions of interest were defined on MRI scans and then applied to coregistered PET scans. Cocaine had pronounced, dose-related effects on blood flow at 5 min post-session that were sustained for over 30 min. Regions of interest with significant increases in blood flow included whole brain, striatum, ventral striatum, and frontal regions. Compared to response-independent cocaine administration, self-administered cocaine had more pronounced and longer-lasting effects, and the pattern of activation differed markedly. This study documents the successful development of PET imaging protocols in behaving monkeys and the importance of response-contingent drug administration paradigms.

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D_4 DOPAMINE RECEPTORS, LABELED BY [^{3}H]U-101,958, ARE DENSE IN PREFRONTAL CORTEX, HIPPOCAMPUS, AND PARAVENTRICULAR THALAMIC NUCLEUS: IMPLICATIONS FOR PSYCHOSTIMULANT ACTIONS

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Dopamine systems have been implicated in the etiology of a number of neuropsychiatric disorders, and contribute to the reinforcing effects produced by several psychostimulants. The D_4 receptor, a direct target of dopamine, has been investigated for its potential role in mediating the effects of cocaine, methamphetamine and alcohol, and in "novelty-seeking" behaviors associated with drug abuse. An accurate map of D_4 distribution and density in primate brain is essential to clarify the role of this receptor subtype in primate models of drug addiction. We investigated the autoradiographic distribution of D_4 receptors in non-human primate (*Macaca mulatta*) brain (N=3), with the D_4 selective probe [^{3}H]U-101,958. Quantification of [3H]U-101,958 binding sites in 77 brain regions revealed dense levels in several cortical areas, especially in subregions of the prefrontal cortex. [^{3}H]U-101,958 binding sites were also prominent in subnuclei of the hypothalamus (i.e., median eminence), the hippocampal formation (i.e., subiculum and fusiform gyrus), and in distinct nuclei of the thalamus (i.e., paraventricular nucleus), but were significantly fewer in number in the striatum. The results correspond well with previous reports of the autoradiographic distribution of D_4 receptors, yet do not coincide with dopamine levels or dopamine transporter densities in brain. The dense localization of D_4 receptors in prefrontal cortex, hippocampus, and paraventricular thalamic nucleus may be of relevance to some effects produced by psychostimulants. Specifically, the prefrontal cortex and paraventricular thalamic nucleus have been shown to be critical components in the neural circuitry mediating the behavioral effects produced by cocaine. A role for D_4 receptors in psychostimulant effects is proposed on this basis as well as reported evidence from D_4 receptor knockout mice and D_4 antagonism studies using behavioral models in rodents.

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EFFECTS OF CHRONIC ETHANOL SELF-ADMINISTRATION ON OPIOID- AND CANNABINOID-STIMULATED [^{35}S]GTPγS BINDING IN RAT BRAIN

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The role of G-protein-coupled receptors in ethanol reinforcement is not clear. These studies were performed to investigate the effect of chronic ethanol self-administration (ESA) on G-proteins activated by the following receptors: mu and delta opioid, cannabinoid, 5-HT$_{1A}$, GABA$_B$ and opioid receptor-like receptor (ORL). Rats were trained to self administer ethanol using the sucrose substitution paradigm. ESA rats received 30 sessions prior to sacrifice; control animals received sucrose only during these sessions. Brains were processed using agonist-stimulated [^{35}S]GTPγS autoradiography. Decreased mu and delta opioid-stimulated [^{35}S]GTPγS binding were found in the prefrontal cortex in ESA brains. No changes in the activity of these receptors were found in other regions examined, including the amygdala and nucleus accumbens. Cannabinoid-stimulated [^{35}S]GTPγS binding was also decreased in the prefrontal cortex, as well as in the caudate-putamen and cingulate cortex in ESA animals. No significant changes in cannabinoid-stimulated [35S]GTPγS binding were found in any other region examined. No significant changes were found for 5-HT$_{1A}$, GABA$_B$ and ORL receptor activity. These results were compared with results from rats treated with the Lieber-DeCarli diet (6% ethanol) for 8 weeks. Following chronic ethanol diet, an increase was found in 5-HT$_{1A}$-stimulated [^{35}S]GTPγS binding in the hippocampus. No changes were found in other receptors examined, although sections containing the prefrontal cortex were not examined. Thus, it appears that differential effects on G-protein-coupled receptors are found for chronic ethanol diet versus ESA. Furthermore, these results indicate that specific G-protein-coupled receptors in the forebrain may contribute to the reinforcing effects of ethanol.

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INVESTIGATIONAL I.V. COCAINE ADMINISTRATION IN I.V-NAIVE SUBJECTS DOES NOT ALTER ILLICIT COCAINE USE PATTERNS

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This study evaluated whether investigational intravenous (i.v.) cocaine (0.2 or 0.4 mg/kg) administration to i.v.-naive cocaine users altered illicit cocaine use patterns. Participants were a group of healthy men (n=17) and women (n=8) with histories of occasional cocaine use (lifetime self-reported use was 12±12 (mean±S.D.) exposures, primarily via nasal insufflation). The recontacted group represented 45% of the total group (n=55) administered i.v. cocaine. Lifetime cocaine use estimates (oral and written questionnaires) obtained prior to and after (mean 39, range 7-107 weeks) cocaine studies were highly concordant (Spearman Rank Correlation ρ =.52 and .78, respectively; P<0.02 and <0.0002, respectively), suggesting stable and reliable self-reported cocaine use. Self-reported illicit cocaine use frequency did not change after the study, and no subject reported post-study i.v. cocaine use. These findings hold for a subgroup of participants (n=14) administered i.v. cocaine on 2-4 separate study days and for a separate group (n=8) who only completed partial follow up interviews. The data in this small sample suggest that investigational iv. cocaine administration to healthy, occasional cocaine users does not promote altered illicit cocaine use patterns.

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NORMALIZATION OF THE QEEG WITH LONG-TERM ABSTINENCE IN COCAINE DEPENDENCE

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The presence of quantitative EEG (QEEG) abnormalities in abstinent cocaine dependent subjects has been demonstrated in our research and reported by others in the literature. We have described the relative persistence of such abnormalities over time for follow-up intervals up to 6 months for a small group of subjects. Further, subtypes with different QEEG profiles have been identified at baseline and a significant relationship shown between length of stay in treatment (continued abstinence) and subtype membership. In our ongoing NIDA study, EEGs were recorded in 103 cocaine dependent subjects at baseline (5-15 days after last cocaine use) and repeated after at 1, 3, 6, 9 and 12 months of abstinence, whenever possible. In order to access whether normalization in the QEEG occurs over time, this report focuses on those subjects who remained in treatment and abstinent for ≥ 9 months. The study group contained 45 subjects (28M, 17F), with a total of 120 evaluations over time. The mean age was 33.5 years and mean years of crack/cocaine use was 12.2 years. Significant trends toward normal were seen in some of the QEEG features across the entire time interval (BL through 12 months), especially mean frequency of the spectrum and posterior slow waves. Change over the first 6 months and changes between months 6 and 12 were also evaluated separately. Different features of the EEG appear to change at different rates, with some changing more in the first 6 months and others taking longer to change and reflected in the 6-12 month analysis only. When separated by gender, significant differences emerge in baseline profiles and in the pattern of change over time. In addition, there are interactions with comorbidity. These results suggest significant gender differences in the effect of chronic exposure to cocaine **on** the brain as well as differences in the degree of normalization of such changes over time.

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INCREASED fMRI RESPONSE TO PHOTIC STIMULATION FOLLOWING COCAINE ADMINISTRATION IN OCCASIONAL USERS

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Cocaine is a powerful vasoactive drug, although the relationship between its vascular and neuronal effects is poorly understood. Functional neuroimaging, which depends heavily upon a stable relationship between brain activation and blood flow, has been used with increasing frequency to attempt to elucidate cocaine's cerebral effects. In order to investigate the effect of cocaine upon this dynamic in real time, we studied 20 men aged 25.6 ± 3.6 yr. (mean ± SD) reporting occasional intranasal cocaine use, with blood oxygenation level dependent (BOLD) fMRI and photic stimulation. Subjects were studied continually for 30 min. around the double blind i.v. administration of either 0.4 mg/kg cocaine (11 subjects) or saline placebo (9 subjects). Cocaine produced significant physiological and subjective effects, including euphoria and craving. Following cocaine administration, we found increased visual cortical activation in 7/11 subjects receiving cocaine, and in 0/9 subjects receiving placebo ($p=0.005$, Fisher's exact test). There was no significant effect of cocaine on BOLD signal outside the visual cortex. These results indicate that cocaine administration augments brain activation in response to a primary sensory stimulus, and that this effect may be neuronal rather than vascular in origin. Discerning the relative vascular and functional contributions, essentially the integrity of this neurovascular coupling, will be critical in understanding how cocaine both acutely and chronically affects brain function.

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EFFECTS OF THE DOPAMINE ANTAGONIST SCH 39166 ON RESPONSE TO IV COCAINE IN HUMANS

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Cocaine's reinforcing effects are mediated through the mesolimbic dopamine system. Consequently the search for anti-cocaine pharmacotherapies often focuses on agents that affect the dopamine system. This study investigates the interaction between the selective D1/D5 dopamine antagonist SCH 39166 and cocaine in cocaine-dependent human volunteers. The objective is to assess the dose-related effects of SCH 39166/placebo on subjective and physiological responses to cocaine. Primary data are from cocaine challenge test sessions conducted under each of the SCH 39166 dose conditions. Each test session provides a dose-effect evaluation of response to cocaine. Cocaine is administered in a single-blind rising dose sequence (0, 25, 50 mg/70 kg iv/1 min.); doses are separated by 60 min. Cocaine test sessions are conducted after 7 days at each SCH 39166 dose level. SCH 39166 doses (0, 10, 25, 100 mg/day p.o.) are administered in randomized, double-blind order, once daily. Subjective and psychomotor effects are assessed prior to and following daily administration of SCH 39166 and repeatedly during each cocaine test session. Plasma is collected for SCH 39166 and cocaine blood levels. The study is near completion and 7 of 10 subjects have completed. The dose codes remain blind at this writing. Results will be presented at the conference.

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ORAL THC VS. SMOKED MARIJUANA: A WITHIN SUBJECTS COMPARISON OF EFFECTS

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Oral tetrahydrocannabinol (THC) has been available by prescription for several years, and more recently, the medical use of marijuana (MJ) has been legalized in several areas of the country. To directly compare the effects of smoked MJ and oral THC, 11 participants lived in a residential laboratory for 21 days. MJ cigarettes (3.1 % THC, q.i.d.) were smoked and THC (20 mg, q.i.d.) was taken orally using a staggered double-dummy, procedure. Four days of placebo separated each active drug condition. Subjective ratings were collected 10 times/day and sleep was measured nightly with a portable sleep monitor. THC and MJ increased ratings of "High," "Good drug effect," "Strong effect" and drug liking. Subjective ratings decreased over 3 days of active drug administration, indicating the development of tolerance to those effects. Peak ratings of "Sedated" were higher under THC than MJ and tolerance developed to the sedating effects of M J, but not THC; total sleep was increased under both active drug conditions and increased over days of THC, but not MJ administration. Ratings of "Anxious" and "Depressed" were significantly elevated during abstinence after MJ, but not THC. The peak effects of MJ and THC were similar, although peak plasma THC levels were much higher after MJ than THC administration. These results expand previous findings demonstrating THC- and MJ-induced tolerance and dependence and indicate that THC plasma levels do not predict the effects of either smoked MJ or oral THC.

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3-PHENYL-2-AMINO(METHYL)-BICYCLO [2.2.2] AND [2.2.1]-ALKANES DOPAMINE UPTAKE INHIBITORS

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A series of 3-phenyl-2-amino(methyl)-bicycle [2.2.2] and [2.2.1]-alkane derivatives was synthesized and tested for inhibitory potency in [^{3}H]WIN 35,428 binding to dopamine transporters, [^{3}H]paroxetinc binding to serotonin transporters, [^{3}H] nisoxetine binding to norepinephrine transporters and synaptosomal [^{3}H]dopamine uptake. Selected compounds were tested for their ability to substitute for cocaine in rat drug discrimination tests. Synthesis was accomplished by two basic procedures. One was a series of Diets-Alder reactions, using *cis* and *trans* cinnamic acid derivatives (nitrite, acid, acid chloride) with cyclohexadiene and cyclopentadiene. Standard manipulations produced the aminomethyl side chain. The other synthetic method was a *bis*annulation procedure using cyclohexenone and aromatic enamines to produce compounds with an amino side chain. The compounds with the amino sidechain also had keto, hydroxyl and ester functionality. Many of the compounds bound with high affinity to the cocaine-binding site as marked by [^{3}H]WIN 35,428. Two of the compounds were shown to substitute for cocaine in drug discrimination tests in rats and one had a very long duration of action. These and related compounds may be promising candidates for further testing as replacement agonists, partial agonists or antagonists of cocaine.

SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF HYDROXYL-CONTAINING DERIVATIVES OF GBR 12909

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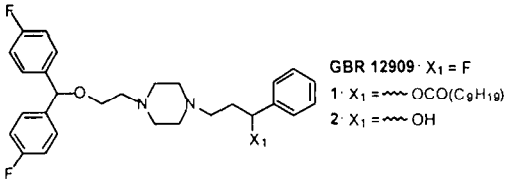
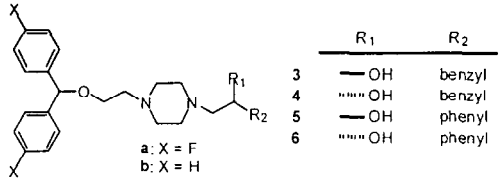
Recently, we found that a single treatment of the depot preparation of the decanoate ester **1** of a racemic benzylic hydroxylated derivative **2** of GBR 12909 effectively decreased cocaine-maintained behavior in the rhesus monkey for nearly a month with less effect on food-maintained performance. With the intent to further study the structure-activity relationships of hydroxyl-containing analogs of GBR 12909 and minimize side effects of racemic compounds, a novel series of optically pure hydroxylated derivatives of GBR 12909 (3-6) were synthesized and their biological activities were investigated. In a dopaminc transporter (DAT) binding assay, the S isomers possessed higher affinities than the corresponding *R* isomers. However, the *S* analogs possessed lower affinities for the serotonin transporter (SERT) than the corresponding *R* analogs. As a result, the *S* isomers displayed much better DAT selectivity relative to SERT. Replacing the phenylpropyl group in compounds **3** and **4** with a phenylethyl group resulted in compounds **5** and **6** with significantly increased SERT affinity and slightly decreased DAT affinity. Of this series, compound **3a** was more potent (IC_{50} = 0.75 nM) and much more selective (309 fold) in the DAT binding assay than GBR 12909, and compound **3b** displayed highest selectivity for the DAT versus SERT (937 fold). These compounds appear to be promising candidates for preparation of novel decanoate esters that can be assessed as potential long-acting agents for the treatment of cocaine abuse.





	R_1	R_2
3	—OH	benzyl
4	····OH	benzyl
5	—OH	phenyl
6	····OH	phenyl

PYRIDYLACRYLOYL DERIVATIVES OF 14-β--AMINOMORPHINONES

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In our extensive investigations of SAR in cinnamoyl derivatives in the 14-β-aminomorphinone series, differences in the effects of orientation of substituents in the cinnamoyl aromatic ring have been noted between a nitro group and chloro or methyl groups. In order to throw light on the cause of these differences, we synthesized 12 pyridylacryloyl derivatives with the pyridyl group attached through the 2'-, 3'- or 4'-positions. The pyridyl group has an electron-withdrawing effect equivalent to the nitrophenyl of the nitrocinnamoyl derivatives and the point of attachment to the etheno group simulates *o-, m-,* and *p*-orientation of the nitro group. The pyridyl derivatives were evaluated in binding assays in cloned human opioid receptors transfected into Chinese hamster ovary cells and also in [^{35}S]GTPγ‰S assays in an equivalent system. In the displacement binding assay, all the new derivatives showed high affinity for μ receptors; the morphinones also had high affinity for κ and δ. None of the NCPM derivatives stimulated [^{35}S]GTPγ‰S binding in cloned μ receptors but were potent antagonists. The NCPM morphinones were also potentκ and δ antagonists in the GTPγ‰S assay, whereas the NCPM codeinones were generally low potency, low efficacyκ and δ agonists. There was little difference between the 2'- and 4'-pyridyl derivatives whereas in the equivalent series of nitro and trifluoromethyl cinnamoylamino derivatives the 2'-isomer had much higher efficacy than the 4'-isomer. Thus, factors other than electron distribution in the cinnamoyl aryl group must contribute to the pharmacological profile in these series.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF CYCLORPHAN DERIVATIVES

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In an attempt to develop compounds for the pharmacotherapy of cocaine addiction, a series of morphinans with varying degrees of kappa and mu opioid activity were synthesized. Cyclorphan, (a N-cyclopropylmethyl morphinan) was modified by replacing the N-cyclopropylmethyl group with a chiral tetrahydrofurfmyl moiety and by the insertion of a keto group at C-10 of the morphinan. In binding experiments, (-)cyclorphan, cyclorphan with a C-10 keto group, and cyclorphan with a N-tetrahydrofurfuryl group had K_i values of less than 0.4 nM for both the mu and kappa opioid receptors. In contrast, cyclorphan containing both a ketone and a N-tetrahydrofurfuryl group had a K_i value of greater than 20 nM for the mu and kappa opioid receptors. All compounds had lower affinity for the delta than either the mu or kappa receptors. In the mouse tail flick and writhing tests, low doses of (-)cyclorphan antagonized morphine-induced antinociception. Higher doses of (-) cyclorphan produced antinociception in the writhing test, which was mediated primarily by the kappa receptor and to a lesser degree the delta receptor. In contrast, the homologs of cyclorphan, containing either a ketone in C-10 or a N-tetrahydrofurfuryl group produced mu and kappa agonist activity, and were devoid of antagonist properties.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF NOVEL 8-AMINO ANALOGUES OF CYCLAZOCINE

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In an attempt to synthesize analogues of cyclazocine with increased bioavailability and varying kappa agonist and mu antagonist properties, a series of 8-amino derivatives of cyclazocine were synthesized. Analogues with either a 1-pyrrolindinyl or a 1-morpholinyl group in the C-8 position of cyclazocine had very low affinity for the multiple opioid receptors as determined by radioligand binding to guinea pig brain membranes. Both compounds had K_i values of greater than 400 nM for the mu, delta, and kappa receptors. In contrast, the 8-phenylamino-cyclazocine bound with high affinity to kappa and mu receptors with K_i values of approximately 1 nM, and it had a 10-fold lower affinity for the delta receptor. The (-)cis entantiomer was determined to be the active enantiomer. In the mouse acetic-acid writhing test, 8-phenylamino-cyclazocine produced antinociception, with an ED_{50} value of 19 nmol, when given i.c.v. The antinociception was kappa-selective, Like cyclazocine, at low doses, the 8-phenylamino derivative antagonized antinociception mediated by mu, but not delta or kappa receptors. 8-Phenylamino-cyclazocine is a kappa-selective agonist and a mu-selective antagonist.

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SPIRO RING CONSTRAINED ANALOGUES OF BUPRENORPHINE

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It has been suggested that buprenorphine derives its unique pharmacological profile partly from restricted rotation about the C7-C20 bond and thus not allowing the *t*-butyl group to access the proposed κ lipophilic agonist site. As part of our program to gain greater insight into this phenomenon we synthesized and evaluated analogues of buprenorphine in which the C-20 lipophilic group has been placed under conformational restraint by being part of an alicyclic system. Spiro ring constrained analogues were prepared by reduction and 3-O-demethylation of the previously reported thevinone adducts. In binding to human opioid receptors transfected into Chinese hamster ovary (CHO) cells, the compounds all displayed high affinity, with some selectivity for the μ-receptor. [^{35}S]GTPγS binding was used to determine functional activity *in vitro*. As expected, the compounds having an NMe group were predominantly potent p-agonists of varying efficacy, whereas an NCPM group caused a shift towards more prominent κ activity. In the NMe series substitution of methyl groups onto the spiro ring led to an increase in μ-potency and efficacy while causing a reduction in efficacy at κ receptors. A similar reduction in efficacy at both κ and δ receptors was the predominant effect observed in the NCPM series. These results suggest that buprenorphine's lack of κ agonist activity in comparison to closely related orvinols may not only be due to restricted access to the region below C-8, but could be as a direct result of the extra methyl groups on the *t*-butyl moiety.

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STRUCTURE-ACTIVITY RELATIONSHIPS OF CANNABINOID ANTAGONISTS

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Synthesis of an antagonist, SR 141716A, that selectively binds to cannabinoid CB1 receptors without producing cannabimimetic activity *in vivo* suggests that binding and activation of cannabinoid receptors are separable events. In the present study, a series of SR141716A analogs were synthesized and were tested for CB1 binding affinity and in a battery of *in vivo* tests, including hypomobility, antinociception, and hypothermia in mice. These analogs retained the central pyrazole structure of SR141716A with manipulations of the 1-, 3-, or 5-substituents. While none of the analogs alone produced the profile of cannabimimetic effects seen with full agonists, several of the 3-substituent analogs with higher binding affinities showed partial agonism for one or more measures. Although some of these 3-substituent analogs also attenuated the effects of Δ^9-THC, partial agonist (vs. antagonist) effects could account for this attenuation. In contrast, antagonism of Δ^9-THC's effects without accompanying agonist or partial agonist effects was observed with substitutions at positions 1 and 5. These results suggest that the structural properties of 1- and 5-substituents are primarily responsible for the antagonist activity of SR141716A.

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NOVEL CANNABINOL PROBES FOR CB1 AND CB2 CANNABINOID RECEPTORS

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The successful development of selective ligands for cannabinoid receptor subtypes provides the impetus for characterizing unique pharmacophores for CB1 and CB2 receptors. Our earlier observation that the phenolic hydroxyl of THC was required for CB1 but not CB2 binding prompted us to extend this finding to the Cannabinol (CBN) series. The binding profile differs in the CBN and THC series and shows that in the CBN series the removal of the phenolic hydroxyl decreases CB1 affinity much more than in the THC series (400 fold versus 30 fold respectively) and the potency for CB2 binding is decreased 57 fold compared to THC's (167 nM versus 2.9 nM). Furthermore, unlike the THC series, the side chain length of desoxy-CBN analogs has relatively little influence on the ratio of CB1/CB2 binding when a hydroxyl is added at position C11, and high potency for CB2 binding was found only when the phenolic hydroxyl was present; the most potent analog was found to be 11-OH-CBN-DMH. Regardless, it is evident that structural requirements for CB1 and CB2 receptors differ between THC and CBN, thus providing a new strategy for further pharmacophore characterization.

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QSAR ANALYSIS OF Δ^{8}-THC ANALOGS: RELATIONSHIP OF SIDE-CHAIN CONFORMATION TO CANNABINOID RECEPTOR AFFINITY AND PHARMACOLOGICAL EFFICACY

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A novel series of 37 predominantly non-branched, alkene and alkyne hydrocarbon and halogenated side-chain substituted Δ^{8}-THC analogs was analyzed using several approaches for defining structure-activity relationships (SARs). The most robust model was developed using comparative molecular field analysis (CoMFA), but models based on a modified active analog approach and a multiple linear regression also yielded consistent results. In these models, increased potency and affinity was generally associated with longer side chains possessing conformational freedom that allowed the side chain to bend back towards the phenyl ring system. Side chains that extended straight away from the point of attachment were associated with decreased predicted affinity and potency. The robustness of the CoMFA model was examined by comparing these results to results achieved with randomly generated numbers in place of the actual pharmacological data describing receptor affinity (K_1 in rat brain) and in vivo potency in the tail-flick, hypothermia and locomotor activity tests in mice; in all instances the actual pharmacological data yielded a substantially stronger predictive model. Attempts were then made to extend these techniques to a series of 13 cyano and carboxamido 1'1'-dimethyl side-chain analogues. However, the model previously developed was unable to predict the affinity or efficacy of these compounds, nor could a new CoMFA model based on the total 50 compounds be developed that was adequately predictive. Finally, a model based solely on the cyano and carboxamido compounds could not be described using the CoMFA technique. It is possible that the 13 1', 1'-dimethyl compounds were unable to be incorporated into any quantitative structure-activity model because they have side chains that possess relatively less conformational mobility (i.e., they are already forced to bend by the dimethyl substituents) and are more varied in their electrostatics then the alkene/alkyne analogs. In conclusion, these experiments describe a novel QSAR for certain cannabinoids; however, they also serve to illustrate the limitations of our SAR approaches.

REFERENCES: Available upon request from senior author.

ORAL COMMUNICATIONS V

OPEN-LABEL MAINTENANCE STUDY WITH BUPRENORPHINE IN PREGNANT OPIATE ADDICTS

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Aims: To access the maternal and fetal safety and neonatal abstinence syndrome (NAS) in neonates born to buprenorphine maintained mothers. Design: Open-label, flexible dosing, inpatient induction with outpatient maintenance. **Participants:** Fourteen opioid dependent pregnant women. **Intervention:** Sublingual buprenorphine tablets and oxazepam for sedation during induction. **Measurements:** Patient self-reports, addiction severity index, blood chemistries, urine toxicology, CTG, sonogram, maternal withdrawal (Wang Scale) and neonatal withdrawal symptomatology (Finnegan Scale) and birth outcome measures. **Findings:** Buprenorphine was well tolerated during pregnancy. Fifteen healthy neonates were born between weeks 36-42 (mean=40 weeks, SD±1.6) with absent, mild (without treatment), and moderate (with treatment) NAS in eight, four and three neonates, respectively: Buprenorphine is safe and efficacious in opioid dependent pregnant women and their fetus. The partial opiate agonist profile (high affinity with low intrinsic activity at the mu receptor) of buprenorphine may account for the mild NAS observed in the neonates. No positive correlation in regard to mean daily dose at delivery and intensity of NAS was detected. Double-blind, double-dummy studies need to be undertaken to confirm our observation.

OUTPATIENT HEROIN DETOXIFICATION WITH CONCOMITANT USE OF METHADONE AND LAAM OR LAAM ALONE

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The New York VA Medical Center was required to close all inpatient substance abuse services in April 1998. Consequently all patients seeking heroin detoxification, in the absence of acute medical or psychiatric co-morbidity must now be detoxified in an outpatient setting. Patients presenting for heroin detoxification at the New York VA have a median 12 years of addiction prior to seeking treatment, an average of 4 previous inpatient and/or outpatient detoxification episodes, and are generally older addicts. Consequently, we reached the decision to use agonists to detoxify, rather than clonidine. Method: We opted for a 30-day agonist detoxification protocol, which does not permit take-home methadone. As staff resources were available to maintain the Clinic for five full days and one half-day, we offered detoxification with five days of methadone and a dose of LAAM on Saturday. Patients were asked to sign an agreement for treatment, given a brief education by nursing on the pharmacological profile of methadone and LAAM prior to the first dose, and evaluated for withdrawal symptoms, side-effects and therapeutic efficacy. During the course of treatment, the option of transfer to LAAM maintenance was also offered if the detoxification discomfort was too great. In September 1998, new admissions were offered the option of detoxification with LAAM only, with 3 day dosing per week. Group and individual counseling were optional. Results: By April 1, 1999, 61 patients had been accepted for outpatient detoxification. Twenty (33%) completed the detoxification- 6 remained opiate positive, 31 (57%) transferred to LAAM maintenance and 10 (16%) terminated early. Of 61 patients, 29 (47.5%) chose LAAM alone, primarily because of 3 day clinic visits vs. 6 for methadone. Overall patients were satisfied with the program. Combination of LAAM and methadone offers dose flexibility for patients seeking detoxification and warrants further study.

DOES BUPRENORPHINE DOSING FREQUENCY AFFECT TREATMENT COMPLIANCE?: DAILY VERSUS 2X- VERSUS 3X- PER-WEEK DOSING

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Recent research suggests less-than-daily buprenorphine (BUP) dosing may be an effective pharmacotherapy for the treatment of opioid-dependence. Previously, we have demonstrated that BUP can be administered as infrequently as every 96 hrs without significantly increasing reports of opiate withdrawal or agonist effects in opioid-dependent outpatients. Abstinence requirements in those studies, however, precluded assessment of the effects of the dosing schedules on illicit opiate use. In this ongoing study, we are comparing the relative effects of 3 weekly dosing schedules on illicit opiate use without abstinence requirements. Outpatients maintained on BUP (4, 8, 10, or 12 mg per day, s.l.) are randomly assigned to daily maintenance dosing (n=24, to date), three-time per week (3x-Wk) dosing (n=20), or two-time per week (2x-Wk) dosing (n=25). Subjects in the 3x-Wk group receive double doses (i.e., two maintenance doses) on Mondays and Wednesday and triple doses on Fridays. Subjects in the 2x-Wk group receive quadruple doses on Mondays and triple doses on Fridays. Subjects were maintained for 24 wks. Urine samples are screened twice weekly for opiates, methadone, and propoxyphene. Preliminary analyses of the urinalysis and retention data suggest 3x-Wk dosing may be superior to daily or 2x-Wk dosing. Fifty percent of the 3x-Wk group achieved at least 8 weeks of continuous abstinence, whereas only 33.3% of the daily and 28% of the 2x-Wk groups achieved this level of abstinence. Moreover, the mean treatment duration for the 3x-Wk group was 22.3 wks, whereas the means for the daily and 2x-Wk groups were 19.8 and 19.4 wks, respectively. Although none of these differences has achieved statistical significance at present, these preliminary results suggest less-than-daily BUP dosing may not be inferior to and, perhaps, may be superior to daily dosing in promoting treatment compliance.

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A RANDOMISED DOUBLE-BLIND TRIAL OF BUPRENORPHINE TABLETS VERSUS METHADONE SYRUP FOR MAINTENANCE THERAPY: EFFICACY AND COST-EFFECTIVENESS

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U.S. research has confirmed the efficacy of sublingual ethanol-based buprenorphine as a maintenance pharmacotherapy for opioid dependence Many of the studies have used fixed dosage regimens, and the ethanol-based solution of buprenorphine (which has greater bioavailability than the buprenorphine tablet). The current study is a parallel group, double-blind, double-dummy, randomised trial of the efficacy and safety of the sublingual buprenorphine tablet compared to oral methadone. Four hundred five patients were randomly assigned to receive either buprenorphine or methadone for a 13 week double-blind period. Dosing was tailored to patient request with those patients assigned buprenorphine dosed on alternate days from the start of week 7. Primary outcome measures were retention in treatment and heroin use based on urine specimens. Self-reported heroin use, other drug use, psychological functioning, HIV risk behaviour and general health were secondary outcome measures. Although there was significant overall improvement, analysis with the intent-to-treat sample revealed no statisticaily significant differences between the two treatments on any of the outcome measures. There was, however, a significantly greater proportion of patients in the buprenorphine group drinking alcohol. Eighty-five percent of buprenorphine patients were maintained on alternative day dosing, with no evidence of dose escalation. Maintenance with buprenorphine tablets is as effective as methadone. Cost analyses indicated that total costs per year for treatment with buprenorphine were US$2883 compared to US$2239 for treatment with methadone.

ACKNOWLEDGEMENTS: Supported by the Commonwealth Department of Health and Aged Care, the S.A. and N.S.W. Health Departments, Reckitt & Colman Pharmaceuticals Pty. Ltd. and NDARC.

IMPACT OF ACCESS TO CONTINGENT TAKE-HOMES AND BLIND DOSE INCREASES DURING BUPRENORPHINE-NALOXONE AND METHADONE MAINTENANCE TREATMENT

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Allowing contingent access to take-home medication and providing medication dose increases are useful strategies for improving outcomes during opioid maintenance treatment. This study evaluated long-term outcomes in 29 opioid-dependent subjects who previously completed a study comparing the buprenorphine-naloxone tablet to methadone for opioid dependence maintenance treatment. Subjects continued participation for at least 16 weeks following the initial study under the same double-blind and double-dummy daily dosing conditions, thrice-weekly urine sampling, and manualized behavioral counseling as in the previous study. However, during this phase, subjects could access take-home medication contingent on opioid-negative urine samples and blind dose increases were provided based on clinical need. Urinalysis results and Addiction Severity Index (ASI) ratings following four months of treatment during the current study were compared to outcomes during four months of participation in the previous study. ASI composite scores of Drug, Opiates and Legal maintained improvement relative to scores in the previous study. Dose increases were provided to 7 patients. In these patients, opioid positive urines decreased significantly from a mean of 39.3 ± 6.3 during the first four months to a mean of 27.3 ± 6.3 during the current study's 4 months. Across all subjects, opioid positive urines decreased significantly from a mean of 23.83 ± 3.4 during the first four months to a mean of 18.1 ± 3.3 during the current study's 4 months. These results suggest that continued treatment improves several aspects of overall psychosocial functioning, maintenance dose increases can reduce opioid use and access to take-home buprenorphine-naloxone tablets or methadone functions as a reinforcer that can be used to increase abstinence during opioid maintenance treatment.

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PREDICTORS OF TREATMENT OUTCOME FOR OPIOID DEPENDENCE: A SINGLE SITE CONTROLLED TRIAL WITH LAAM, BUPRENORPHINE, AND METHADONE

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The comparison of methadone, LAAM, and buprenorphine (BUP) for the treatment of opioid dependence within a single randomized controlled trial (RTC; previously described) of 220 opioid dependent subjects, provides a unique opportunity to assess for predictors of outcome between medications. Currently, no controlled within study design has examined predictors of outcome between these medications. This report describes a multi-step approach, used to identify variables that predicted treatment outcome and their potential use in future analyses and studies. First, we identified, *a priori,* 3 critical variables (study retention, opioid and cocaine urinalysis results) important for successful outcome and 18 variables (taken from demographic, drug use, employment, treatment compliance, psychiatric, and study medication data) believed important or previously reported to predict treatment outcome. Second, within each study group, correlational analyses were conducted comparing the 18 variables and 3 outcome measures. Third, Fisher's z' transformation were used to compare correlation coefficients between groups. Results from these analyses showed significant differences ($p<0.05$) between medications on one or more of the three outcome measures with nine of the variables, suggesting that subgroups of patients responded differently to the medications. Meta-analysis of >1000 subjects maintained on either methadone, LAAM, or BUP and who participated in RTCs in this outpatient clinic is planned using these nine variables, as well as others shown to be associated with treatment outcome, to determine their predictive power. Results from this analysis will be strengthened by consistencies in collection procedures, dose equivalency, demographics, and outcome measures. Ultimately, variables found to predict outcome in the meta-analysis will be tested prospectively with the hope of developing treatment algorithms.

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COMBINING BEHAVIORAL TREATMENTS WITH AGONIST MAINTENANCE

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Buprenorphine (BUP), the Community Reinforcement Approach (CRA), and Contingency Management (CM) have shown promise as treatments for cocaine and opioid dependence. This 22-week, random assignment clinical trial evaluated the efficacy of adding CM vs. a non-monetary voucher control (VC) to CRA, and compared daily maintenance on BUP 12-16 mg SL and methadone (METH) 65-85 mg PO in patients with concurrent opioid and cocaine dependence (N=162). Patients assigned to CM received vouchers for urine samples free of both illicit opioids and cocaine, with the value of the vouchers and schedule for increasing and decreasing the value during the first 12 weeks similar to that used studies of CM and CRA in Vermont. During weeks 12-24, the value of the voucher was decreased to $1. The groups were comparable at baseline on most demographic measures and measures of drug use and psychiatric severity. There was a non-significant trend favoring better retention in methadone vs. buprenorphine treated patients (Wilcoxon $\chi^2=6.6$, df=3, p=.08). There were significant effects of treatment condition, time and their interaction on rates of opioid-positive and cocaine-positive urine samples. Rates of opioid-positive samples averaged 50% and 56% in METH-CM and METH-VC and 60% and 72% in BUP-CM and BUP-VC ($p<.001$). Rates of cocaine-positive samples averaged 48%, 58%, 70% and 69% in the four groups ($p<.001$) Rates of $\geq$3 consecutive weeks abstinence from illicit opioids and from cocaine were higher in the two methadone groups compared to the two buprenorphine groups (Opioids: 58%, 58%, 41%, 28%, $P<.025$; Cocaine: 50%, 48%, 26%, 28%, $p<.05$). CM was associated with a significantly more rapid decline in rates of both opioid-positive and cocaine-positive samples and with significant overall effects at 12 weeks. A slight rebound in opiate-positive and cocaine-positive samples in the CM but not VC groups after week 12 resulted in no significant overall differences between CM and VC. These results support the superiority of methadone compared to buprenorphine and the modest efficacy of CM during the period of escalation in the value of the voucher but point to the possibility of rebound in drug use following discontinuation of CM.

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COMPLICATIONS ASSOCIATED WITH CONTINGENCY MANAGEMENT FOR HEROIN DEPENDENT POLY-DRUG ABUSERS

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The present study used Voucher Based Reinforcement Therapy (VBRT) to target poly-drug use. Poly-drug use often complicates substance abuse treatment for opiate abusers. This study targeted poly-drug abstinence with a 12-week VBRT phase versus a yoked control (YC) condition. Overall, there were no significant group differences for longest continuous abstinence, total abstinence, or percentage who achieved ≥ 1 cocaine, heroin, or poly-drug abstinent urine samples. However, many participants never produced a poly-drug-free sample, and, therefore, never came into contact with the reinforcement contingencies. Separate analyses were conducted on the sub-sample of participants who achieved ≥ 1 poly-drug-free UDS results (8 VBRT and 6 YC participants) and were therefore exposed to the reinforcement contingencies. Even with this small sample size, results reached significance for total number of cocaine-free UDS samples produced ($t=3.23$, $df=12$, $p=.007$), but not for heroin or poly-drug abstinence, although all results were in the predicted direction. Strategies to promote early abstinence and consequent exposure to contingent reinforcement may be critical for poly-drug abusing patients. Results suggest that, for those who achieve poly-drug abstinence, VBRT can enhance treatment outcome. However, an improved protocol will be necessary to promote initial poly-drug abstinence. Pilot data are presented comparing early reinforcement of cocaine versus poly-drug abstinence.

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ORAL COMMUNICATIONS VI

CHILDHOOD INTENTIONS PREDICT TOBACCO SMOKING ONSET IN URBAN ADOLESCENTS

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Before adolescents take their first puff or experiment with cigarette smoking, many of them progress through a preparation stage of expressing interest. Prospective studies of adolescents (age 12 and above) indicate susceptibility to smoking (intentions and expectations) as a precursor of taking up smoking. However, many youth begin smoking by age 11 or 12; therefore, it is important to understand this progression in younger children. This research investigated the association between the intentions to use cigarettes and smoking onset in a predominantly African-American epidemiologic sample of 2,150 urban youth. Annual assessments were made as part of a private interview starting in third and fourth grade (mean age 9). Thirty-six percent smoked their first cigarette during the five year follow-up. By age 11, 8% expressed intentions to smoke and 14% had smoked their first cigarette. As the children aged, the likelihood of smoking increased. much more rapidly among those expressing intent. The odds of smoking were eight times greater (95%, CI 6.6-10.4) for those who had expressed an intention to use (73%), as compared to those who became smokers without expressing intent (24%). Despite boys being more likely to express their intention to smoke, there was no male-female difference in the mean age of first use when intention was expressed. Prevention efforts with a focus on pre-smoking intentions to smoke maybe important in children as early as grade four.

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ACTIVITY AND ALCOHOL AVAILABILITY PREDICT ALCOHOL USE OF ADOLESCENTS BY DIRECTLY AND INDIRECTLY MODIFYING PEER CONSUMPTION, ATTITUDE AND OWN NORMS

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Laboratory studies with humans and animals have shown that drug availability and competing activity modify drug consumption. We hypothesized that involvement in activities, and perceived limitations on alcohol availability would either directly or indirectly moderate alcohol consumption of adolescents. A questionnaire was administered to 3,336 grade 8 and grade 11 students attending Newfoundland schools. They were asked about their involvement in school, family and church-related activities, the availability of various drugs, the extent of drug and alcohol use by themselves, their parents and peers, and the attitudes about drug and alcohol use of themselves, their parents and their peers. A path analytic model was developed using a randomly chosen subset of half the respondents and tested on the remaining half. This model accounted for 90% of the variance of a latent variable derived from both quantity and frequency of drinking. In the model, alcohol consumption was predicted primarily by peer drinking (beta= .81) and parental norms (beta= .45), and to a lesser extent by own norms (beta=. 16) and own preferences (beta=. 14). Student activities (job, church, school and family) indirectly inhibited drinking through own preferences and peer norms and were directly inhibited by own drinking and parental drinking. Alcohol availability facilitated drinking indirectly through peer norms, own norms and own preferences. The model was similar when applied to males and females except that the amount of drinking variance accounted for was greater for males (96% for males and 71% in females). The model also accounted for more drinking variance for older students (16 to 17 years) than younger students (13 to 14 years).

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GENDER DIFFERENCES IN SUBSTANCE USE, MENTAL HEALTH AND CONDUCT-RELATED PROBLEMS: A MULTITRAIT MULTIMETHOD ANALYSIS AMONG ADOLESCENTS IN A JUVENILE JUSTICE SETTING

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Studies with adolescents at high risk for substance use have consistently found that females have a higher risk for mental health or internalizing behavior problems while males have a higher risk for aggressive or externalizing behavior problems. The present study examines these gender differences using a multitrait multimethod (MTMM) approach among 1,136 girls (mean age=15.3) and 1,132 boys (mean age=15.9) entering the Kansas juvenile justice system. The first method involved the Short POSIT (Problem Oriented Screening Instrument for Teenagers) scales on substance use, mental health, and aggressive behavior problems. The second method involved the Kansas juvenile intake questionnaire that included questions such as drug use frequency, history of child abuse, prior arrests, and suicide attempts. MTMM models following Widaman's (1985) hierarchically nested covariance structure models were evaluated for convergent and discriminant validity. A model with correlated traits and uncorrelated methods had the best fit based on a series of chisquare difference tests and evaluation of practical fit. Simultaneous modeling of this MTMM structure for substance use, mental health and conduct-related problems was then tested for boys and girls. Models in which factor loadings and/or covariances among factors were constrained versus an unconstrained model were compared for goodness of fit based on the chi-square difference tests and examination of loadings for practical fi. The model with unconstrained parameters had the best fit indicating that factor loadings on mental health and conduct-related problems were not invariant across gender groups. Results support the use of dual sources of information when assessing problems in the areas of substance use, mental health and aggressive behaviors. Results also suggest that previous findings on gender differences in internalizing and externalizing behavior problems may be due to these differences in factor loadings.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON INITIATION OF AND PERSISTENCE IN MARIJUANA USE: AN EXAMINATION OF ADOLESCENT FEMALE TWINS

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As with many aspects of behavior, illicit substance use is likely to be influenced by both genetic and environmental factors. The Missouri Adolescent Female Twin Study (MOAFTS) provides an opportunity to test the relative contributions of these factors to marijuana use in young women. The present analyses were based on data from 1057 pairs of twins (MZ=603, DZ=454; mean age=17.1 years) who completed a one-year follow-up telephone interview and a questionnaire that included an assessment of the respondent's marijuana use (never, once, or more than once). Logistic regression analyses indicated that marijuana use was predicted by age, increasing levels of conduct problems, number of oppositional-defiant symptoms, and depression. Familial logistic regression analyses indicated that genetic influences on marijuana initiation were significant ($p < .05$), with a trend for repeated use. Further model fitting analyses supported a two-stage model of marijuana use, with separate but overlapping genetic and environmental influences on initiation and persistence indicating the importance of distinguishing between influences on initiation and those associated with continued drug use.

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PERSONALITY CHARACTERISTICS OF ADOLESCENTS IN TREATMENT FOR ALCOHOL AND OTHER DRUG MISUSE: GENDER AND ETHNIC DIFFERENCES

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Relatively little is known about personality characteristics of adolescents in treatment for alcohol and other drug (AOD) misuse. Utilizing the Drug Abuse Treatment Outcome study for Adolescents (DATOS-A), intake data was examined for 3,288 adolescents, aged 11-19, in 6 nationwide geographical areas, and in 3 drug abuse treatment modalities, to assess a variety of personality characteristics. Included in this study were scales representing religiosity, locus of control, self-esteem, hostility, and empathy. The findings document significant personality scale differences as a function of gender and ethnicity. Females (n = 885) had higher scores on empathy, hostility, and religiosity, whereas males (n = 2,497) scored higher on self-esteem and an internal locus of control. By ethnicity, African-American adolescents (n = 807) reported the highest religiosity and self-esteem, and lowest hostility. White adolescents (n = 1,745) had the highest hostility, lowest religiosity, and most internal locus of control. Hispanic adolescents (n = 694) typically scored between the other two ethnic groups. These results provide evidence of the possible utility of designing differential adolescent AOD treatment as a function of gender and ethnic personality characteristics. Further studies will address the relationship between these findings and severity of dependence and other negative consequences of misuse, and treatment outcome.

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ADOLESCENT DRUG PROBLEMS INCREASES RISK FOR ADULT ANTISOCIAL PERSONALITY

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Subtypes of alcoholics and drug addicts often include one type whose drug use stems from antisocial tendencies. Although conduct disorder before age 1.5 is required for antisocial personality disorder diagnosis, recent studies have reported on men and women drug users who exhibited adulthood antisocial tendencies without experiencing conduct problems. This reanalysis of Epidemiological Catchment Area data (community sample) retrospectively investigated the association between adolescent drug problems (including alcohol) and adulthood antisocial personality criteria among groups with sub-clinical configurations of conduct disorder symptoms. Analyses were conducted separately for 7,277 men and 10,096 women who reported a) having conduct problems before age 13 (early onset conduct problems; ECP), b) having conduct problems first between ages 13 and 20 (later onset conduct problems; LCP), or c) having no conduct problems (NCP). Data indicated that adolescent drug problems were most prevalent in ECP men and second most prevalent in LCP men. For women, regardless of onset age, conduct problems were associated with adolescent drug problems. Regardless of conduct problem onset and gender, however, drug problems originating in adolescence increased risk for adulthood antisocial personality. Even with a history of ECP, absence of adolescent drug problems protected against adulthood antisocial personality. These findings persisted after accounting for other risk factors such as cognitive dysfunction and adolescent depression. Future research should investigate if risk for adulthood antisocial personality might be reduced with prevention or decreased adolescent drug use.

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PREDICTORS OF TREATMENT USE AMONG ADOLESCENT MALES

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Major gaps continue to exist in our knowledge base regarding utilization of health treatment services and unmet need for these services among children and adolescents. We hypothesized that correlates of mental health treatment utilization and unmet need for this treatment would include factors similar to those found by the recent MECA study, such as parental psychopathology. Our subjects included 196 boys, ages 14 to 16 years old, and their biological parents. These families are participating in an ongoing, longitudinal study (CEDAR) funded by NIDA, which assesses the etiology and correlates of substance use disorders. Four factors were significantly associated with increased mental health treatment utilization in our sample, including the diagnosis of ADHD and ODD in the adolescent, father's alcohol use disorder, and mother's amphetamine use disorder, while father's cannabis use disorder was significantly associated with decreased utilization. Four factors were significantly associated with unmet treatment need in our sample, including a diagnosis of conduct disorder in the adolescent, mother's amphetamine use disorder, mother's and father's history of an anxiety disorder and a greater number of siblings in the family. These findings suggest that paternal substance use, paternal psychopathology, and an increased number of siblings act as barriers to receiving adequate mental health services among adolescent boys.

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COMORBIDITY AMONG ADOLESCENTS IN DRUG TREATMENT: TREATMENT PROCESSES AND OUTCOMES FROM THE DRUG ABUSE TREATMENT OUTCOME STUDY

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This study examined treatment processes and outcomes of adolescents in residential drug treatment programs who have a comorbid mental disorder in the national Drug Abuse Treatment Outcome Study for Adolescents (DATOS-A). Adolescents were sampled from 13 residential drug treatment programs for adolescents in 6 cities. The sample consisted of adolescents who were at least weekly marijuana users; 46% met DSM-III-R criteria for conduct disorder; 16% had some combination of either conduct disorder, major depression, or attention deficit hyperactivity disorder; and 38% had none of these disorders. Any type of comorbidity was associated with being younger, white or Hispanic, marijuana dependence, having problems with family, having a negative reference group, and engaging in more illegal activities. Although there was a positive correlation between mental health needs and receipt of mental health services, in multivariate analyses the presence of a mental disorder was not associated with receipt of mental health services. Comorbidity was associated with receipt of health services and HIV risk reduction services. Treatment retention was negatively associated with more education; need for mental health, health, or family services; and with being white or male. Use of alcohol, marijuana, cocaine, and hallucinogens were all reduced at follow-up, however, rates of use continued to be higher for the comorbid adolescents. Post-treatment abstinence from alcohol and drugs was associated with the total number of services received while in treatment and with treatment retention for comorbid adolescents; whites were less likely to be abstinent as compared with African Americans. The findings suggest that comorbid youth in drug treatment have higher rates of alcohol and drug use and more service needs, but that receipt of services promotes enhanced treatment retention and outcomes.

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ORAL COMMUNICATIONS VII

COCAINE RECIPROCALLY MODULATES GENE EXPRESSION OF THE BETA CHEMOKINES AND THEIR RECEPTORS IN THE HUMAN ASTROCYTOMA CELL LINE, U87

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Although cocaine has been linked as a co-factor in the immunopathogenesis of HIV-1 infections, the molecular mechanism(s) underlying the actions of cocaine in the induction of immunodeflciency and encephalopathy in HIV-infected patients have not been fully defined. Recently, two unique HIV-1 entry co-receptors (CCR3 and CCRS) and a trio of HIV-1 specific suppressor chemokines (RANTES, MIP-1α and MIP-1β were identified. The β chemokines are the natural ligands for the HIV entry co-receptors, CCR3 and CCR5. Restricted HIV-1 infection of neuronal or glial cells *in vitro* also has been reported. We hypothesize that cocaine mediates these effects through down-regulation of HIV-1 suppressing chemokines and/or up-regulation of HIV-1 entry co-receptors in HIV-1 infected persons. U87 cells ($3.2x10^6$ cells/60mm dish) were cultured with 10^{-5} to 10^{-8} M concentrations of cocaine. Total RNA was extracted, reverse transcribed and cDNA was amplified by PCR using CCR3, CCRS, MIP-1beta, and RANTES primers. Our results show that cocaine significantly down- regulates the expression of the HIV-1 suppressing chemokine genes, MIP-1β, and RANTES and up-regulates the expression of the HIV-1 entry co-receptors, CCR3 and CCRS by U87 cells. These studies support a role for cocaine as a co-factor in the pathogenesis of HIV infection and suggest that the mechanisms of cocaine-associated susceptibility to and progression of HIV-1 infections may be mediated through the inhibition of HIV-1 suppressing chemokines and the concomitant up-regulation of HIV-1 entry co-receptors.

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ADHERENCE TO HIV MEDICATIONS AMONG PATIENTS IN METHADONE MAINTENANCE

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New medications and combination therapies for HIV are often followed by complex schedules and instructions, creating problems with adherence. Preliminary data suggest that HIV+ individuals in methadone maintenance may have difficulty with a crucial element of adherence: knowledge about their prescriptions. This study investigated adherence to anti-retrovirals in a proposed sample of HIV+ patients from the methadone maintenance program at San Francisco General Hospital. Adherence data was collected from 19 patients during the baseline phase of a pilot project aimed at increasing medication adherence. When self-reported data were compared with the recommended prescription requirements for individual anti-retrovirals medications, 10% of the patients were inaccurate in their dosage requirements, 44% were inaccurate in reporting the scheduling requirements, and 56% were inaccurate in reporting the special dietary instructions for their protease inhibitors (PI). Patients reported taking 83% of their PI doses yesterday; however, only 40% of doses were taken according the medications' scheduling requirements and 26% were taken according to the special dietary instructions (i.e., "take with food"). Although patients reported relatively good adherence to PI doses, their inability to attend to the medications' scheduling and dietary instructions may contribute to sub-therapeutic outcomes, leading to possible drug resistance. Patients must know how to correctly take their medications in order to adhere to their prescribed regimens. Thus, adherence should be measured in various ways to help researchers better understand the difficulties patients experience.

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MONETARY REINFORCEMENT COMBINED WITH STRUCTURED TRAINING INCREASES COMPLIANCE TO ANTIRETROVIRAL THERAPY

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BACKGROUND AND OBJECTIVES: Strict compliance to anti-retroviral therapy is thought to be crucial for optimal medical response, but few compliance interventions have been rigorously tested. We used a randomized controlled trial to test the ability of cue-based training with or without cash reinforcement to improve compliance to anti-retroviral therapy. **PARTICIPANTS:** Thirty HIV-infected subjects on stable anti-retroviral therapy regimens treated in VA clinic. **INTERVENTION:** Four weekly sessions of either: a) non-directive inquiries about compliance (control group), b) cue-dose training using MEMS caps (CD), or c) cue-dose training with cash reinforcement for correctly timed bottle opening (CD+CR). **RESULTS:** MEMS documented baseline compliance was high (73%). Compliance improved in the CD+CR group compared to controls at weeks 1-4 and remained numerically higher for eight follow-up weeks. Similar improvement was seen with other anti-retroviral drugs. There was no significant improvement in the CD group. Unexpectedly, viral load increases were seen in the CD+CR group despite high compliance. **CONCLUSION:** Cue-dose training with cash reinforcement improved compliance to anti-retroviral therapy. Questions of generalizability, feasibility and effect on medical outcomes remain.

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SEROPREVALENCE OF HEPATITIS C VIRUS INFECTION IN OPIOID DEPENDENT PATIENTS

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Introduction: Hepatitis C virus (HCV) infection has become an pubic health issue of increasing concern because of its prevalence and association with significant excess morbidity and mortality. However, questions remain about its epidemiology and natural history. Objective: In a cross-sectional and retrospective study design, this investigation is 1) to determine the prevalence of HCV infection in a large population of patients enrolled in methadone maintenance treatment; 2) to determine the demographic, behavioral, and clinical factors associated with HCV infection; and 3) follow the clinical course of infected patients. Methods: All patients admitted to a large methadone maintenance program (seven clinics) in New York City were screened for HCV antibody prevalence. Through chart abstraction, demographic, behavioral, and clinical information was collected. As of this writing, data was analyzed to determine whether significant associations exist. Further analysis will be pursued to determine the strengths of these associations. Results: As of this writing, serological data exists for 455 patients (38% female, 46% African American, 43% Hispanic, and mean age of 42.3 years of age). The overall seroprevalence was 65%. Age ($p<.01$) and gender ($p=.004$) were associated with infection with older patients and males more likely to be infected. Conclusion: The overall seroprevalence is consistent with what has been reported in other populations of former injection drug users. While further analysis is still underway, it is clear that this population is at substantial risk to incur hepatic cancer in light of what is currently known about the natural history of HCV infection.

HEPATITIS C VIRUS AND VIRAL COMORBIDITY IN PATIENTS IN METHADONE MAINTENANCE TREATMENT: A COMPARISON OF TWO CLINICS

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Hepatitis C (HCV) infects approximately 4 million people in the US, which results in roughly 10,000 deaths/year, and is the leading reason for liver transplantation. The major route of HCV transmission is bloodborne (parenteral), and the group most at risk for HCV infection is intravenous drug users (IVDUs), with a number of studies showing a worldwide HCV prevalence among IVDUs of 50-98%. However, to date, there are no systematic studies in the US of the prevalence of HCV in IVDUs in chronic opioid agonist treatment (primarily methadone maintenance or MMT). In this study, we reviewed viral marker serology results in new admissions (only) from 1991-1998 in one MMT clinic associated with our laboratory (the ADP, mdn age = 29y). In this clinic, 74-84% of patients are being tested for HCV. The annual rate of HCV is 20-35%, anti-HIV-1 is 0-18%, the rate of HBV ranges from 25-45% and the rate of hepatitis A (HAV) is <5%. We then compared the current patient population in the ADP (n=113) and in 68/251 patients in another MMT clinic associated with our lab (the AC, mdn age = 45y). Of those patients tested, the percent with positive viral marker serology in the ADP as compared to the AC is 41% vs. 76% (HCV), 14% vs. 26% (anti-HIV-1) and 51% vs. 72% (HBV). We conclude that testing for HCV, along with HIV-1, HBV and HAV, needs to be performed in the MMT population, and that vaccination, which is safe and effective, should be done in all patients who test seronegative for HAV and HBV (Borg *et al.,* 1999). Also, further evaluation is needed to determine which HCV-positive patients may benefit from double therapy treatment (ribavirin and interferon alfa-2b).

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PREDICTORS OF HEAVY TOBACCO USE AMONG ADOLESCENTS

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Factors predicting the initiation of light smoking among adolescents have been studied fairly extensively, but factors predicting the progression to heavy smoking remain less clear. The purpose of this research was to assess the predictors of the heavy tobacco use at baseline and a 3-year follow-up among a sample of adolescents. The subjects consisted of 718 adolescents, ages 13 to 18, who participated in a longitudinal study at the Pittsburgh Adolescent Alcohol Research Center (PAARC). About half of the subjects were recruited from various alcohol treatment programs in the greater Pittsburgh area, and the other half from a representative community sample. At baseline, 506 subjects (70.5%) had a lifetime history of having ever smoked a cigarette, while one-third (33.4%) had a history of heavy smoking, defined as smoking 10 or more cigarettes per day. Stepwise logistic regression analyses were conducted to determine predictors of heavy use. Significant predictors of baseline heavy use were: older age, higher levels of aggressive behavior, Caucasian ethnicity, and higher depression scores (BDI). Significant predictors of heavy use at the 3-year follow-up evaluation were: Caucasian ethnicity, higher levels of aggressive behavior, lower SES, and older age. However, when heavy use at baseline was included as one of the potential predictors of heavy use at 3-year follow-up, then heavy use at baseline predicts heavy use at follow-up very well, while all other variables have no significant effect. These findings suggest that a variety of factors predict initiation of heavy use, but that continuation of heavy use is predicted primarily by previous heavy use.

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COTININE ELIMINATION TRENDS IN BLACK AND WHITE WOMEN CIGARETTE SMOKERS

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Higher cotinine levels in African American cigarette smokers compared to Caucasian smokers may indicate greater exposure to smoke constituents, even though daily smoking rate is lower in African Americans. Differences in nicotine intake and elimination may be influencing factors. The purpose of this study was to compare cotinine elimination trends in African American and Caucasian women during 6 days of smoking abstinence in the Clinical Research Center (CRC). Preliminary data of 31 women (16 black and 15 white women) indicate an average age of 32.1 yrs, an average of 20.4 cpd for 16.2 yrs beginning at age 16. Sixty-five percent were menthol smokers. Average time to first cigarette of the day was 11.6 min (med=5 min) with shorter times indicating increased dependence. Plasma for cotinine assays was obtained every 8 hr during the study, including Day 1 of ad lib smoking. Mean plasma cotinine at the end of Day 1 was significantly ($p=.018$) higher for black women (356 ng/ml) compared to white women (243 ng/ml) and significantly higher for menthol (342 ng/ml) vs non-menthol (238 ng/ ml) smokers. During Days 2 through 7, women were smoking abstinent as confirmed by expired air carbon monoxide. Time to reach non-smoker levels <14 ng/ml of cotinine ranged from 48 to >136 hrs. Predicted cotinine half-life was similar for black women (22.7 hrs) and for white women (20.1 hrs), while menthol smokers had significantly longer predicted half-life compared to non-menthol smokers (23 vs 18 hrs, $p=.04$). Admission GGT values were in normal range for all subjects. Daily urine pH averaged 5.4-5.9 and did not differ by ethnicity or menthol preference. Exploration of factors influencing cotinine levels beyond elimination is needed.

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SUBJECTIVE AND DISCRIMINATIVE STIMULUS EFFECTS OF TWO DE-NICOTINIZED CIGARETTES WITH DIFFERENT TAR CONTENTS

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The role of tar content in the subjective and discriminative stimulus effects of cigarette smoking was examined. Current smokers (N = 18) smoked 2 non-nicotine cigarettes with FTC yields of 0.06 mg nicotine and 12.4 mg (low tar) or 17.9 mg tar (high tar). Physiological measures and visual analog scales were completed over a 30 min period. Dosing order was determined randomly and counterbalanced. After sampling both cigarettes, volunteers smoked a third test cigarette. Half of the volunteers received the low tar cigarette and half, the high tar cigarette. Volunteers guessed the identity of the test cigarette (i.e., A or B) at 1, 5, 10, 20, and 30 minutes after the first puff. Eight of the 18 participants correctly guessed the identity of the test cigarette. No significant differences in VAS scores were found among the non-discriminators. However, among the discriminators, the low tar cigarette produced significant positive effects including Good Drug Effects, Stimulation, and Desire to Smoke the Cigarette You Just Smoked. The high tar cigarette produced negative effects including Harshness, Heaviness, and Intensity of Flavor. The average tar yield of these participants' usual cigarettes was 9.75 mg, lower than that of the low tar cigarette used here, possibly accounting for their greater liking for the low tar cigarette. No changes in blood pressure or pulse were observed and both cigarettes produced similar increases in carbon monoxide, indicating similar depth of inhalation when smoking each. Results suggest cigarette tar yields may play an important role in cigarette smoking preferences.

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A COMPARISON OF THE REINFORCING EFFICACY OF NICOTINE-CONTAINING AND DE-NICOTINIZED CIGARETTES

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The relative reinforcing efficacy of nicotine-containing and de-nicotinizcd cigarettes was compared to examine the potential conditioned reinforcing effects of smoking-produced sensory stimulation. Operant responding of 8 cigarette-deprived smokers was reinforced with two puffs on nicotine-containing or de-nicotinized cigarettes. The two cigarette types were available independently, in the first phase, across a range of increasing prices as arranged by a progressive-ratio schedule of reinforcement. In the second phase, the two cigarette types were available, concurrently, at a range of prices as arranged by selected ratio requirements. Repeated measures analyses of variance and post-hoc comparisons revealed that the two types of cigarettes were similarly affected by increases in price and produced similar measures of elasticity, breakpoints, and peak response rates when presented independently. However, nicotine-containing cigarettes were preferred over de-nicotinized cigarettes over a range of prices when the two types of cigarette were available concurrently. Results suggest that, when presented alone, the conditioned reinforcing effects of the sensory stimulation provided by the de-nicotinized cigarettes played an important role in cigarette consumption, but preference was likely determined in part by nicotine content in the choice situation.

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EFFECTS OF HALOPERIDOL ON CIGARETTE SMOKING

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Studies with laboratory animals suggest that dopamine mediates the rewarding effects of nicotine (e.g., Corrigall 1995), and three studies with human subjects support a role for dopamine in cigarette smoking (Dawe *et al.,* 1995; McEvoy *et al.* 1995; Caskey *et al.* 1999). The present study, which is ongoing, is evaluating the effects of the D2 dopamine antagonist, haloperidol, on acute responses to smoking and on rates of *ad lib* smoking in the laboratory. During six laboratory sessions, subjects receive pretreatment with placebo or haloperidol (1 and 2 mg orally) three hours prior to inhaling controlled doses of smoke from a nicotine-containing or denicotinized cigarette, according to a 3 x 2 repeated-measures design. After controlled smoking, subjects smoked *ad lib* over a 3 hr period. All drugs and cigarettes are administered under double-blind conditions. Preliminary data from 16 subjects (total N will be 24) provide partial support for our hypotheses. Two mg haloperidol significantly decreased the number of cigarettes smoked and the inter-cigarette-interval relative to placebo. The higher dose of haloperidol also attenuated the effects of nicotine in reducing craving for cigarettes under controlled conditions. However, haloperidol did not affect ratings of smoking satisfaction at either dose. Our preliminary results confirm a role for dopamine in mediating the reinforcing effects of cigarettes, and suggest that dopamine may play a differential role in the positive reinforcing versus withdrawal-relieving effects of nicotine.

REFERENCES: Available from senior author upon request.

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EFFECTS OF ABSTINENCE ON THE RELATIVE VALUE OF CIGARETTES

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It is commonly believed that when drug users are deprived of drugs they become more likely to perform rash, impulsive behaviors. These impulsive behaviors may be related or unrelated to obtaining drugs, e.g., committing crimes to drugs vs being aggressive towards family members. To examine whether abstinence does increase both types of impulsive behavior, 8 smokers (≥15 cigarettes/day) participated in 3 sessions. On each session, they completed computer tasks, which examined impulsivity by measuring the tendency to choose a small, immediate reward over a large, delayed reward. In the drug-related behaviors task, they chose between cigarettes available immediately (range 0 - 60) and $10.00 available following a delay (0, 7, 30, 180 or 365 days). In the unrelated behaviors task, they chose between money available immediately (range $0.01 - $10.50) and $10.00 available following a delay. Smokers then remained in the laboratory for 6 h. The first session was a practice session in which choices were hypothetical and smokers smoked ad libium in the following 6 h. Counterbalanced, there followed a session on which participants did not smoke for 24 h and another on which they could smoke until the session began. In both these sessions, choices on the task determined the number of cigarettes smokers could have in the following 6 h. Smokers chose cigarettes more on the deprivation session, discounting the value of delayed money relative to that of the cigarettes. This increased preference for the immediately available drug during abstinence may be viewed indicating an increase in impulsive behavior. This increase did not generalize to the unrelated behaviors task (money now vs. money delayed). These findings indicate that increases in impulsivity during abstinence were limited to drug-related behaviors. Interestingly, from a methodological standpoint, discounting was systematically less on all tasks during the practice session when choices were hypothetical.

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GENDER, WOMEN, AND TOBACCO WITHDRAWAL SIGNS AND SYMPTOMS

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Women are less likely to quit smoking than are men and may receive less benefit from nicotine replacement therapy (NRT). Although tobacco withdrawal has not been particularly powerful in differentiating gender and individual differences in cessation, it has been assessed almost exclusively with self-report. The current research investigated objective signs and subjective symptoms of tobacco withdrawal as potential mechanisms underlying: a) gender differences in response to NRT (Study 1; n=34); and, b) the effects of depression history on quitting among women (Study 2; n=13). These studies are unique in that withdrawal signs were assessed using polysomnographic measures of sleep. Sleep is a fundamental index of disturbed behavioral regulation. In both studies, signs and symptoms were collected pre- and post-cessation, Withdrawal trajectories over time were compared using Generalized Estimating Equations. In Study 1, 34 male and female smokers were randomized to active or placebo NRT. Polysomnographic sleep indices indicated that NRT might be less effective at suppressing certain withdrawal responses and produce some iatrogenic effects among women (e.g., sleep fragmentation and efficiency). In Study 2, seven depression history positive (Dep+) and six history negative (Dep-) women quit smoking without pharmacotherapy. Withdrawal trajectories differed by depression history. Dep+ women displayed abstinence-induced changes in REM sleep parameters that are consistent with greater vulnerability to depression. Valid and reliable self-report measures did not reveal gender differences in response to NRT or differences due to depression history. In sum, tobacco withdrawal may be a mechanism underlying gender differences in response to NRT and the influence of depression history among women. Greater emphasis on the measurement of withdrawal signs might benefit the development of the theory and treatment of nicotine dependence.

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ORAL COMMUNICATIONS IX

SEPTAL AND AMYGDALA TRH IN MORPHINE WITHDRAWAL IN THE RAT

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Systemic thyrotropin-releasing hormone (TRH) ameliorates somatic symptoms of opiate withdrawal (WD) in rats. To further define how TRH mediates WD, Sprague-Dawley rats were implanted with one 75 mg morphine pellet daily for 5 d. On day 6, WD was induced with naltrexone (2-100 mg/kg, i.p.). Rats were sacrificed at various times into WD, and preproTRH mRNA was quantified by RNase protection assay and *in situ* hybridization. PreproTRH mRNA increased to twice control levels at 3 h WD, and peaked at 10 and 18 times control at 12 h, in rostral and caudal amygdala sections, respectively. Induction was localized to the central amygdaloid nucleus, posteromedial cortical amygdaloid nucleus, and bed nucleus of the accessory olfactory tract. TRH peptide in the amygdala region, assayed by RIA, did not increase until 36 h WD. However, marked reductions in TRH were found in the septal area at 30 min WD. In behavioral studies, we blocked this reduction during WD by medial septum pre-infusions of TRH, and found teeth chatters and chewing were reduced, compared to rats receiving vehicle pre-infusions. Further, TRH pre-infusion into the septum blocked the development of conditioned place aversion in morphine-pelleted rats given septal infusions of methylnaloxonium. We hypothesize that somatic and aversive aspects of morphine WD are mediated in part by changes in TRH signaling in amygdaloid and septal nuclei.

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REPEATED SOCIAL DEFEAT STRESS INCREASES MU-OPIOID RECEPTOR mRNA EXPRESSION IN VENTRAL TEGMENTAL AREA OF INTRUDER RATS

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Stress in the form of social defeat induces behavioral sensitization to psychostimulant challenge. This salient stressor selectively alters the activity of mesocorticolimbic dopamine projections from the ventral tegmental area (VTA), which has been implicated in the development of sensitization and drug-seeking behavior. Opioids can modulate the activity of dopamine neurons in VTA by stimulating mu-opioid receptors located on GABAergic interneurons. This action reduces inhibitory input to VTA dopamine neurons. Previously, we have shown that brief episodes of defeat stress induced expression of mu-opioid receptor mRNA in VTA, lasting up to 6 hours. Repeated social defeat stress was hypothesized to induce mu-opioid receptor mRNA expression in the VTA for a much longer period. Defeat stress consisted of a short confrontation with an aggressive resident animal, and subsequently 30 min of exposure to threats behind a protective cage. Rats were exposed to repeated social stress once daily for 5 days, and the neurobiological consequences were studied 7 days later. Regional mu-receptor mRNA levels were detected by *in situ* hybridization histochemistry, and amount of labeling was measured in the VTA and the substantia nigra (SN). Expression of mu-opioid receptor mRNA in the VTA was two-fold higher in defeated rats compared to naive control animals. In contrast, repeated social stress exposure did not affect mu-receptor mRNA expression in the SN. These results suggest that mu-opioid receptor expression in the VTA is a long-term consequence of social stress, which might be implicated in the development of sensitization via regulation of mesocorticolimbic neuronal activity.

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DYNORPHIN-INDUCED PROLACTIN RELEASE IS DECREASED IN COCAINE ADDICTED METHADONE MAINTAINED PATIENTS

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Endogenous dynorphin has been demonstrated to modulate cocaine-induced dopaminergic activity in animal models. “Binge” pattern cocaine administration is associated with lowered central dopaminergic tone, as well as counterregulatory changes in the dynorphin/kappa opioid receptor system. Previous work from this laboratory has shown that intravenous administration of dynorphin A_{1-13} to normal volunteers results in increases in serum prolactin through an opioid receptor mediated mechanism. In the present study, we administered a placebo, 120microgm/kg, and 500microgm/kg of dynorphin A_{1-13} (the shortened form of the naturally occurring dynorphin A_{1-17}) on separate days to three groups of human volunteers: healthy subjects with no history of addictions (2 females, 10 males), stable methadone maintained patients with no ongoing substance problems (1 female, 6 males), and methadone maintained patients with no ongoing illicit opiate use but with active cocaine addiction, in early abstinence from cocaine (3 females, 3 males). Dynorphin-induced prolactin release was measured as a peripherally accessible window into central kappa-opioid-modulated dopaminergic tone. In a preliminary analysis of the data, low dose dynorphin appeared to result in lower peak prolactin responses in methadone maintained patients both with and without ongoing cocaine addiction. In contrast, in response to high dose dynorphin, stable methadone patients with no ongoing drug abuse had peak prolactin levels comparable to normal volunteers, whereas, those with ongoing cocaine addiction did not. There also appeared to be gender differences in dynorphin-induced prolactin release in patients with ongoing cocaine addiction compared with normal volunteers.

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FEMALE CONADAL HORMONES MODULATE COCAINE-INDUCED BEHAVIOR

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Sex differences in response to cocaine have been reported both in humans and animals. Following the same dose of cocaine, male subjects achieve higher peak plasma cocaine levels and detect cocaine effects faster than females. Gonadally intact female rats show higher levels of cocaine-induced locomotor activity compared to male rats and self-administer cocaine to higher breaking points. The present study was undertaken to investigate cocaine effects in female rats of genetically distinct inbred (Fischer 344, F344; Lewis, LEW) and outbred (Sprague-Dawley, SD) strains. All female rats were bilaterally ovariectomized (OVX) and randomly assigned to one of four experimental groups: (i) estradiol benzoate (EB) group, (ii) progesterone (P) group, (iii) EB+P group, and (iv) OVX group. To determine gender-related differences in cocaine's acute and chronic effects, data obtained from female rats were compared with those from strain-matched, weight-matched male rats. EB+P female rats showed greater locomotor effect to both acute cocaine as well as to repeated-cocaine than male rats. Bilateral removal of ovaries abolished cocaine sensitization. In all strains of rats studied, progesterone alone did not alter the OVXinduced attenuation of cocaine behavior. Estrogen alone restored cocaine-induced behavioral sensitization. There were significant strain effects on the degree of gonadal hormonal-induced modulation of cocaine effects in female rats. Female LEW rats were extremely sensitive to repeated cocaine effects whereas the F344 females showed only marginal effects. The SD rats ranked intermediate in their behavioral sensitivity. The present study strongly supports the hypothesis that female rats are more sensitive to both acute and chronic behavioral effects of cocaine compared to male rats and that the effects are strain dependent. It also shows that estrogen plays an important role in the increased cocaine sensitivity in female rats. Together, these data indicate significant interactions between ovarian steroid hormones and cocaine-induced behavioral effects.

INVESTIGATION OF POTENTIAL MONOAMINE MECHANISMS UNDERLYING THE COCAINE-INDUCED ACTIVATION OF THE HPA AXIS IN RHESUS MONKEYS

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Previously, we reported a positive correlation between intake of self-administered cocaine and plasma cortisol and ACTH levels in male rhesus monkeys. Pharmacological inhibition of the cocaine-induced increase in ACTH with the CRH antagonist, astressin, led us to investigate a role for monoamines in the release of CRH following cocaine administration. It has been reported that serotonergic neurons projecting to the paraventricular nucleus of the hypothalamus innervate CRF-containing cells (Liposits *et al.,* Histochemistry, 86: 541-549, 1987), and there is evidence that 5-HT_2 receptors are responsible for cocaine-induced ACTH and corticosterone increases in the rat (Levy *et al.,* J Pharmacol Exp Ther, 259: 495-500, 1991). Other studies have indicated that $alpha_1$ adrenergic receptors may mediate the increases in HPA activity following alcohol consumption (e.g. Grossman and Besser, Clin Endocrinol, 17: 287-290, 1982). Three male rhesus monkeys, each with a surgically-implanted venous catheter, were subjects in this study. Cocaine (0.1 or 0.3 mg/kg/inj) was available on a fixed-ratio 30 time-out 600-s schedule. The 5-HT_{2A} antagonist, ketanserin (0.1, 0.3 and 1.0 mg/kg), $alpha_1$ adrenergic antagonist, prazosin (0.01, 0.03, 0.1 mg/kg) and the D_2 and 5-HT_2 blocker, risperidone (0.01, 0.03, 0.1 mg/kg), were each administered 15-30 min prior to the start of the 10 am cocaine self-administration session. Venous blood was sampled before, during and after each 130 min session; plasma cortisol and ACTH levels were measured by RIA. Ketanserin dose-dependently blocked the increase in both cortisol and ACTH in one of three monkeys. However, neither prazosin nor risperidone were effective in this respect. All three antagonists stimulated ACTH release at the highest doses tested. Risperidone (0.1 mg/kg) attenuated cocaine-maintained behavior. These studies were unable to demonstrate a clear role for NE, DA or 5-HT in mediating the cocaine-induced increases in HPA activity.

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REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR USING A CONDITIONED REINFORCER: ROLE FOR THE HYPOTHALAMO-PITUITARY-ADRENAL (HPA) AXIS

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Adult male Wistar rats were trained to self-administer cocaine (0.25 mg/kg/infusion) under a FR4 schedule of reinforcement. A light above the response lever indicated the availability of cocaine. A house light and tone stimulus was paired with each cocaine injection and the subsequent 20-sec timeout that followed each injection. Sessions lasted 2 hours and were conducted 5 days per week. When stable self-administration was observed, extinction training began whereby responding resulted in no programmed consequences. Extinction training continued for 10 sessions or until responding decreased below 20% of baseline self-administration. Reinstatement was tested in two ways. During non-contingent reinstatement, the tone and house light stimulus was presented every 15 min regardless of responding. During response-contingent reinstatement, responding resulted in the contingent presentation of the tone and house light stimulus. Rats were pretreated with ketoconazole (25 mg/kg, ip) 30 min before the start of the reinstatement test session to determine the potential role for corticosterone. The response-contingent presentation of a light and tone stimulus previously paired with cocaine during self-administration reliably reinstated extinguished cocaine-seeking behavior. However, the non-contingent presentation of the same stimulus did not. Rats could be retrained using this procedure for multiple reinstatement testing. Conditioned increases in plasma corticosterone were evident during cocaine extinction as well as during reinstatement. However, while plasma corticosterone returned to basal levels by the end of the session during extinction, it remained elevated through the end of the session during reinstatement. Pretreatment with ketoconazole reversed the conditioned cue-induced reinstatement of extinguished cocaine-seeking behavior and also attenuated the conditioned increases in plasma corticosterone observed during reinstatement. These data suggest an important role for corticosterone in the ability of environmental cues to stimulate cocaine-seeking behavior in rats. The HPA axis may therefore also be involved in cocaine craving induced by exposure to cocaine-associated cues in humans.

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EFFECTS OF INTRAVENOUS COCAINE ON STRESS HORMONES IN HUMANS

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Cocaine has been shown to activate the sympathoadrenal system and increase plasma catecholamines in preclinical studies. Controlled human studies have been inconclusive on whether cocaine activates the sympathoadrenal system. The purpose of this study was to investigate whether commonly abused doses of cocaine increase plasma catecholamines in humans in a double-blind, placebo-controlled study. Six male cocaine users were given an intravenous injection of 0.46 mg/lcg dose of cocaine or placebo, on two consecutive days. Multiple plasma samples for epinephrine and norepinephrine were obtained to determine the extent and time course of the changes in the concentrations of these hormones following cocaine or placebo (saline) injection. Plasma epinephrine and norepinephrine concentrations were significantly increased in response to cocaine injection compared to placebo. Peak plasma epinephrine and norepinephrine concentrations were reached 3 and 12 min after cocaine injection, respectively. These results suggest that the sympathoadrenal system is activated after the administration of dose sizes of cocaine that are commonly abused by humans.

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THE ASSOCIATION BETWEEN PSYCHOLOGICAL DISTRESS AND COCAINE USE DURING TREATMENT

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Although psychological distress is identified as a common reason for continued drug use and relapse, the direct association between stress and drug use remains understudied. In a sample of 68 cocaine abusing men and women entering a treatment engagement study, we examined the relationship between perceived stress and baseline individual characteristics as well as drug use treatment outcomes. The Perceived Stress Scale (PSS) was completed at intake along with assessment of psychiatric severity and substance use diagnoses. PSS scores were significantly correlated with ASI psychiatric severity, Beck depression scores, cocaine dependence severity and baseline cocaine craving and cocaine use (p's<.01). Further, baseline PSS scores significantly predicted weekly cocaine use during the 3-week engagement study period (p<.03) and weekly cocaine craving during treatment (p<.01) and during the 1 month follow-up period (p<.01). These data are initial evidence that 'psychological distress' may be an important clinical construct in perpetuation of drug use behaviors. Also, the findings complement recent preclinical and human laboratory research indicating a direct relationship between stress and cocaine-seeking behavior.

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ORAL COMMUNICATIONS X

GENDER DIFFERENCES IN THE DRUG EVALUATION NETWORK SYSTEM: A NATIONAL ADDICTION TREATMENT INFORMATION SYSTEM

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Data from the Drug Evaluation Network Study (DENS), a nationwide electronic system providing clinical information on substance abuse patients, supports the growing body of evidence that drug abuse history, personal health, and social function factors are quite different between males and females. Four treatment modalities are represented in DENS: methadone maintenance, inpatient/residential, outpatient and intensive outpatient abstinence oriented. The Addiction Severity Index (ASI) is the primary source of data collection, with a system that allows for the addition of 35 questions based on contemporary areas of concern. The data set from DENS is in the public domain. This presentation highlights the substantial differences between male and female clients in the 40 treatment programs across the country participating in DENS. While not yet a nationally representative sample, our pilot findings show significant differences in many areas. For example: women report entering treatment at an earlier age than men do. At treatment entry, the number of years women report using alcohol, heroin, and marijuana is less than those reported by men; however, there are no differences in years of use for amphetamines or cocaine. More women than men report experiencing medical problems (39% vs. 29%) and more women report taking prescription medications for medical problems (30% vs. 23%). A greater percentage of women reported inpatient psychiatric hospitalizations (23% vs. 17%) symptoms of depression (40% vs. 30%), and having attempted suicide (3% vs. 1.6%). Data presented will reflect approximately 10,000 treatment admissions collected up to the week prior to the conference.

GENDER DIFFERENCES AND PATTERNS OF HEALTH CARE UTILIZATION AMONG DRUG USERS IN PUERTO RICO

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Different antecedents and consequences of drug abuse between males and females have been reported on previous studies. This study aims to identify gender differences in drug treatment and health care utilization among drug users in Puerto Rico. A total of 1,115 drug users not currently in treatment were recruited following a targeted area sampling based on copping areas (settings where illicit drugs are sold). Participants were followed-up six months after baseline in order to determine the factors associated to health care utilization. Statistical analyses were performed using Chi-square and independent sample t-tests. Baseline data showed that females were more likely to smoke crack while males were more likely to inject cocaine or heroin. Females were more likely to recognize an alcohol problem and showed higher scores on the Alcohol Composite Scale of the Addiction Severity Index (ASI) ($p<0.001$). Females also had a higher rate on the Psychiatric Composite Scale (ASI) ($p<0.001$). Follow-up data did not show gender differences in the utilization of methadone programs, detoxification, outpatient (not methadone) program, or hospital-based drug treatment. Women reported criminal justice system and agency referrals as the main mechanisms to enter drug treatment and were more likely to receive drug treatment in prisons and jails. Furthermore, females were significantly more likely to be hospitalized and to receive mental health services than males. Promoting referrals for drug abuse treatment among women in human service organizations will help increase access to drug treatment services among this population.

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GENDER DIFFERENCES IN SYMPTOMS PRESENTATION AMONG ALCOHOL AND NON-ALCOHOL ABUSING BIPOLAR DISORDER PATIENTS

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This study examined gender differences of bipolar disorder patients with comorbid alcohol use (n=60; males = 40; females = 20) to a group of bipolar disorder patients without comorbid alcohol use (n=195; males = 80; females = 115). We hypothesized that those with comorbid alcohol use will report higher incidence of other drug use, and of impulsive, and violent behavior than the non-comorbid group. Subjects were selected from consecutively evaluated patients, using a validated semi-structured evaluation procedure. Those who met study inclusion criteria of bipolar disorder, manic subtype, were included in the study. The severity of concurrent maladaptive alcohol use among these patients was rated on a four-point severity scale, from absent to severe. The results revealed that both female and male bipolar alcoholic patients were more likely to report other drug use as well as impulsive and violent behavior than female and male non-alcohol abusing bipolar patients. These results suggest that impulsive behavior may be an important dimension for females and males bipolar patient with alcohol abuse, and that these patients are also likely to abuse other drugs in conjunction with alcohol.

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DIFFERENTIAL ENGAGEMENT OF SUBSTANCE ABUSING MALES AND FEMALES IN PATIENT PLACEMENT-DRIVEN TREATMENT PLANNING

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Gender differences are being analyzed in relation to treatment entry and outcome in a study of the validity of the Patient Placement Criteria of the American Society of Addiction Medicine. During subject recruitment, a smaller percentage of women engaged in treatment (attended at least their first treatment appointment) compared with men. We attempted to determine the reasons for this post hoc, as barriers to treatment may be importantt in placement criteria as well as treatment design. Predictive factors considered included demographic characteristics, drug of choice, family obligations, psychiatric distress and environmental issues. **Method:** Indigent patients were recruited from 5 publicly funded sites. They were randomized to Level II (day treatment) or Level III (residential rehabilitation) after detoxification. **Results:** Of 442 men recruited so far, 54% engaged in treatment, while 44% of 234 women engaged in treatment. (p=.015). Within Levels, the difference in engagement rates was significant for Level III only (p=.003). Using logistic regression, the following variables were associated with lower percentages of engagement overall: female gender, heroin as primary drug, more days of family conflict in the last 30 days. A combination of alcohol plus another drug as primary problem and randomization to Level III were associated with higher percentages of engagement. No variables were found to mediate the effect of gender on engagement. **Discussion:** Engagement rates for women did not appear to be accounted for by variables usually associated with gender differences. This indicates the need for prospective studies designed to specifically measure variables related to women's issues to determine their effect on treatment engagement and outcome. Greater understanding of such factors may help develop more effective ways to engage women in treatment and may be important in developing valid placement criteria.

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GENDER DIFFERENCES IN RELAPSE AMONG COCAINE DEPENDENT OUTPATIENTS

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Gender differences have been found in a variety of aspects of drug dependence, although results are equivocal. Several studies have suggested that female drug abusers report higher rates of negative affect, have higher prevalence of co-existing psychiatric disorders (Rounsaville et al. 1991), attribute drug use and relapse more often to negative affect (McKay *et al.* 1996) and are more likely to attend group therapy (Fiorentine *et al.* 1991), compared to males. In the present study, analysis of variance was used to evaluate gender differences among 141 cocaine dependent outpatients, with regard to demographic variables, therapy participation, rate of relapse, stage of change as measured by a readiness score, level of negative affect, and the concordance rate of self-reported drug use and urine drug screens. Participants received 12 weeks of one of two therapies: relapse prevention (RP) or discussion support (DS), and Naltrexone or placebo. At baseline, men reported using alcohol, cocaine and marijuana for more years than women had. However, there were no baseline gender differences on drug or alcohol use severity, readiness to change, or level of depression. There was an interaction ($p<0.05$) between therapy type and gender for several measures of retention, relapse to cocaine use, and treatment effectiveness. Women stayed in treatment longer and relapsed later when they received RP compared to DS therapy, whereas men performed relatively similarly within both types of therapies. There were no gender differences on the concordance rate between self-reported drug use and urine drug screens. It appears that women may benefit more from psychosocial and behavioral treatments that emphasize implementing coping skills and increasing self-esteem.

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GENDER DIFFERENCES IN COCAINE DEPENDENT OUTPATIENTS

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The purpose of this study was to examine gender differences in treatment outcome among cocaine-dependent outpatients. One hundred eighty-five males and 73 females, who sought treatment at a university-based research clinic, were compared on baseline characteristics. A subset of 85 males and 40 females who received the CRA plus vouchers treatment for cocaine abuse were compared on selected measures of treatment outcome. A greater proportion of men than women were employed full-time (63 vs. 42, $p< .01$), and had never married (53 vs. 39, $p<.0.5$). With regard to cocaine use severity at intake, men reported spending more money per week on cocaine ($p=.05$), and greater proportion of men received prior treatments' for cocaine abuse (55 vs. 40, $p<.05$). With regard to other drug use, men reported more cannabis and alcohol use in the last 30 days, and more years of regular cannabis and alcohol use ($p<.05$). Greater proportion of men than women were also cannabis dependent (28 vs. 4, $p<.01$) or cannabis and alcohol dependent (18 vs. 1, $p<.01$). With regards to adverse consequences of cocaine use, more women experienced depression, low energy, and unwanted sexual relations, while men experienced more paranoia, and were more likely to report having physically harmed someone ($p< .05$). Women had higher BDI scores than men ($p<.01$), while men scored higher on the MAST ($p< .05$). With regard to treatment outcome, no gender differences were found in either treatment retention or cocaine abstinence achieved during treatment or during follow-up timepoints. Though men report greater severity of other drug use and dependence at intake, men and women respond equally well to the CRA plus vouchers treatment.

GENDER EFFECTS OF DESIPRAMINE ON OPIATE USE IN BUPRENORPHINE - VS. METHADONE-MAINTAINED COCAINE ABUSERS

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This controlled clinical trial determined the relative efficacy of administering a cocaine anti-craving medication, despiramine (DIM), in combination with burprenorphine (BUP) or methadone (MTH) to decrease cocaine and opioid use among cocaine-abusing opioid-dependent patients using a randomized cross-over design. One hundred eighty cocaine-abusing opioid addicts (69% male; 69% W/22% AA/9% H) were enrolled in a double-blind, 26-week trial in which they received either BUP (12 mg. s.l.) or MTH (65 mg., p.o.) daily. Half the subjects in each opiate condition received DIM (150mg/day) for the first half of the trial and placebo during the second, whereas the other half received the converse. Urine samples were obtained thrice weekly. Groups did not differ on demographics, baseline drug use or retention. Analyses using hierarchical linear modeling indicate that reductions in cocaine use were significantly greater in those receiving DIM than placebo ($Z=2.16$, $p<0.05$), regardless of opioid agent or gender. In contrast, opioid use showed a gender X opioid med X DIM X time interaction ($Z=-2.86$, $p<0.01$). Methadone maintained males on despiramine significantly reduced opioid use relative to methadone-maintained males on placebo. ($Z=2.25$, $p<0.05$), but had opioid use similar to opioid-maintained females, and buprenorphine-maintained males. These results suggest that DIM facilitation of cocaine abstinence is unaffected by gender or opioid maintenance agents; however, DIM appears to increase opioid abstinence in males, but not females maintained on methadone.

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THE EFFECTS OF TRIPLE THERAPY AND GENDER ON METHADONE LEVELS IN METHADONE MAINTAINED PATIENTS

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Heroin dependence, for which methadone remains the main pharmacological treatment, and AIDS are two of the leading health problems today. The general belief among methadone subjects is that the potency of methadone is reduced by AIDS medications. A fall in methadone level may result in heroin relapse, poor compliance, dropout from treatment and poor HIV outcomes. This study determined the effects of three groups of medications commonly used for HIV prophylactic treatment on methadone blood levels. In addition, gender differences in methadone levels were examined to assess possible differences in the rates of metabolism of methadone. This cross-sectional study assessed the following groups of patients, a) methadone-maintained AIDS patients receiving triple therapy, b) methadone-maintained HIV patients yet to commence medication treatment, and c) HIV negative methadone-maintained patients. The main findings were: 1) There were no significant differences in rate of methadone metabolism based on gender, and 2) Triple therapy significantly increased the rate of methadone metabolism. The results of this study may be useful in patient education and the development of a comprehensive treatment that takes into account gender differences and medication interaction in the delivery of care.

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ARE THERE GENDER DIFFERENCES AMONG OUTPATIENT DRUG-FREE TREATMENT CLIENTS THAT AFFECT THEIR POST-TREATMENT OUTCOMES?

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Previous findings from the NIDA-sponsored Drug Abuse Treatment Outcome Study (DATOS) indicated that there were substantial gender differences among clients in each of four treatment modalities with respect to demographic and background characteristics and pretreatment behaviors. This study investigated the impact of these differences on post-treatment outcomes for men and women in the outpatient drug-free modality of DATOS. It was hypothesized that men and women in drug abuse treatment have different pre-treatment characteristics and behaviors that affect their post-treatment outcomes. Subjects were 496 men and 268 women who entered treatment in the outpatient drug-free treatment programs that participated in DATOS from 1991 to 1993. Subjects were administered a comprehensive psycho-social and behavioral assessment battery through interviews conducted at entry to treatment, during treatment, and 12 months following treatment. The results indicated that men and women were both different and similar on key pre-treatment characteristics and behaviors and post-treatment outcomes. For example, chi-square tests indicated that men and women differed significantly in such areas as history of physical and/or sexual abuse, mental health problems, and involvement with the criminal justice system. However, men and women, were found to be similar in the areas of cocaine and marijuana use. Results also indicated that both men and women reported decreases in their substance use and related behavior during the year following treatment. Multivariate logistic regression modeling indicated that the pretreatment gender differences did not have a wholesale impact on post-treatment outcomes for men and women.

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MENTAL HEALTH PROBLEMS AMONG ADOLESCENT CHILDREN OF ALCOHOL DEPENDENT PARENTS: EPIDEMIOLOGICAL RESEARCH WITH A NATIONALLY REPRESENTATIVE SAMPLE

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In this study, we seek confirmatory evidence about specific mental health problems of children of actively alcohol-dependent parents ('AAD' children) as compared to control ('NAD')children whose parents are not alcohol-dependent. Treatment sample research leads us to expect the most prominent AAD-NAD differences with respect to externalizing symptoms. In 1995 and 1996, the National Household Survey (NHSDA) used probability sampling to select nationally representative samples of U.S. households and members of eligible participating households. A total of 1,729 parent-child pairs were assessed, with both the parent and adolescent child living in the same household. Children's problems were assessed with an NHSDA version of Achenbach's Youth Self-Report; parental alcohol dependence was assessed via items adapted from the Diagnostic Interview Schedule. There were 79 parent-child pairs in which the interviewed parent reported a history of three or more active alcohol problems. Analysis of variance (ANOVA) showed 79 AAD children to have higher delinquency scores ($p = 0.001$) and aggressive behavior scores ($p = 0.014$) as compared to 1,650 NAD children. Multivariate analysis of covariance (MANCOVA), with age, sex of child, sex of parent, and ethnicity as covariates, confirmed the presence of independent delinquency excesses among children with alcohol dependent parents ($F = 9.23$, $df = 1,1659$, $p = 0.002$). The evidence of this study favors the hypothesis that adolescent children living with an alcohol dependent parent have more delinquency problems than other adolescents. It is of interest that we did not find similar patterns of association for the internalizing symptoms, nor for aggression, once delinquency was held constant.

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INDIVIDUAL TRAITS AND FAMILY CONTEXTS PREDICT SONS' EXTERNALIZING BEHAVIOR AND PRELIMINARY RELATIVE RISK RATIOS FOR CD AND SUD OUTCOMES

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An ontogenetic framework for elucidating the etiology of substance use disorders (SUD) requires identifying how individual traits and family contexts combine to increase risk for SUD outcomes. In this study, we examined individual traits in family context to identify processes that account for the relationship between fathers' SUD+ status and sons' externalizing behaviors. Results obtained from SUD+ (n=89) and SUD- (n= 139) families show that fathers' abusive propensities toward their sons mediated the relationship between fathers' SUD+ status and sons' externalizing behavior scale (EBS) scores 2 years later. Moreover, individual traits (e.g., temperament), family contextual variables (e.g., marital adjustment, quality of parent-offspring relationship) and deviant peer affiliations combined to accounted for 58% of the variance on sons' EBS scores. Also, High Risk Cluster (HRC) and Low Risk Cluster (LRC) memberships were derived from cluster analyses of the continuous risk factor scores that predicted sons' EBS scores. Sons classified into the HRC at age 10-12 had significantly higher cannabis and alcohol QxF scores, consequences of consumption scores, setting in which consumption takes place scores, motivation for substance abuse scores and subjective reinforcing effects scores at age 16 compared with sons classified into the LRC at age 10-12. Preliminary relative risk estimates show that sons in the HRC at age 10-12 were at greater risk for DSM-III-RCD (5.11) and SUD (4.33) outcomes at age 16 compared to sons classified in the LRC, SUD+ or SUD- groups. Moreover, when sons' EBS scores obtained at age 12-14 were included in HRC and LRC classifications, sons assigned to the HRC had substantially increased relative risk ratios of 8.12 for CD and 18.73 for SUD diagnoses at age 16. Implications for selected family-based prevention initiatives are presented.

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MATERNAL LINKAGE AMONG FEMALE ALCOHOLICS

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Subtyping studies have identified at least two types of alcoholics, those with either an early or late onset. Examination of male alcoholics has supported greater biological pre-disposition to disease among early compare one with late onset alcoholics, suggesting that this is the more heritable form. However, a few contemporary studies have been conducted among women and the influence of nurturing may have been underestimated. From a cohort of 327 alcoholics, we identified 137 with an early onset (m = 95) and 180 of late onset (m = 130). Women with parental alcoholism developed the disease earlier than men (25.5 years vs. 27.5 years, respectively; p = 0.05). Focusing on the sub-sample of females, those of early compared with late onset were more likely to have mothers who had been problem drinkers (22.3% vs. 12.2%; p = 0.05). No significant differences were found in paternal drinking between early and late onset females, or when gender among late onset alcoholics were compared (p = 0.3). These results would suggest that, like their male counterparts, women with early onset alcoholism are distinguishable from those on late onset. Additionally, having a mother who drinks raises the potential for female offspring to become alcoholics. The presentation will also provide an analysis of the relative contribution between psychosocial and heritable-factors for the early development of alcoholism in women.

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MATERNAL SMOKING AS A RISK FACTOR FOR EARLY SMOKING INITIATION

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Using prospective data, we test (1) whether exposure to maternal smoking in early childhood increases children's risk of early smoking initiation, and (2) whether prenatal exposure to maternal smoking increases children's risk of smoking beyond that, due to maternal smoking during the child's early years. A total of 801 mothers completed baseline interviews when their children were 6-7 years of age and 717 (90%) children participated at a 5-year follow-up at age 11-12. Maternal smoking status was ascertained at the baseline interview and mothers were classified as (1) prenatal smoker, defined as smoking at least two months during pregnancy (n=205); (2) current daily smoker when the child was 6-7 years of age, but not during pregnancy (n=83); and (3) non-smoker, defined as not smoking at baseline or during pregnancy (n=409). Incidence of smoking was 7.3% for children whose mothers were non-smokers compared to 15.7% for children whose mothers smoked, but not during pregnancy (OR=2.3, CI: 1.3-4.0), and 15.1% for children exposed to maternal smoking prenatally (OR=2.4, CI: 1.2-5.0). These findings did not change when social class was taken into account. Our results indicate that prenatal exposure to maternal smoking contributes no additional risk of children's smoking beyond that due to environmental exposure. These findings point to the importance of early smoking cessation programs for mothers, before their children begin school, as a preventive strategy for reducing children's risk of smoking.

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INITIATION AND PERSISTENCE OF MARIJUANA AND OTHER ILLICIT DRUG USE IN AUSTRALIAN TWINS

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Telephone interview data on measures of initiation and persistence of marijuana use and use of other illicit drugs were obtained from over 1,400 Australian twin pairs, aged 23-34. Statistical model fitting was used to test the hypothesis that different genetic factors may influence initiation versus persistence of drug use. We tested a correlated liabilities model which proposed that the liability for persistence of use was influenced by its own specific genetic and environmental factors in addition to those that also influenced initiation of use. We also tested an alternative model which proposed that the initiation and persistence of use could be represented via a single liability dimension influenced by common genetic and environmental factors, with persistent users being, on average, more extreme in their genetic liability. The results suggested that, for marijuana use, about 50% of the variance in initiation could be attributed to additive genetic factors for both men and women. The results were similar for illicit drug use in women but, in men, additive genetic factors accounted for only 17% of the variance in initiation while shared and unique environmental factors accounted for 47% and 36% of the variance, respectively. In general, there was little evidence to suggest that persistence of drug use is influenced by separate factors beyond those that also influence initiation although, in the case of male illicit drug use, environmental factors specific to persistence accounted for approximately 32% of the variance. In all cases, models proposing a single liability dimension fit the data adequately.

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TOBACCO SMOKING AS A GATEWAY TO THE WORLD OF ILLICIT DRUG USE

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Expanding initial evidence reported at last year's CPDD meeting, this report presents estimates regarding the transition from tobacco smoking to marijuana use, and from marijuana use to cocaine use. Self-report data from the 1991, 1992, 1993, and 1994 National Household Surveys on Drug Abuse (NHSDA) were analyzed using survival analysis methods. The subjects were youths and young adults 12-25 years at assessment in these nationally representative samples. Evidence from this more recent research, again, links tobacco smoking with increased risk of having an opportunity to try marijuana (adjusted Relative Hazards, aRH = 2.78, 95% CI, 2.6, 3.0, with comparable estimates obtained in the four independent replication samples), with actually using marijuana once the opportunity has occurred (aRH= 4.34; 95% CI, 3.58, 5.26). In turn, marijuana users who have smoked tobacco have increased risk of having an opportunity to try cocaine (aRH = 7.81, 95% CI, 7.15, 8.52) and to actually use cocaine once the opportunity has occurred (aRH = 19.23, 95% CI, 14.25, 25.95). This evidence highlights markers for two separate causal mechanisms that can account for 'gateway' observations about tobacco smoking as a step toward the world of illicit drug use: (1) increased tobacco-associated likelihood of exposure to an opportunity to try illicit drugs, and (2) increased likelihood of initiating illicit drug use among tobacco smokers given the opportunity to start. We speculate that current tobacco smoking prevention initiatives might reduce occurrence of marijuana use by influencing the first mechanism only.

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BUPRENORPHINE DOSE-DEPENDENT OCCUPANCY OF μ-OPIOID RECEPTORS AND CLINICAL EFFECTS IN HEROIN-DEPENDENT VOLUNTEERS

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A central principle of pharmacotherapy of opioid dependence is that the clinical efficacy of medications is directly related to μ opioid receptor (μOR) occupancy. In this study, we gathered preliminary data on CNS μOR occupancy by sublingual liquid buprenorphine (BUP) 2 mg, 16 mg and after detoxification on 0 mg under double-blind conditions, in 3 healthy opioid-dependent volunteers, and age-matched control subjects. CNS measures of μOR binding were obtained with [^{11}C]carfentanil (CFN) and PET, using a modified Logan plot model with occipital cortex as the input function, 4 hrs after the last BUP dose. Opioid withdrawal symptoms and heroin craving were rated for 3 days prior to PET in an inpatient unit. Regional μOR occupancy by BUP was dose-dependent in both cortical and subcortical regions (repeated measures ANOVA, $p < 0.05$) and ranged from 40-50% at the 2 mg dose to 80-95% at 16 mg, compared to placebo. Mu opioid receptor availability at 0, 2 and 16 mg doses also correlated positively with opioid withdrawal symptoms and heroin craving. Under placebo conditions, and compared with non-dependent subjects, opioid-dependent subjects showed increased μOR binding in several brain areas, although with considerable individual and regional variability, with regional means ranging from 14 to 70%. The present data suggest that BUP administration is associated with dose-dependent reductions in μOR availability, which arc correlated with reductions in measures of opioid withdrawal and craving. In addition, greater μOR availability is observed in opioid-dependent subjects during the placebo condition, in comparison with non-dependent control subjects.

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COMPARISON OF THE PHARMACOKINETICS (PET NEUROIMAGING WITH "C-DIPRENORPHINE) AND PHARMACODYNAMICS (HYDROMORPHONE CHALLENGE) OF METHADONE DEPENDANT INDIVIDUALS

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Currently, the best established treatment for opiate addiction is a harm reduction approach using the opiate agonist methadone as a substitute therapy. However, there are many questions about its action in terms of brain opiate receptor function. This study was designed to investigate some of these questions. We used neuroimaging techniques to investigate the relationships between receptor binding, degree of occupancy by different doses of methadone (as measured by both daily dose and blood levels of the methadone's active R-enantiomer), and tested receptor function by measuring sensitivity to opiate agonists. Patients on stable, but different, doses of methadone were investigated. Each subject was given a test of opioid tolerance using the short acting opioid agonist, hydromorphone. Imaging was done using both PET scanning and a recently developed neuroimaging technique, the Multiple Organs Coincidences Counter (MOCC) as an altemative to PET. The main advantage of the technique is that it is possible to perform multiple scans on subjects. The scans were performed using ^{11}C-labelled diprenorphine, an opiate receptor antagonist, for the measurements of receptor binding. One of the findings is that one of the objective measures (Saccadic Eye Movements) shows a significant decrease of Peak eye velocity from baseline for 10mg of hydromorphone when measured against Methadone R-Enantiomer blood levels (R^2=0.6025 $p<0.005$). Also, preliminary analysis of the PET scans seem to show that global Volume of Distribution measures are similar to naïve controls. R-enantiomer blood levels correlate significantly with oral methadone dose and subjective measures (VAS) seem to correlate with the dose of hydromorphone. Objective measures of tolerance (SEM changes) correlate significantly with oral dose and blood levels. Overall, the results from this study demonstrate that it is possible to do combined PK and PD assessments on methadone dependant individuals.

PROLONGED OCCUPANCY OF [11C] COCAINE IN ORBITOFRONTAL CORTEX OF PRIMATE BRAIN

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The dopamine transporter, expressed at high levels in striatum, is a major target of cocaine in primate brain. Accumulating *biochemical* evidence of extrastriatal targets of [^{3}H]cocaine (Kaufman and Madras, 1994, Madras *et al.,* 1997) and *behavioral* evidence that dopamine transporter "knock-out" mice retain a proclivity to self-administer cocaine (Rocha *et al.,* 1998) offer compelling reasons to investigate other brain targets of cocaine. To pursue this goal, we conducted PET imaging with [^{11}C]cocaine in living brain of three cynomolgus monkeys. Magnetic resonance imaging (MRI) validated neuroanatomical regions using T1 and T2 weighted imaging procedures. Predictably, [^{11}C]cocaine accumulated and disengaged rapidly in the caudate-putamen, with peak activity arising within 10-15 min of i.v. injection and declining thereafter. A similar pattern of rapid onset and offset was observed in cerebellum and other brain regions. In contrast, accumulation and dissociation of [^{11}C]cocaine in the orbitofrontal cortex was unique as the labeled probe accumulated within 2 min. and was retained for at least 70 min. without significant decline. Further research is needed to determine whether the radioactivity is [^{11}C]cocaine or a metabolite and whether these findings are observable in human brain. In preliminary radioreceptor assays conducted in the orbitofrontal cortex of a post-mortem human brain, [^{3}H]cocaine bound to specific targets, which also bound phenyltropane analogs with relatively high affinity. Others have reported that the orbitofrontal cortex of primate brain displays pronounced decreases in glucose utilization (^{18}FDG) during acutely administered cocaine. Conversely, in orbitofrontal cortex of human brain, increases in (^{18}FDG) are observed during withdrawal from and craving for cocaine. Based on our findings and these other reports, cocaine targets in the orbitofrontal cortex of brain merit further investigation.

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REDUCTIONS IN DOPAMINE D2 RECEPTORS FOLLOWING COCAINE EXPOSURE IN MONKEYS AS DETERMINED BY POSITRON EMISSION TOMOGRAPHY (PET)

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Previous research in humans (Volkow *et al.,* 1993) suggests that cocaine abuse can cause a down-regulation in dopamine D2 receptor number, as determined by positron emission tomography (PET). One goal of the present experiment was to study the longitudinal changes in D2 receptors as a consequence of cocaine exposure in a nonhuman primate model of cocaine abuse. Initially, experimentally-naive adult male rhesus monkeys (n=12) were scanned twice with the D2 ligand [^{18}F]fluoroclebopride (FCP). After baseline scans, the monkeys (n=8) were prepared with subcutaneous vascular access ports and trained to self-administer cocaine under a multiple fixed interval 3 min schedule of food (20 min components) and cocaine (0.2 mg/kg/inj; 60 min components) presentation. Monkeys were rescanned after 1-wk, 1-, 3-, 6-, and 9 months of cocaine exposure. Prior to cocaine, the D2 receptor binding potential was 2.62 (± .29). Following cocaine self-administration, binding potential decreased at all time points (from 8-26% reduction), and was not correlated with total cocaine intake. These results extend previous PET findings in humans by demonstrating decreases in D2 receptor binding potential after a very short (1 wk), as well as following chronic (e.g., 9 mo) cocaine exposure. In behavioral sessions, food-maintained responding was disrupted in all monkeys, with no evidence of tolerance developing to cocaine's effects. In contrast, for some monkeys, total session intake showed increasing trends with continued cocaine exposure (i.e., tolerance). In no case did tolerance (or lack of tolerance) to the effects of self-administered cocaine correlate with changes in D2 binding potential.

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S.P.E.C.T. IMAGING OF AMPHETAMINE-INDUCED DOPAMINE RELEASE IN COCAINE ABUSERS WITH ADULT A.D.H.D. COMPARED TO CONTROLS

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Adult attention-deficit hyperactivity disorder is over-represented in substance-abusing populations, including those with cocaine dependence. Converging data in the imaging literature suggest that ADHD and cocaine abuse may involve deficiencies in the dopamine (DA) system. We hypothesized that cocaine abusers with ADHD would have an underlying dysfunction in DA activity compared to healthy controls. To obtain an index of presynaptic DA terminals, single photon emission computerized tomography (SPECT), the D_2/D_3 [^{123}I]IBZM radiotracer, and a dextroamphetamine challenge were used. Four cocaine abusers with adult ADHD (2 Caucasian males and 2 African-American females) and 4 healthy controls (1 African-American and 3 Caucasian males) were studied. Individuals were evaluated for adult ADHD and cocaine dependence using the SCID for DSM-IV and a SCID-like module for child and adult ADHD symptoms. Cocaine abusers. with adult ADHD, had significantly less amphetamine-induced DA release compared to the control group (0.26 ± 0.3% versus 11.2 ± 6.3%; $p<.02$), suggesting lower activity of the DA neurons following exposure to amphetamine. Further, cocaine abusers, with ADHD, reported less subjective effects from the amphetamine challenge compared to the control group. At present, our data are preliminary and more research needs to be carried out with larger samples and additional groups, i.e., cocaine abusers without ADHD and individuals with ADHD who do not abuse cocaine, to determine if dopaminergic abnormalities are due to one or both of these disorders.

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EVIDENCE FOR LONG-TERM NEUROTOXICITY ASSOCIATED WITH METHAMPHETAMINE USE IN HUMANS: A PROTON MRS STUDY

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Methamphetamine (METH) abuse is a re-emerging epidemic worldwide. However, little biological data are available on the potential toxic effects of METH on the human brain. We performed proton magnetic resonance spectroscopy (MRS) in 25 previously METH dependent, abstinent subjects (lifetime exposure 3,640 grams; last METH use 4.25 months) and in 25 control subjects without a history of drug abuse. Compared to the control subjects, METH users showed reduced concentration of N-Acetyl (NA) compounds, a neuronal marker, in the frontal gray and white matter and the basal ganglia (approximately –10% in all 3 regions). In frontal white matter, the [NA] correlated inversely with the Log lifetime METH exposure. METH users also showed reduced creatine concentration in the frontal white matter and basal ganglia, reduced choline concentration in the basal ganglia, and reduced myo-inositol concentration (a glial marker) in the frontal gray matter and in the basal ganglia. Our findings provide the first *in vivo* evidence for long-term neuronal damage, with reduced [NA], and glial abnormalities, with reduced myo-inositol concentration, in long-term abstinent METH users. The persistence of these neurochemical abnormalities in METH users underscores the potential long-term impact of the methamphetamine epidemic on public health.

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ALTERED COGNITIVE TASK INDUCED FUNCTIONAL ACTIVATION IN COCAINE USERS

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Experienced cocaine users (n=11) and controls (n=11) completed a visuospatial working memory (VSWM) task after each of three separate films that portrayed either individuals smoking crack cocaine, outdoor nature scenes, or explicit sexual content. This task tested (a) if prolonged cocaine abuse has persistent effects on cognitive abilities, and (b) if cognitive impairments might be exacerbated by a craving state induced by the cocaine film. Cocaine users and controls have been shown to perform equally well on this task. Contiguous 7 mm saggital slices covering the entire brain were collected. Percentage signal changes corresponding to the active task and interdigitated rest periods were calculated and subjected to a 2-way (group x preceding film) ANOVA. This VSWM task produced significant areas of activation that were predominantly bilateral and included occipital, superior parietal, and frontal (premotor and pre-SMA) cortices. Comparisons revealed greater activations in cocaine users relative to controls throughout this network with the exception of the pre-SMA. This region showed a main effect for film content showing the greatest activation following the Nature film. The greater activation in users did not change as a function of the preceding movie. Consequently, this "trait-like" difference may suggest greater "effort" was required from users to perform this cognitive task, a conclusion consistent with neuroimaging experiments with normal controls that have demonstrated a link between activation magnitude and effort. Controls to determine if the activation differences may reflect vascular, rather than neurological aberration are ongoing. These results also suggest that as a complement to performance measures, long-term effects of cocaine may be observable with cognitive, task-induced activation.

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HOW SPECIFIC IS THE BRAIN SIGNATURE OF CUE-INDUCED COCAINE CRAVING?

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We have recently shown that cocaine videos triggered (appetitive) cocaine craving and differential increases in limbic (amygdala, anterior cingulate and temporal pole) rCBF (regional cerebral blood flow) in cocaine users (but not in cocaine-naive controls), as measured by PET (Positron Emission Tomography). Since limbic regions are involved in multiple motivational and affective states, we - and other labs now working in this arena - need to determine the **specificity** of the brain responses. Which of the observed brain changes are specific to appetitive craving, and which may simply reflect generalized arousal, or other features of the stimulus (its modality, its temporal characteristics) unrelated to craving *per se?* Some ***anatomical specificity*** *is* supported by the findings (ours and others) that brain changes to cocaine stimuli are regionalized, with amygdalar activation a positive finding in each study, thusfar able to examine the structure. We will be testing ***state specificity*** by imaging the response to both appetitive (sexual) and aversive videos in separate cohorts, predicting overlaps in brain activation for the appetitive (sexual) video, and some regional dissociation for the aversive one. Initial results from the sexual desire cohort (n=18, cocaine-naive controls) do suggest overlap with some of the regions (particularly anterior cingulate) activated during cocaine desire; striking overlap in deactivations by both appetitive stimuli are being further analyzed. Finally, some of the differences in findings across imaging laboratories may be due to ***stimulus-specific*** brain responses. For example, cocaine videotapes presented in intermittent or repeated clips may activate "working memory" regions (dorsolateral prefrontal cortex, DLPFC). In our lab, an extended, uninterrupted narrative video does not activate the DLPFC, though it triggers robust craving. Separating out the brain signature of the craving state from that of the craving *stimulus is* a current and critical challenge for imaging studies of cue-induced cocaine craving.

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EFFECTS OF TOBACCO SMOKING ON BRAIN BENZODIAZEPINE RECEPTORS IN SCHIZOPHRENIC PATIENTS MEASURED BY [^{123}I]IOMAZENIL SPECT

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Our objective was to assess whether smoking changes the regional cerebral central $GABA_A$/benzodiazepine receptor distribution volume (BZR-V_T-p) in schizophrenia. Twenty-five male schizophrenic patients were studied: 15 cigarette smokers (age 44 ± 10 y; 9 C, 5 AA, 1 H; 5 on atypical antipsychotics, 7 on typical antipsychotics, and 3 not on antipsychotics; amount 26 ± 12 cigarettes per day; duration of smoking 20 ± 11 years) versus 10 nonsmokers (age 38 ± 15 y; 6 C, 3 AA, 1 H; 6 on atypical antipsychotics, 2 on typical antipsychotics, and 2 not on antipsychotics). Single Photon Emission Computed Tomography (SPECT) was acquired for 36 min on the Prism 3000 camera starting 6 h after bolus injection of [^{123}I]iomazenil, using the constant infusion/sustained equilibrium method (total activity 6 mCi, bolus/infusion ratio 3.8 h). After non-uniform attenuation correction, the SPECT was co-registered with a T1-weighted MRI. Preliminary data, using Statistical Parametric Mapping with a 2 groups, I scan per subject design, and either no global normalization or proportional scaling, did not show any significant BZR-V_T-p differences in smokers versus nonsmokers. Age and antipsychotic medication did not exert any significant influence on BZR-V_T-p. Therefore, smoking does not seem to substantially affect BZR-V_T-p in schizophrenia.

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PATTERNS OF NICOTINE USE AMONG OUTPATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

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To assess current patterns of nicotine use in men and women with chronic psychotic illness, we administered measures of nicotine use and dependence, mood/psychotic symptoms, alcohol/drug use, and obtained cotinine levels. An outpatient sample of 30 cigarette smokers with schizophrenia or schizoaffective disorder had a mean age of 47.3; 50% were white, 33.3% Hispanic, and 16.7% African-American. Mean number of cigarettes smoked daily was 22.4, 63.0% smoked >1 pack/day, and 96% of smokers met DSM-IV criteria for nicotine dependence. Mean age of onset of smoking was 17.6 yrs. Of the 70.8% of patients who had made at least 1 serious (>24 hrs.) attempt to quit, 25.0% tried >5 times. With respect to readiness to quit, 20.8% report having decided to stop smoking now. A smoking-related medical problem was present in 45.8% of the sample. Pearson correlation between number of cigarettes smoked daily and negative symptoms was 0.40, significant at P=0.05. No significant correlation was found between number of cigarettes smoked daily and depressive symptoms (0.10). On multiple regression analysis, thought disorder PANSS subscale was significantly positively correlated (0.44) with cotinine level. These data point to the strong need for therapeutic interventions to support nicotine cessation attempts and abstinence maintenance in patients with chronic psychosis.

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NEURONAL ACTIVATION AND DESENSITIZATION IN THE RAT BRAIN FOLLOWING ETHANOL CONSUMPTION

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Our previous studies have identified nuclei of the rat brain that are affected by ethanol, and have shown that chronic intraperitoneal (IP) injections of ethanol desensitizes these regions to a subsequent acute ethanol treatment. Chronic IP ethanol administration does not represent the route of intake in humans and can produce detrimental side effects (i.e. ulcers) in animals. The goal to establish a model of chronic ethanol consumption such that these repercussions can be eliminated was achieved, using a liquid ethanol diet as a means of ethanol administration. Adult male Harlan Sprague-Dawley rats were randomly assigned to receive either (a) a liquid Lieber-Decarli (L-D) ethanol diet (6.4% $^{v}/v$), (b) a L-D control diet containing an isocaloric quantity of dextrin, or (c) a control diet of rat chow and water for 8 wk. After chronic exposure, the animals received an acute IP injection with either ethanol or saline. The animals were then perfused transcardially with saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer, and the brain was removed and fixed. The expression of FOS protein has been used as a neuroanatomical marker for activated nuclei. Coronal brain sections were stained immunocytochemically for FOS immunoreactivity (FOSir). In animals given a rat chow control diet, an acute IP injection of ethanol produced FOSir in the bed nucleus of the stria terminalis, hypothalamic paraventricular, supraoptic, locus coeruleus, parabrachial, and Edinger-Westphal (EW) nuclei. Following a chronic L-D ethanol diet, FOS desensitization was observed in all of these nuclei, except for the EW, following a subsequent acute IP injection of ethanol, in addition to the previously mentioned nuclei, FOSir was also induced in the globus pallidus and layer 6 of the cerebral cortex. In animals fed an ethanol diet, desensitization to acute ethanol exposure occurred. The lack of desensitization in the EW by chronic ethanol exposure is of particular significance because the EW modulates oculomotor functions. Our results show that a liquid ethanol diet, rather than an IP injection, can be used as a representative animal model in which the underlying neuronal effects of ethanol consumption can be explored.

DISCRIMINATIVE STIMULUS EFFECTS OF THE GABA UPTAKE INHIBITOR CI-966

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Depressant drugs of abuse, such as the barbiturates and benzodiazepines, have as one of their principal actions the facilitation of GABAergic inhibitory neurotransmission. On the other hand, not all GABA agonists have abuse potential and, depending on their specific cellular mechanism for enhancing GABA, many of these drugs produce a profile of acute effects that differs from that of the abused depressants. To further understand the unique pharmacology of site-selective GABAergic drugs, the discriminative stimulus effects of the GABA uptake inhibitor CI-966 were studied in rats. Rats were trained to discriminate 5.6 mg/kg U-966 from vehicle using a standard lever selection task with correct-lever responding reinforced under a FR-32 schedule of food pellet presentation. To our knowledge, this is the first report of successful drug discrimination training using a GABA uptake inhibitor. Full substitution was obtained with another GABA uptake inhibitor, NO-711. Interestingly, no substitution was obtained with either the direct $GABA_A$ agonist muscimol or $GABA_B$ agonist baclofen. Partial substitution associated with response rate decreases was obtained with diazepam, apomorphine, and phencyclidine, whereas, no substitution was obtained with pentylenetetrazol or chlorpromazine, showing the pharmacological specificity of the discrimination. Evidence is emerging that CI-966 may represent a unique class of discriminable drugs, sharing effects with another GABA uptake inhibitor but differing in varying degrees from other GABA agonists such as diazepam, muscimol, and baclofen.

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INTERACTIONS BETWEEN NEGATIVE AND POSITIVE $GABA_A$ MODULATORS: DRUG DISCRIMINATION STUDIES IN RHESUS MONKEYS TREATED CHRONICALLY WITH DIAZEPAM

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The gamma-aminobutryic acid,, ($GABA_A$) receptor complex contains several distinct receptor sites at which drugs can either facilitate or inhibit the actions of GABA. The biphasic nature of $GABA_A$ modulation as well as possible interactions among modulators that act at distinct sites on the complex are not well understood, particularly *in vivo*. The purpose of the current study was to characterize the interactions between positive modulators that act at different sites on the $GABA_A$ receptor complex and negative modulators that are presumed to vary in efficacy. Three rhesus monkeys received 5.6 mg/kg/day of diazepam (p.o.) and discriminated between 0.32 mg/kg of flumazenil (s.c.) and vehicle while responding under a fixed ratio 5 schedule of food presentation. The neutral modulator flumazenil and the negative modulators Rol5-4513 and beta-CCE dose-dependently increased responding on the flumazenil lever without modifying response rates. The rank order potency was flumazenil (ED_{50}=0.03±0.01 mg/kg)<Rol5-4513 (ED_{50}=0.10±0.02 mg/kg)<beta-CCE (ED_{50}=0.27±0.03 mg/kg). When administered 45 min prior to test sessions, a supplemental injection of 10.0 mg/kg of either diazepam or pentobarbital (s.c.) shifted the flumazenil, Rol54513 and beta-CCE dose-effect curves 3- to 10-fold to the right of the respective control curves, and 1.0 mg/kg of pregnanelone shifted the flumazenil dose-effect curve 3-fold to the right. Ketamine (1.0 mg/kg) did not attenuate the discriminative stimulus effects of flumazenil. Thus, positive modulation at different sites on the $GABA_A$ receptor complex attenuates comparably the discriminative stimulus effects of negative modulators.

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SELF-ADMINISTERED ETHANOL AS A DISCRIMINATIVE STIMULUS

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This study determined if self-administered ethanol would serve as a discriminative stimulus in rats. Twelve adult male Long-Evans rats were trained to self-administer 10% ethanol (0.1 ml deliveries) under an FR 1 schedule. Rats were allowed to self-administer 750 mg/kg ethanol during a 30 min. self-administration session. Ethanol self-administration was then double alternated with water self-administration sessions. After each SA session, the rats were placed in standard 2-lever operant chambers for 15 min and trained to respond under an FR 16 schedule of 45 mg food pellet delivery. The lever that produced food pellets was determined by whether ethanol or water had been available during the preceding self-administration session. Within 90 sessions, 10 of the 12 rats had acquired the discrimination between self-administered ethanol and water. A self-administered ethanol dose-effect curve was then completed. Self-administered ethanol doses of 750, 1,000 and 1,320 mg/kg fully substituted for the 750 mg/kg ethanol training dose. Lower self-administered ethanol doses partially substituted for the training dose. Injected i.p. ethanol doses of 750 mg/kg and higher also fully substituted for self-administered ethanol. The results indicated that ethanol's pharmacological, rather than peripheral (taste, smell, etc.) effects were primarily responsible for maintaining the discrimination between self-administered ethanol and water.

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ALCOHOL-INDUCED CONDITIONED TASTE AVERSIONS: A COMPARISON BETWEEN LEW/N AND F344/N RAT STRAINS

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Previously, we have reported that cocaine-induced taste aversions significantly differed between Lewis and Fischer rat strains (Glowa *et al.* Psychopharmacology 114:229-232, 1994). Doses of cocaine ineffective in the Fischer strain produced robust taste aversions in the Lewis strain, suggesting differential sensitivities to the aversive effects of cocaine. The present study assessed whether such differential sensitivities are specific to cocaine by examining alcohol-induced taste aversions in the Lewis and Fischer strains. Specifically, 84 Lewis and 84 Fischer rats were adapted to water restriction and then allowed limited access to a novel saccharin solution. Different groups within each strain were then injected intraperitoneally with either vehicle or various doses of alcohol (0.56 to 1.8 g/kg; Experiment 1 and 0.30 to 1.3 g/kg; Experiment 2). These pairings were repeated every fourth day for a total of four conditioning trials. For both strains (in both experiments), alcohol-induced aversions were dose dependent with the higher doses of alcohol producing greater suppression of saccharin consumption. There were no differences between strains in the minimally effective dose producing an aversion. Further, there were no significant differences between strains in the strength or rate of acquisition of aversions induced by alcohol. These data with alcohol are different from those produced by cocaine (see above), suggesting that the strain differences in cocaine-induced aversions may be a function of their relative sensitivities to cocaine.

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EFFECTS OF THE BENZODIAZEPINE-SITE LIGAND PAGOCLONE IN SQUIRREL MONKEYS

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Pagoclone, a cyclopyrrolone derivative, binds with high affinity to benzodiazepine binding sites on the $GABA_A$ receptor complex. Preliminary studies in rodents suggested that pagoclone (RP 62955) is a partial positive allosteric modulator of GABA. The present studies examined the effects of pagoclone on schedule-controlled responding in squirrel monkeys. Results were compared to those obtained previously with the cyclopyrrolone, zopiclone, and with the imidazodiazepines, midazolam, and bretazenil. Midazolam and zopiclone are putative full benzodiazepine agonist, and bretazenil is a putative partial benzodiazepine agonist. In monkeys responding under a fixed-ratio (FR) schedule of punished and non-punished food-maintained responding control response rates were 3.18±0.55 (nonpunished) and 0.08±0.08 (punished) resp/sec. Pagoclone, 0.03-1.0 mg/kg, i.m. produced dose-related anti-suppressant effects; a peak dose, 0.3 mg/kg, increased rates of punished responding to 1.27±0.71 resp/sec amd decreased rates of non-punished responding to 1.23±0.58 resp/sec. The onset of effects of pagoclone was relatively slow and often were not evident until 20 min post-injection; these effects lasted at least 90 min. Midazolam and zopiclone also produced anti-suppressant and rate-decreasing effects under this schedule, whereas bretazenil had only anti-suppressant effects. In a second group of monkeys responding under an FR schedule of stimulus-shock termination, pagoclone, midazolam, and zopiclone had rate-decreasing effects. Pretreatment with bretazenil antagonized the rate-decreasing effect of midazolam; however, pretreatment with 0.03 mg/kg pagoclone resulted in a slight leftward shift of the midazolam dose-effect curve. These data suggest that the effects of pagoclone are more similar to the effects of midazolam and zopiclone than to bretazenil in nonhuman primates.

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A DOUBLE-PEAK PHENOMENON IN THE PHARMACOKINETICS OF ALPRAZOLAM AFTER ORAL ADMINISTRATION

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The pharmacokinetics of alprazolam following i.v. and p.o. administration in rats were characterized. Alprazolam decayed biexponentially following the i.v. dose (1.25 mg/kg), but the concentration-time profiles following the oral doses (7 and 12.5 mg/kg) exhibited a double-peak phenomenon. The presence of two peaks was confirmed by statistical analysis of the serum concentration data of alprazolam, as well as by observed double peaks in the serum concentration-time profiles of the two active metabolites (α-bhydroxyalprazolam and 4-hydroxyalprazolam). An absorption model incorporating a delay site is proposed to describe the data, and the absolute oral bioavailability estimated to be about 30%. The two peaks were approximately 80 to 115 min apart, and there was a delay in the absorption of close to 80% of oral alprazolam, regardless of dose. We hypothesize that the mechanism underlying the double-peak phenomenon is due to reduction in gastric motility caused by the muscle relaxant effect of alprazolam. This hypothesis is supported by the observed longer delay in the appearance of the second peak at the higher p.o. dose. Enterohepatic recycling is precluded from being the underlying mechanism, due to the presence of double peaks after the p.o. doses, but not after the i.v. dose. This is the first reported case of double peaks for oral alprazolam, and this phenomenon has not been reported for other benzodiazepines (BZs). The double-peak phenomenon caused by the hypothesized mechanism may have important therapeutic and drug interaction implications, especially because BZs are commonly co-administered with other drugs.

FLUMAZENIL-PRECIPITATED WITHDRAWAL EFFECTS IN HEALTHY VOLUNTEERS

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Chronic use of benzodiazepines at therapeutic doses can produce physical dependence leading to a withdrawal syndrome upon cessation of use. Flumazenil, a benzodiazepine receptor antagonist, has been useful in non-humans for characterizing benzodiazepine withdrawal effects and investigating dosing parameters that affect the intensity of withdrawal effects. The present study is designed to assess the influence of the duration of agonist exposure on flumazenil-precipitated withdrawal effects in healthy volunteers. Two groups of volunteers receive either 15 mg/day diazepam, or placebo, p.o., for 28 consecutive days. During this exposure period, intravenous flumazenil challenge sessions occur after 0, 1, 7, 14, and 28 days of diazepam or placebo exposure. Flumazenil is administered in 0.2 mg/70 kg doses each minute for five minutes (total dose = 1 mg/70 kg). Blood samples are drawn before each session to determine serum levels of diazepam and nordiazepam. Subjective effects are assessed using visual analog scales, adjective ratings, and the Speilberger State-Trait Anxiety Inventory (STAI). In addition, observer ratings are conducted by research staff, and cognitive and psychomotor performances are assessed using number recall, DSST, and balance. Physiological measures include heart rate, blood pressure, respiration rate, and skin temperature. Thus far, preliminary results indicate that flumazenil-precipitated withdrawal effects occur after one week of diazepam exposure and are sustained through four weeks of diazepam exposure. Subjective effects associated with withdrawal are well correlated with diazepam serum levels.

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ANXIETY AND OTHER PREDICTORS OF SELF-MEDICATION IN ANXIOUS OUTPATIENTS

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It is commonly thought that anxious patients self-administer benzodiazepines (BZ's) for anxiety relief. However, there are questions about the extent to which positive drug reinforcement influences patterns of BZ use. Epidemiological studies have shown that BZ use by anxious patients is generally conservative. However, some patients use more BZ's than others and are, therefore, at greater risk for dependence on these drugs. The present study was designed to evaluate the relative importance of patients' intake characteristics and subjective drug responses as predictors of BZ self-administration. In particular, we were interested in knowing whether anxiety poses a risk factor for dependence by virtue of its association with patterns of use. Fifty-five M, F patients seeking treatment for generalized anxiety or panic disorder participated in 3-week Choice Procedures in which alprazolam (Alz) and placebo were available for self-medication "as needed." Initial drug sampling involved one week of each drug dispensed in color-coded capsules. During the third week, patients received both medication colors and were free to choose between them. Findings showed that 56% of the sample had an Alz preference greater than 80%. Patients consumed capsules an average of 64% of available days and took an average of 2 capsules on days of use. Results of intake regression analyses showed that drug preference (R^2=32%) was predicted by trait-like measures, while frequency (R^2=53%) and quantity (R^2=28%) of use were predicted by state anxiety and certain personality features. These findings suggest that preference represents a different dimension of self-administration behavior than frequency or quantity of use. They also suggest that state anxiety and certain personality characteristics may be risk factors for BZ dependence. Sample period anxiety and drug effect scores (i.e., like, help, relax) correlated with medication use, but did not improve prediction of frequency and quantity of use over what was achieved with the intake models alone. However, drug "helpfulness" scores did improve prediction of preference (R^2=45%).

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ORAL COMMUNICATIONS XIV

PHARMACOLOGICAL CHARACTERIZATION OF SENSITIZATION TO OPIOID ANTAGONISTS

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Acute or chronic treatment with morphine (MS) can sensitize organisms to the behavioral effects of classical opioid antagonists. These changes in the potency and/or maximal effects of antagonists probably reflect withdrawal indicative of physiological dependence. The present experiments compared the ability of compounds with a range of activities at *mu* opioid receptors to precipitate withdrawal during chronic treatment with MS. Lever pressing by rats was reinforced under FR schedules of food delivery in sessions comprised of several 5-min trials; each preceded by a 10-min time-out. Cumulative dose tests examined the potency and maximal rate-decreasing effects of compounds before, during, and after continuous infusion of saline or 1 to 20 mg/kg/day MS. These doses of MS produced tolerance to MS, methadone and etorphine, a large dose-dependent sensitization to naltrexone, and no change in potency of the putative neutral antagonist CTAP (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2). Treatment with 10 mg/kg/day MS produced tolerance to the partial agonists buprenorphine, dezocine, GPA 1657, *dl*-pentazocine, and *dl*-profadol. In contrast, 10 mg/kg/day MS produced sensitization to nalorphine and did not change the potency of nalbuphine. Increasing the dose of MS to 20 mg/kg/day produced further sensitization to nalorphine and sensitization, rather than tolerance, to nalbuphine and buprenorphine. MS doses of 10 or 20 mg/kg/day did not change the potency or maximal effect of CTAP. These variations in responsiveness to MS treatment parallel reported differences among the compounds in relative intrinsic efficacy and suggest that behavioral procedures provide a sensitive assessment of the ability of compounds with low intrinsic efficacy to produce withdrawal.

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IN VIVO CONFIRMATION OF NALTREXONE SUSTAINED RELEASE BY MICROENCAPSULATION IN POLY(D,L-LACTIDE) FOR PROLONGED DRUG ADDICTION THERAPY

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Naltrexone is an opioid antagonist which reversibly attenuates or blocks the subjective effects of opioids. Treatment of narcotic addiction disorders and alcoholism using naltrexone is greatly enhanced when medication compliance is reinforced. In order to improve treatment prognosis, therefore, a sustained-release microparticulate intramuscular depot formulation (Naltrel™) has been developed consisting of naltrexone dispersed in a biodegradable polymer matrix. The goal is to obtain sustained release of naltrexone sufficient to maintain therapeutic systemic levels for at least one month. Microencapsulation was performed using a continuous, in-line process in which an organic phase containing polymer and drug was homogenized into an aqueous surfactant solution followed by thorough washing using fresh water. Preliminary *in vitro* and *in vivo* (dog) formulation screening studies indicated that poly(D,L-lactide) (DL-PLA) and naltrexone free base were suitable candidates for further formulation development. Consequently, additional formulations were prepared in which DL-PLA molecular weight and drug loading were varied. One formulation consisting of 17% naltrexone in a low molecular weight DL-PLA displayed a small initial burst following IM administration and provided sustained plasma naltrexone concentrations of between 0.5-2.5 ng/mL for greater than 120 days. These results were highly encouraging and demonstrated the potential of developing a long-acting naltrexone depot formulation which will be confirmed in human clinical trials.

THE EFFECTS OF NALTREXONE AND ISRADIPINE ON THE BEHAVIORAL RESPONSES TO COCAINE IN HUMAN SUBJECTS

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We examined the effects of isradipine (ISR) and naltrexone (NX), each alone and in combination, on the behavioral effects of cocaine. Eight cocaine-abusing volunteers underwent up to 7 experimental sessions in which either NX (0, 50 mg, p.o.), ISR (0, 10 mg, p.o.), or NX (50 mg, p.o.) in combination with ISR (10 mg, p.o.) was administered prior to cocaine (cocaine placebo or cocaine 100 mg/70 kg, I.N.) administration, Relative to placebo, NX alone decreased cocaine-induced ratings of euphoria, ratings of good drug effects and performance on a psychomotor task, and increased cocaine's effects on ratings of dysphoria. ISR alone decreased cocaine-induced changes in systolic blood pressure and increased cocaine's effects on heart rate. Relative to placebo, NX in combination with ISR did not appear to alter cocaine-induced effects. These preliminary finding suggest that NX may be a useful agent in reducing some of the positive cocaine-induced subjective effects.

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NALTREXONE COMBINED WITH RELAPSE PREVENTION FOR THE TREATMENT OF COCAINE DEPENDENCE

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Interventions to reduce cocaine use have been pharmacological, based on hypothesized biological mechanisms of action, and psychological, based on behavioral and cognitive-behavioral theory. It is reasonable to predict that the combined effect of these two types of interventions will be greater than their independent effects. We conducted a double-blind, placebo-controlled clinical trial examining the joint action of naltrexone (NTX) in combination with relapse prevention (RP) therapy for the treatment of cocaine dependence. Participants first completed a "detoxification" phase where they abstained from cocaine use for at least five days prior to being randomly assigned to one of four combined medication (0 vs. 50 mg) by therapy (RP vs. Drug Counseling) experimental conditions for the treatment phase of the study. The 12-week outpatient treatment involved twice weekly therapy and medication clinic visits. RP techniques emphasized coping skills training, handling drug use episodes, and general lifestyle changes to maintain abstinence. Drug Counseling (DC) was non-directive and supportive. During treatment, biweekly urinalysis testing was conducted, along with weekly measurement of cocaine craving, side effects, and mood state. Short-term outcome was assessed at end-of-treatment, followed by repeated assessments over a 1-year period. Of the 85 participants, 12 (16.4%) remained abstinent (based on cocaine-negative urines) throughout treatment, with comparable rates found across the four treatment groups. A random effects regression model was used to test for group differences on percentage of cocaine-positive urines as a function of treatment. These analyses indicate a significant time by medication by therapy interaction, suggesting less cocaine use over time among subjects receiving RP-NTX than those in the other conditions. These results are consistent with the notion that substance use in dependent patients can be reduced with a combination of coping skills training and pharmacologic treatments.

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ORAL COMMUNICATIONS XV

MODULATION OF COCAINE'S DISCRIMINATIVE STIMULUS EFFECTS BY DOPAMINE D1 AGONISTS IN RHESUS MONKEYS

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The interactions between dopamine D1 agonists and cocaine have received much recent attention in the search for an effective cocaine pharmacotherapy. In general, D1 agonists classified as high-efficacy on the basis of *in vitro* functional measures have cocaine-like behavioral effects in non-human primates, while those classified as low-effficacy do not. The present study investigated, in adult male rhesus monkeys, the cocaine-like discriminative stimulus effects of high- and low-efficacy D1 agonists, and the ability of a low-efficacy D1 agonist to alter the discriminative stimulus effects of cocaine. Subjects (n=3-4) were trained to discriminate cocaine (0.2-0.3 mg/kg i.m., 10- or 15-min pretreatment) from saline under a fixed-ratio schedule of food reinforcement. The high-efficacy agonist SKF 81297 (0.01-1.0 mg/kg) fully substituted for cocaine in 2 animals (>80% cocaine-appropriate responding) and occasioned 77% cocaine-appropriate responding in the third. In contrast, the low-efficacy agonist SKF 38393 (0.3-10.0 mg/kg) occasioned <50% cocaine-appropriate responding in all subjects. When given as a pretreatment, SKF 38393 shifted the cocaine dose-response curves to the left and/or upward in 2 of 3 monkeys. Thus. SKF 38393 presented a unique profile, in that it partially substituted for cocaine but did not antagonize cocaine's discriminative stimulus effects. These results demonstrate that D1 agonists have cocaine-like discriminative stimulus effects in rhesus monkeys which are consistent with their *in vitro* efficacies.

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MODULATION OF COCAINE SELF-ADMINISTRATION BY FULL AND PARTIAL D1 AGONISTS

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Dopamine D1 agonists and partial agonists have been proposed as candidate pharmacotherapies for the treatment of cocaine addiction. The present study assessed the effects of D1 full agonists (SKF 82958, SKF 81297) and partial agonists (SKF 83959, SKF 77434) on intravenous cocaine self-administration. Squirrel monkeys were trained to respond on a second-order schedule (FI 10 min, FR 30:S) of i.v. cocaine injection. Initially, the effects of a full range of doses of self-administered cocaine and vehicle were determined in each subject. Subsequently, the effects of daily treatment with D1 agonists were determined on self-administration of doses of cocaine that maintained maximum rates of responding. All D1 agonists, regardless of efficacy, suppressed cocaine self-administration in a dose-related manner, resulting in marked reductions in response rate. Daily treatment with effective doses of SKF 83959 and SKF 77434 during re-determinations of the cocaine dose-response functions resulted in overall rightward and downward shifts of the functions. On the other hand, daily treatment with SKF 82958 and SKF 81297 produced downward shifts of the functions only. In observational studies, SKF 83959 and SKF 77434 produced dose-related decreases in overall activity along with increases in species-typical sleep postures, but did not induce catalepsy or ataxia at doses 10-33 times greater than those required to suppress cocaine self-administration. Only small changes in activity levels were observed with SKF 82958 and SKF 81297. The results show that D1 full and partial agonists are similarly effective in reducing self-administration of cocaine in monkeys, but can be distinguished on the basis of their capacity to alter the shape and position of the cocaine dose-response function and the incidence of sedative-like side effects.

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THE D3R PARTIAL AGONIST, DO897, REDUCES COCAINE SELF-ADMINISTRATION AND STIMULANT DISCRIMINATIVE EFFECTS BUT LACKS STIMULANT ACTIVITY

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DO897 (N-(4-(methoxyphenyl-2)piperazinyl-l)butyl-2)naphtamide-2; a.k.a. BP 4.897) was found to be highly selective for the dopamine D3 receptor (D3R) in binding assays and to have partial D3R agonist activity in *in vitro* mitogenesis assays using transfected NG108-15.hD3 cells. In order to characterized the *in vivo* pharmacology of this compound, DO897 was tested for its locomotor activity effects in mice (0.01-10 mg/kg i.p.), its ability to produce cocaine- and d-amphetamine-like discriminative stimulus effects in mice (.01-17 mg/kg i.p.), and for its ability to support self-administration in rhesus monkeys (0.3-30 µg/kg i.v.). DO897 dose-dependently reduced locomotor activity in mice and partially produced the d-amphetamine and cocaine discriminative stimuli evoking <20% drug lever responding of each. None of the four rhesus monkeys tested self-administered D0897. Because of this interesting pharmacological profile, DO897 was further tested (10 mg/kg i.p) in combination with d-amphetamine and cocaine in discrimination procedures, and also as a continuous co-treatment (1-560 µg/kg/h) during cocaine self-administration. The dose-response curves for both d-amphetamine and cocaine were downwardly displaced by DO897 co-treatment and did not exceed 50% levels. Self-administration of 30 µg/kg cocaine were reduced to low levels by 300 µg/kg/h i.v. DO897 in one monkey, and by 560 µg/kg/h i.v. in the other three monkeys. In some instances, food-maintained responding was also reduced by DO897. These results suggest that DO897 has a profile of activity suitable for consideration as a potential treatment for cocaine dependency disorders.

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EFFECTS OF THE LONG-ACTING MONOAMINE REUPTAKE INHIBITOR INDATRALINE ON COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS

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The utility of oral methadone for the treatment of opioid dependence suggests that a slow-onset, long-acting cocaine-like medication may be useful in the treatment of cocaine dependence. Accordingly, the present study examined the effects of indatraline on cocaine self-administration in rhesus monkeys. In initial drug discrimination experiments, indatraline (0.1-1.0 mg/kg, i.m.) dose-dependently substituted for cocaine in four rhesus monkeys trained to discriminate 0.4 mg/kg cocaine from saline. Indatraline (1.0 mg/kg) produced peak effects after 30 min. and these effects lasted up to 48 hr. In drug self-administration studies, indatraline (0.0032 0.032 mg/kg/inj) maintained low rates of responding when substituted for cocaine in three monkeys trained to respond for cocaine (0.032 mg/kg/inj) and food during multiple daily sessions of cocaine and food availability. However, chronic treatment with saline or indatraline (0.1-0.56 mg/kg/day, i.v.; 7 days; N=4) dose-dependently decreased self-administration of 0.01 mg/kg/inj cocaine. Effective doses of indatraline also decreased food maintained responding and produced signs of psychomotor toxicity (e.g. stereotypies and weight loss). Subsequent dose-effect studies (N=3) indicated that indatraline (0.32-0.56 mg/kg/day) produced a dose-dependent downward shift in the cocaine self-administration dose-effect curve (0.0032-0.1 mg/kg/inj cocaine). These findings suggest that indatraline decreases cocaine self-administration in monkeys, but only at relatively high doses that may also produce undesirable side effects.

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EFFECTS OF HYDROXYLATED ANALOGS GBR 12909 ON RESPONDING MAINTAINED UNDER MULT CHAIN FI, FR30 SCHEDULES OF FOOD, AND COCAINE PRESENTATION

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Previous studies have shown that the decanoate of a hydroxylated analog of GBR 12909 selectively decreased daily cocaine self-administration for up to 30 days. The current studies sought to extend these findings by assessing the acute effects of additional analogs for enhanced potency and/or selectivity, as compared to GBR 12909. Both stereoisomers of two analogs, hydroxylated at the alpha and beta carbons of the phenylpropyl moiety of GBR 12909, were assessed for activity under a mult chain FI 10-min, FR 30 schedule of food and cocaine delivery in 3-4 rhesus monkeys. Rates of responding and numbers of reinforcer deliveries under the FR component were used to assess selectivity, and the FI component was used to assess psychomotor stimulant effects of these drugs. Hydroxylation of the alpha position (DL754 and DL796) increased potency over GBR 12909. Hydroxylation of the beta position (LWH88 and LWH90) resulted in one isomer (LWH88) that was more potent than GBR 12909. DL754, DL796 and LWH88 generally decreased cocaine-maintained responding at doses less than those that decreased food-maintained responding. No agent increased FI responding. The ability of these compounds to selectively decrease self-administration at doses without psychomotor stimulant effects suggests that they will be effective precursors for the development of long-term, decanoate-formulated agonist treatments for cocaine abuse.

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SUSTAINED COCAINE EXPOSURE OF 12 OR 24 HOURS CAN DECREASE SELF-ADMINISTRATION AND DESIRE FOR COCAINE

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This study tested the hypothesis that cocaine could be effective as a substitution pharmacotherapy, analogous to nicotine and opiate substitution treatments. The efficacy of cocaine substitution therapy was defined as decreased cocaine self-administration and craving and/or decreased subjective effects. Seven non-dependent cocaine abusers (6 subjects completed study, I discharged prior to completion, his data not included) were administered iv deuterated cocaine (6 mg/kg or placebo) at a constant rate over 12 or 24 hours. Effects of, and craving for, cocaine were measured with probe doses of smoked cocaine (two 100 mg pipeloads) available 1 hour before and 25 hours after the start of infusions. Except for one episode of atrial tachycardia with the 12 hour infusion, infusions were generally well tolerated. When the pre-infusion smoking effects are compared with post-infusion, in 4 of 6 subjects one or both infusions decreased the number of self-administered cocaine inhalations (vs 1 of 6 subjects with placebo). Visual analog, 'desire for cocaine', decreased in all 6 subjects after one or both infusions (vs 2 of 6 with placebo). No consistent effects on cocaine craving were seen with any infusion condition. We conclude that continuous, but brief, exposures to cocaine may decrease cocaine self-administration or desire for cocaine, but that craving for cocaine is not affected.

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AMANTADINE AND PROPRANOLOL IMPROVE TREATMENT OUTCOME IN PATIENTS WITH SEVERE COCAINE WITHDRAWAL SYMPTOMS

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BACKGROUND: Severe cocaine withdrawal symptoms at treatment entry, determined by high scores on the Cocaine Selective Severity Assessment (CSSA), predict poor outcome in outpatient cocaine dependence treatment. Amantadine and propranolol may be able to reduce cocaine withdrawal symptoms and, therefore, may be more useful in patients with high baseline CSSA scores. **METHODS:** Subgroup analyses of patients with baseline CSSA scores above the 67th percentile (high CSSA) in 2 separate trials of amantadine and propranolol were conducted. Amantadine (300 mg daily) was evaluated in a 4-week, double-blind, placebo-controlled trial, including 20 high CSSA cocaine dependent patients. Propranolol (80 mg daily) was evaluated in an 8-week double-blind, placebo-controlled trial including 36 high CSSA patients. Outcome measures included treatment retention and urine toxicology screens. **RESULTS:** Among high CSSA patients in the amantadine study, amantadine treated patients submitted significantly more clean urine samples than did placebo patients (50% vs. 7%, $p < 0.05$). In the propranolol trial, treatment retention among high CSSA patients was significantly better with propranolol than placebo (73% vs. 37%, chi square = 5.2, $p = .02$). Neither amantadine nor propranolol was superior to placebo in patients with low CSSA scores. **CONCLUSIONS:** Amantadine and propranolol may be useful in the treatment of cocaine dependent patients with severe cocaine withdrawal symptoms.

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DOUBLE-BLIND PLACEBO CONTROLLED STIMULANT TRIAL FOR COCAINE DEPENDENT ADHD ADULTS

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In previous work, we have shown that approximately 1/4 of adults entering substance abuse treatment have attention deficit hyperactivity disorder (ADHD). Our pilot studies have also shown that patients with the dual diagnosis of cocaine dependence and ADHD can be safely and effectively treated with stimulant medications (e.g., pemoline or methylphenidate). The successfulness of these open trials led us to conduct an ongoing 12-week controlled clinical trial of psychomotor stimulant medications in a population of cocaine dependent adults with current ADHD. There are three treatment arms: placebo, pemoline (75 mg t.i.d.), and methylphenidate (30 mg t.i.d.). All volunteers participate in weekly substance abuse group counseling and individual cognitive-behavioral psychotherapy for problems related to ADHD. To date, 34 Intention-to-Treat (i.e., received initial dose of medication) participants have been enrolled; 12 assigned to placebo, 12 to methylphenidate, and 10 to pemoline. Preliminary results indicate greater efficacy of methylphenidate versus pemoline or placebo to reduce ADHD symptoms in these cocaine dependent patients. Despite the reduction in ADHD symptoms, rates of cocaine abstinence and treatment retention do not differ by treatment condition. Results suggest that ADHD symptom relief and cocaine abstinence are independent treatment outcomes requiring different treatment strategies.

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ORAL COMMUNICATIONS XVI

MU OPIOID RECEPTOR-MEDIATED G-PROTEIN ACTIVATION BY HEROIN METABOLITES: 6-MONOACETYLMORPHINE DISPLAYS HIGHER EFFICACY THAN MORPHINE

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This study examined whether heroin is potentially a more efficacious opiate than morphine. Stimulation of [^{35}S]GTPγS binding by heroin and its metabolites 6-monoacetylmorphine (6-MAM), morphine and morphine-6-glucuronide (M-6-G) was measured in membranes prepared from rat thalamus. The efficacy of these drugs was compared to the p-selective full agonist, DAMGO. Morphine and M-6-G were both partial agonists, producing approximately 55% of the stimulation observed with DAMGO. Interestingly, both heroin and 6-MAM were higher efficacy partial agonists than morphine ($P < 0.01$). Both of these drugs stimulated [^{35}S]GTPγS binding by about 75% of the stimulation produced by DAMGO, although 6-MAM was 20-fold more potent than heroin. HPLC analysis showed that the effect of heroin was probably due to hydrolysis to 6-MAM. The increased efficacy of 6-MAM was due to its actions at μ receptors, as determined by the following evidence. Naloxone produced a parallel rightward shift in the concentration-effect curve of 6-MAM, with a resulting K_e value of approximately 1 nM. This value is similar to that obtained for naloxone-induced reversal of DAMGO-stimulated [WS]GTPγS binding in thalamus, and is close the K_D value for naloxone binding to μ receptors. Moreover, inclusion of 1 nM of the δ antagonist naltrindole (a concentration approximately 20-times its K_D value for binding to δ receptors) did not change the potency or relative efficacy of 6-MAM. Finally, the relative efficacy values obtained with DAMGO, morphine, 6-MAM and M-6-G in membranes prepared from human μ receptor-transfected C6 glioma cells were identical to those obtained in rat thalamus. These results demonstrate that, at the G-protein level, the heroin metabolite 6-MAM is a more efficacious μ agonist than either morphine or M-6-G. This finding suggests that heroin may be a more efficacious μ agonist than morphine *in vivo,* with greater therapeutic and/or abuse potential.

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ENHANCED TYROSINE PHOSPHORYLATION OF THE DELTA OPIOID RECEPTOR (DOR) IS ASSOCIATED WITH ITS DESENSITIZATION AND INTERNALIZATION

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Chronic opiate abuse produces biochemical and cellular changes which are believed to contribute to the development of tolerance and addictive behaviors. Three separate phenomena – receptor desensitization, internalization and down-regulation – all contribute to a decrease in opioid receptor function. Desensitization is a rapid loss of agonist function, produced by an uncoupling of the receptor from its effector system and occurs closely with the internalization of the receptor into clathrin-coated endosomes. Longer periods of exposure produce a physical loss (down-regulation) of receptor binding sites from the cell surface. Both processes appear dependent on the phosphorylation of residues in the C-terminus of the opioid receptor. Protein tyrosine kinases (TYK) are among several phosphorylating enzymes that are activated by opioid agonists; however, the importance of tyrosine phosphorylation in receptor function and regulation is poorly understood. Our laboratory has focused on determining whether the DOR acts as a substrate for TYKs and whether this activity is involved in opioid receptor regulation. We have shown that the delta-specific opioid agonist DSLET increases tyrosine phosphorylation within the DOR in a time and concentration dependent manner. In addition, the presence of the TYK inhibitor, genestein, also attenuates the rapid and reversible internalization of the DOR, which occurs shortly after the desensitization of this receptor. In contrast, although the DOR remains in state of hyper-tyrosine phosphorylation for up to 120 minutes, genestein does not attenuate DOR down-regulation produced by a 24-hour exposure to DSLET. Furthermore, we have demonstrated that the activation of mitogen-activated protein kinases (MAP-K) by opioids is produced through the activity of the same tyrosine kinases responsible for the phosphorytation of the δ-opioid receptor. Finally, we have ascertained that opioid-mediated MAP-K activation is not dependent on DOR internalization, since morphine, which does not induce receptor endocytosis but does activate the receptor, produces a robust phosphorytation of the MAP kinase protein.

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CHRONIC COCAINE ADMINISTRATION DECREASES $CABA_B$ RECEPTOR STIMULATED ^{35}S-GTPγ¦S BINDING IN THE RAT VENTRAL TEGMENTAL AREA

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Results of numerous studies indicate that the inhibitory neurotransmitter γ-aminobutyric acid (GABA) modulates central dopamine (DA) systems, and that $GABA_B$ receptors may play a primary role in decreasing levels of DA activity. To determine if chronic cocaine administration alters the coupling of $GABA_B$ receptors to G-proteins in central DA systems, male F-344 rats received cocaine (15mg/kg, ip) or saline 3 times a day at 1 h intervals for 14 consecutive days. Rats were decapitated 1 h after the last injection and the substantia nigra, caudate-putamen, ventral tegmental area (VTA), nucleus accumbens, and frontal cortex were separately dissected on ice. Crude membrane preparations from individual animals were incubated for 2 hrs at 30°C in assay buffer in the presence of 0.05 nM ^{35}S-GTPγS. Basal binding was determined in the presence of GDP, agonist-stimulated binding was determined in the presence of GDP and increasing concentrations of the $GABA_B$ receptor agonist baclofen, and nonspecific binding was determined in the presence of GDP and an excess of unlabeled GTPγS. Two-way ANOVA revealed a significant decrease in $GABA_B$ receptor stimulated ^{35}S-GTPγ¦S binding in the VTA of cocaine treated rats compared to saline controls. Preliminary results from an autoradiographic study, examining 3H-GABA binding to $GABA_B$ receptors in an additional two groups of rats receiving either chronic cocaine or saline as described above, indicate no difference in binding in the VTA. These data suggest that the decrease in $GABA_B$ receptor stimulated ^{35}S-GTPγ¦S binding seen in the VTA is likely due to a functional uncoupling of the receptor from the G-protein and not to a down-regulation of $GABA_B$ receptors. Therefore, chronic cocaine administration may, in turn, impair $GABA_B$ receptor regulation of DA activity.

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COPING SKILLS AS A MEDIATOR OF TRAUMA AND DEPRESSION

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Substance dependent persons experience more traumatic events in their lives than non-dependent persons. They also experience higher levels of depression. Depression in a dependent person is, at least, partly associated with experiencing traumatic events. The causal path may be direct, or it may involve other variables. The purpose of this data analysis was to explore the influence of coping skills on the relationship between traumatic events and depression. The data set consisted of 280 male patients enrolled in a substance dependence treatment program at a mid-sized VA Medical Center. Upon intake, the patients were given the Traumatic Events Screen Inventory (TESI), the Zung Depression Scale, and the Coping Strategies Inventory (CSI). Coping skills could be either a "moderator" or a "mediator" variable in terms of the relationship between trauma and depression. It was predicted that coping skills would be a moderator variable, i.e., the same amount of trauma would produce higher levels of depression for a person with poor coping skills and lower levels of depression for a person with good coping skills. However, the data showed no evidence for coping as a moderator variable. Instead, coping skills appeared to be a mediator variable, i.e., trauma produced a deterioration in coping skills which in turn produced more depression. In this sample, trauma was correlated r = .36 with depression. Of this effect, 19% was mediated by coping skills. The remaining 81% of the effect was either due to a direct link between trauma and depression, or due to mediation by unknown variables. The current analysis lends further support to the recommendation that substance dependent persons can benefit from coping skills training.

DEPRESSION IN PREGNANT SUBSTANCE DEPENDENT WOMEN

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Depression in pregnant substance dependent women negatively impacts on the physical health of both the mother and the child. This study examined the prevalence of depression in a population of pregnant substance dependent women seeking substance abuse treatment at the comprehensive, interdisciplinary Center for Addiction and Pregnancy. Comparisons were made among different clinical assessment instruments measuring depression (Scheduled Clinical Interview for DSM-III-R (SCID), Addiction Severity Index (ASI), Beck Depression Inventory (BDI), and Minnesota Multiphasic Personality Inventory -2 (MMPI-2)). Clinical correlates, including treatment retention were also examined. The BDI was used to measure intensity of depressive symptoms in 155 women entering treatment. Women were divided into two groups, those scoring <20 on the BDI and those scoring 220. Thirty-three percent of women in the group scored ≥ 20 on the BDI. The BDI had poor-fair sensitivity and fair-good specificity for various diagnoses of depression using the SCID. T-test statistical analyses revealed that higher BDI scores correlated with younger age, with Opiate and/or Cocaine Abuse and Dependence Diagnoses on the SCID, and higher Depression T-scores on the MMPI-2. In addition, a survival rate analysis using the Wilcoxon (Gehan) statistic revealed that higher BDI scores did correlate with treatment retention at one year. Pregnant substance dependent women, especially those with moderate to severe depressive symptoms, may be more likely to stay in treatment due to their higher level of distress or some other characteristic of either the women or of the treatment program. Future studies examining depressive symptoms over time, and the impact of treatment of depressive disorders in this population are planned.

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PSYCHOPATHOLOGY AND PSYCHOSOCIAL STATUS IN SUBTYPES OF PREGNANT DRUG DEPENDENT WOMEN

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Psychiatric comorbidity is prevalent among pregnant substance dependent women and may have negative effects on their outcome for addiction treatment (Haller *et al.,* 1993; Ouimette *et al.,* 1997). Thus, a clinically useful strategy to identify those women who need psychiatric care to supplement their substance abuse treatment is needed. The current study examined the concurrent validity of drug abuser subtypes derived from cluster analysis of the self-report Minnesota Multiphasic Personality Inventory-2 (MMPI-2). The study sample consisted of 170 treatment-seeking opiate and/or cocaine dependent pregnant women aged 18 to 42 ($\underline{M}$=29.1, $\underline{SD}$=4.6). Based on k-means cluster analysis, seven of ten MMPI-2 clinical scales (hypochrondriasis, depression, hysteria, psychopathic deviate, paranoia. psychasthenia, and schizophrenia) significantly contributed to separating three clusters. The three-cluster solution based on the seven-variable model included a low symptom group ($\underline{n}$=40, 24%) with no significant elevation on any clinical scale, a moderate symptom group ($\underline{n}$=72, 42%) with only psychopathic deviate scale in the clinical range, and a high symptom group ($\underline{n}$ =58, 34%) with clinically elevated average scores on all seven scales. Thus, the clusters varied along dimensions of psychopathic deviance and Axis I psychiatric severity. Consistent with their MMPI-2 profiles of antisocial tendency, the moderate and high symptom groups were rated as having more legal and family/social problems on the Addiction Severity Index (ASI) than the low symptom group. The high symptom group was rated as more psychiatrically impaired on the ASI, was diagnosed with more lifetime depression disorders, and reported more inpatient and psychopharmacological treatments than the low and moderate symptom groups. These results show that MMPI-derived subtypes have good concurrent validity with interview measures of psychosocial and psychiatric functioning. The study findings support MMPI-2's use with pregnant drug dependent women for assessment and treatment planning.

IMPLICATIONS OF SUBSTANCE DEPENDENCE FOR SEVERE AND PERSISTENT MENTAL ILLNESS

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Substance dependence (SD) disorders are prevalent and pernicious for severe and persistently mentally ill (SMI) adults. SD disorders in SMI adults may exacerbate psychotic symptoms, hinder medication compliance, and cause crisis episodes. As part of a clinical trial, we compared 141 SD and 127 non-dependent (ND) SMI adults. We hypothesized that SD subjects would have poorer psychosocial, and drug use outcomes than ND subjects, and that the primary drug dependence disorder would moderate these effects. Subjects were recruited at discharge from an acute inpatient episode and randomly assigned to one of two case management programs. These data are results of the first 6 months of case management treatment. SD subjects reported lower levels of quality of life (p = .001), higher levels of psychological distress (p < .0001) received fewer outpatient services (Mean = 18 versus 24 visits) and were 1.85 times more likely to require a psychiatric emergency visit. The most prevalent DSM III-R SD diagnoses were alcohol (57%), cocaine (45%), stimulants (27%) and marijuana (27%). SD subjects were divided into 3 subgroups based on the prevalence of dependence diagnoses: cocaine-dependent (including those dependent on other drugs as well); one or more drugs other than cocaine, and alcohol-dependent only. Main findings revealed that cocaine-dependent subjects experienced more adverse events and more negative outcomes than ND subjects. For example, cocaine-dependent were more likely than ND subjects to have been homeless in the 6 months prior to study entry (OR, 4.7) and at 6 months follow-up (OR, 4.3) and they had significantly higher levels of psychological distress and lower levels of life satisfaction at 6 months follow-up (p <05) than ND subjects. A majority of the analyses revealed that other drug dependent and alcohol-only subjects were not significantly different than ND subjects in the domains of adverse events, drug use, and psychosocial functioning. The immediate clinical significance of these findings is that it is important for those who treat SD adults with SMI to differentiate among dependence diagnoses because cocaine-dependent patients are more likely to have more severe problems than ND patients and to require specialized interventions.

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THE ROLE OF PSYCHIATRIC DISORDERS IN PREDICTING TREATMENT OUTCOMES

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Previous research has demonstrated that psychiatric disorders are common among persons who abuse alcohol and drugs, but few studies have examined the relationship of psychiatric disorders to drug treatment outcome. We successfully re-interviewed 401 drug dependent persons (95% of the baseline in-treatment sample) and determined their drug abuse status at follow-up 12 months later. Analyses indicated that several baseline psychiatric disorders predicted worse outcomes at follow-up: Major depression predicted using a larger number of substances ($p = .009$), and having more drug dependence diagnoses ($p = .008$) and symptoms ($p = .007$). Antisocial personality disorder (ASPD) predicted using a larger number of substances ($p = .01$), but phobias predicted using a smaller number of substances ($p = .04$). Other psychiatric disorders, including alcohol dependence, were not significantly associated with drug abuse outcomes. Controlling for gender, outcomes among men were more closely associated with psychiatric status than among women. These results are unique in their assessment of persons dependent on illicit substances; and overall, we found that those with phobias had better outcomes and those with major depression or ASPD had worse outcomes.

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DRUG TREATMENT OUTCOME AND DUAL DIAGNOSES AMONG HOMELESS PERSONS

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Homeless subjects were recruited to participate in a randomized control trial of a day treatment vs. day treatment with abstinence contingencies for housing and work. The day treatment was adapted from a day hospital model and used structured goal setting in domains expected to address concerns especially relevant to those with non-psychotic psychiatric symptoms. The following analyses' purpose was to examine whether subjects who met a DSM III-R Axis I Mental Disorder diagnosis and an Axis I Substance Related Disorder diagnosis i.e., those with dual diagnoses, responded differently from those that did not meet criteria for an Axis I Substance Related Disorder only, i.e., single diagnosis. Of the 128 (90.8%) subjects who completed a DSM III-R Axis I interview at baseline, 82 (64.1%) were classified as Dual Diagnosis subjects (DD) and 46(36.0%) as Single Diagnosis (SS). Addiction Severity Index (ASI) composite scores at baseline were significantly more severe on most composite measures, including the psychiatric composite scores ($p=.0001$), validating the distinction between the dual and single diagnosis subjects. Six month follow-up ASI composite scores showed significant improvement for both SD and DD subjects in the medical, alcohol, drug, family, psychiatric, and employment domains with significance levels of at least $p<.05$ for each. Average composite score changes were between .1-.2 for each scale showing significance. There were no treatment by diagnostic group interactions and there were no significant differences between DD and SD at follow-up on the ASI composite scores. Results imply that despite the differences at baseline, both SD and DD benefit from this behavioral day treatment and show improvements in the same functional domains. Moreover, a carefully crafted treatment program for dual diagnosis patients may provide a framework for single diagnosis patients to address psychiatric issues.

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IN-VITRO AND IN-VIVO ACTION OF CANNABINOIDS

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In our continuing effort to understand the molecular basis of the neurobehavioral effects of cannabinoids, we are using multidisciplinary approaches to study cannabinoid receptor (*Cnrs*) gene expression and function. We are testing the general hypothesis that the *Cnr*, CB1 alone may not be responsible for all the myriad cannabinoid induced neurobehavioral alterations. In this study, we have used mouse *in-vivo* models of motor function and anxiety tests and *in-vitro Xenopus laevis* oocytes expression system to examine the influence of *Cnr* agonists and antagonist SR 14116A for CB1. For the *in-vivo* study, the effect of SR 141716A (0.03-3.0 mg/kg) in two mouse models of anxiety was evaluated. The ability of the antagonist to block the effect of the *Cnr* agonist, methanandamide was determined. SR 141716A induced an anxiolytic profile that was dependent on the mouse strain and test utilized. The acute anxiogenic and cataleptogenic effects of methanandamide were antagonized by pre-treatment with SR 141716A. In the voltage clamp studies we investigated the effects of anandamide on recombinant AMPA GluR3 subunit currents generated by kainic acid in oocytes expressing the AMPA glutamate receptor. We present evidence that anandamide inhibited the kainate activated currents in oocytes expressing AMPA glutamate receptor via a cannabinoid independent mechanism. WIN 55,212-2 and arachidonic acid had no significant effects on the kainate activated currents. SR 141716A had no effect on the anandamide inhibition. However, the effect of anandamide was potentiated by forskolin whereas MDL-HCl reversed the anandamide effects. These findings indicate that SR 141716A is a putative anxiolytic *in-vivo*. The *in-vitro* study indicate that anandamide's action which may involve cAMP transduction is independent of a *Cnr* mechanism.

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CANNABINOIDS MODULATE BOTH PHASIC AND TONIC NOCICEPTION IN MICE

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Cannabinoids have long been known to produce antinociception in many animal models of pain. In the present studyΔ^{9}-THC and anandamide were assessed in the formalin test of nociception. As previously reported, mice injected with formalin (1.25-5%) into the dorsal surface of a hind foot exhibited a concentration dependent increase in paw licking that occurred in two phases, a phasic component that occurred within the first 5 min and a tonic component that occurred from 20 to 40 min after the injection. Δ^{9}-THC elicited dose-related antinociceptive effects with an equivalent ED50 value of 0.3 mg/kg for both nociceptive phases. Anandamide also produced antinociception in both phases. The CB1 antagonist, SR 141716A (3 mg/kg, i.p.) antagonized the antinociceptive effects of 3 mg/kg Δ^{9}-THC. Interestingly, SR 141716A given alone significantly increased nociceptive responses compared to the vehicle controls, with mice in each respective group spending a mean ± S.E.M. of 326 ± 36 and 190 ± 43 s licking the afflicted paw. Although these results are consistent with the involvement of a tonically active endogenous cannabinoid system in tonic nociception, inverse agonistic activity or non-cannabinoid mechanisms of SR 141716A cannot be ruled out. These findings taken together suggest that cannabinoids can modulate both tonic and phasic nociception.

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EXPOSURE TO MARIJUANA SMOKE CAUSES PHYSICAL DEPENDENCE IN MICE

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Repeated administration of delta-9-THC, the major psychoactive constituent in marijuana *(Cannabis sativa),* causes dependence as demonstrated by precipitated withdrawal. Therefore, the purpose of the present study was to assess whether repeated exposure to marijuana smoke will cause dependence as evidenced by precipitated withdrawal. Acute administration of the CB1 receptor antagonist, SR141716A, precipitated withdrawal illustrated by a significant increase in paw tremors in mice given 5 daily exposures to smoke generated by burning 200 mg marijuana (3.46% delta-9-THC). Additionally, mice challenged with SR141716A following exposures to 1, 3, 5, or 10 days of marijuana smoke (200 mg leaf, once/day) showed an exposure-dependent withdrawal relationship. By day 3, animals were showing approximately 50% of the estimated Emax for paw tremors. A dose-response relationship was also found when exposing mice for 5 days to smoke from varying amounts of marijuana with an EA_{50} (Effective Amount) of 105.0 (95% C.L. of 77.1-142.9). An exposure to marijuana smoke (200 mg) following precipitation of withdrawal was insufficient to significantly attenuate the precipitated increase in paw tremors. However, an i.v. injection of 10 mg/kg delta-9-THC was sufficient to reverse the precipitated increase in paw tremors. Blood level data shows that an acute exposure to 200 mg marijuana smoke only generates delta-9-THC levels comparable to approximately a 5 mg/kg i.v. injection, possibly explaining the insignificant attenuation of withdrawal following smoke exposure. These findings demonstrate that repeated exposure to marijuana smoke induces physical dependence, as demonstrated by a precipitated increase in paw tremors.

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CANNABINOID AND D2-TYPE DOPAMINE RECEPTOR AGONISTS INTERACT TO PRODUCE PROFOUND SEDATION IN NONHUMAN PRIMATES

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Although use of both dopamine agonist medications and cannabinoid agonists is mounting, information on dopamine-cannabinoid receptor interaction in primates is scant. We investigated the effects of a CB1 cannabinoid agonist, levonantradol alone and in combination with dopamine agonists on unconditioned behaviors in cynomolgus monkeys (*Macaca fascicularis;* n=3-4). Various i.m. doses of levonantradol, a CB1 agonist, significantly decreased locomotor and general activity and promoted sedation, but did not induce rigidity. In contrast, the D3/D2 dopamine agonist quinelorane, the D2/D1 agonist pergolide or the D1 agonist SKF 81297 neither promoted sedation nor reduced motor activity. In contrast, both quinelorane and pergolide precipitated sedation and a marked loss of spontaneous activity following i.m. levonantradol at a (sub-threshold) dose that alone produced no sedation. These paradoxical findings suggest that D2 dopamine and CB1 cannabinoid receptors interact uniquely in primate brain. They also signify that cannabinoid and dopamine agonist combinations should be used with caution.

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THE GENETIC ARCHITECTURE OF SENSATION SEEKING AND MARIJUANA USE

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Sensation seeking and risk taking traits have consistently been reported as significant factors in adolescent drug use. However, although these traits highly correlate with drug use the underlying relationship between these personality factors and drug use is unknown. We assessed the genetic and environmental architecture between risk taking traits and marijuana use in adolescents (ages 13-21) who participated in the National Longitudinal Study of Adolescent Health, a school based study representative of the US general adolescent population. Two waves of data were available from 738 twin pairs (144 monozygotic male; 145 monozygotic female; 131 dizygotic male; 114 dizygotic female; 204 dizygotic opposite sex). Several items were used to assess sensation seeking and risk taking traits, such as sexual promiscuity, birth control use, seat belt use, bicycle helmet use, riding a motorcycle, risk taking attitude, and participation in dangerous dares. Structural equation modeling using the program Mx revealed that univariate heritabilities ranged from zero (birth control use) to .77 (participation in dangerous dares) for risk taking traits and was moderate for marijuana use (.31). Common environmental effects ranged from zero (participation in dangerous dares) to .71 (bicycle helmet use) and were moderate for marijuana use (.47). Bivariate analyses suggested that the genetic covariation between sensation seeking and marijuana use was negligible for some items, while other items were greatly influenced by shared genetic factors. Common environmental influences also showed variable amounts of covariation with marijuana use for each item of risk taking. These results suggest that the trait defined as risk taking is not a simple concept, but rather consists of several factors that differ in the contribution of unique genetic and environmental influences as well as in the influences shared with substance abuse.

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MARIHUANA WITHDRAWAL SYMPTOMS IN ADOLESCENTS RECEIVING TREATMENT

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It is estimated that 42% of 12th graders in the U.S. have smoked marihuana and that 4.6% smoke it on a daily basis. In addition, rates of past year dependence on marihuana are much higher in adolescence than at any other age. It is still undetermined, however, whether abstinence from marihuana results in a clinically significant withdrawal syndrome in adolescents. We have previously reported increases in irritability, anxiety, physical tension and aggressive behavior during the first week of abstinence in chronic adult marihuana smokers. The present study was conducted to investigate whether adolescents who smoke marihuana daily experience abstinence symptoms and to compare these symptoms to those seen in adult chronic marihuana users. Subjects were residents in the Substance Abuse Track of the Acute Adolescent Residential Program at McLean Hospital and met DSM-IV criteria for Cannabis Dependence. Withdrawal symptoms were assessed with a 13-item daily diary measuring changes in mood, ability to concentrate, sleep, appetite, anxiety, irritability, physical tension, physical symptoms, and desire to smoke marihuana. Data collection began on admission day and abstinence was verified by supervised daily urines. Results indicate that compared to the adult chronic marihuana users, the adolescents had significantly lower urinary THC levels, even though both groups reported similar frequency of marihuana use. In addition, the adolescent subjects experienced slight increases in irritability and anxiety peaking on days 3 and 4 of abstinence. This is in contrast to peak symptom severity occurring on days 7 and 8 of abstinence in adults. These findings suggest that chronic marihuana use is associated with some abstinence symptoms in adolescents. The role these symptoms play in relapse among adolescents needs to be identified.

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ABSTINENCE-BASED VOUCHERS INCREASE MARIJUANA ABSTINENCE DURING OUTPATIENT TREATMENT FOR MARIJUANA DEPENDENCE

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Abstinence-based vouchers have demonstrated efficacy in the treatment of cocaine dependence. The present study tested the efficacy of this behavioral intervention in the treatment of marijuana dependence. Sixty individuals seeking outpatient treatment for marijuana dependence were randomly assigned to one of three 14-week treatments: motivational enhancement (M), M plus behavioral coping skills therapy (MBT), or MBT plus abstinence-based vouchers (MBTV). The voucher program involved providing monetary-based incentives contingent on subjects submitting cannabinoid-negative urine specimens. MBTV engendered significantly greater periods of documented marijuana abstinence during treatment than the MBT and M groups. For example, 50% and 40% of MBTV patients achieved greater than 4 and 7 weeks of abstinence respectively, compared with 30% and 05% in the MBT group and 10% and 05% in the M group. In addition, a greater percentage of participants in the MBTV group compared with the MBT or M groups were abstinent at the end of treatment. No significant differences in outcome were observed between the MBT and M treatment groups. The positive effect of the abstinence-based voucher program extends the scientific evidence supporting the utility of incentive-based interventions for the treatment of substance abuse.

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ASSESSING ATTITUDES TOWARD MARIJUANA USE AMONG OPIOID MAINTENANCE PATIENTS

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Approximately 50-80% of clients in opioid maintenance programs report recent use of marijuana (Budney *et al.,* 1998). The consequence of such use on treatment outcomes is unclear. One study indicated that marijuana use can increase tendencies to relapse to heroin (Wasserman *et al.,* 1998); whereas, others have found no effect for marijuana use on treatment outcomes (Budney *et al.,* 1998 and Saxon *et al.,* 1993). The present study was designed to develop a self-report questionnaire to assess attitudes toward marijuana use among opioid maintenance patients. A 124-item inventory was developed from structured interviews with clients in opioid replacement therapy and then administered to 30 additional clients, approximately half of whom reported current use of marijuana and half of whom reported no current use. Questions about marijuana were organized along seven domains: 1) the physical effects of use, 2) the psychological effects of use, 3) the personal consequences of use, 4) the relationship of use to the use of other drugs, 5) the effects of use on drug treatment therapy, 6) putative medicinal properties, and 7) social policy issues. After discarding psychometrically inadequate items, a 59-question inventory was retained. Cronbach's alpha for the individual subscales ranged from .60 to .90, indicating adequate internal consistency. Users vs. non-users differed only on the medicinal properties subscale. Users were more likely to positively endorse the medicinal value of marijuana than non-users ($p < .04$). Future studies will assess the psychometric properties of the instrument with a larger sample and examine whether attitudes toward marijuana can be used to predict outcomes in opioid replacement therapy.

COCAINE- AND ETHANOL-INDUCED BEHAVIORAL SENSITIZATION AND REWARD: NEW EVIDENCE FOR COMMON NEURAL SUBSTRATES

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Various classes of abused substances are thought to produce a similar effect on the mesolimbic dopamine (DA) pathway, increasing DA transmission in the nucleus accumbens from DA neurons in the ventral tegmental area. In the present study, we investigated: a) if repeated administration of cocaine, ethanol or nicotine yields behavioral cross-sensitization between these agents, and b) whether the rewarding effects of cocaine and ethanol are suppressed by inhibition/ablation of the neuronal nitric oxide synthase (nNOS). Results of locomotor activity studies in Swiss Webster mice indicated that among the drugs tested, only cross-sensitization between cocaine and ethanol was observed. The sensitized response we assessed was 'drug-dependent' rather than 'context-dependent'. Both cocaine- and ethanol-induced behavioral sensitization was accompanied by a marked increase (71-108%) in striatal dopamine transporter (DAT) binding sites detected by [^{3}H]mazindol binding. The rewarding effects of cocaine and ethanol were determined by conditioned place preference (CPP) studies. Cocaine (20 mg/kg)-induced CPP in Swiss Webster mice was completely blocked by pre-treatment with the nNOS inhibitor 7-nitroindazole (7-NI; 25 mg/kg). Moreover, nNOS knockout mice did not acquire cocaine-induced CPP compared to wild-type mice. Ethanol (2.5 g/kg)induced CPP in DBA mice was also blocked by pre-treatment with 7-NI. The findings that cocaine and ethanol a) generated cross-sensitization with each other, b) caused a similar regulation of striatal DAT binding sites, and c) produced nitric oxide-dependent reward, support the hypothesis that these drugs may share common neural substrates/second messengers in evoking their rewarding effects.

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MOLECULAR MECHANISMS MEDIATING GENETIC SENSITIVITY TO COCAINE-INDUCED CONVULSIONS

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The initiation of cocaine-induced convulsions is mediated by serotonin (5-HT) neurotransmission, acting primarily at 5-HT$_2$ receptors. This effect of cocaine, however, is attenuated by cocaine binding to muscarinic sites. We found that C57BL/6J (65) mice are nearly twice as sensitive to the convulsant effects of cocaine relative to the genetically similar C57BL/6ByJ (6ByJ) mice. The present study examined whether this genetic sensitivity to cocaine convulsions is related to 5-HT and/or muscarinic mechanisms. We first compared 5-HT$_2$ receptor densities in the amygdaloid ridge, brainstem, cerebellum, frontal cortex, hippocampus, hypothalamus, midbrain, and striatum of 65 and 6ByJ mice. We then compared phosphoinositide (PI) hydrolysis turnover produced by 5-HT or the muscarinic agonist carbacol in the same brain regions as used in the receptor density studies. Overall, the density of 5-HT$_2$ receptors is higher in 6ByJ mice relative to 65 mice across all brain regions examined. A significantly higher density and 5-HT$_2$ receptor-mediated PI turnover was observed in the amygdaloid ridge, hypothalamus, and midbrain of 6ByJ mice relative to 65 mice. However, a higher muscarinic receptor-mediated PI turnover was also observed in the amygdaloid ridge, frontal cortex, and hypothalamus of 6ByJ mice relative to 63 mice. Thus, 6ByJ mice are less sensitive to the convulsant effects of cocaine, despite the fact that these mice exhibit a higher density and coupling of 5-HT$_2$ sites relative to 65 mice. We suggest that 6ByJ mice are less sensitive to cocaine-induced convulsions relative to 6J mice due to a greater involvement of muscarinic receptors, which appear to play an inhibitory role in mediating this toxic effect of cocaine.

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EXTRACELLULAR FLUID LEVELS OF DOPAMINE IN THE VENTRAL PALLIDUM DURING AND THE EFFECTS OF 6-OHDA LESIONS ON COCAINE, HEROIN, AND SPEEDBALL SELF-ADMINISTRATION

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The brain mechanisms relevant to drug self-administration have been subject to intensive investigation during the last decade. Although much attention has focused on the role of dopaminergic innervations of the nucleus accumbens (NA), recent experiments suggest that dopaminergic innervations of the ventral palladium (VP) may be important in the processes underlying rat cocaine self-administration. The purpose of the following experiments was to detennine the extent to which dopaminergic innervations of the VP are important in the self-administration of heroin and cocaine/heroin combinations (speedball), as well as cocaine. Rats were implanted with intravenous catheters and bilateral stainless-steel guide cannulas and allowed to self-administer three different doses of cocaine or heroin, or speedball, in each daily session. Microdialysis probes were inserted into the guides 15 hrs prior to selected sessions and extracellular fluid was collected every 10 min for 1 hr preceding sessions, during the session, and for 90 minpost-session and analyzed for dopamine (DA) concentration using HPLC. Subsequently, 6-OHDA lesions of the VP were produced by injection of 4.0 µg of 6-OHDA. A sham treated group received infusions of the vehicle. VP DA elevated rats self-administering cocaine but were highest in the rats self-administering speedball. DA was not elevated in rats self-administering heroin alone. Sham-lesioned animals showed only small, transitory, decreases in drug intake. 6-OHDA lesions significantly attenuated cocaine and speedball self-administration while similar lesions have no effect on heroin self-administration or responding maintained by food presentation. DA innervations of the VP may have a significant role in the self-administration of cocaine and speedball but not heroin.

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LATE EMBRYONIC COCAINE (COC) EXPOSURE SUPPRESSES LIPOPOLYSACCHARIDE (LPS)-INDUCED FEVER IN THE YOUNG CHICK: INVOLVEMENT OF $5HT_2$ RECEPTORS

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Prenatal exposure to abused drugs, such as COC, may interfere with coordinated multisystem responses which have survival value. One such beneficial response is fever following exposure to pathogens or pathogen products. This study determined if prenatal COC alters postnatal fever response to LPS and if 5-HT_2 receptors are involved. Eggs were injected on embryonic day 18 (E18) with COC (5 equal doses, total=60 mg/kg egg, 1.5 h apart; n=57) or saline (n=56). E18 COC injected, thusly, did not affect hatchability nor hatch weight. On day 4 (D4) and D24 chicks (n=7-8) were injected with saline or LPS and temperature measured every 2 h for 10 h. A significant Postnatal treatment x Post-injection time interaction was found at D4 ($F_{4,96}$=3.01, $p<0.03$) and D24 ($F_{4,88}$=9.97, $p<0.0001$). E18 COC did not affect temperature of postnatal saline-treated chicks, but E18 COC-treated chicks had a 70% reduction in the peak fever response to LPS on both days ($p<0.05$ vs. controls). In prior studies, we blocked adverse outcomes of prenatal COC by pretreatment with the 5-HT_2 antagonist ritanserin (RIT). On E17 we treated with 0, 0.3, 0.9, or 2.7 mg RIT/kg egg prior to E18 injections (n=55-61 per group). RIT alone did not effect hatching measures or temperature in D4 or D24 saline- or LPS-treated chicks. However, 0.9 and 2.7 mg RIT/kg on E17 attenuated the reduced peak LPS-fever response induced by E18 COC; RIT + COC groups did not differ from controls. Thus, prenatal COC exposure may adversely affect a neonate's ability to mount an adaptive fever response, increasing risk for negative disease outcome. 5-HT_2 receptors may mediate this effect and antagonists may be useful in a high risk pregnant cohort.

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CHANGES IN BETA-ENDORPHIN (ß-E) RELEASED FROM THE PREOPTIC ANTERIOR HYPOTHALAMUS (POAH) OF RATS DURING CHRONIC MORPHINE ADMINISTRATION

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Tolerance has been reported to body temperature (Tb) effects of morphine (MOR), a prototypic mu-opioid receptor agonist. Acute low doses of MOR given peripherally and centrally produce hyperthermia in rats, but the same dose causes less of an increase in Tb response in rats treated chronically with MOR. We have demonstrated that mu-opioid receptor agonists given centrally induce hyperthermia and increase ß-E release from the POAH. In the present study, we investigated whether ß-E release from this region changed during chronic peripheral MOR administration. MOR or saline was given to male S-D rats by a s.c. implanted osmotic pump at 2.5 mg/kg/h for 7 days. Microdialysis samples were collected from the POACH of freely moving rats every 60 min for 4 h each day during days I, 2, 4 and 7, and then analyzed for ß-E by radioimmunoassay. Release of ß-E in chronic MOR-treated rats was increased 7-fold at day 4 and 2.5-fold at day 7, compared with the baseline of 18 pg/fraction. ß-E release in rats treated with saline was increased 1.5-fold at day 4 and 0.4-fold at day 7, with the baseline of 13 pg/fraction. Withdrawal signs were observed after s.c. injection of naloxone (1 mg/kg) in the chronic MOR group after 7 days, but not in the saline group. At day 7, a MOR injection (5 mg/kg, s.c.) induced 1.8 °C Tb increase in saline group, but only 0.6 °C increase in MOR group. These results indicate that increased R-E release in the POAH may contribute to tolerance to the MOR Tb effect resulting from desensitization of the mu-receptors.

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EXPRESSION OF GLIAL CELL DERIVED NEUROTROPHIC FACTOR MRNA IN SPINAL CORD, STEM AND CORTEX DURING MORPHINE WITHDRAWAL IN RATS

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The recent studies have demonstrated that certain neurotrophic factors such as brain-derived neurotrophic factors and related neurotrophins can modify opiate action in the mesolimbic dopamine system. Glial cell derived neurotrophic factor (GDNF) has been shown to protect dopaminergic neurons from natural death and neurotoxicant induced cell lesions. The present study was initiated to observe the expression of GDNF gene in spinal cord, stem and cortex during morphine dependence and withdrawal in rats. The level of GDNF mRNA was assayed by reverse transcription polymerase chain reaction (RT-PCR) with the actin mRNA as an internal control. The basic expressions of GDBF mRNA in spinal cord, stem and cortex were lower in normal adult rats, the levels of GDNF mRNA in spinal cord and stem were decreased, and GDNF mRNA level in cortex was slightly increased during morphine dependence. While the GDNF mRNA levels in spinal cord, stem and cortex were increased significantly at 1 hour and at peak at 2 hour after injection of naloxone during morphine withdrawal. The administration with L-N-nitric arginine methylester, an inhibitor of nitric oxide synthase, the GDNF mRNA levels in spinal cord and stem were not different from those of the morphine withdrawal animals, but the GDNF mRNA level in cortex decreased compared with those of morphine withdrawal animals. The GDNF mRNA levels were not changed in each group. Therefore, the continuous expressions of GDNF mRNA were increased during morphine withdrawal which may be account for the neuroadaptation associated with the morphine chronic use.

THE ABUSED INHALANT, ISOBUTYL NITRITE, IMPAIRS CELL-MEDIATED IMMUNITY, PROBABLY BY INHIBITING MACROPHAGE SIGNAL TRANSDUCTION

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Nitrite inhalants are widely abused by male homosexuals. Epidemiological studies have identified nitrite inhalant abuse as a risk factor for HIV seropositivity and for Kaposi's sarcoma. Nitrite inhalants could act as a risk factor by reducing host resistance to viral replication or tumor growth. Using a mouse model, we have shown that inhaled isobutyl nitrite severely depressed immunity, including macrophage function. A syngeneic tumor grew 4-fold faster in mice exposed to abuser levels of inhaled isobutyl nitrite. The tumoricidal activity of peritoneal macrophages from mice exposed the inhalant was reduced by 40%, which corresponded to a 30% reduction in inducible nitric oxide (iNO). The production of iNO depends upon the enzyme, iNO synthase, the synthesis of which is regulated by the nuclear binding factor, NF-kB. Macrophages from mice exposed to isobutyl nitrite had a 40% reduction in the nuclear translocation of NF-kB. This was not related to altered phosphorylation of the NF-kB inhibitor, IkB-alpha, but may be related to reduced proteasome function.

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ORAL COMMUNICATIONS XX

ACUTE EFFECTS OF D-AMPHETAMINE DURING THE EARLY AND LATE FOLLICULAR PHASES OF THE MENSTRUAL CYCLE

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Stimulant drugs such as amphetamine and cocaine are used by a growing percentage of women. However, to date, few studies have investigated variables that influence responses to stimulant drugs in women. Recently, it has been shown that the ovarian hormone estrogen interacts directly with specific neurotransmitter systems in the central nervous system, including the dopamine system which also mediates the effects of stimulant drugs. For example, estrogen facilitates the release of dopamine, and also increases the neurochemical and behavioral responses to amphetamine in rats. Furthermore, our laboratory has recently demonstrated that the stimulating and euphoric effects of amphetamine in normal healthy women are greater during the follicular phase than during the mid-luteal phase, and that these effects are associated with estrogen level during the follicular phase. The present study was designed to determine whether the subjective effects of amphetamine are greater during the late follicular phase, when estrogen levels are high, than during the early follicular phase, when estrogen levels are low. Nineteen healthy women participated in a 4-session, within-subject design, in which they received 15 mg amphetamine and placebo orally at the menses and pre-ovulatory phases of the menstrual cycle. Dependent measures included self-report questionnaires, physiological measures, and plasma hormone levels. At both the menses and pre-ovulatory phases amphetamine increased subjects' ratings of feeling and liking the drug effects. However, women report increased ratings of unpleasant stimulantion (e.g., restlessness, anxiety, etc) during the late follicular phase than during the early follicular phase after amphetamine. These results suggest that there are interactions between estrogen and responses to amphetamine.

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INDIVIDUAL DIFFERENCES IN REACTIVITY TO A NOVEL ENVIRONMENT IN PREDICTING EFFECTS OF &AMPHETAMINE

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Individual differences in the reinforcing and behavioral-activating effects of *d*-amphetamine (AMPH) have been predicted in animals based on level of locomotor responding in a novel environment. In an analogous assessment of healthy young adults (not drug abusers), we are measuring wrist motor activity levels (automated recording device) for 2 hrs in a novel recreational environment (in the absence of drug) to characterize individual differences in reactivity and relating these to differences to subsequent AMPH (5-20 mg)-induced motor activity, acoustic probe-startle eyeblink reflex, prepulse inhibition (PPI) of the startle reflex and subjective effects measures. Similar to previous animal studies, a median-split was used to classify participants as High Responders (HR; n=7) or Low Responders (LR; n=7) in the novel setting. Preliminary results suggest that HR exhibit significantly greater activity levels in a novel environment compared to LR and that activity levels following AMPH and placebo were significantly greater in HR compared to LR. Peak acoustic startle eyeblink reflexes on probe-alone trials (no prepulse presentation) were significantly greater in HR compared to LR under both AMPH and placebo conditions. Conversely, prepulse inhibition of the acoustic startle reflex was significantly less in HR compared to LR following AMPH and placebo. In addition to typical AMPH dose-dependent subjective effects, LR report significantly more negative subjective effects (e.g., "Irritable") compared to HR. Finally, we are exploring individual differences in AMPH reinforcing effects as a function of motor activity in the novel environment to determine whether previous animal data generalize across species. Overall, these preliminary results suggest that individuals can be classified as HR or LR with regard to motor activity in a novel environment and that activity levels in a novel environment predict subsequent levels of motor activity, acoustic startle reflex and prepulse inhibition responding, and reports of negative subjective effects following AMPH.

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ISRADIPINE DOSES NOT ALTER D-METHAMPHETAMINE-INDUCED HUNGER STATE IN HUMANS

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We studied the effects of isradipine (0.12 mg/kg orally), an L-type calcium channel blocker, on d-methamphetamine-induced changes in somatic ('I feel hungry') and psychological ('I feel a strong urge to eat') perceptions of hunger state using a placebo-controlled, double-blind, Latin Square, cross-over design in 18 healthy male and female volunteers. D-methamphetamine (0.21 and 0.42 mg/kg orally) significantly reduced subjective ratings of 'I feel hungry' ($F = 7.08$, $p = 0.02$) and 'I feel a strong urge to eat' ($F = 8.91$, $p = 0.0008$), presumably by increasing monaminergic turnover. Specifically, effects on hunger are hypothesized to be primarily mediated by norepinephrine, and to a much lesser extent, dopamine. Isradipine, an inhibitor of dopamine release, had no significant effect on either 'I feel hungry' ($F = 0.53$, $p = 0.97$) or "I feel a strong urge to eat' ($F = 1.37$, $p = 0.1$). In addition, isradipine pretreatment did not significantly alter d-methamphetamine's anorexic effects ('I feel hungry' - $F = 1.63$, p - 0.21, and 'I feel a strong urge to eat' - $F = 0.88$, $p = 0.53$). These results suggest that isradipine may, therefore, not significantly modify the control on hunger state in humans.

BEHAVIORAL AND SUBJECTIVE EFFECTS OF METHAMPHETAMINE ADMINISTERED TO HUMANS IN A RESIDENTIAL LABORATORY

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The effects of oral methamphetamine (10 and 20 mg) were investigated in 7 healthy research volunteers (4F, 3M). Participants lived in a residential laboratory for 15 days, where their daily routines consisted of completing 5 psychomotor tasks during daytime hours (0900-1700) and engaging in private or social recreation activities in the evening (1700-2330). Subjective effects were assessed 10 times/day. Food was available *ad libitum* between 0815 and 2330. Study medications (placebo and methamphetamine) were administered twice daily (1000 and 1800). Participants received methamphetamine on days 4-6 and 10-12. Placebo was administered on all other study days. The order of methamphetamine dosing was counterbalanced across participants and each dose was administered for three consecutive days. Methamphetamine, relative to placebo, increased ratings of "High," "Stimulated," and "Good Drug Effect" on the first day of administration, but by the third day ratings decreased to baseline levels. Ratings of "Trouble Sleeping" and "Bad Drug Effects" were significantly higher on the third day of methamphetamine administration compared to the first day of administration. Methamphetamine had little effect on performance. These data suggest that the pattern of methamphetamine's acute subjective effects are altered with chronic administration such that "positive" effects are decreased and "negative" effects are increased over time.

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ORAL ADMINISTRATION OF THE SUBSTITUTED PHENETHYLAMINE MDMA HAS CARDIOVASCULAR EFFECTS SIMILAR TO DOBUTAMINE 20 µG/KG/MIN

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Despite widespread nonmedical use and case reports of medical complications, the cardiovascular psychopharmacology of the substituted phenethylamine MDMA has not been systematically investigated in humans. Cardiac effects were measured using quantitative two-dimensional echocardiography 1 hour following two oral doses of MDMA (0.5 and 1.5 mg/kg) or placebo in 8 healthy MDMA users. The cardiovascular response to oral MDMA was compared to the effects of the sympathomimetic beta agonist dobutamine (5, 20, and 40 µg/kg/min) administered iv using a standard clinical protocol at least 1 week before MDMA. MDMA produced dose-dependent increases in cardiac output, ejection fraction, and heart rate qualitatively similar to dobutamine 20 µg/kg/min. MDMA did not produce any wall motion abnormalities or apparent cardiotoxicity. We conclude that oral doses of 0.5 to 1.5 mg/kg of MDMA have modest cardiostimulatory effects comparable to 20 µg/kg/min of dobutamine.

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SUBJECTIVE RESPONSES TO MDMA AND mCPP--A HUMAN DOSE RUN-UP STUDY

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3,4-Methylenedioxymethamphetamine (MDMA) is a widely used drug of abuse. The psychoactive effects of MDMA have been attributed to its actions on 5-HT systems as well as DA systems. In animals, MDMA has been shown to share discriminative stimulus and reinforcing effects with amphetamine as well as fenfluramine. In addition, humans have reported that MDMA products hallucinogenic-like effects but few controlled laboratory studies have examined a complete profile of subjective effects in human volunteers in comparison to either amphetamine or fenfluramine. In order to select an optimal dose of MDMA for such studies, and as well, to determine whether metachlorophenylpiperazine (mCPP), a 5-HT releaser and semi-selective 5-HT agonist is a possible laboratory substitute for fenfluramine, two dose run-up studies were conducted. After giving informed consent, experienced MDMA user volunteers participate in a three-session experiment. During the first two 6-hour sessions, subjects receive either MDMA (75 mg/70 kg; 110 mg/70 kg; 145 mg/70 kg; or 175 mg/70 kg), mCPP (I 7.5 mg/70 kg; 35 mg/70 kg; or 52.5 mg/70 kg) or placebo under double-blind conditions in a balanced order. The third session is a safety evaluation one-week following the second laboratory session. At baseline and hourly, the following parameters are obtained: heart rate and blood pressure, POMS, ARCI, visual analogue scales, and the Hallucinogen Rating Scale. Preliminary analyses indicate that MDMA produces a distinct pattern of subjective effects as well as increases in cardiovascular indices. To date, mCPP has produced few consistent effects across subjects.

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MDMA PHARMACOKINETICS AND PHYSIOLOGICAL AND SUBJECTIVE EFFECTS IN HUMANS

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The purpose of this study was to describe the pharmacokinetics of 3,4-methylenedioxymethamphetamine (MDMA) and its physiological and subjective effects. Eight volunteers experienced with the use of MDMA each received either placebo, low dose (0.5 mg/kg) MDMA, or moderate dose (1.5 mg/kg) MDMA in a double-blind, crossover study. The moderate dose (but not the low dose) MDMA produced statistically significant increases in systolic and diastolic blood pressure, heart rate, and rate pressure product when compared to the placebo condition, comparable to those produced by stimulants. Mean peak increases in heart rate, systolic, and diastolic blood pressure were 26 bpm, 20 mmHg, and 13 mmHg, respectively, for the moderate dose. Peak physiological values for the moderate dose occurred 1 hour (heart rate) to 2.5 hours (diastolic blood pressure) after dosing. The moderate dose MDMA produced a number of significant subjective effects, including those associated with the use of stimulants and those associated with the use of LSD. Our moderate dose was thought to be comparable to that typically used by most of our participants and produced peak subjective effects at 2 hours after dosing. In this condition, global intoxication rating rose from 0 to a peak of 52 on a 100 point rating scale. Pharmacokinetics and cortisol responses are described.

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MDMA AND ALCOHOL INTERACTIONS IN HUMANS: A DOSE-FINDING PILOT STUDY

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3,4-Methylenedioxymethamphetamine (MDMA) is a synthetic amphetamine derivative commonly abused by young people. Epidemiological data in Spain show that MDMA is usually consumed simultaneously with other drugs, as alcohol and cannabis. There are no experimental data of the pharmacological interactions of MDMA and alcohol in humans and its possible implications in terms of road safety. This pilot study was designed to obtain preliminary data on the interactions between MDMA and alcohol, and to determine the doses to be used in future investigations. Eight healthy male recreational users of MDMA participated in two or four different experimental sessions. They received different single oral doses of MDMA (75, 100 mg), alcohol (0.5, 0.8 g/kg), the combination or placebo. Drugs were administered double-blind, double-dummy and randomized (lower doses were allocated before higher doses for safety reasons). Study variables included: vital signs (blood pressure, heart rate, temperature, pupil diameter), psychomotor performance (reaction time, DSST, Maddox-wing), and subjective effects (visual analog scales, ARCI-short form). When administered in combination, alcohol seemed to increase the effects of MDMA on heart rate. MDMA did not reverse the alcohol effects on psychomotor performance. The results of subjective questionnaires seemed to indicate that MDMA and alcohol combination induced greater scores in pleasurable-related scales (ARCI-MBG, "good effects", "liking"). Moreover, a reduction in alcohol-induced sedation was produced by the combination. A definitive study including more subjects may confirm these finding and determine if the combination could have a higher abuse liability than MDMA or alcohol alone.

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COGNITIVE CORRELATES OF CHRONIC METHAMPHETAMINE USE

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The most effective treatments available for stimulant abuse are psychosocial interventions. These treatments rely on many of the same cognitive skills that have been found to be impaired in methamphetamine (MA) abusers (Simon *et al.* under review). This project is designed to evaluate the duration of these deficits. Twenty-two MA abusers in treatment and a comparison group of 22 participants, who had never used drugs, were given a battery of tests designed to tap the cognitive functions necessary to benefit from cognitive treatment. Participants were tested at baseline, then after three months, and six months. Weekly urine samples were obtained and urine samples were collected at each testing. Deficits were found at baseline for tests involving memory, perceptual speed, manipulation of information, and the ability to ignore irrelevant information. The MA group's performance on perceptual speed and the ability to ignore irrelevant information was within the normal range by three months. Their ability to manipulate information and to recall and recognize pictures was within the normal range at six months. Word recall and recognition returned to normal limits after six months of abstinence. These findings have implications for the treatment of MA, and definitely suggest that strategies known to mediate deficits in learning and memory should be utilized.

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STABILITY AND FACTOR STRUCTURE OF NEO-PI-R SCORES OF OPIOID DEPENDENT PATIENTS

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There is considerable interest in the measurement of personality traits of drug abusers. This interest raises important questions about the reliability of trait measures in drug abusers entering treatment. The purpose of the present study was to examine the short-term retest reliability and factor structure of the NEO-Personality Inventory-Revised (NEO-PI-R) in opioid dependent, treatment-seeking patients. The NEO-PI-R is a 240-item empirically developed measure of the Five Factor Model of personality (Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness). Data are presented from 239 active drug-using participants admitted to a drug abuse treatment-research program in Baltimore. Participants completed the NEO-PI-R at intake and again four months later. Results yielded moderate to high indices of reliability for all NEO-PI-R factor and facet scores. Retest correlation coefficients ranged from .68 to .74 for the five factor scores. For 26 of 30 facet scales, retest correlation coefficients ranged .53 to .72. The hypothesized five factor structure of NEO-PI-R was replicated using factor analysis with a Procrustes rotation solution. Congruence coefficients for 28 of the 30 facet scales were significant demonstrating a very good fit with the predicted factor structure. The results show good short-term stability and factor structure of the NEO-PI-R in patients seeking drug abuse treatment indicating its potential utility in treatment outcome research.

ANTISOCIAL PERSONALITY DISORDER, AIDS RISK BEHAVIORS AND OUTCOME DURING BUPRENORPHINE-NALOXONE TABLET AND METHADONE MAINTENANCE TREATMENT

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Substance dependent adults are nearly 16 times more likely to be diagnosed with Antisocial Personality Disorder (ASPD) than the general population. However, recent work has suggested that a subtype of ASPD that does not require the presence of Conduct Disorder (CD) would expand this number significantly. This study examined 101 opioid-dependent outpatients diagnosed with either ASPD, Adult Antisocial Behavior Only (i.e., no CD) (AABO), or no ASPD and the relationship of their diagnosis to HIV risk behaviors, treatment outcomes, and addiction severity. ASPD criteria were assessed using a structured interview during the second week of participation in a controlled 118 day trial comparing the efficacy of the buprenorphine-naloxone tablet to methadone for opioid maintenance treatment. Of the 101 patients, 61% (62/101) were diagnosed with ASPD, 34% (34/101) met criteria for AABO, and 5% had no diagnosis. Patients with ASPD had significantly more antisocial behaviors as measured by the Diagnostic Interview Schedule ($x = 7.5 \pm .17$) than those receiving an AABO diagnosis ($x = 6.6 \pm .28$). These two groups did not differ in days of treatment completed, number of DSM-IV criteria met, number of opioid positive urine samples provided, self-reported opioid use in the 30 days preceding intake, Addiction Severity Index composite scores, or on the number of HIV risk behaviors reported. Thus, the presence of an average of one additional antisocial behavioral symptom did not measurably influence opioid treatment outcomes or HIV risk behaviors. Overall, the similar treatment performances amongst ASPD and AABO opioid users suggests that a early onset or late onset specifier of ASPD may be diagnostically useful and facilitate treatment planning focusing on antisocial behaviors.

ASPD AND DRUG TREATMENT ENTRY AMONG STREET-RECRUITED INJECTION OPIATE USERS

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The DSM-IV defines Antisocial Personality Disorder (ASPD) as a pervasive pattern of disregard for and violation of the rights of others. ASPD requires a diagnosis of Conduct Disorder occurring prior to age 15 and, after age 15, at least three of the following symptoms: aggressive, unsafe, unlawful, deceitful, impulsive, irresponsible and lacking remorse. Four hundred fifty-three opiate injection drug users (IDUs) were recruited through street outreach in Denver, CO. They averaged 18 years of drug use, a median of 10 lifetime arrests and more than a third were homeless. Seventy-seven percent had ASPD, with an average of five symptoms. All subjects were offered drug treatment incentives (immediate intake, transportation and no intake fee) and half were given a coupon for 90 days of free drug treatment. Among participants with ASPD, twice as many entered when it was free (42%), compared to when it was not free (19%). This study showed evidence of an extremely high prevalence of ASPD in this population. Free treatment was an effective motivator for IDU with ASPD to enter treatment; however, further research into treatment outcomes is needed to determine the effectiveness of free treatment for IDUs with ASPD.

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EFFECTS OF ETHANOL AND AMPHETAMINE ON A MOTOR INHIBITION TASK IN HUMANS: A MEASURE OF IMPULSIVITY?

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Drugs of abuse may increase impulsive behavior. One form of impulsive behavior, which can be measured using the Stop Task (Logan, 1981), involves impaired ability to inhibit responses. Individuals who are highly impulsive (e.g., ADHD children and adults high on personality measures of impulsivity) perform poorly on this task. We used the task to assess the acute effects of d-amphetamine (AMP; 10 and 20 mg; N=20) and ethanol (ETH; 0.2 - 0.8 g/kg; N=17) on impulsive behavior in healthy volunteers. The stop task assesses the time to make a prepotent response (Go RT) and the time it takes to inhibit this response (Stop RT). Participants press a key (the go response) as quickly as possible in response to a visual stimulus (Go RT). On some trials, the visual stimulus is followed by a tone, which signals the participant to stop execution of the go response. The delay between presentation of the go and stop signal is adjusted until the participant succeeds in inhibiting the response on 50% of trials, and the time it takes the participant to inhibit the prepotent go response (Stop RT) can be inferred. Go and Stop RT times vary independently of each other. In this study, ETH increased Stop RT without affecting Go RT, extending previous reports that ETH impairs response inhibition. AMP did not significantly affect either Go or Stop RTs in the group as a whole (N=20). However, in participants with slow Stop RTs (determined by a median split) AMP decreased Stop RT without changing Go RT. The AMP results are consistent with the known ability of AMP to improve sub-asymptotic performance, and with its effects in children with ADHD. The findings suggest that ETH, but not AMP, increases impulsive behavior.

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FUNCTIONAL AND DYSFUNCTIONAL IMPULSIVITY: CORRELATIONS WITH DRUG TREATMENT OUTCOME AND PATIENT CHARACTERISTICS

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The lack of impulse control may play a role in drug use. Self-reports of impulsivity have been shown to correlate positively with drug use (Patton, *et al.,* 1995). Self-reported impulsivity also discriminated subjects with and without drug use histories (Allen, *et al.,* 1998). Reductions in cocaine use in a trial of methylphenidate (Levin *et al., 1998)* were concomitant with reductions in self-reports of impulsivity. The present study further investigates the relationship between impulsivity and drug use in an outpatient treatment setting. Self-reports of impulsivity were gathered using the Dickman Impulsivity inventory (Dickman, 1990). It is a 46 item questionnaire from which functional and dysfunctional impulsivity scales are scored. The Dickman Inventory questionnaire was administered to 153 females and 365 males as part of a standard intake procedure for cocaine medication treatment trials. Other data collected at intake, used in these analyses, included: demographic information, items from the ASI, and drug taking history information. Outcome data included: study completion status, retention length, proportion cocaine positive urine screens, proportion of missed urine screens, and missed medication sessions. Psychometric properties of both derived scales were adequate, Cronbach's alpha=.69 and .80 for functional and dysfunctional scales, respectively. Males and females differed in their scores on both scales. The pattern of correlations, with patient characteristics and outcome data, was different for functional and dysfunctional scales as a function of gender. Further analyses comparing subjects who scored in the upper and lower quartiles show gender differences in some correlations of impulsivity and drug use measures.

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CURRENT CIGARETTE SMOKERS ARE MORE IMPULSIVE THAN NEVER AND EX-SMOKERS

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The understanding of drug abuse may benefit from the study of the impulsivity that frequently characterizes drug dependence. The present experiment examined delay discounting in 23 current, 22 never, and 21 ex-smokers of cigarettes with matched demographic characteristics. The subjective value of delayed hypothetical monetary rewards was determined in a psychophysical titration procedure. Participants indicated their choice of immediate and delayed rewards. The amount of the immediate reward was adjusted until the indifference point was found. This process was repeated at each of 7 delays ranging from 1 week to 25 years. The hyperbolic decay model (Mazur, 1987) was fit to data from each participant to yield a derived discounting rate (k). Median discounting rates for current smokers were higher than rates for never and ex-smokers (Wilcoxon Rank-Sum test). Never and ex-smokers did not differ in discounting rates (Wilcoxon Rank-Sum test). This result confirms the reduced sensitivity to delayed outcomes found in other drug-dependent populations, and implicates foreshortening of the temporal horizon as a pervasive feature of drug addiction. Never and ex-smokers could discount similarly because cigarette smoking is associated with a reversible increase in discounting or due to selection bias.

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ANGER PROBLEMS IN SUBSTANCE ABUSE TREATMENT

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Anger problems have been correlated with substance abuse and relapse to substance abuse. We studied the prevalence of anger problems and other negative emotions in 349 substance abuse patients enrolled in treatment at the San Francisco VA Medical Center. Substance use was measured with the Addiction Severity Index (ASI, McLellan, Luborsky, O'Brien, & Woody, 1980). Trait-anger and anger expression were assessed with the State-Trait Anger Expression Inventory (STAXI, Spielberger, 1988). Results show that 67% of our sample reported a score of 22 or above on the STAXI, which indicates dysfunctional anger. We also studied length of time in treatment for angry versus non-angry patients. Contrary to our original hypothesis, results of a survival analysis showed that patients with very high levels of anger tended to stay longer in substance abuse treatment than their non-angry counterparts (median = 71 days versus 58 days, respectively). We propose a separate diagnostic DSM category for anger disorders.

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DRUG-RELATED SUICIDAL AND HOMICIDAL BEHAVIOR IN PSYCHIATRIC INPATIENTS

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A number of studies have shown that CNS hyposerotonergic tone is associated with a greater risk of impulsive suicide and impulsive violence, suggesting the possibility of a common neurobiological pathway for both behaviors. A preliminary, retrospective study of 44 inpatients examining drug-related suicidal/homicidal behavior using the Drug-Related Suicidal and/or Homicidal Behavior (hereafter, DRSHB) Questionnaire yielded the following results: (a) Demographics: Male 68%, Female 32%; Age (avg.) 43; Ethnicity: white 93%, black 1%; Not Married 50%; Unemployed 61%; Education: At least HS/GED 55%; (b) Most problematic drug prior to admission: Alcohol 60%; Heroin 16%; Cocaine 12%; Benzodiazepines 7%; (c) Most problematic drug in relation to suicidality: Alcohol 37%; Cocaine 9%; Heroin 7%; Benzodiazepines 7%; (d) Suicidality: Lifetime-61%; Current SI-30%; Previous Suicide Attempt, -36%; Current Suicide Attempt, -14%; (e) Relationship of Suicidality & Violence: Suicidal: 36%; Violent: 11%; Suicidal & Violent: 23%; Non-suicidal & Nonviolent: 30%. Although the data should be viewed with caution as the sample was small and non-random, the study demonstrates the overlap of drug-related suicidal and homicidal behavior in a clinical population.

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THE NATURE OF THE RELATIONSHIP BETWEEN SUBSTANCE ABUSE AND DOMESTIC VIOLENCE

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The present study explores the relationship between substance abuse and domestic violence. Forty-six female residents of an urban domestic violence shelter were interviewed about the frequency of substance use by both partners in the relationship, rates of substance abuse in their families of origin, and the participants perceptions of the specific ways in which substance abuse contributed to the relational violence. Fifty percent of participants reported that their partners' substance abuse served as a catalyst to domestic abuse. Specifically, three clusters of catalysts were identified: 1) The batterer, after drinking or using drugs, becomes argumentative which leads to abuse, 2) The batterer becomes abusive when asked to seek treatment and, 3) The batterer exerts force on the victim to use or withdraw from substances or prevents victims from seeking substance abuse treatment. Finally, participants reported high rates of substance abuse in their families of origin as well as in their batterers' family of origin. These statistical trends underscore the need for a collaborative approach among service providers in the substance abuse and domestic violence fields.

RELATIONSHIP OF SELF-REGULATION TO ALCOHOL AND NICOTINE DEPENDENCE

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Addiction to substances can be viewed as repeated attempts by individuals to regulate an intolerable internal state. Deficiencies in the ability to self-regulate may influence propensity for, and ability to recover from, addiction. This study looked at how different forms of self-regulation are related to alcohol and nicotine dependence. Subjects were 321 participants in a study on the genetics of alcoholism, 58% female and 42% male, with an average age of 46. For the alcohol dependence analyses, subjects were grouped according to DSM-IV alcohol dependence: Current dependence, Past dependence, and Never dependent. Nicotine groups were formed using DSM-IV criteria for nicotine dependence: Current dependence, Past Dependence, Never dependent and Smoked, but not dependent. DSM-IV dependence was diagnosed by structured interview; dimensions of self-regulation including affect regulation, object relations, reality testing and defense styles were measured by paper and pencil questionnaire. ANCOVAs controlling for age and gender were conducted. Current and Past alcoholics reported higher frequency of attempts to regulate affect, particularly with somatic, aggressive, and sexual methods, than Never-dependents, and also scored higher on impaired reality testing. Current alcoholics scored higher than Past and Never dependents on three out of four scales measuring impairments in object relations, as well as four out of five personality psychopathology scales related to self-regulation. Past differed from Never on two of these scales, constraint (lower) and aggression (higher). Current alcoholics also scored higher than Past and Never on use of immature defense styles. Scales measuring impairments differentiated among alcoholics, whereas scales measuring strengths did not. Differences among nicotine dependence groups on several scales were removed when alcohol dependence was added to the model, suggesting that the differences observed between nicotine groups could be accounted for by the variability in alcohol dependence. Results suggest that there is a strong relationship between self-regulation and alcohol dependence, and a weak relationship with nicotine dependence that warrants further study in a more representative sample.

COMPARISON OF PSYCHOSOCIAL VARIABLES FOR HOMELESS VS. DOMICILED PREGNANT SUBSTANCE ABUSERS

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Previous studies have shown that homelessness is associated with both substance abuse and psychosocial dysfunction (Milbum, 1991). The present study examined psychosocial functioning in a sample of pregnant drug-dependent women reporting homelessness at treatment enrollment (n=76). Data were compared to a matched sample of domiciled women using Student's t-tests and Chi-Square analyses; a Bonferroni Correction corrected for Type 1 Error. Homeless women presented with higher medical severity ratings than non-homeless women (4.4 vs. 4.1, $p < .05$) and more frequent recent days with medical problems (7.8 vs. 2.9, $p < .002$). Homeless women also reported less institutional (Social Services) support ($p < .002$). The homeless group was less likely to have experienced close, long-term relationships with parents ($p < .001$) and were more likely to have experienced serious conflicts with mother, siblings and sexual partner ($p < .001$). Homeless women had higher rates of emotional ($p < .001$) and physical abuse ($p < .022$). The two groups differed psychiatrically, with homeless women reporting more inpatient psychiatric treatment episodes (1.3 vs. 0.3, $p < .002$), and a higher incidence of both recent and lifetime suicidal ideation and attempts ($p < .001$). Logistic regression analyses indicated that DSS income, family/social and psychiatric severity contributed significantly to homelessness status ($\chi = 41.3$. $p < .001$). Treatment should address the housing needs of this population as well as related social and psychiatric challenges.

CHILDHOOD ABUSE HISTORIES AND QEEG IN COCAINE DEPENDENCE

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Childhood abuse apparently has a high relative prevalence in populations in treatment for substance use disorders. In the context of our ongoing NIDA funded study of neurophysiology on crack cocaine dependence in drug abstinent subjects in residential treatment, quantitative EEG was obtained in 16 subjects who disclosed a history of abuse in childhood and compared to 16 subjects who denied such a history. Subjects were matched for gender, age, and reported lifetime cumulative exposure to cocaine. The methodology utilized to define sexual and physical abuse is described in [1]. In comparison to subjects who denied a history of abuse, those who disclosed a history of abuse exhibited increased relative theta (3.5 - 7.5 Hz) power in posterior leads, and increased beta (12.5 - 25 Hz) mean frequency. These results are of possible interest in view of prior reports of increased EEG abnormalities, and MRI evidence of hippocampal atrophy in individuals with childhood abuse histories. The hippocampus/amygdala is an important generator of the theta EEG rhythm, and theta is reportedly increased with cortisol exposure. Cortisol has been associated with the acquisition or expression of stimulant sensitization, and stress induced activation of hypothalamo-hypophysial-adrenal axis has been observed to reinstate drug seeking behavior in animals. One hypothetical interpretation of the above QEEG findings is a model in which stress during development results in enduring functional changes in the hippocampus/amygdala which are associated with an increased liability towards the acquisition or expression of sensitization and vulnerability to addiction. In addition to presenting important psychodynamic issues, childhood abuse may also be involved in neurobiological processes thought to mediate risk toward drug dependence.

THE EFFECT OF BIRTH ORDER ON DEPRESSION AND ANXIETY SCORES IN SCHOOL-AGED CHILDREN OF ALCOHOLICS

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Early descriptive literature on Children of Alcoholics (COAs) suggested that children raised by alcoholic parents take on "roles" within the family. Empiric studies have documented an increase in depressive symptoms in children of alcoholic parents as compared to children of non-alcoholics (NCOAs). However, differential symptomatology related to birth order among children of alcoholics has not been empirically studied. This study examined the relationship between birth order and increased depressive and anxiety symptoms among children of alcoholic parents. Data for this analysis was obtained from an existing database of psychological measures on 98 school-aged children. Subjects were between the ages of 6 and 18 years (average age 13.20, SD 3.31) from alcoholic-headed (COA) and control (NCOA) families. The sample included 50 children of alcoholics (24 females, 18 males) and 48 children of non-alcoholics (20 females, 28 males). Subjects were further grouped as being the oldest, middle, or youngest child in their family. Depressive and anxiety symptoms were measured using an extensive psychosocial battery, including both self and parental reports. Analysis of Variance (ANOVA) covarying for age and a secondary analysis using the Mann-Whitney U test, comparing all possible birth order groups were performed. This study found 1) increased depressive and anxiety symptoms among COAs, and 2) increased depressive and anxiety symptoms among middle children of alcoholics as compared to all other groups. This study supports the theory that children of alcoholics experience differential psychological morbidity based on birth order.

THE EFFECT OF LIFETIME HISTORIES OF PARENT AND SIBLING SUBSTANCE ABUSE AND/OR DEPRESSION ON ADULT ROLE FUNCTIONING IN A LONGITUDINAL SAMPLE

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This study examined the relationship of substance abuse and depression among parents and siblings of probands and the effect of such dysfunctions among the probands. Data were obtained from a random, non-clinical, sample of 1,200 male and female subjects who were originally tested in 1979-8, at the age of 12, 15 or 18. Subjects returned 3, 6, and 13 years later to provide longitudinal information up to the age of 31. Lifetime diagnoses of substance abuse (alcohol and other drugs) and depression were obtained for each natural parent and sibling using the Family History Research Diagnostic Criteria (FH-RDC). Each family member was characterized as symptom free, substance abuse only, depressed only or comorbid for substance abuse and depression. The "dysfunctional family" was defined as symptom free, sibling problem only, parental substance abuse only, parental depression only, parental comorbidity or both parent and sibling problem. Subjects were then examined vis-a-vis these groupings regarding longitudinal measures of alcohol and marijuana, depression, stress, life satisfactions, social isolation, negative affect, and deviant behaviors. Of the 613 subjects who reported no problem with substance use or depression, 46% had some problem within the family (indicating subject resilience). However, 42% of subjects from symptom free families reported a lifetime occurrence of substance abuse and/or depression (indicating subject risk).

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PREDICTORS OF CHANGE IN PSYCHOSOCIAL ADJUSTMENT AMONG DUALLY DIAGNOSED PATIENTS IN A MODIFIED THERAPEUTIC COMMUNITY

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Although the efficacy of the traditional drug-free therapeutic community (TC) model has been demonstrated to be effective in treating patients with chemical dependence and in rehabilitating persons with criminal histories, less is known concerning the factors influencing treatment outcomes in TCs designed to treat patients dually diagnosed (DD). A sample of 54 homeless male DD patients, who completed 6 months of treatment in a residential TC modified for DD, were evaluated for change in level of psychosocial functioning over the course of treatment, with particular reference to criminality status and type of nondrug Axis I disorder. Sources of data included 1) information obtained during intake interview concerning sociodemographics, history of criminality, prior substance use and prior treatment, 2) DSM-III-R diagnoses based on psychiatric evaluation, and 3) psychosocial adjustment (a composite of staff-rated interpersonal behaviors) assessed at baseline, 3 months and 6 months. Primary drug of choice for the majority (62%) of patients was crack/cocaine. History of prior drug treatment was positively related to improvement in adjustment. Repeated measures MANCOVA analyses indicated that patients demonstrated significant improvement in the level of psychosocial adjustment over the 6 month period that was unrelated to criminality status and Axis I disorder (schizophienia vs. affective disorder). A significant time by Axis I disorder interaction indicated that affective disorder patients exhibited greater improvement between baseline and 3 months whereas patients with schizophrenia exhibited more improvement between 3 and 6 months. These findings suggest that neither, history of criminal conduct nor type of nondrug Axis I diagnosis necessarily compromise DD patients' response to modified TC treatment. However, the rate of improvement in psychosocial adjustment may vary across diagnostic groups.

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RELAPSE EPISODES OF DRUG IMPAIRED ANESTHESIOLOGISTS COMPARED WITH PHYSICIANS OF OTHER SPECIALTIES

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Approximately 8-15% of physicians are impaired, primarily as a result of substance abuse but also due to psychiatric problems and dementia. Although few studies have evaluated treatment outcome for this population, it is generally accepted that anesthesiologists are at greater risk for developing drug use problems and may have less chance of positive treatment outcome, compared with physicians of other specialties. This study sought to evaluate whether or not anesthesiologists differed from physicians of other specialties regarding relapse rates while enrolled in a state monitoring program. One hundred and twenty-five anesthesiologists were compared with 894 physicians in other specialties (mostly internal medicine, family practice, or emergency medicine) recruited from four state monitoring programs. Groups did not significantly differ regarding gender, race, marital status, or legal status. Differences were found for age ($p<.0001$), employment status ($p<.002$), and primary substance of abuse ($p<.001$). Anesthesiologists were younger than other physicians in the monitoring program and a smaller percentage were employed full-time. As would be expected, the most frequently reported primary substance was opioids for the anesthesiologists and alcohol for the other physicians. The groups did not differ regarding other substances of abuse, nicotine use, number of prescription medications, and number of over-the-counter medications. There were no group differences in relapse rates during the monitoring program. Thirteen and six-tenths percent of the anesthesiologists and 13.2% of the physicians in other specialties relapsed at least once. There was a significant difference between mean number of relapse episodes; anesthesiologists relapsed fewer times compared with other physicians. No differences were found between groups regarding substance(s) abused during the relapse episode, amount of drug use during relapse episode, duration of relapse episode or method of relapse detection. These data suggest that, although anesthesiologists may be at greater risk for substance abuse, treatment outcome among this group appears to be similar to physicians of other specialties.

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GENDER-RELATED DIFFERENCES IN THE CHARACTERISTICS OF INDIVIDUALS WITH GAMBLING PROBLEMS IDENTIFIED THROUGH USE OF A GAMBLING HELPLINE

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Disordered gambling behavior is four- to ten-fold more frequently exhibited by individuals with drug or alcohol problems. The economic impact attributable to gambling problems in the United States, alone, is estimated conservatively at $5 billion per year. Historically, studies of problem and pathological gambling have predominantly or exclusively involved men, generating a deficiency in our understanding of disordered gambling behaviors in women. We hypothesized that groups of males and females with gambling problems would differ. We analyzed data obtained from callers to a 24-hour Gambling Helpline serving the greater southern New England region of the United States. One thousand two hundred sixty helpline phone calls were received over a year-long period from February 1998 to February 1999. Data obtained from responses, received at intake, were analyzed with respect to gender of the individuals with identified gambling problems. Male/female differences were observed in reports of patterns of gambling and indebtedness, drug and alcohol problems, mood and anxiety, mental health treatment, and legal problems. These findings have implications for not only the theoretical framework in which disordered gambling is viewed, but also the treatment strategies used for different groups of individuals with gambling problems,

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INCARCERATED VETERANS: SUBSTANCE DEPENDENCE TREATMENT NEEDS

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Substance abuse remains one of society's most pervasive social concerns and is commonly associated with criminal behavior. Research has demonstrated that addictions treatment has a positive impact on substance use and on criminal recidivism. Within a program evaluation approach, we conducted assessments of veterans in the King County Jail system with the following goals: determination of substance abuse, identification of areas of treatment concern/need, and assessment of utilization of VA services. The Addiction Severity Index was administered to 131 incarcerated veterans. Alcohol, heroin, and cocaine were the primary substances of use, and lifetime heroin and cocaine use were related to the number of lifetime months of incarceration ($\underline{r} = .45$, $\underline{p} < .01$ and $\underline{r} = .23$, $\underline{p} < .05$, respectively). Sixty-two (51%) veterans had not recently utilized VA services, Seventeen (29%) vets, not using VA services, indicated addictions treatment was moderately-extremely important. Of the 41 vets reporting such treatment was not important, eight (22%) endorsed use of alcohol to intoxication or of cocaine within the past month. Fifty-nine (63%) of the 93 vets, who provided complete data, endorsed at least one psychiatric symptom in the previous 30 days. Thus, overall results suggest substance use and psychiatric symptoms are prevalent issues for this population but a large number of veterans are not accessing available services despite indications of treatment need. Given the connections clearly established between addictions treatment and reduction in criminal recidivism, focus on facilitating substance use treatment is warranted.

REMISSION FROM ILLICIT DRUG USE OVER A 24-YEAR PERIOD. PART I. PATTERNS OF REMISSIONS AND PSYCHIATRIC PREDICTORS

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A dearth exists in comprehensive epidemiologic studies on patterns of remission over time and their predictors, in part due to the relative rarity of long-term follow-ups of chronic drug users ascertained from community populations. The ongoing Washington University Vietnam Era Study Phase III (VES-III) provides an opportunity to examine processes of hard drug use over a 24-year period, with relative economy, because a large proportion of the cohort members were addicted to narcotics while stationed in Vietnam. The VES study cohort (N=1,227) consisted of two samples of Vietnam War enlisted men who departed from Vietnam in 1971, and a civilian comparison sample, first surveyed in 1972 and 1974. The results of the current study were drawn from respondents of VES-III (N=841), carried out in 1996-97. Measures of remission were obtained separately for sedatives, stimulants, marijuana, cocaine, and opiates from year-to-year assessment; predictors included use frequency, mode of administration, alcoholism, depression, post-traumatic stress disorder (PTSD) and antisocial personality. Treatment use was assessed for the last quit attempt and from larger health care utilization measures. Among those who reported years of most frequent use since 1972, the mean duration per remission lasting 1 year or longer was lowest (10.6 years) for cocaine. The marginal success rate of continuous remission increased over time for cocaine, but the rate appeared stable for marijuana. Across 5 classes of drugs, more frequent use was detrimental to early remission. Alcohol dependence/abuse, childhood antisocial personality and war-time related PTSD had negative impacts on early remission. A majority of illicit drug users (72-78% across five drugs) intentionally attempted to quit; however, most did not use traditional drug treatment when making the last quit attempt (no treatment from 65% for opiates to 90% for stimulants). Over 87% of remission without treatment was associated with continuous remission to present. A considerable portion of those maintaining remission reported the last year of most frequent use was prior to the last quit attempt. Health care was found to be underutilized. Less than 9% of drug users, active during the past 5 years, were treated for drug problems with hospitalization in this time period; 3% of current drug users received counseling/treatment in clinics during the past 6 months. The results suggest considerable unmet needs for chronic drug abusers with comorbid psychiatric disorders.

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DO HARDCORE DRUG USERS CLAIM TO USE DRUGS ONLY OCCASIONALLY?

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Self-reports of drug use frequency are central to treatment outcome evaluations, estimates of the prevalence of heavy use, estimates of treatment need, and other questions with direct relevance to drug policies. Nevertheless, surprisingly little is known about the validity of these self-reports. This study examines the accuracy of 701 frequency self reports made by a sample of methadone maintenance clients. Self-report accuracy is evaluated by comparing rates of positive urinalyses found for each case with rates that would be expected had drug use occurred only as often as reported. Expected rates of positive urinalyses are derived from conservative Monte Carlo models of drug use for each case. This procedure reveals extensive heroin and cocaine use frequency underreporting. After adjusting for frequency underreporting, 51% of 249 cases reporting only occasional heroin use (1-10 days in the past 30), and 22% of the 133 cases reporting occasional cocaine use, are found to be using these drugs with frequencies corresponding to what the Office of National Drug Control Policy defines as "hardcore use" (more than 10 days in the past 30). Drug use frequency underreporting appears substantial, and might constitute an important threat to the validity of some treatment outcome evaluations, needs assessments and other analyses that rely on drug use frequency self-reports.

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MODELS EXPLAINING HELP SEEKING AMONG LATINO AND AFRICAN-AMERICAN ADDICTS ENTERING HOSPITAL-BASED DETOXIFICATION

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This presentation represents a first attempt at predicting treatment entry among addicts leaving detoxification. Several theoretical models of help seeking attitudes and behaviors are tested, in terms of their ability to improve the predictive capacity of social statuses and past behaviors ("fixed" variables) alone. These models are the theories of reasoned action, planned behavior, and interpersonal behavior, and a modified health belief model that incorporates the transtheoretical model of stages of change. Data presented here were collected as part of a larger study of persons seeking detoxification from heroin and cocaine/crack in two hospitals in The Bronx, New York. The dependent variable is entry vs. non-entry into long term treatment in the 30 days following discharge from the hospital. Independent variables are all measured at baseline. Four logistic regressions are conducted, one for each theory tested. Fifty-seven percent of the 99 subjects interviewed at follow-up entered treatment, a higher percentage than was expected based on preliminary hospital data. In the logistic regression of treatment entry on the fixed variables, homelessness is found to be a strong predictor of treatment entry. Of the four theories tested, only the theory of planned behavior results in a significant improvement of the model based on the fixed variables alone. Both behavioral beliefs favoring treatment and self-efficacy have significant coefficients in this improved model. Interventions targeted to substance abusers entering detoxification and on the street that are designed to increase levels of behavioral beliefs and self-efficacy regarding long term treatment are indicated as likely to increase rates of treatment entry.

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READINESS FOR CHANGE IN CONTINGENCY MANAGEMENT AND RELAPSE PREVENTION TREATMENTS WITH COCAINE USERS

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The University of Rhode Island Change Assessment scale (URICA) was administered to: a) 120 cocaine users in methadone maintenance treatment who received either relapse prevention (RP), contingency management (CM), RP&CM, or methadone treatment only (MM); and b) 162 primary cocaine users who received RP, CM, or RP&CM. Treatment response was reflected by a Treatment Effectiveness Scores (TES, total number of stimulant-free urine out of a possible maximum of 48). It was hypothesized that the primary cocaine users would have a greater readiness for change and that readiness would be less predictive of treatment response in the CM conditions compared to the RP conditions. Implications for selective application of CM interventions based on treatment readiness will be discussed.

REDUCING COCAINE USE IN METHADONE PATIENTS: CONTINGENCIES VS COUNSELING

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Developing effective strategies for reducing cocaine use among patients in methadone maintenance treatment is an important priority for this patient group. One hundred twenty cocaine dependent MMTP patients were randomly assigned to 1 of 4 16-week treatment conditions. The conditions were contingency management only (CM), relapse prevention only (RP), both conditions together (CM+RP), or neither (None). CM procedures were comparable to those developed by Higgins and colleagues,: RP procedures consisted of a thrice weekly group cognitive-behavioral intervention. In-treatment measures of cocaine use (self-report, ASI drug scale, and Urinalysis) all showed that CM conditions were superior to non-CM conditions (P<.01) and RP was superior to the None condition. Other data on the durability of these treatment effects at 6 and 12 month follow up will be presented as well as data assessing the impact of these interventions on secondary dependent measures.

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LONG-TERM ABSTINENCE REINFORCEMENT IN METHADONE PATIENTS

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Abstinence reinforcement interventions, using reinforcers such as take-home methadone doses or monetary vouchers, have been shown effective in promoting sustained abstinence from illicit drugs in methadone patients. However, like other drug abuse treatments, abstinence reinforcement interventions have not been effective in all patients and effects have not reliably persisted over time. This study evaluated effects of providing long-term exposure to abstinence reinforcement contingencies as a means of promoting and maintaining long-term abstinence. In a three-group randomized-controlled study, methadone patients with evidence of on-going cocaine abuse were assigned to receive no reinforcement (control), contingent take-home reinforcement for opiate- and cocaine-free urines (usual-care abstinence reinforcement) or the usual care take-home contingency plus voucher reinforcement for cocaine-free urines. A key feature of the study is that the abstinence reinforcement contingencies were maintained and studied for a full year, instead of being restricted to the first few months of treatment. Voucher reinforcement subjects could earn up to $5,800 in vouchers for providing cocaine-free urines over a 52-week period according to a schedule of escalating reinforcement for sustained abstinence. Take-home reinforcement for opiate and cocaine-free urines increased the overall percent of cocaine-free urines relative to controls (P<.05), although the effect appeared to diminish over time. Adding voucher reinforcement for cocaine abstinence substantially increased (P<.01) abstinence from cocaine and from opiates (longest duration of sustained abstinence and percent of negative urines) relative to both the control and take-home only groups. Drug abstinence in the take-home plus voucher reinforcement group increased across the first 26 weeks of treatment and effects were maintained throughout the 52-week intervention period. These results suggest that long-term exposure to abstinence reinforcement contingencies may be extremely useful as a maintenance intervention to prevent relapse.

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CONTINGENCY MANAGEMENT AND RELAPSE PREVENTION TRAINING IN A SAMPLE OF COCAINE-USING METHADONE CLIENTS

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Clients in outpatient methadone treatment (OMT) who use cocaine arc difficult to engage and retain in treatment. Specialized interventions such as contingency management (CM) and relapse prevention have shown promise in engaging and retaining these clients. This study investigates the effectiveness of using CM in combination with a cocaine-specific relapse prevention training module entitled Counseling on Cocaine Abuse (COCA) to increase treatment participation and reduce cocaine use. Based on indicators of cocaine use at admission, 61 clients were randomly assigned to 1 of 4 treatment conditions. Clients participated in their assigned interventions for 8 weeks and progress was followed for 8 weeks post-intervention. Analysis of variance (ANOVA) examined differences in cocaine use and treatment retention. Results indicated the COCA intervention was positively related to 6 months retention rates and that CM was significantly related to reductions in cocaine use during the 8-week intervention. Cocaine use was also reduced during the 8-week post-intervention period. Both techniques were associated with positive treatment response but had different focal points of influence.

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SELF-PERCEIVED NEEDS FOR ANCILLARY SERVICES BY CLIENTS

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Substance abuse treatment centers are often required to provide ancillary services in addition to primary treatment of alcohol and/or drug abuse. Clients, however, may not view services addressing employment, legal, medical, family/social, and psychological problems as immediately relevant. For this study, we defined self-perceived need as a client rating a problem as "considerable" or "extreme". Of 10,967 clients presenting to Detroit's central intake unit from February 1, 1996 to December 21, 1997, 29% had no self-perceived need for services, 36% for one service, 32% for 2-3 and 3% for 4-5 services. The greatest self-perceived counseling or treatment need was for employment (45% of clients), followed by family/social (23%), medical (21%), psychiatric (17%), and legal (15%). Subgroups found to have self-perceived need for significantly more services were women, clients abusing more than one drug, clients whose primary drug of abuse was crack cocaine, and clients abusing alcohol. In addition, clients abusing alcohol alone or in combination with crack reported needing significantly more services than those abusing crack alone or those abusing neither drug. These data can be used to plan services congruent with the self-perceived needs of people presenting for publicly funded substance abuse treatment.

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HELPLINES: HOW HELPFUL ARE THEY?

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Two raters (RLR and MJC) called 35 helplines from a website designed to assist substance abusers and their families. Each rater called five times, once each for stopping alcohol, cocaine, heroin, marijuana, and tobacco. The raters then categorized the written responses received into a) incorrect information (tobacco is not a drug dependence), b) inadequate response (e.g., never returned the call), c) state that they do not deal with the drug, d) unhelpful written material (e.g., about pharmacology of marijuana), e) helpful, but not very (e.g., refer to another hotline), f) helpful written material (e.g., quit smoking booklet), g) referral to 12-step program, and h) helpful referral (to program or therapist). The raters agreed on 90% of the ratings. Ties were broken by a third rater (JRH). Overall, 38% (21/56) of cocaine, 41% (23/56) of heroin, 27% (16/60) of marijuana, 36% (23/64) of alcohol, and 20% (13/64) of tobacco calls were helpful (categories f and h). When category g is added 46% (26/56) of cocaine, 46% (26/56) of heroin, 27% (16/60) of marijuana, 63% (40/64) of alcohol, and 30% (19/64) of tobacco calls were somewhat helpful. Only 39% (11/28) of cocaine, 36% (10/28) of heroin, 17% (5/30) of marijuana, 38% (12/32) of alcohol, and 22% (7/32) of tobacco helplines were somewhat helpful to both callers. We conclude that, the large majority of the time, helpline advice is not helpful.

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SUBSTANCE ABUSE TREATMENT OUTCOMES IN A MANAGED CARE ENVIRONMENT: PRELIMINARY FINDINGS

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As managed care vendors have been interposed between the client and the provider of treatment, there has been uncertainty about the quality and nature of services being delivered; this study seeks to assess those services. The data analyzed here are an initial subset of paired intake and six month follow-up data (N=314 pairs) of primarily alcohol-dependent clients who had been authorized for services by a large managed behavioral health care provider (MBHO) operating in the Philadelphia metropolitan area. Health status, problem severity and usage consequences are assessed with the multi-part Substance Abuse Outcomes Module (SAOM), which provides for patient and clinician baselines and patient follow-up report. These data are being merged into the MBHO authorization and claims file for study of outcome by provider, risk and benefit characteristics; claims data will also be evaluated (not yet done). In the outcome study so far, 93% of the sample had a baseline substance dependence diagnosis (90% concordance between clinician and patient assessment). Based on DSM status at the six month post survey, 48% of the post treatment sample (60% followup compliance) showed neither abuse nor dependence (41% were still dependent, 11% abuse). For the full group of clients at six months after treatment initiation, the past 30 day drinking and heavy drinking days were reduced by 50% ($p<.001$), the 100 point problem severity scale scores declined from 64.8 - 27.0 ($p<.001$), all five reported composite "consequences" variables (physical, interpersonal, intrapersonal, impulse control, social responsibility) improved by 50% ($p<.001$), and 7 of 8 health status measures were improved ($p<.01$. Neither risk, benefit type, nor demographics predicted outcome. So far, it appears that the proportion of clients benefiting from managed care services is approximately normative. Relationships between services received and outcome has not yet been examined, nor have co-pay or other potential management barriers to services access.

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PERCEPTIONS OF CONTROL AND ADDICTION TREATMENT OUTCOMES

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Given the extreme individual and societal consequences of drug and alcohol abuse, the nature and treatment of these problems warrants high priority. Because loss of control over a substance is a defining feature of addiction, treatment approaches have proposed various methods to counter this loss of control. In general, the various approaches differ in their assumptions regarding why control is lost, and whether it can be regained. The behavioral model proposes control can be regained as it was lost, namely, through principles of learning. The disease model, explaining lost control as part of a "disease," rejects the idea that control can be regained, and treatment, instead, focuses on the addict's acceptance of powerlessness over their substance. Since loss of control over a substance holds an important place in addiction treatment models, perhaps addicts' perceptions of control over a substance are important as well. After reviewing psychological research suggesting perceptions of control bestow many physical and psychological benefits, research that specifically examines perceptions of control and addiction was reviewed. Many studies have found substance-specific perceptions of control (such as self-efficacy) are associated with better treatment outcomes among addicts. However, research on the treatment effectiveness of 12-step groups seems to contradict these findings. The "perceived source" of self-efficacy beliefs is offered as an explanation for the contradictory empirical evidence.

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DRUG TREATMENT AND TWELVE-STEP PROGRAM PARTICIPATION: THE ADDITIVE EFFECTS OF INTEGRATED RECOVERY ACTIVITIES

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The historical rise in the number of Twelve-step programs and participants raises questions concerning client participation in drug treatment and Twelve-step programs, and their separate and combined effects on recovery. The results of a prospective treatment outcomes study (n = 356) indicate that rather than recovery alternatives, drug treatment and Twelve-step programs are often utilized by the client as integrated recovery activities. Treatment participants with pretreatment Twelve-step involvement stayed in treatment longer, and were more likely to complete treatment. An additive effect of these recovery activities was documented such that those who participated concurrently in both drug treatment and Twelve-step programs had significantly higher rates of posttreatment abstinence than those who only participated either in treatment or Twelve-step programs. Weekly or more frequent attendance at Twelve-step meetings was significantly associated with drug and alcohol abstinence over the two-year follow-up period regardless of the level of participation in additional treatment or aftercare activities. Less than weekly meeting attendance, or the cessation of participation in Twelve-step groups was significantly associated with relapse to drug and alcohol abuse.

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CHARACTERISTICS OF INDIVIDUALS WITH AND WITHOUT A HISTORY OF REPEATED DETOXIFICATION TREATMENT: IMPLICATIONS FOR TREATMENT POLICY

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In the current context of limited resources for substance abuse care, the relatively expensive treatment option of detoxification has come under increasing scrutiny, especially because its efficacy is questionable. We are examining intake ASI results from an adult substance abusing population to determine how persons with a history of multiple detoxifications differ from those with no detox treatments. In a preliminary analysis, 671 Medicaid eligible individuals were grouped into four categories: no detoxification history, one lifetime detox, 2-4 lifetime detox experiences, and more than 4 detoxes. Results indicated that as expected, the group with no detoxification history tended to report less lifetime drug and alcohol use. Also, a significantly larger percentage of the group with more than 4 detoxes reported overdosing on drugs. While severity of psychiatric symptoms also tended to increase as the number of detox experiences increased, the overall prevalence of psychiatric symptoms, even in the no detox group, was remarkably high. Sixty-six percent of the respondents in the no detox group reported experiencing serious depression; over half reported serious anxiety; almost one quarter experienced hallucinations; and one third had attempted suicide. In the group with more than 4 lifetime detoxifications, psychiatric symptoms were even more severe, with 87% reporting serious depression; 77% serious anxiety; 51% hallucinations; and 57% attempting suicide. Other differences between groups will also be explored and implications for treatment and policy discussed.

DIFFERENTIAL RECRUITMENT INTO THE "BREAKING THE CYCLE" (BTC) PROJECT

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The National Institute of Justice sponsored "Breaking the Cycle" (BTC) demonstration projects for adults in Birmingham, AL; Tacoma, WA; and Jacksonville, FL. BTC was conceived as a system-wide effort to provide intensive case management, treatment, and community-based monitoring to a substantial proportion of substance abusing offenders in lieu of pre-trial detention, prosecution, or incarceration. The present study compared baseline data on pre-trial defendants (N = 399) recruited into the first BTC project in Birmingham to a comparison sample of pre-trial defendants (N = 192) recruited in the months immediately preceding BTC implementation. Inclusion criteria for both groups were: (1) at least 18 years of age, (2) resident of Jefferson County, AL, (3) charged with a felony offense, (4) provided a drug-positive urine at intake, and (5) provided at least one locator contact. Comparison subjects were recruited soon after booking or their initial court appearance. BTC subjects were recruited at their first contact with the BTC program, scheduled within 24 hours of release from jail. Results revealed that there were significantly more racial minorities and individuals, with lower incomes, in the comparison sample. Moreover, comparison subjects had significantly more lifetime criminal charges and significantly greater ASI composite severity scores in nearly all domains (Drug Use, Alcohol Use, Medical, Psychological, Family/Social, Employment/Support). The comparison subjects also exhibited significant improvement in several ASI domains (Drug Use, Employment/Support, Legal, Psychological) at 9 months post-admission, and these improvements were generally maintained at 15 months post-admission (follow-up data are not yet available on the BTC subjects). Notably, these changes were not related to treatment services received by these individuals, suggesting that non-specific effects of arrest or imprisonment may have been sufficient to bring about improvements for a substantial proportion of these defendants. These findings have important implications for all three BTC adult demonstration projects. In particular, future BTC efforts must focus on identifying barriers to serving the targeted population, and on statistically controlling for non-BTC related changes in client status.

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HALLUCINOGENS ON THE INTERNET: A VAST NEW UNDERGROUND PSYCHEDELIC RESOURCE

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Hallucinogenic drug use remains a public health concern, with over 1.2 million Americans estimated to have ingested them for the first time in 1997. We sought to demonstrate the extent of "underground" information now readily available to hallucinogen users through the Internet. Using standard search techniques, familiar to even most American teenagers, we promptly located 46 web sites devoted to hallucinogens, and then used a "snowball" approach to locate dozens of additional hallucinogen-related sites. We found highly detailed information on all aspects of hallucinogen use. These included guides on how to locate and identify hallucinogen-containing plants in the United States, isolation and synthesis techniques for scores of hallucinogenic compounds, offers for grow kits to allow users to grow hallucinogenic plants at home, and offers to sell actual drugs to users via mail order. Additional web pages covered "drug tourism," descriptions of drug experiences and dosage recommendations; religious-based information; and numerous other more scientific and legal topics. Much of this information – such as extraction of hallucinogens from legally available grasses (*Phalaris* spp.) and ornamental cacti (*Trichocereus* spp.) – has yet to be described in textbooks, and is likely unknown to clinicians who treat hallucinogen users. Strikingly, in contrast to the vast array of Internet information effectively endorsing hallucinogen use, federal agency information, and other information on the dangers of hallucinogens, were only minimally present.

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INTERNET SUPPORT FOR NEW AND MINORITY DRUG ABUSE RESEARCHERS

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Danya International, Inc., in collaboration with Aspen Systems Corporation, Inc. has been developing a user-friendly Internet application to provide support to new and minority drug abuse researchers. Funded by the National Institute on Drug Abuse, this website (www.drugnet.net/dar) provides a set of robust Internet resources available to new and minority researchers who are seeking opportunities that address the mission and priorities of the Institute. Danya proposes to give a presentation of this website which will include an electronic grant writing tutorial system for new drug abuse researchers, web-based opportunities for seeking mentoring and consulting support, searchable databases for seeking funding opportunities and information, searchable bibliographic databases, and access to a wealth of other related links and databases. It is anticipated that this website wilt help researchers to collaborate on an ongoing basis, share ideas and experiences, stay informed in areas of particular interest, and access valuable resources in an easy-to-use format.

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PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF ACUTE TOLERANCE TO CLOZAPINE AFTER INTRAVENOUS AND ORAL ADMINISTRATION

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We investigated the pharmacokinetics (PK) of intravenous and oral clozapine in rats. The terminal half-life and absolute oral clozapine bioavailability are 82.7 min and 5.32%, respectively. Parallel pharmacodynamics (PD) was conducted using performance on a timing behavior, a differential reinforcement of low rate schedule (DRL 45-s) in 3-hr sessions, characterizing both dose- and concentration-effect relations of i.v. (1-5 mg/kg) and p.o. clozapine (2.5-10 mg/kg). Clozapine was described by our alprazolam PK-PD model due to their similar behavioral and pharmacological profiles. A unique concentration-effect relation was described for clozapine across doses and routes. Reference concentrations (i.e., $EC_{50,st}$, $EC_{50,sd}$, and IC_{50}) increased as a function of dose. Consequently, the relative potency of clozapine decreased significantly and linearly with the logarithm of $AUC_{(0-\infty)}$or bioavailable dose for the three PD functions regardless of route of administration. The reference concentration is an index for the sensitivity of DRL performance to clozapine, while the relative potency provides an index for estimating the extent of acute tolerance. As reference concentration increases, relative potency consequently decreases, and acute tolerance increases. Thus, acute tolerance is greater for i.v. clozapine than for p.o. clozapine; additionally, a larger dose produces greater acute tolerance for each route of administration. The PK-PD analysis allows the identification of both stimulatory and sedative actions of clozapine and the delineation of its consequences on timing performance under the DRL 45-s schedule. Furthermore, effects of dose and routes of administration on acute tolerance presented herein may have direct implications in optimizing therapeutic dose regimens for clozapine.

PHARMACOKINETICS OF METHYLECGONIDINE, THE CRACK COCAINE PYROLYSIS PRODUCT

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Smoking cocaine base ("crack") results in the formation of a pyrolysis product, methytecgonidine (MEG; anhydroecgonine methyl ester). MEG has been identified in urine of crack smokers and in meconium of infants of crack smoking mothers. MEG contains a double bond that is subject to a Michael addition reaction, demonstrated here *in vitro* with propanethiol in methanol. Thus MEG may bind covalently to biological substrates, accounting for the irreversible non-competitive antagonism observed *in vitro.* This phenomenon would not be detectable in conventional pharmacokinetic analyses in the absence of a labeled pyrolysis product, and could complicate analytical methods for determining concentrations in biological samples. Indeed, previous analyses of body fluids have identified MEG's presence; however, its presence in blood was elusive. We developed an assay capable of determining MEG levels in sheep plasma using ethylecgonidine (also containing a double bond) as an internal standard, and have used it to study the pharmacokinetics of MEG in sheep. Sample plasma is treated with chilled methanol, spun to pellet plasma protein, and the supernatant extracted using solid phase extraction columns. A GC/MS selected ion monitoring method is used to determine MEG concentrations. Sheep were prepared with indwelling venous catheters and then administered MEG in physiological experiments. At least 30 samples were drawn following each MEG administration. A two-compartment model has been fit to the log transformed data for all dosing experiments analyzed. Four of six experiments demonstrated that a three-compartment model better described the elimination, as evidenced by the proportion of variance accounted for by the model ($p< 0.05$). There was no obvious saturation; upon inspection the elimination curves were parallel and dose-related 3.0, 5.6, and 10.0 mg/kg. Modeling bingeing patterns of self-administration suggests that MEG may bioaccumulate; whether bioaccumulation occurs via covalent incorporation remains to be determined *in vivo.*

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USE OF QUANTITATIVE BENZOYLECGONINE LEVELS FOR THE ASSESSMENT OF COCAINE USAGE IN CLINICAL TRIALS

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To reduce or eliminate cocaine use is the major goal in the treatment of cocaine addiction. Although abstinence is the most desirable outcome, a 50% reduction in cocaine use is considered a successful treatment effect (FDA DAAC, July 1997). Currently, the only biological surrogate marker which objectively monitors patient cocaine use is urine benzoylecgonine (BE) concentration. However, urine BE levels arc highly variable. This study is to investigate the utility of using individual urine BE data for the assessment of a 50% reduction of cocaine use in sets of simulated data. Analyses were also performed for actual clinical data. A set of urine BE data was simulated from a simple clinical model to mimic a trial where the treatment medication is effective in reducing patient cocaine use by 50%. The simulated baseline BE levels were comparable to those observed in the actual trials. The individual BE data was analyzed by comparing the BE during the treatment period with that for the baseline period. A reduction of BE of 50% or more of the baseline period is defined as a treatment "positive." The simulated data demonstrated that only approximately 50% of the subjects, who in fact reduced cocaine use by 50%, could be detected by using the individual BE data and a target concentration of 50% reduction from baseline. When intrasubject variability increases, the probability of "false positive" -- subjects who did not reduce cocaine use but showed a reduction of urine BE of more than 50% of the baseline value -- increases. The statistical power to detect a treatment effect, therefore, decreases. Since the intrasubject variability for BE in real clinical trials in general is larger than that of the simulated data, the use of individual BE may not provide adequate statistical power to detect a 50% treatment effect. In fact, analyses of the data from an actual clinical trial suggest that the use of a group mean of the quantitative BE data provides more statistical power in detecting a treatment effect than the use of individual BE data. Research to develop a reliable and sensitive method to assess cocaine usage is ongoing.

WEEKLY URINE TOXICOLOGY SCREENS IN COCAINE TREATMENT TRIALS

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We examined the level of weekly variation in urine benzoylecgonine (BE) from samples collected within a week over the course of multiple weeks in data from a randomized clinical trial of a treatment for cocaine abuse. Eleven weeks worth of data from 68 participants was assayed for quantitative BE levels. Agreement between pairs of samples was estimated for both quantitative and qualitative measures. Results indicated substantial intra-week variation with correlations never exceeding $r = 0.50$ and approximately 20% disagreement when converted to cut-off values. Unlike the evidence from opioid studies, multiple assessments for cocaine treatment trials are required.

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INDIVIDUAL URINARY EXCRETION PROFILES OF COCAINE AND METABOLITES FOLLOWING INTRAVENOUS, INTRANASAL, SMOKED AND ORAL ADMINISTRATION

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Urine drug testing is employed widely in treatment and forensic investigations for the detection of cocaine use. Information on the excretion of cocaine and metabolites is generally based on studies involving intravenous (IV) administration. We evaluated urinary excretion profiles of cocaine administered as single doses by the IV (25 mg), intranasal (IN, 32 mg), smoked (SM, 42 mg), and oral (OR, 200 mg) routes to 3-8 cocaine-experienced subjects. Specimens were collected and analyzed by gas chromatography-mass spectrometry for cocaine and 8 metabolites plus anhydroecgonine methyl ester (AEME), a pyrolysis product of "crack" cocaine. Benzoylecgonine (BZE) and ecgonine methyl ester accounted for the greatest portion of the dose (25-58%) across all routes; whereas, small amounts (<2%) of cocaine and nor-BZE were also excreted. Oxidative/hydrolytic metabolites (norcocaine, m- and p-hydroxy-cocaine, and m- and p-hydroxy-BZE) were also present in small amounts. AEME was only detected in trace amounts (<0.1%) following smoked administration. Overall, ca. 63% of the dose was recovered from urine by OR administration, 57% by IV, 45% by IN, and 27% by SM. Although greater variability was noted by the SM and IN routes compared to IV for total drug recovery, urine Cmax and Tmax, there were no differences in mean detection times (time to detection of last positive specimen). These data indicated that commonly used drug testing methods work equally well for different routes of cocaine administration.

INHIBITION OF COCAINE BRAIN UPTAKE AND FACILITATION OF COCAINE EFFLUX FROM THE BRAIN BY A SYSTEMIC SPECIFIC ANTIBODY

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There are presently no established therapeutic treatments for cocaine abusers, particularly for acute overdoses. Two new concepts are presently evaluated (1) the administration of enzyme esterases which increase the catabolism rate of cocaine and (2) the active or passive use of specific antibodies to cocaine. These two strategies aim to neutralize the free cocaine molecules circulating in the bloodstream and consequently decrease the cocaine level in tissue by diminishing it tissue uptake and/or facilitating its tissue to blood redistribution. A cocaine antibody product (COC-AB^{TM}) is being developed based on the second strategy indicated above. To substantiate this immunotoxicotherapy (ITT) approach we are evaluating the ability of a mouse monoclonal benzoylecgonine specific IgG_1 to alter cocaine disposition in several rat models. By using the in situ brain perfusion technique, it was demonstrated that the brain uptake of cocaine decreased when increasing amounts of cocaine specific IgG_1 were infused. The brain cocaine distribution volume which was calculated to be 930 ± 77 µl/g when no antibody was given decreased to 74 ± 21 µl/g when a dose of antibody was infused. By using a more conventional in vivo technique, it was demonstrated that the infusion of the cocaine-specific IgG_1 one minute after iv cocaine significantly decreased the cocaine level by 64% (brain), and 51% (heart). This redistribution effect was confirmed by the parallel increase of the plasma antibody bound cocaine. The data substantiate that the cocaine tissue distribution and overall disposition is rapidly and substantially altered by systemic specific antibody. ITT is being further developed via a specific immunoconjugate to be a targeted antidote therapy for cocaine overdoses.

THE EFFECT OF CHRONIC COCAINE USE ON MAO-A ACTIVITY IN THE HUMAN BRAIN: A POSTMORTEM STUDY

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The major route of elimination of monoamines after release is by reuptake into the presynaptic neurons and storage in vesicles for re-release. Cocaine, a widely abused drug, is a powerful monoamine reuptake inhibitor. Repeated cocaine use could alter the normal physiological reuptake process and in turn upregulate the enzymes involved in monoamine metabolism in postsynaptic neurons and glial cells to eliminate the excess monoamines released. Since MAO-A and B play important roles in the metabolism of both intracellular and extracellular monoamines, chronic exposure to cocaine may affect the levels of these enzyme activities. To investigate this hypothesis, MAO-A activity was measured in the caudate, putamen, nucleus accumbens, orbitofrontal cortex, temporal cortex, and anterior cingulate from cocaine overdose victims and age-matched and drug-free controls. Briefly, MAO-A activity was characterized in the human brain by measuring the conversion of [^{14}C] serotonin. Initial kinetic studies showed that the Km for MAO-A was approximately equal in all of the brain regions (mean = 99.2 ± 6.75 μM), whereas the amount of MAO-A activity varied, in order of magnitude: anterior cingulate > nucleus accumbens > temporal cortex > orbitofrontal cortex = caudate > putamen. Activity was selectively inhibited by clorgyline and not by deprenyl. MAO-A activity was increased in the caudale and putamen, and decreased in the temporal cortex of cocaine overdose victims, as compared to drug-free controls. There were no significant changes in MAO-A activity in the nucleus accumbens, orbitofrontal cortex, or anterior cingutate. These data suggest that the rate of monoamine metabolism is significantly altered in select brain regions from cocaine overdose victims. This may be a compensatory effect following chronic uptake inhibition by cocaine. An increase in the rate of metabolism in dopaminergic brain regions may account for some of the dysphoria associated with withdrawal from the drug, and may contribute to relapse.

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PHARMACOKINETICS AND DYNAMICS OF METHADONE ENANTIOMERS FOLLOWING A SINGLE ORAL DOSE TO HEALTHY FEMALE VOLUNTEERS

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Methadone is administered as a racemic mixture, although only the R-(-)-enantiomer is therapeutically active. Eight healthy female volunteers completed a study of the pharmacogenetic determinants of methadone disposition and effects. Concentrations of methadone enantiomers were determined by a chiral HPLC method from serum and urine samples, collected for 96 hours, following an oral dose of 0.2 mg/kg. Non-compartmental pharmacokinetic analyses were performed. The hypothesis of enantioselective disposition was confirmed as concentrations of (R)-methadone were consistently higher than (S)-methadone (area under the concentration vs. time curve R:S = 5.7 ± 3.3, n = 6) and the half-life prolonged (R: 42.1 ± 12.9 hr *vs.* S: 21.1 ± 3.8 hr; n = 8). The percent unbound in plasma of (R)-methadone varied from 10.0 to 33.0 % and was higher than the fraction unbound of (S)-methadone with an R:S ratio (mean ± SD) of 1.74 ± 0.50. Pupillary constriction and decrease in oral temperature correlated better with serum concentrations of (R)-methadone than with total (R+S)-methadone. Additional analyses considering α_1--acid glycoprotein phenotype and cytochrome P-450 2D6 genotype are expected to improve our understanding of the concentration: effect relationships among tnethadone enantiomers.

STEADY-STATE METHADONE CONCENTRATION-EFFECT RELATIONSHIPS

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There are significant changes in a number of opioid effects over the 24 hour inter-dosing interval in methadone maintenance patients. The present analysis examined concentration (racemic and R)-effect relationship for a range of subjective and objective responses in 18 methadone maintenance patients. At each of 11 time points during a single inter-dosing interval, opioid effects were measured and a blood sample collected. The sigmoidal Emax model was used to relate plasma concentrations and effects and to calculate the slope factor (N). Curve fitting was carried out for individual subject data on each of the measures. For racemic methadone, the mean N values (±SE) were 5.1±1.1 (n=10) for the MBG scale of the ARCI, 2.8±0.7 (n=6) for pain threshold, 1.2±0.1 (n-12) for pupil diameter, 2.2±0.5 (n=14) for total mood disturbance of the Profile of Mood States and 5.5±0.9 (n=9) for withdrawal. For R-(-)-methadone concentrations the corresponding values were 4.8±0.8 (n=10; MBG), 2.2±0.3 (n=4; pain), 1.4±0.2 (n=10; pupil), 2.3±0.4 (n=9; mood) and 6.1±0.7 (n=9; withdrawal). As expected, EC50 values for R-(-)-methadone were approximately half the magnitude of those calculated for racemic methadone. The results indicate that different opioid effects vary in their sensitivity to changes in methadone concentration and that these effects relate well to racemic as well as R-(-)-methadone. Small changes in methadone concentration are likely to result in relatively large changes in MBG scores and withdrawal, but much smaller changes in pupil diameter, pain threshold, and total mood disturbance.

OPIOID EFFECTS ON ZIDOVUDINE (ZDV) DISPOSITION

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We have shown that methadone treatment increases ZDV exposure. To enhance the care of opioid dependent patients with HIV infection, we are examining interactions between ZDV and other long acting opioids used in the treatment of opioid dependence (1-alpha-acetyl-methadol (LAAM) and buprenorphine). ZDV 200 mg has been administered to non-opioid dependent controls (14) and to subjects chronically maintained on either LAAM (9) or buprenorphine (9). Blood samples have been collected over an 8 hour interval to determine pharmacokinetic parameters of ZDV.

Para-meter	Control Mean (SD)		LAAM Mean (SD)	p	Buprenorphine Mean (SD)	
AUC	1562 (522)		1534 (733)	0.912	1230 (343)	0.107
Cmax	1147 (374)		1097 (513)	0.789	884 (348)	0.106
Cl/F 139 (50.3)	155 (79.8)	0.56	167 (43)	0.184		
V/F 221 (73)	263 (128)	0.326	242 (73)	0.508		
t1/2 1.13 (0.2)	1.17(0.19)	0.638	1.01(0.16)	0.145		

Interim analysis does not show a statistically significant effect of LAAM or buprenorphine on ZDV pharmacokinetics parameters. However, a trend for lower ZDV AUC and Cmax has been observed in the buprenorphine-maintained sample. These findings underscore the clinical importance of understanding the interaction of antiretroviral therapies in patients with HIV disease who are chronically maintained on opioids.

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ACUTE DOSE VARIATIONS DURING METHADONE MAINTENANCE: EFFECTS OF INSTRUCTIONS (EXPECTANCY) ON HEROIN CRAVING AND HEROIN USE

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Craving may be a relapse marker during methadone (METH) treatment. This ongoing study examines whether single-day METH dose changes affect heroin craving/use and whether instructions (expectancy), maintenance dose and individual differences modulate craving. Opioid-dependent outpatient volunteers (10M, 6F) were stabilized on METH doses (30 to 120 mg/day) tailored to suppress withdrawal symptoms and heroin use. Each subject participated in all test conditions in randomized order under double-blind conditions. In each session, subjects were told whether their METH dose would Increase (2 sessions), Decrease (2 sessions) or stay the same as Usual (1 session). On Increase/Decrease days, the usual METH dose was given one day (false instruction), whereas a 25% dose change (Increase/Decrease) was delivered the other day (true instruction). On Usual days, the usual METH dose was given. Craving and other subjective effects were measured prior to instruction, for one hour after (anticipation of METH), for 2 hrs post-METH, and next visit 24 hrs later. Urine samples were tested before the instruction (required to be drug-free) and 24 hrs later (no contingency stated). Heroin craving was significantly related to pharmacological factors: Dose instructions had no significant effect on craving (anticipation); post-METH craving decreased after usual and increased METH doses. There were sex differences in post-METH subjective effects: Relative to males, females reported greater craving decreases (especially after usual and increased doses) and greater positive mood and agonist symptoms. Subjects maintained on higher methadone doses tended to report increased craving 24 hrs after true dose decreases, and had greater decreases in METH reinforcing value during detoxification. During detoxification (4 weeks), heroin craving showed significant linear increases as methadone dose decreased (measured at 75, 50, 25 and 0% of the maintenance dose).

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LAAM TREATMENT WITH OR WITHOUT TAKE-HOME PRIVILEGES

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Levo-alpha-acetylmethadol hydrochloride (LAA
M) has been approved for use in the treatment of opiate dependence since 1993. However, less than 5% of the opiate addicts in treatment receive LAAM and fully 80% of opiate addicts are in no treatment program. There is a clear need for developing strategies to increase the percentage of opiate addicts in treatment. One complication that continues to interfere with the implementation of LAAM is the labeling restriction on offering "take-home" or "carry-out" dosing with LAAM. A randomized clinical trial evaluating the feasibility of providing take-home LAAM in 158 opiate dependent individuals in Los Angeles was recently completed. Patients were inducted on LAAM after a period of methadone treatment;. following a two-week stabilization on LAAM. One hundred fifty patients were randomized to standard LAAM treatment (3 times weekly in-clinic dosing) or to a program where they could earn take home privileges based on no illicit drug use for a period of six weeks (3 times weekly urinalysis). Most of the patients completed the 48-week protocol (89 of 150 patients; 59.3%). Early termination was usually due to similar reasons seen at methadone clinics (jail, moving, etc.). The primary objective of the project was to evaluate the extent to which providing take-home dosing led to LAAM diversion, to differential treatment outcome, or to increased adverse event reports. Nearly all patients tolerated a standard induction schedule and there was no difficulty in recruiting patients for LAAM treatment. Results clearly indicate that there was no indication of diversion and there were no significant differences in the incidence of adverse events. Further, self-reported drug/alcohol use, treatment effectiveness scores (TES), and retention in treatment all reflected better outcome for those assigned to the take-home condition.

UTILIZATION OF LAAM IN THE MANAGEMENT OF METHADONE TAKE-HOME DOSES

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Take home doses of methadone have been controversial, primarily because of the potential for diversion. Six-day opiate substitution clinics have had no option, but to give a methadone take-home dose for Sunday to patients that have yet to qualify for take-home privileges. The introduction of LAAM, a synthetic mu agonist with a longer duration of action than methadone, to the treatment armamentarium provides a potential alternative to Sunday take-home dose of methadone in this group of patients. We evaluated 60 patients utilizing a 48-hour dose of LAAM given on Saturday. Doses of LAAM were calculated using 1:1.2 conversion factor. Patients were evaluated at two intervals: 1) prior to receiving their dose of LAAM (P1) and 2) upon return to clinic (P2). The following instruments were used: a) Objective Opiate Withdrawal Scale, b) Subjective Opiate Withdrawal Scale and c) Visual Analog Craving Scale. The statistical comparison of the means of the sums of the various craving and withdrawal instruments scores at P1 and P2 favor LAAM ($p \leq .05$). LAAM is an effective alternative to a take-home dose of methadone for Sunday in methadone maintained patients in 6 day/week clinics.

OUTCOMES FOR OPIOID ADDICTS TREATED IN AN AMBULATORY DETOXIFICATION PROGRAM UTILIZING LAAM

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The success of opiate assisted detoxification utilizing methadone has been well documented in selected populations. Pharmacokinetics of LAAM suggest that it could be an equally effective agent for detoxification. In order to evaluate this hypothesis, we studied opioid dependent veterans who were referred to an ambulatory detoxification program. Patients received three 48-hour doses of LAAM during the first week. Subsequent doses of LAAM were tapered by 2-4 mg utilizing the standard 48 hours and 72 hours dosing intervals. In addition to the pharmacological treatment, patients were required to participate in an ambulatory detoxification group thrice weekly. Throughout their treatment, patients were monitored for level of opioid craving, assessment of confidence in ability to resist drug use, self-report of opioid use, and were subjected to random urine drug testing. Patients were classified into two groups: completers (C) vs. noncompleters (NC). Thirty-seven patients were enrolled in this program during the months of January to April 1999. Over one-third of the patients successfully completed the program and had a mean length of treatment as 34 days and attended 13 groups compared to 13 days of treatment and attendance at 4 groups for the NC. There were no significant differences in baseline demographics between the two groups in regards to age, years of opiate use or history of polysubstance use. There were differences in route of administration, history of previous methadone treatment, presence of other drug users in household and employment status. Level of opiate craving decreased significantly during the first week of detoxification for both groups but remained at constant level for the rest of the treatment period. Neither group achieved total abstinence but there was a significant decrease in the frequency of opiate use as evidenced by self-reports and urine toxicologies. In regards to patient's response to potential triggers for drug use (as measured by the DTCQ), C had less confidence at baseline compared to NC. At the end of treatment, C reported an increase in their confidence level but the majority did not identify definite aftercare plans. We conclude that LAAM should be considered as a viable treatment option for detoxification of opiate addicts.

PRELIMINARY FINDINGS FROM A CONTROLLED TRIAL OF METHADONE MEDICAL MAINTENANCE

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The most effective therapy for chronic heroin dependence is methadone maintenance (MM). Unfortunately, MM is not available to many who might benefit from it. One way to increase the availability of MM is extensive implementation of methadone medical maintenance for well-functioning, drug abstinent patients. Medical maintenance reduces the reporting schedule to once per month with counseling done by medical staff (physician or nurse). Shifting patients to medical maintenance will produce savings in staff resources that can be used to expand the capacity of existing treatment programs and to improve the present therapeutic continuum. Data are lacking on controlled trials of medical maintenance which might guide changes in U.S. federal regulations. We report on the first 41 MM patients enrolled in a one year, randomized, controlled trial of methadone medical maintenance in patients recruited from 3 community-based methadone treatment clinics. Patients were eligible if, for the previous 12 consecutive months, they 1) had been in MM treatment, 2) worked full time, 3) had no urine screens positive for illicit drugs. Study patients are randomly assigned to I of 3 conditions: routine care, medical maintenance at the MM clinic, and medical maintenance at a private doctor's office. All patients submit two random urine samples and receive one random medication recall each month. The sample reported an average of 14 years total of MM treatment, 9 current consecutive years of MM treatment, 5 current consecutive years of illicit drug abstinence, and received a mean current methadone dose of 58 mg. Study patients were 34% female, 20% minority, had a mean age of 45, and, on average. had a high school education and earned approximately $20,000 yearly. To date, 88% (21124) of patients successfully completed the first 6 weeks of randomized treatment, while 12% (3/24) submitted a positive urine specimen and/or failed a medication recall. Study patients assigned to the medical maintenance conditions are satisfied with the advantages medical maintenance offers, but a small percentage of patients exhibited indices of treatment instability during the first 6 weeks of the study.

CONTINGENT INTENSIVE OUTPATIENT TREATMENT WITH VOUCHERS: A PILOT STUDY

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A reinforcement-based intensive outpatient treatment was delivered to 37 recently-detoxified, inner city, heroin abusers. Attendance was scheduled daily for the first two weeks, four times weekly for the next two weeks, and then thrice weekly for the final eight weeks. Individual cognitive-behavioral counseling, transportation assistance (bus tokens), and vouchers (up to $30 per wk) were delivered for attendance. Group skills training, social/recreational activities, lunch, vouchers (up to an additional $45 per wk) and rent or utilities payment ($150 over 4 weeks), were available for heroin & cocaine abstinent clients. Sixty-five percent (N=24) remained in treatment for more than two weeks, attending an average of 30 out of 44 sessions; 43% (N=l6) completed 3 months of treatment. Treatment completers submitted 92% (SD=l9) drug-negative urines during the enrollment compared with 56% (SD=42) drug negative urines submitted by dropouts, $F(1,35)=9.99$, $p=.003$. Ninety-four percent of treatment completers were employed at the end of their treatment episode compared to 14% of non-completers. Opportunity to earn voucher incentives does not appear to interfere with employment. Eighty percent (N=13) of participants who were drug-positive, as compared to 18% of those who were drug-negative at intake, left treatment within the first two weeks. Clients who are drug-positive at intake arc at risk for early dropout and may need interventions to enhance motivation.

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VOUCHER-BASED REINFORCEMENT OF OPIATE ABSTINENCE DURING METHADONE DETOXIFICATION: FOLLOW-UP

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This study evaluated voucher-based reinforcement of opiate abstinence before, during, and after a 90-day methadone detoxification. After 4 weeks of methadone maintenance treatment (baseline), patients (N=51) were randomly assigned to either the Abstinence Reinforcement or Control Group. Abstinence Reinforcement patients received a 22-week intervention in which they could earn vouchers for providing opiate-free urines before, during, and after a methadone detoxification. Patients could earn vouchers three times per week under a schedule of escalating reinforcement for sustained abstinence (maximum earnings of $2,200). Control patients received non-contingent vouchers (i.e., independent of urinalysis results) to match those obtained by the Abstinence Reinforcement group. Methadone doses were maintained during the first 6 weeks of the voucher intervention (maintenance period), and gradually reduced to 0 mg during the following 71 days according to a percent schedule (detoxification period). All patients received placebo (cherry syrup) for the next 19 days while the voucher contingencies remained in effect. Finally, during the last 3 weeks, the voucher contingencies remained in effect but no medication was provided. Follow-up contacts were programmed at 4 and 8 weeks thereafter. Patients in the Abstinence Reinforcement group provided significantly (p =0.05) more opiate-free urine samples during the maintenance period than during baseline. During the maintenance and detoxification periods, Abstinence Reinforcement patients provided significantly (p =0.05) more opiate and cocaine-free specimens than controls. Patients in the Abstinence Reinforcement Group sustained significantly (p=0.05) longer periods of continuous abstinence from opiates than controls. When the methadone dose reached 0 mg, 81.5% and 82.6% of the patients were still in treatment in the Abstinence Reinforcement and Control group, respectively.

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A GROUP INTERVENTION OF A REINFORCEMENT PLAN FOR METHADONE PATIENTS

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As an extension to a cognitive-behavior based treatment for dually-addicted enrollees into methadone maintenance, a treatment reinforcement plan (TRP) group was established. This intervention adapted Iguchi *et al's* (1997) contingency management model which uses vouchers redeemable for goods and services to shape behavior consistent with a treatment service plan. In a group modality counselors and patients collaboratively develop realistic treatment goals, break them down into weekly achievable tasks, and set up a modest ($5 value) reward structure for task completion. Examples of beneficial group processes were: 1) Establishing priorities - patients sorted through an array of problems and identified one small important area to work on; 2) Sharing goals and weekly tasks with the group elicited advice on resources and strategies to complete a particular task. Sometimes group members would accompany one another to give support; and 3) Social reinforcement (e.g., praise, recognition) which patients received from group members and counselors upon completion of their tasks. In order for groups to be run effectively, certain issues had to be addressed. E.g. 1) Avoidance of overly ambitious goals and tasks; 2) Time management - without structure, patients would spend the entire group period talking about whatever issues were troubling them; 3) Keeping patients focussed - A certain amount of time had to be devoted to each individual patient in order to identify a specific task. Some subjects would lose interest and engage in disruptive activities (e.g., putting on make-up, sleeping, side conversations) when the focus was not on them. Counselors had to be alert to re-engage group members in the group process. Subjects completed 43% of scheduled TRP tasks. Subjects who had earlier participated in TRP activities delivered in an individual session format with a higher incentive ($15) completed significantly more scheduled TRP tasks with individual sessions (63%). The most frequent group TRP tasks were related to housing, health care, and employment issues. A TRP within a group format appears to be a feasible intervention; greater success is likely to occur with higher incentives.

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HUMAN METHADONE SELF-ADMINISTRATION: INTERACTING EFFECTS OF METHADONE AND MONETARY ALTERNATIVES

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The effects of pre-loads of 0, 40, 80 mg methadone and availability of monetary alternatives on human methadone self-administration were examined. Methadone-maintenance patients stabilized at a dose of 80 mg methadone per day participated. Patients received 0, 20, 40 or 80 mg of methadone before the methadone self-administration trial. Completing a response requirement of 64 responses on one button dispensed 10 ml of 0.054 mg/ml methadone solution. Completing the equivalent response requirement on a concurrently available response button dispensed vehicle or earned points exchangeable for $0.05, $0.10, and $0.20. When the monetary alternative to methadone was vehicle or $ 0.05 patients consumed greater amounts of methadone solution following methadone preloads. However, increases in the monetary value of the alternative resulted in decreased methadone self-administration. The magnitude of these decreases was greatest following preload doses of 40 to 80 mg methadone. In other contexts the profile of results would be interpreted as priming. However, the decreases in methadone consumption as the value of the monetary alternative increased suggests that methadone preloads decreased the reinforcing effects of each methadone delivery.

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BUPRENORPHINE VERSUS METHADONE MAINTENANCE FOR THE TREATMENT OF OPIOID DEPENDENCE

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Aims: To evaluate whether buprenorphine is equivalent effective as methadone in maintenance therapy in opiate addicts over a treatment period of 24 weeks. Design: Patients were externally randomized either to buprenorphine or methadone in an open, comparative study design. Participants: Sixty subjects (19 females and 41 males) who met DSM-IV criteria for opioid dependence and were seeking treatment. Intervention: Patients received either sublingual buprenorphine (2 and 8mg tablets) with a maximum daily dose of 8 mg or oral methadone (D-/+L racemat) with an upper daily dose of 80 mg. A stable dose design was required apart from the induction phase of 6 days. Measurement: Retention in treatment and illicit substance use (opiates, cocaine and benzodiazepines) as determined by urine toxicology. Correlation of results in plasma levels and retention rate was carried out. Findings: The retention rate was significantly better for the methadone maintained group ($p < 0.05$) but patients who completed the study in the buprenorphine group had significantly less additional consumption of opioids ($p = 0.04$). Conclusion: The findings support the superiority of methadone in regard to retention rate, as well as prior reports about buprenorphine being an alternative in maintenance therapy, but suggest that a special subgroup might be primarily benefiting from buprenorphine.

SECONDARY OUTCOME MEASURES FOR OPIOID DEPENDENCE: A SINGLE SITE CONTROLLED TRIAL WITH LAAM, BUPRENORPHINE AND METHADONE

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Preliminary data for three *a priori* primary outcome measures collected in a study of 220 opioid dependent (DSM-IV) subjects comparing LAAM, buprenorphine and methadone were reported in 1998. This report compares secondary outcomes from the original study. This study used a randomized, stratified, parallel group, double-blind, triple-dummy design. The buprenorphine and LAAM groups were dosed three times per week and the two methadone groups (high and low dose), which provided control conditions for gauging treatment effectiveness, were dosed daily. Treatment consisted of a 2-week dose induction and 15-weeks of maintenance. The secondary outcome measures incjuded: 1) dose adequacy ratings (DAR), 2) opiate withdrawal symptoms (OWS), 3) other drug use (ODU), 4) dose change requests, 5) symptom checklist (SC), and 6) adverse events (AE). Multi-level analyses were conducted for DAR, OWS, and SC using SAS PROC MIXED with a heterogeneous autoregressive covariance structure for repeated measurements. Proportion of missed clinic visits and study retention were used as covariates to adjust for missing data, drop-outs, and when rescued (poor responders). Tukey-Kramer procedure was used to compare means. Chi Squares were used to analyze dichotomous data and ANOVA's for all other variables. There was a time effect for DAR, OWS and SC with improvement across time. There was a significant condition effect for OWS (buprenorphine greatest) and cocaine craving (DAR; high dose methadone greatest). For ODU, ETOH use was tow for all 4 groups while benzodiazepine use was significantly greater for the high versus low dose methadone group. The buprenorphine group requested significantly more dose increases than the high dose methadone group. SC and AE were similar across the four groups. Overall, the profile of effects on secondary outcome measures was similar across all three medications. Potential differences between medications for benzodiazepine use needs further investigation. High dose methadone appeared most effective in preventing requests for dose increases.

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PHARMACOKINETICS OF LIQUID VS. TABLET BUPRENORPHINE

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Prior buprenorphine studies, including pivotal clinical trials to establish its clinical efficacy and safety, have used a sublingual liquid preparation. The anticipated formulation to be approved for clinical use; however, will be a tablet. In previous single dose studies, the tablet formulation has been shown to have bioavailability of approximately 50% (range 12-80%) relative to the liquid preparation. The relative bioavailability with chronic dosing of the two formulations remains unknown. The present study compares the steady state pharmacokinetics and bioavailability of buprenorphine following multiple dosing of two 8mg sublingual tablets and 8mg of buprenorphine in a 1ml sublingual solution (in 30% ethanol). Based on the single dose observation of 50% bioavailability for the tablet, the two preparations are expected to yield comparable steady-state blood levels. The results indicate that the tablet formation with repeated dosing achieves blood levels approaching 75% of that achieved with the liquid preparation and produces corresponding greater clinical effects.

BUPRENORPHINE: LIQUID VS. TABLET FORMULATION

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Nineteen ninety-nine looks to be a big year for buprenorphine. Final pieces of data are being readied for filing and FDA approval is anticipated later this year. It would appear that NIDA may have another winner on its hands. Much of the pivotal clinical research supporting buprenorphine's safety and efficacy has been conducted with the sublingual solution even though the anticipated market product will be a tablet, alone or combined with naloxone. Earlier work by Jones *et al.* comparing single doses of the liquid vs. tablet formulations showed that the bioavailability of the tablet, compared to the liquid, ranges from 20 to 80% giving the tablet an estimated clinical effect of about half that of the liquid. A multiple dose steady-state pharmacokinetic study (reported elsewhere at this meeting) suggested that, with chronic dosing, the bioavailability of the tablet formulation approaches 70% of that of the liquid. To compare the bioavailability, clinical effects, and patient preference between the two formulations in patients treated with chronic dosing, we completed a study at our Pizarro clinic using a double-dummy, double-blind design. One hundred eighty-four opioid dependent patients were randomly assigned to receive either active liquid buprenorphine or active tablet buprenorphine. Patients began treatment, after a brief introduction, with either 8mg of liquid or 16mg of tablet buprenorphine. They remained on the assigned dose for 4 weeks and were then given a dose increase to 12mg liquid or 24mg tablet for 4 weeks. From weeks 9-12, the doses were raised to 16mg liquid and 32mg tablet. For the final 4 weeks (weeks 13-16), patients were switched to the alternate formulation at their highest assigned dose. Outcome measures included clinic attendance, drug use, signs and symptoms of over- or under-medication and patient preferences. This report presents results of the study in these key observations and on the correlation between drug bioavailability and clinical response. It appears that the buprenorphine approval process may escape the Y2K problem just in the nick of time.

A CONTROLLED COMPARISON OF THE BUPRENORPHINE-NALOXONE TABLET AND METHADONE FOR OPIOID MAINTENANCE TREATMENT: INTERIM RESULTS

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A combination buprenorphine-naloxone tablet (BNX) containing 8 mg of buprenorphine and 2 mg of naloxone is pending approval by the FDA for opioid dependence treatment. This ongoing, controlled study of 300 patients is comparing the efficacy of BNX to methadone (METH) for opioid maintenance treatment. An interim analysis was conducted of 162 opioid-dependent outpatients assigned randomly to either BNX8, BNX16, METH45 or METH90 mg dose groups for 118 days. Daily dosing was double-blind and double-dummy. Urine samples were collected thrice weekly, manualized behavioral counseling was provided twice per month, and Addiction Severity Index (ASI) ratings were collected at intake, 8 and 16 weeks. There were no significant differences across groups in the number of patients completing the study, medication compliance, rates of opioid use, or self-reported drug use. All groups improved significantly over time on ASI composite scores of Drug, Opiates, Employment and Legal, with a trend toward improvement on the Family measure. Fifty-five of the 162 patients (34%) completed the entire study. For treatment completers, patients receiving BNX tended to have higher rates of opioid abstinence (64% for BNX8 and BNX16) than those receiving METH (36% for METH45 and 52% for METH90). Patients receiving BNX were also significantly better at achieving at least 2 weeks of continuous opioid abstinence (84% for BNX8 and 70% for BNX16) than patients on METH (41% for METH45 and 67% for METH90). Finally, Treatment Effectiveness Scores (TES) for opioids were significantly higher for patients receiving BNX (32.2 ± 3.6) as compared to patients receiving METH (21.4 ± 2.7). These interim results suggest that BNX is as efficacious as METH and that treatment improves several aspects of psychosocial functioning. Further, for a subset of patients receiving at least 4 months of treatment, 8-16 mg of BNX is at least as effective as 90 mg METH in reducing illicit opioid use.

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DOSE PROPORTIONALITY OF 4, 8, 16, AND 32 MC SUBLINGUAL BUPRENORPHINE SOLUTIONS

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Sublingual buprenorphine is a promising treatment for opiate dependence. This study was performed to assess the contribution of nonlinear absorption to the observed ceiling on pharmacodynamic effects seen with buprenorphine doses greater than 24 mg. The dose proportionality of sublingual liquid formulations of 4 to 32 mg of buprenorphine was evaluated in 12 opiate-experienced, but not dependent, subjects. Plasma buprenorphine levels were measured by LC/MS/MS, standard pharmacokinetic parameters were determined, and opiate-specific subjective and physiologic effects measures were obtained. Mean buprenorphine AUC and Cmax increased with dose of buprenorphine, but dose-corrected AUC and Cmax decreased with each increase in dose ($p<0.01$). Pharmacodynamic effects increased with all doses but were not consistently maximal with the 32 mg dose of buprenorphine. We conclude that there is a decrease in sublingual bioavailability with increasing doses of buprenorphine which may at least partially explain the observed ceiling on buprenorphine's opiate agonist effects. The deviation from dose proportionality may be due to the sublingual mode of administration or to the pharmacologic characteristics of the drug itself.

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BUPRENORPHINE DOES NOT COMPLETELY ANTAGONIZE THE REINFORCING EFFECTS OF IV HEROIN IN HUMANS

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Heroin-dependent individuals, maintained on 8 and 16 mg sublingual buprenorphine tablets, participated in a 6-week inpatient study evaluating the reinforcing effects of intravenous (0, 6.25, 12.5, 25 mg) heroin. Half of the participants received 8 mg first, and half received 16 mg first. All participants received both buprenorphine doses, and were stabilized on each buprenorphine dose for 1 week, during study weeks 1 and 4. Testing occurred during weeks 2, 3, 5, and 6 on Mon, Tues, Thurs, and Fri mornings and afternoons (2 sessions per test day). On Mon and Thurs mornings during test weeks, participants received a sample dose of heroin and $20, and for the next 3 sessions they could self-administer all, or part of the sampled heroin dose or money amount. Participants responding under a progressive-ratio schedule (PR 50, ..., 2800) during a 10-trial self-administration task could choose 1/10th of the sampled heroin dose or 1/10th of the sampled money amount during each trial. The PR value increased independently for each option. The total amount of heroin and/or money chosen during the self-administration task was given as a bolus dose at the end of the task. Relative to placebo, 12.5 and 25 mg heroin produced statistically significant increases in break point values under both maintenance dose conditions. The heroin break point values were significantly lower under the 16 mg buprenorphine-maintenance dose, compared to 8 mg. These results demonstrate that the reinforcing effects of heroin were reduced, but not completely antagonized by buprenorphine.

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EFFECTS OF BUPRENORPHINE ON OPIOID DRUG-SEEKING BEHAVIOR

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Buprenorphine (BUP) is a μ opioid partial agonist being developed as a treatment for opioid dependence. BUP can attenuate the subjective and reinforcing effects of subsequently administered opioids. Because BUP is long-acting, it does not have to be administered daily to retain its effectiveness. The purposes of this study were to examine the effects of BUP on opioid drug-seeking behavior, to determine if these effects are dose-dependent, and to determine the effects of alternate-day dosing on opioid drug-seeking behavior. This study examined the effects BUP has on choice between hydromorphone (HYD) injections and money. During the first week of the 9-week study, while subjects were maintained on 2 mg/day BUP, they participated in 2 sessions during which they sampled 4 and 24 mg HYD (counter-balanced and referred to as drug "A" and drug "B") injected i.m. During the next 8 weeks subjects were maintained on 4 BUP maintenance conditions (2 mg daily, 4 mg alternating with 0 mg, 16 mg daily, and 32 mg alternating with 0 mg) each for 2 weeks. The first two conditions were completed first with the order counter-balanced and the second two conditions were completed last with the order counterbalanced. During the second week of each of the 4 maintenance conditions subjects participated in 4 sessions during which they could make 8 choices between HYD injections (4 or 24 mg maximum on separate days) or money ($ 16 maximum). Subjects responded on a progressive ratio schedule for 2.5 hours (100, 200, 400,... 12,800 responses were needed for each consecutive reinforcer). Each completed ratio on the drug keys produced 118 of the total available HYD dose and each completed ratio on the money keys produced $2.00. Based upon the results from the first 8 subjects, BUP produced a non-significant trend toward a dose-related decrease in opioid drug-seeking behavior. During the alternate day dosing regimens, subjects did not choose more HYD on days when they received 0 mg BUP compared with days when they received active BUP.

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COUNSELING REQUIREMENTS FOR BUPRENORPHINE MAINTENANCE: A PILOT STUDY

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Background: Buprenorphine (BUP) is a promising alternative to methadone, as it allows for less-than-daily dosing, it has lower abuse liability, and it can more easily be provided outside of traditional maintenance clinics. However, the counseling requirements for BUP maintenance with less-than-daily dosing or outside of maintenance clinics need to be evaluated. The specific aims of this pilot study were to develop a draft manual for Medical Management (MM), a brief, nurse-administered counseling approach we intended for use in later studies of BUP in Primary Care settings, and to pilot test the feasibility and efficacy of MM in a Methadone Maintenance Program. **Methods:** We developed an initial MM manual designed to approximate counseling provided to patients in Primary Care clinics. In MM, the RN: 1) established a therapeutic alliance; 2) educated patients about opioid dependence and BUP maintenance; 3) monitored drug use and encourage participation in self-help groups; and 4) gave brief advice for achieving abstinence. Fourteen opioid-dependent patients were treated for 12 weeks with thrice-weekly BUP plus either MM, provided thrice-weekly (5-10 min) by an RN, or MM+DC. DC was provided weekly (45 min) by Certified Alcohol & Drug Counselors. **Results:** Seven of seven MM and 6/7 MM+DC patients completed all 12 weeks of the study. Rates of opioid-positive urine toxicology tests averaged 72% for MM and 54% for MM+DC ($p=.367$). Two of seven MM and four of seven MM+DC patients achieved ≥ 3 consecutive weeks of opioid-negative urine toxicology tests. Conclusions: This preliminary study demonstrates the feasibility and acceptability of MM and suggests that, as with methadone, DC may be a necessary component of buprenorphine treatment of opioid dependence.

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EFFECTS OF PRAMIPEXOLE ON CUE-ELICITED COCAINE CRAVING

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Previous studies have shown that dopamine (DA) agonists increase and dopamine antagonists decrease cue-elicited cocaine responses in a short-term human laboratory setting. To evaluate whether the latter is true in the context of longer-term clinical trials, agents are needed that are better tolerated than conventional dopamine antagonists such as haloperidol. If cocaine cues elevate dopamine as suggested by our previous studies (cues elevated plasma homovanillic acid), medications that inhibit dopamine release may be sufficient to attenuate cocaine cue responses without the side effects of continuous receptor blockade. Subjects were treated in a double blind, counter-balanced, two session placebo-controlled design with a low dose of pramipexole (0.1 mg). This dose is hypothesized to be sufficient to inhibit the tiring of dopaminergic pathways at presynaptic dopamine autoreceptors in the midbrain without stimulanting postsynaptic dopamine receptors in the basal ganglia and cortical regions. Subjective cravings, anxiety, and euphoria were reported, and objective physiological measures (cortisol, heart rate, temperature, and galvanic skin response) were recorded before and after the conditioned cues. The cocaine cues significantly elevated plasma cortisol, galvanic skin response, and subjective reports of craving and euphoria consistent with past studies. Unexpectedly, pramipexole selectively attenuated cue induced euphoria without affecting any other measure. Earlier imaging studies implicate dopaminergically innervated cortical regions in craving. These mesocortical pathways as opposed to mesolimbic dopaminergic projections (to the nucleus accumbens) are not believed to have dopamine autoreceptors, the receptor target of pramipexole. Conceivably, mesolimbic pathways may mediate cue induced euphoria responses and mesocortical pathways may mediate craving. Some have questioned the relationship between craving and drug self-administration. The ability to tease these responses apart, pharmacologically, may enable later studies to determine which response, if any, is relevant to drug self-administration.

EFFECT OF A SELECTIVE DOPAMINE D1 ANTAGONIST (SCH 39166) ON SMOKED COCAINE SELF-ADMINISTRATION IN HUMANS

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Data in laboratory animals suggest that dopamine D1 antagonists may be useful as treatment medications for cocaine abuse. This study investigated the effects of the D1 antagonist, SCH 39166, in a laboratory model of cocaine self-administration in humans. Non-treatment seeking cocaine abusers (n=10) were maintained on placebo and SCH 39166, each for eight days. Participants received SCH 39166 (0, 100 mg po) each day at 2200. There were 8 laboratory sessions in which participants had the opportunity to choose between repeated doses of smoked cocaine (0, 12, 25, 50 mg) and a voucher worth $5. Cardiovascular and subjective responsivity to cocaine, and cocaine craving were also assessed. In the presence of placebo cocaine, SCH 39166 significantly decreased cocaine craving and ratings of irritability, bad drug effect and hunger, while increasing alcohol and tobacco craving. In the presence of active cocaine, SCH 39166 increased cocaine self-administration (12 mg), and increased ratings of good drug effect, high, stimulated and dose quality (25, 50 mg). SCH 39166 also increased blood pressure and heart rate across most cocaine doses. Although SCH 39166 alone had effects on mood and drug craving that could facilitate cocaine abstinence, the combination of SCH 39166 with active cocaine resulted in enhanced cocaine self-administration and subjective effects. These data, combined with our earlier study with the D1 agonist, ABT-431, suggest that enhancing rather than blocking the effects of cocaine at the D1 receptor may be a more useful approach to treating cocaine abuse.

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CLOMIPRAMINE FOR THE TREATMENT OF COCAINE DEPENDENCE

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The efficacy of clomipramine was investigated in an open pilot study of cocaine dependence because cocaine dependence features compulsive repetitive drug use. The results were compared with a similar historical control group who received multi-vitamins as a medication. Both groups had identical psychosocial treatment and outcome measures. **METHODS:** This was a seven-week open trial involving 20 cocaine-dependent subjects. Clomipramine dosage was titrated over the initial 3 weeks to a maximum of 150mg per day. Study visits were conducted twice weekly. Psychosocial treatment consisted of twice weekly, individual, manual based, cognitive behavioral therapy. Urine toxicology screens were obtained at each visit. The primary outcome measure was semi-quantitative urinary benzoylecognine levels. Secondary outcome measures included treatment retention, results from Addiction Severity Index, and scores on a cocaine withdrawal scale. **RESULTS:** The treatment effectiveness and the treatment retention did not differ significantly between the two groups. The ASI drug composite scores declined in both groups; the self-reported days of cocaine use declined in both groups from the baseline ASI to week 7 ASI. There was no significant group by time intervention. **CONCLUSION:** Clomipramine was not more efficacious than multi-vitamin in this pilot trial.

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PERGOLIDE/HALOPERIDOL FOR THE TREATMENT OF COCAINE DEPENDENCE

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Pre-clinical studies of D_1 and D_2 agonists suggest that a pure D_1 agonist might be beneficial in preventing cocaine relapse in humans. We hypothesized that Pergolide (a potent D_1/D_2 agonist) in combination with haloperidol (a D_2 antagonist) would provide a D1 effect that would be beneficial in treating cocaine addiction. We examined this in a sample of male and female crack cocaine users without other Axis I diagnosis enrolled in a double blind study. There were no significant differences between the Pergolide/Haldol (treatment) group and the Placebo/Haldol (placebo) group with respect to age (M=32.35, SD=8.15 and m=33.83, SD=7.15), years of drug use (M=7.56, SD=.5.67, and M=7.50, SD=5.59), money spent on cocaine in the past month (M=$912, SD=$1222 and M=$523, SD=$415), Beck Anxiety (M=20.70, SD=10.29 and M30.17, SD= 20.14) or Beck Depression scores (M=13.33, SD=11.62 and M=13.73, SD=14.27)) at baseline. Dropout rate was high with 47% of treatment and 56% of the placebo subjects terminating by the end of study week 2. Side effect rate was also high with 31/35 subjects reporting at least one medication related side effect at week 1. In the placebo group, two subjects had acute dystonic reactions requiring oral or parenteral medication management. There were no differences between the groups in weekly benzoylecgonine levels (Pergolide/Haldol M=2.587.64 ng/ml, SD=1937.25 Placebo/Haldol, M=1760.67 ng/ml, SD=2168.66); treatment effectiveness score and Pergolide/Haldol M=3.73, SD=4.49 and Placebo/Haldol M=2.63, SD=4.19 out of possible score of 16 points). The proportion of negative urine drug screens did not differ between groups. These findings indicate that in our population of crack cocaine users, the combination of Pergolide and Haloperidol, in these doses, was not a feasible therapy because of high drop-out rates and numbers side effects. Subjects appeared less likely to drop out of the Pergolide/Haldol group than the Placebo/Haldol group and demonstrated lower rates of extrapyramidal symptoms. This may be related to amelioration of some D_2 antagonist effects of Haldol by the Pergolide.

LAMOTRIGINE TREATMENT OF COCAINE DEPENDENCE

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The purpose of this project was to study the effectiveness of lamotrigine in reducing relapse in newly abstinent cocaine dependent patients. The hypothesis is that glutamate plays a role in cocaine dependence and; therefore, lamotrigine (via decreased glutamate release) may also decrease relapse to cocaine dependence. Nineteen cocaine abusing male and female subjects were recruited and initially admitted to the day rehabilitation program at the West Haven campus of VA Connecticut Health Care for three weeks. Subjects who achieved a minimum of ten days abstinence from cocaine during the day program were then entered into a 14-week clinical trial of lamotrigine randomized into two (double-blind) groups: a low dose of 50mg daily and a high target dose of 300mg. A six-week slow induction schedule was used. The primary outcome measure was length of time until relapse (2 consecutive weeks with cocaine positive urines) and number of relapses. Craving was also measured by self-report (visual analog scales and quantitative cocaine use inventory, as well as Tiffany Craving Scale). Other possible predictors of clinical response such as depression, cocaine high and side effects were also measured weekly. Lamotrigine levels were measured at weeks 7, 11 and 14, or at the time of discontinuation from the study. Of 19 subjects entering day treatment, 15 completed the 3 week day treatment. Of the 11 who began medication, 7 (2 on 50mg and 5 on 300mg) completed 6 weeks and 5 (4 on 300mg) completed all 14 weeks. Average retention was 8.5 ± 1.6 weeks. These 11 subjects were 64% male, 36% divorced and 64% never married, 55% African-American, 18% Hispanic and 27% Caucasian. Side effects were mild and were not given as reasons for dropout. Serum lamotrigine levels confirmed compliance. While the number is too small to determine efficacy or to compare dose groups, 4 of 7 patients who completed at least 6 weeks (avg. = 11.8 weeks) had a relapse. However, the average length of time until relapse was 8.5 weeks and 6 of 7 had an average of 87% of weeks retained abstinent from cocaine. Patients improved or maintained initial improvement with respect to most outcome measures. In conclusion, lamotrigine was well tolerated and may have potential for development as a pharmacotherapeutic agent for relapse prevention in cocaine-dependent patients.

GLYCOPROTEIN PHARMACOTHERAPY FOR COCAINE ABUSE

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A luteinizing hormone (LH) glycoprotein subunit is structurally analogous to the cocaine binding site of the dopamine transporter in brain. The LH glycoprotein subunit rapidly binds cocaine in blood of rhesus monkey and prevents cocaine from crossing the blood brain barrier (J. Mendelson, N. Mello, and S. Negus, Journal of Pharmacology and Experimental Therapeutics, 289:791-799, 1999). Stimulation of increased LH levels in blood occurs following administration of synthetic luteinizing hormone releasing hormone (LHRH), Factrel 500 mcg. The effects of LHRH stimulation of LH in humans was carried out with procedures analogous to the investigations conducted with rhesus monkey. Adult male cocaine abusers provided informed consent for assessment of plasma cocaine levels following administration of placebo or LHRH (Factrel) pretreatment. LHRH stimulated an increase in LH to peak levels of 129.8 ng/ml in contrast to placebo administration when peak LH levels were 52.4 ng/ml. Peak plasma cocaine levels following placebo administration were 261.3 ng/ml. Peak plasma cocaine levels after LHRH (Factrel) treatment were 183.3 ng/ml. Thus LHRH induced an increment of LH of 77.6 ng/ml which resulted in the decrement in peak plasma cocaine levels of 78 ng/ml. The virtually identical increment and decrement in ng/ml of LH and cocaine, respectively, suggest that cocaine is binding to the LH glycoprotein subunit in a equimolar manner in humans.

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GABAPENTIN TREATMENT OF COCAINE DEPENDENCE

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The current project was designed to evaluate the use of GABAPENTIN (GBP) to modify relapse to cocaine use in an 8-week open-label clinical trial in patients who met DSM-IV criteria for a diagnosis of cocaine dependence. The dose of GBP used was 300 mg b.i.d. for three days, then 600 mg b.i.d., thereafter. Subjects were followed weekly with follow-up assessments done at study termination (8 weeks) and at 3 months. The primary dependent variable, relapse to cocaine use, was determined by self-report as well as urine drug screening. Other dependent variables (e.g., analog rating scales and psychologic assessments) were assessed for secondary analyses, as well. Preliminary data on eleven subjects at week 4, in this ongoing trial, indicate the amount of money spent weekly on cocaine decreased from $384/week during the 30 days prior to study entry to $54/week during the first 4 weeks of the study. An average of 27% of urine screened in the first four weeks were cocaine positive. Baseline rating of amount of craving and percent of time craved decreased from 78 to 24 and 75% to 24% respectively by week 4. The medication and dosing strategy was well tolerated. This preliminary study indicates that GBP is well tolerated and may be efficacious in the treatment of cocaine dependence. A placebo-controlled trial would be of interest.

COCAINE WITHDRAWAL SEVERITY AS A PREDICTOR OF OUTCOME IN PHARMACOTHERAPY TRIALS FOR COCAINE DEPENDENCE

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This study evaluated the predictive validity of the CSSA and initial urine toxicology results in 76 cocaine dependent patients participating in medication trials for cocaine dependence. Subjects participated in one of four, 7-week, open medication trials for cocaine dependence. Predictor variables included baseline CSSA scores, initial urine toxicology results, and medication assignment. The outcome variable measured was three continuous weeks of self-reported abstinence from cocaine confirmed by urine toxicology screens. Predictor variables were evaluated individually, and in combination, utilizing logistic regression. Medication assignment was not a significant predictor of abstinence. The initial urine toxicology result was a significant predictor of abstinence; sensitivity = .69, specificity = .94, and the probability of correctly predicting abstinence = 76.3% (model χ^2 = 25.3, $p < .0001$). The baseline CSSA scores, dichotomized at 18, also predicted abstinence; sensitivity = .59, specificity = .88, and probability of correctly predicting abstinence = 75.0% (model χ^2 = 13.9, p = .0002). Including both the baseline urine result and the baseline CSSA score improved the predictive validity of the model (improvement χ^2 = 9.99 p = .02). The final model, including both variables, was a robust predictor of abstinence; sensitivity = .84, specificity = .89, probability of correctly predicting abstinence = 85.5% (model χ^2= 3 1.7, $p < .0001$). The initial urine toxicology result and the CSSA are both useful predictors of abstinence in cocaine medication trials and the combination of these two measures predicts abstinence better than either measure alone.

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REDUCED BLUE-CONE ERG AMPLITUDE IS ASSOCIATED WITH CUE-ELICITED COCAINE CRAVING

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Determining methods for subtyping cocaine addicts who may display a dysregulated dopamine system could have implications for pharmacotherapy cocaine treatment matching. In the eye, the retina has a high concentration of dopamine, which is thought to be involved in blue-cone b wave Electroretinogram (ERG) amplitude. This study examined whether cocaine addicts with reduced b wave amplitude may have higher cue-elicited craving than those without reduced b wave amplitude. Withdrawn cocaine dependent patients (n=36) completed an ERG, a cocaine craving questionnaire at baseline and following the cue-exposure procedure. Patients with a blunted blue cone b wave ERG response >.50 microvolts (N=20) had significantly more cue-elicited craving than patients without blunted response (N=16) (m=-.39 ± .87 vs .50 ± .91 t=-3.00, d.f.= 34, P=.005). The ERG and other non-invasive measures of blue cone retinal functioning may be a biological marker of predicting which cocaine addicts will have a stronger reaction to cocaine cues. Future research could examine whether this sub-group has a higher relapse potential and may require more intensive psychosocial or pharmacological treatments.

CRACK COCAINE USE AND NEUROPSYCHOLOGICAL FUNCTIONING

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The effects of chronic cocaine use on neuropsychological functions have not been well-established, secondary to a number of contradictory findings. This study examined the relationship between cocaine use variables and neurocognitive functioning in a group (n=20) of cocaine dependence (crack smoking) outpatients recruited as part of a larger study of the efficacy of amlodipine and cognitive-behavioral therapy in the treatment of cocaine dependence. Subjects with a history of alcohol addiction, neurological illness, head injury, or other illness with known effect on cognition were excluded. The sample was: 15% female, 85% male, 65% African American, 35% Caucasian, mean age 36.6±8.8 yrs, mean education 12.2±2.2 yrs, mean lifetime use of cocaine 9.4±6.4 yrs; mean cocaine use in the preceding month 7.0±9.1 days; mean benzoylecgonine levels at baseline 2186.5 ng/ml±2495.2, and mean Beck Depression score 11.8±6.3. Initial results for this ongoing study revealed that compared to normative data, 60% of the sample had impaired performance (T score ≤ 33) on a measure of visual memory (Rey-Osterreith Complex Figure) and 42-52% were impaired (T score ≤ 33) on a measure of complex attention (Paced Auditory Serial Addition Test). In contrast, performance on the California Verbal Learning Test, Symbol Digit Modalities Test, Wisconsin Card Sorting Test, and Trail Making AtB was within normal limits as compared to normative data. Estimate IQ was in the average range (92.0±6.3). Nonparametric analyses indicated performance on neurocognitive measures was not significantly associated with baseline cocaine use factors, visual analog craving, depression, or patient initiated study drop out. Results are consistent with other reports of limited deficits in cocaine dependent individuals. Also of note, there was no significant relationship between amount of cocaine usage, neurocognitive status or demographic variables and study drop out, suggesting that a representative sample of those subjects initially recruited continue in the study past the baseline assessment. As these preliminary findings are based on pilot data, future analyses will determine if these relationships hold over the course of a 12-week clinical trial.

THE SUBSTANCE CLINICAL GLOBAL IMPRESSION (SCGI) SCALE: MEASURING GLOBAL FUNCTIONING IN SUBSTANCE RELATED CLINICAL TRIALS

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Much difficulty has occurred over accurately assessing global functioning of individuals with substance disorders, specifically cocaine related disorders. Although the CGI scale has been used in other psychiatric populations, it has not been standardized, nor modified, to address the needs of substance using populations. A committee of staff from NIDA Medication Development Research Units modified the CGI for use in multi-center cocaine clinical trials. Included are the following areas: reported use of cocaine and other drugs, cocaine seeking behavior, observable and reported psychiatric symptoms, physical/medical problems, maladaptive coping in family/social and other areas, and an exploratory option. Each item is rated for severity. Overall severity and improvement items are also rated. Weekly SCGI ratings from 155 subjects in cocaine clinical trials across four sites were compared to other common outcome measures for cross validation. The results indicate that SCGI global severity ratings decreased across the course of the 8-10 week clinical trials. The SCGI item and global scores compared to the ASI composite scores yield correlations ranging from .51 to .06. The self rated cocaine seeking behavior item which is comprised of craving for cocaine, effort to stop, and drug-seeking behavior was related to BSCS intensity of craving score ($r=.62$, $p<.0001$). BE levels were related to the observer rated cocaine use item ($r=.43$, $p<.0001$). The SUR was related to similar SCGI items ($r=.40$ to $r=.28$, $p<.0001$) The SCGI is a valid measure of global functioning, correlates with actual use/related functioning problems, and provides a time efficient outcome measure for short term trials.

NALTREXONE DOES NOT BLOCK "BINGE" COCAINE-INDUCED ELEVATION OF DYNORPHIN AND MU OPIOID RECEPTOR mRNA

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We have previously reported that one day "binge" cocaine administration led to a significant increase in mu opioid receptor (MOR) mRNA in the nucleus accumbens, frontal cortex and amygdala in rats, with **no** changes in the caudate putamen. It has been hypothesized that a rapid increase in receptor mRNA may be a compensatory response to rapid internalization of the receptor following binding with its released endogenous ligands. To test this, we have examined the effect of an opioid antagonist naltrexone (NTX) on MOR mRNA and for purposes of contrast, on preprodynorphin (Dyn) mRNA levels in the rat brain after one day "binge" pattern cocaine administration (three 15 mg/kg injections i.p. at 1h intervals). To minimize the effects of injection stress, male Fischer rats were injected with saline for 6 days prior to the test day. On the 7th day, rats received injections of either saline (1ml/kkg, i.p.) or NTX (10 mg/kg, i.p.), 15 min prior to start of the "binge" administration of cocaine or saline in four treatment groups: a) saline/saline; b) NTX/saline; c) saline/cocaine and d) NTX/cocaine. Rats were sacrificed 30 min after the final injection. MOR mRNA and Dyn mRNA in selected brain regions was quantitated by a solution hybridization RNase protection assay. MOR mRNA in the nucleus accumbens and frontal cortex, and Dyn mRNA levels in the caudate putamen, were both increased following "binge" cocaine administration ($p<0.05$). NTX did not alter cocaine-induced increase in MOR mRNA and Dyn mRNA levels in these brain regions nor did NTX alone affect these mRNA levels. These results suggest that the rapid increase in both MOR and Dyn mRNA by acute cocaine are not mediated by receptor binding of endogenous opioids.

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EFFECTS OF KAPPA OPIOID AGONISTS ON COCAINE SELF-ADMINISTRATION IN RHESUS MONKEYS: RAPID ASSESSMENT OF COCAINE DOSE-EFFECT CURVES

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Kappa opioid agonists attenuate some behavioral effects of cocaine, and we previously reported that kappa agonists reduced responding for cocaine doses at the peak of the cocaine self-administration dose-effect curve in rhesus monkeys (Negus *et al.,* 1997; Mello and Negus, 1998). The present study employed a novel procedure to assess the effects of kappa agonists on complete cocaine self-administration dose-effect functions in rhesus monkeys (n=3). Responding was maintained by food and up to four doses of cocaine in multiple components of each session, and full cocaine dose-effect functions were determined in a few sessions with overlapping dose ranges. Cocaine (0.001-0.32 mg/kg/injection; i.v.) dose-dependently maintained responding, resulting in characteristic inverted U-shaped dose-effect curves. The mixed kappa agonist/mu antagonist 1-cyclorphan (0.0032-0.032 mg/kg, i.m.) and the kappa selective agonist enadoline (0.00032-0.0032 mg/kg/hr, i.v.) decreased cocaine- and food-maintained responding. 1-Cyclorphan exhibited a selective reducion in cocaine self-administration at 0.01 mg/kg. In monkeys (n=5) trained to discriminate cocaine (0.4 mg/kg, i.m.) from saline, 1-cyclorphan did not substitute for or antagonize the discriminative stimulus effects of cocaine. These results suggest that further evaluation of kappa opioid agonists as potential treatments for cocaine abuse is warranted.

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PROCEDURAL EVALUATION OF INTRAVENOUS DRUG SELF-ADMINISTRATION BEHAVIOR IN MICE

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Mouse behavior is sensitive to both genetic and procedural influences. Procedural variables in drug self-administration include, dose and drug availability, operant manipulanda and behavioral training history. The contribution of these variables to intravenous drug self-administration performance was examined in C57BL/6JxSJL/J F1 hybrid mice. In general, nose-poke response rates were higher than lever press (4-5g force) response rates. In naive mice, both lever press and nose-poke responding was relatively stable over 15 sessions when saline was contingently infused and decreased only in the third week of testing. Substitution of cocaine and heroin following saline availability demonstrated dose-related responding and discrimination indexes which paralleled the number of injections. Nose-poke and lever press responding were also compared under conditions of speedball (cocaine + heroin) availability. Speedball acquisition profiles were qualitatively similar regardless of the operant response emitted, although quantitatively the fixed ratio associated with drug delivery was set at three to one for nose-poke vs. lever responding. No differences in dose-effect curves for speedball self-administration were observed when compared across operant groups. Interestingly, the shape of the dose-effect curve was similar regardless of whether subjects reached a criterion of $\geq$ 70% discrimination for lever press acquisition. Dose effect curves generated for nose-poke responding were identical whether the first day or all three days of dose substitutions were considered. These latter results support the use of a more streamlined drug self-administration protocol for mice. In sum, the overall characteristics of self-administration behavior are similar, regardless of operant employed. However, it is likely that expansion of these studies to other mouse strains, reinforcement schedules, and drugs may reveal more complex interactions associated with drug taking behavior.

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ISOBOLOGRAPHIC ANALYSIS OF COCAINE AND HEROIN CO-SELFADMINISTRATION IN RATS

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The concurrent use of cocaine and heroin, referred to as speedball, has continued to gain popularity in recent years. The pharmacological interaction between these drugs has not been evaluated across a range of doses that generate the entire inverted U-shaped dose-effect function; however, for this purpose, rats were trained to self-administer three combinations of cocaine and heroin under an FR10 schedule of reinforcement. Self-administration of cocaine and heroin alone was also assessed in these animals for comparison. The A50's for cocaine self-administration alone were 0.06 (0.04-0.08) and 0.318 (0.22-0.42) mg/inf on the ascending and descending limbs, respectively. Heroin maintained responding with respective A50's of 0.003 (0.002-0.004) and 0.03 (0.025-0.036) on the ascending and descending limbs. Isobolograms are generated using the A50's of cocaine and heron alone for both the ascending and descending limbs of each dose-effect curve. Plots of the A50's for cocaine and heroin in combination fell below the theoretical line of additivity on the descending limb of the dose-efect curves, but did not reach statistical significance from additivity. The A50's for the drug combination fell almost exactly on the theoretical line of additivity for the ascending limb. Therefore, cocaine and heroin appear to function in an additive manner pharmacologically maintaining self-administration under this schedule of reinforcement.

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THE REINFORCING EFFECTS OF A COMBINATION OF METHADONE AND COCAINE

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Polydrug abuse is common. In particular, patients in methadone programs often abuse cocaine, thus undermining the effectiveness of methadone treatment. In our study, with a FR 8 schedule, the oral self-administration of combinations of methadone and cocaine was studied in two rhesus monkeys. First, methadone (0.2 mg/ml) was established as a reinforcer. Next, cocaine was fade in, and methadone was fade out, thus cocaine came to function as a reinforcer. In the next phase, the monkeys had a choice of drinking the vehicle (deionized water), a drug solution, or a combination of methadone/cocaine. Only two liquids were tested at each session. All drug solutions, methadone (0.2 mg/ml), cocaine (0.0125, 0.05, 0.2, and 0.8 mg/ml), and a mixture of methadone plus one concentration of cocaine, were strongly preferred to the vehicle which indicates reinforcing effects. The highest rate of cocaine maintained responding was shifted from an intermediate concentration to a lower concentration after cocaine was combined with a reinforcing concentration of methadone (0.2 mg/ml). When monkeys had a choice of drinking the methadone solution or drinking the combination of methadone plus cocaine, the combination was preferred in all but one test condition (when methadone was combined with a lower dose of cocaine, the combination was not preferred to methadone alone with M-NL). When monkeys had a choice between drinking a cocaine solution or drinking the combination of methadone plus cocaine, there was a marked preference for the combination (except for one condition with M-NL where methadone combined with the 0.8 mg/ml cocaine, and the 0.8 mg/ml cocaine were equally selected). In the third phase, two combinations of methadone plus cocaine were made concurrently available. The combination with the higher cocaine concentration was always preferred. In summary, the combination of methadone plus cocaine served as an effective reinforcer, and had higher intrinsic reinforcing strength than either component alone.

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DISULFIRAM FOR COCAINE USE IN OPIATE-DEPENDENT SUBJECTS TREATED WITH BUPRENORPHINE

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Background: In this double-blind, randomized clinical trial, we examined the effects of disulfiram versus placebo on cocaine and illicit opioid use in buprenorphine-maintained subjects. Methods: Opiate dependent subjects (N=20), who were abusing or dependent on cocaine, were induced onto buprenorphine-maintenance (24 mg daily) and randomized to disulfiram (250 mg daily; N=11) or placebo (N=9) for a total of 12 weeks. Results: The groups were comparable at baseline on demographic measures. A total of 15 subjects completed the study, including 8 subjects randomized to disulfiram (72.7%) and 7 subjects randomized to placebo (77.8%). Disulfiram was well-tolerated, and there were no adverse reactions in these buprenorphine-maintained subjects. The total number of weeks abstinent from cocaine was significantly greater on disulfiram vs. placebo [Mean±SD: 7.8±2.6 vs. 3.3±0.5, $p<0.05$] and the number of days to achieving 3 weeks [24.6±15.1 vs. 57.8±7.7, $p<0.01$] of cocaine abstinence was significantly lower in disulfiram as compared to placebo. Subjects in the disulfiram group achieved consistently higher rates of cocaine negative urine tests in each 3 week interval, and that the increase over time was faster in the disulfiram as compared to placebo. There were no significant differences between disulfiram vs. placebo group on measures of illicit heroin use. Conclusions: This preliminary study suggests the efficacy of disulfiram vs. placebo for treatment of cocaine use in buprenorphine-maintained patients.

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COCAINE ABSTINENCE INITIATION IN METHADONE PATIENTS

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Many methadone patients continue to use drugs, especially cocaine, during treatment. Behavioral techniques that could reliably initiate abstinence in drug abusers would be clinically useful. This study examined efficacy of an abstinence initiation procedure based on behavioral principles that offered a large monetary reward for relatively small amount of behavior change. In a within-subject design, methadone maintenance patients, with evidence of on-going cocaine use, were exposed to four incentive conditions in random order. In one condition, a $100 incentive was available for evidence of 2-day abstinence based on quantitative urinalysis testing. In two other conditions, a total of $400 in vouchers was available for evidence of continuous abstinence over an 11-day period. In a final comparison condition, no voucher incentives were offered. Descriptive data are available for 32 subjects who completed at least 1 experimental condition. Approximately 80% of subjects stopped cocaine use for 2 days (Monday to Wednesday) when offered the $100 voucher incentive. In contrast, 50% were abstinent for 2 days under the no voucher condition. Subjects maintained abstinence for longer durations when incentives were continued following the initial abstinence initiation than when only a single incentive could be earned. Using the typical 300ng/ml benzoylecgonine cutoff criteria, a higher percentage of subjects (approximately 50%) were abstinent from days 4-11 in the extended voucher conditions than in the single or no voucher conditions, where approximately 20% were abstinent at these measurement time points. The procedure appears efficacious for initiating and sustaining abstinence from cocaine in methadone patients and may both clinical and scientific application.

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NEUROANATOMICAL LOCALIZATION OF QEEG ABNORMALITY RELATED TO TREATMENT FAILURE IN COCAINE DEPENDENCE

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As reported by Prichep *et al.* (1998) in the adjacent poster in this session, a cluster analysis of clectrophysiologic variables on 57 patients evaluated at entry into residential treatment for crack cocaine dependence yielded 3 groups; a favorable prognostic (FP) group in which 20 of 25 (80%) subjects were retained in treatment for >25 weeks, and two poor prognostic (PP) groups in which a total of 25 of 32 (69%) subjects prematurely terminated treatment at <25 weeks. Both PP groups shared the feature of increased relative power in beta which distinguished them from the FP group. The PP groups were further distinguished from one another on the basis of a relative excess of theta power in one of two PP groups. The FP group was characterized by a relative and absolute alpha power excess, which was not encountered in either PP group. Increased beta power has been associated with treatment failure in two independent studies of alcohol dependence, suggesting the possibility of a general marker for negative outcome in substance dependence. The neuroanatomical localization of beta activity, estimated by low resolution tomographic analysis (LORETA), revealed maximal beta activity localized to the temporal poles in the high theta PP group, and maximal beta activity localized to the left dorsolateral prefrontal cortex in the low theta PP group, which arc regions that are reportedly activated by exposure to cocaine cues in PET and fMRI studies. The alpha excess in the FP group was maximal in central and parietal cortical regions. It is suggested that neural sensitization is a mechanism that can explain and integrate these results on PP subjects with EEG and metabolic imaging results reported by other laboratories.

OUTCOME RELATED ELECTROPHYSIOLOGICAL SUBTYPES OF COCAINE DEPENDENCE

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A previous study demonstrated the existence of 2 QEEG subtypes of cocaine dependent males, identified at baseline (5-14 days after last use), displaying differential proneness to relapse and independent of length of drug exposure. This further study includes females and adds baseline somatosensory EP features to the QEEG measures. 57 cocaine dependent adults (16 F, 41 M), mean age 31.2 years, with DSM III-R cocaine dependence, were evaluated 5-14 days after last cocaine use, while inpatients at Phoenix House, a drug-free therapeutic community. The median length of stay in treatment (continued abstinence) for this group was 25 weeks. Cluster Analysis (SAS) on a small subset of QEEG and SEP baseline features identified 3 clusters. CLUS 2 (n=23) and CLUS 3 (n=25) replicated the earlier subtypes, while, CLUS 1 (n=9) was previously undescribed. Among the distinguishable features were excess % power in theta and beta in CLUS 1, excess % power in beta CLUS 2 and excess absolute and % power in alpha in CLUS 3. Cluster membership was significantly associated with length of stay in treatment (χ^2=13.789, P<0.001) but not with length of exposure or any demographic or clinical data. 78% of Cluster 1 and 65% of Cluster 2 left treatment ≤ 25 weeks, whereas 80% of Cluster 3 remained in treatment > 25 weeks. The existence of outcome related subtypes may reflect differential neurophysiological vulnerability predisposing individuals to cocaine addiction or drug-seeking behavior, differential neurosensitivity to the effects of cocaine exposure, and associated differences in treatment outcome. The application of a source localization algorithm to this data will be reported elsewhere (Alper *et al.,* 1998).

SUBJECTIVE, PSYCHOMOTOR AND PHYSIOLOGICAL EFFECTS OF INTRAVENOUS HYDROMORPHONE AND MORPHINE IN NON-DRUG-ABUSING VOLUNTEERS

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Hydromorphone is an opioid mu agonist commonly used for post-operative analgesia. Its effects have been well-characterized in opioid abusers, but not in non-drug abusers. Accordingly, we examined hydromorphone's effects in healthy volunteers using an abuse liability testing methodology which comprehensively assesses a drug's subjective, psychomotor, and physiological effects. In addition, we tested two doses of morphine to compare the effects of the two full mu agonists. With approval from the IRB, healthy volunteers with no history of drug abuse (n=17), whose ages ranged from 21-34 yrs (mean age=25.1 yrs), were enrolled in a randomized, double-blind, placebo controlled, crossover trial. In a semi-recumbent position, subjects received an injection of hydromorphone (0.33, 0.65, and 1.3 mg/70 kg), morphine (5 and 10 mg/70 kg), or saline. Behavioral and physiological measures were assessed before and for 5 h after the injection. In a dose-related manner, hydromorphone increased PCAG and LSD scores on the ARCI and several ratings on an opiate adjective checklist. A number of VAS ratings, including "heavy, sluggish feeling," "sleepy," and "coasting" were also increased. Hydromorphone had little effect on psychomotor performance, but did induce miosis. Morphine had a similar profile of subjective effects to that of hydromorphone. The magnitude of effect on many measures was greater with 1.3 mg of hydromorphone than with 10 mg of morphine, but the differences rarely achieved statistical significance. We conclude that hydromorphone has similar qualitative and quantitative effects to those of morphine. This result replicates similar findings with post-addicts (cf. Preston and Jasinksi, 1991).

REFERENCE: Preston, K.L. and Jasinski, D.R. (1991) Drug and Alcohol Dependence, 28, 49-82.

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BEHAVIORAL AND PHYSIOLOGICAL EFFECTS OF CUMULATIVE DOSES OF MORPHINE AND THREE MIXED AGONIST-ANTAGONIST OPIOIDS IN NON-DRUG-ABUSERS

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Subjective, psychomotor, and physiological effects of three mixed agonist-antagonist opioids were examined in comparison with morphine, a full mu agonist, using a cumulative-dosing procedure. Thirteen healthy volunteers received i.v. injections of saline (S), morphine (M), butorphanol (B), nalbuphine (N), or pentazocine (P) in a randomized, double-blind, crossover design. Subjects received one injection per hour for the first four hours, and a 3-hr recovery period followed. S was injected first during each session; then S or increasing doses of the opioid were administered. These putatively equianalgesic doses (actual amount per injection) were M and N 2.5, 5, and 10 mg/70 kg; B 0.5, 1, and 2 mg/70 kg; and P 7.5, 15, and 0 mg/70 kg. (The largest dose of P was omitted to avoid the risk of psychotomimesis.) Subjects completed mood forms and psychomotor tests, and vital signs were recorded following drug injection and during recovery. Dose-related effects were observed for all drugs. Butorphanol produced stronger subjective effects or influenced mood at smaller doses than the other opioids. MOR produced the least psychomotor impairment, and BUT produced the most, a result that replicates those found in our single-dosing studies. Some effects of BUT and NAL showed a ceiling effect, which is consistent with other research showing ceiling effects of these drugs. Although PEN effects could not be fully characterized because the largest dose was omitted, no obvious differences were observed in quality or magnitude of effects, compared with the other opioids.

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EFFECTS OF BUTORPHANOL AND NALBUPHINE IN OPIOID-DEPENDENT HUMANS UNDER A NOVEL-RESPONSE NALOXONE DISCRIMINATION PROCEDURE

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The pharmacological specificity of the instructed novel-response naloxone discrimination procedure was examined by determining the effects of mixed-action opioids in opioid-dependent subjects trained to discriminate the opioid antagonist naloxone (NX) from placebo. Five male opioid-maintained volunteers were trained to distinguish between a low dose of NX (0.15 mg/70 kg, i.m.; e.g., Drug A) and placebo (e.g., Drug B) under an instructed novel-response drug discrimination procedure, in which subjects identify the drug condition as "A", "B", or "N" (neither A nor B - 'novel'). Once the discrimination was acquired, doses of NX (0-0.15 mg/70 kg, i.m.), butorphanol (BUT; 0-1.5 mg/70 kg, i.m.), and nalbuphine (NAL; 0-3.0 mg/70 kg, i.m.) were tested. NX produced dose-related increases in NX-appropriate responding, little or no 'novel'-appropriate responding and increases in self-reported opioid antagonist adjective ratings. BUT produced approximately 60% NX-appropriate responding at the highest dose tested, a dose-related increase in 'novel'-appropriate responding to approximately 40% at the highest dose tested, and increases in self-reported opioid agonist adjective ratings at the lowest dose and in antagonist adjective ratings at the highest dose. NAL produced 80% NX-appropriate responding at the middle dose tested, 40% novel-appropriate responding at the highest doses, and increases in self-reported opioid agonist adjective ratings at the lowest dose and in antagonist adjective ratings at the highest dose. These results suggest that mixed-action opioid agonist/antagonists may be distinguished from the opioid antagonist naloxone based on their discriminative stimulus and self-reported effects under a novel-response naloxone discrimination procedure.

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EVALUATION OF THE PHENCYCLIDINE (PCP)-LIKE DISCRIMINATIVE STIMULUS EFFECTS OF THE ISOMERS OF METHADONE AND PENTAZOCINE

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Methadone and pentazocine have been shown to have affinity for both opioid receptors and the PCP-site on the NMDA receptor complex. To further evaluate possible NMDA antagonist-like effects of these drugs, the racemates and enantiomers of methadone and both alpha- and beta-pentazocine were tested in rats trained to discriminate PCP from saline in a standard two-lever drug discrimination procedure. Testing of (±)-, (+)- and (-)-methadone, alone and with naloxone, failed to produce greater than 40% substitution for PCP. Similarly, alpha-pentazocine (Talwin®) and its isomers produced at best 28% PCP-lever responding. Co-administration with naltrexone produced inconsistent results. (±)-beta-pentazocine alone produced partial levels of substitution and full substitution when combined with naltrexone. The PCP-like discriminative stimulus effects were associated only with the (-)-isomer. Overall, production of PCP-like discriminative stimulus effects appeared to be related primarily to absolute affinity for the PCP-site rather than the ratio of PCP-site to mu opioid affinity. The response rate suppressing effects of the methadone compounds reflected their relative affinity for the mu opioid site, while for the pentazocine compounds, the response rate effects did not reflect their affinity for either the PCP-site or mu opioid receptor consistent with an alternative CNS site of activity.

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ROLE OF NMDA AND SIGMA RECEPTORS IN THE DISCRIMINATIVE STIMULUS EFFECTS OF U-50,488H

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It is well known that kappa receptor agonist U-50,488H produces aversive 'and psychotomimetic effect. To clarify the role of NMDA receptor and sigma receptors in the discriminative stimulus effects of U-50,488H, we examined the effects of non-competitive NMDA antagonists and sigma I receptor agonists on the discriminative stimulus properties of U-50,488H (3 mg/kg, i.p.) which produces a significant aversion. Eight male Fischer 344 rats were trained to discriminate between U-50,488H (3 mg/kg, i.p.) and saline under a fixed ratio (FR) 10 schedule. After the animals attained the criterion (accuracy of at least 83 %), dose-response and generalization tests were initiated. Phencyclidine (PCP) generalized to the discriminative stimulus effects of U-50,488H. This finding suggests that the discriminative stimulus effect of U-50,488H may be related to PCP-like psychotomimetic effects, which may result in aversive effects. Moreover, dizocilpine (non-competitive NMDA receptor antagonist) and (+)pentazocine (sigmal receptor agonist) also generalized to the discriminative stimulus effect of U-50,488H. However, (±) and (-) pentazocine partially generalized to the discriminative stimulus effects of U-50,488H. On the other hand, SA 4503 (sigma, receptor agonist) did not generalize to the discriminative stimulus effects U-50,488H, suggesting that there may be two receptor subclasses in the sigmal receptor subtype. These findings indicate that blockade of NMDA receptors and activation of sigma receptors, especially (+) pentazocine binding site, may play an important role in the discriminative stimulus effects of U-50,488H.

COCAINE-LIKE DISCRIMINATIVE STIMULUS EFFECTS PRODUCED BY THE PARTIAL MU AGONISTS DEZOCINE, MEPERIDINE AND PROFADOL

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The present study evaluated the ability of several partial mu agonists with known non-opioid actions to produce cocaine-like discriminative stimulus effects. In rats trained to discriminate 10 mg/kg cocaine from saline, cocaine and the D2/D3 agonist (-)-quinpirole produced dose-dependent increases in cocaine-appropriate responding. When administered alone, the partial mu agonist dezocine (1.0 - 10 mg/kg) failed to substitute for the cocaine stimulus. Pretreatment with naltrexone antagonized dezocine's rate-decreasing effects such that higher doses could be tested. The highest dose of dezocine (17.5 mg/kg), tested in combination with naltrexone, produced high levels of cocaine-appropriate responding. The partial mu agonists meperidine and profadol alone, and in combination with naltrexone, produced intermediate levels of cocaine-appropriate responding, though to a lesser extent than that observed with dezocine. In contrast, the partial mu agonists butorphanol and (+)-propoxyphene, the mu agonist morphine, the kappa agonist U50,488, and the barbiturate pentobarbital, alone or in combination with naltrexone, failed to produce appreciable levels of cocaine-appropriate responding. These findings suggest that the cocaine-like discriminative stimulus effects produced by dezocine, meperidine and profadol, while not related to their activity at mu or kappa opioid receptors, could be due to an unspecified action in the dopaminergic system.

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STIMULUS CONTROL OF DRUG ABUSE: STIMULUS COMPOUNDING PRODUCES COMPARABLE INCREASES IN HEROIN AND COCAINE SELF-ADMINISTRATION

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Recently, it was shown that combining previously-established discriminative stimuli can substantially increase cocaine self-administration in rats. The present study further assessed the generality of this effect by systematically replicating it with opioid self-administration. Rats' nose-poke responding produced heroin (0.025 mg/kg/infusion, iv) on a variable-ratio schedule when either a tone or a light was present, but not in the absence of these stimuli. Once the tone and light had acquired discriminative control of responding, they were presented in compound during extinction (with heroin discontinued) or under maintenance conditions (with heroin available during test-stimulus presentations). In extinction, the tone-light compound increased responding approximately 3-fold compared to tone and light alone. Under maintenance conditions, compounding increased heroin intake approximately 2-fold. These effects closely matched those obtained earlier with cocaine and in a preliminary study with morphine. Furthermore, these results replicate those obtained earlier with food reinforcement and shock avoidance. This consistency across pharmacological classes and across drug and non-drug reinforcers provides further evidence that: 1) self-administered drugs support conditioning and learning in a manner comparable to that of other reinforcers; and 2) multiple drug-related cues interact in lawful and predictable ways to affect drug seeking and consumption.

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MODULATION OF MORPHINE BEHAVIORAL EFFECTS BY FLUOXETINE

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The role of serotonin in the opioid dependence/withdrawal signs is documented already for a longer time. The serotonergic influence of S.S.R.I. fluoxetine on morphine behavioral effects was investigated in the present study. Changes of morphine effects caused by fluoxetine co-administration were evaluated in the models of 'agonistic behavior' in singly-housed male mice on dyadic interactions with non-aggressive group-housed partners, and I. V. drug self-administration in rats. Fluoxetine at the dose of 5 mg/kg, did not significantly alter behavior of neither 'aggressive' nor 'timid' singly-housed mice. In the combined treatment fluoxetine potentiated the anti-aggressive effect of morphine (5 mg/kg), and the inhibiting effects on locomotion in both, 'aggressive' and 'timid' mice. Morphine I. V. self-administration in rats (in the Coulbourn Instruments's cages) during 2h daily sessions was increasing, already, since the 3rd experimental day. The drug intake and preference of the active hole maintained stable on increasing 'fixed ratio' (FR 1, 2, 3) of nose-pokes required for receiving an injection. Fluoxetine pretreatment suppressed morphine self-administration at doses (2 mg/kg) which did not inhibit locomotor and exploratory behavior of rats in the staircase test. The withdrawal of fluoxetine caused return to morphine self-administration of the previous level. This effect was shown in the each rat repeatedly.

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ETHANOL AND DIZOCILPINE ALTER THE LOCOMOTOR EFFECTS OF MORPHINE

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The noncompetitive NMDA antagonist, dizocilpine (DZ), attenuates chronic morphine (MS) effects. Like DZ, pretreatment with ethanol, a putative NMDA antagonist, attenuates MS dependence. We examined whether ethanol would attenuate MS locomotor sensitization. Separate groups of rats (n=6 ea) were injected with DZ (0.1 mg/kg IP), ethanol (1 g/kg IP), or vehicle followed 30 min later by MS (0 or 10 mg/kg SC) for 14 days. One week later, rats were given MS (0 or 3 mg/kg SC) and locomotor activity was assessed for 60 min. In vehicle pretreated rats, MS led to a prolonged enhanced activation, which was greater in the group with chronic MS administration demonstrating locomotor sensitization. This "morphine pattern" was eliminated by chronic DZ, but not by chronic ethanol pretreatments. Both DZ and ethanol depressed activity levels. These effects occurred whether or not MS was administered chronically. In separate groups, neither DZ nor ethanol altered the acute biphasic locomotor effects of MS (hypoactivity followed by hyperactivity). The possible motivational consequences of the MS biphasic effect were assessed using Pavlovian conditioning procedures and measuring ultrasonic vocalizations (USVs). An immediate group received 3 pairings of MS (10 mg/kg SC) in the presence of a CS from 0-15 min post-injection and a delayed group received 3 pairings of MS in the presence of a CS from 210-225 min post-injection. On other days, 3 pairings of saline in the presence of another CS were given. There were more CS-elicited USVs than UR-elicited USVs. The MS-paired CS+ elicited more USVs than the saline-paired CS-. MS's "biphasic" locomotor effect was mimicked by the CS-elicited USVs; fewer USVs were produced to the CS+ in the immediate compared to the delayed condition. Because previous research shows that different USV frequency levels are associated with different affective values (24 kHZ-aversive; 55 kHz-appetitive), USVs may provide a rapid way in which to measure affective dynamic states induced by drugs and the CSs associated with them.

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NATREXONE SUPPRESSION OF DRUG SELF-ADMINISTRATION IS DETERMINED BY ECONOMIC CONDITIONS

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The purpose of this study was to investigate the effects of naltrexone (NTX) on ethanol, phencyclidine (PCP), and food intake in an open vs closed economy using progressive-ratio (PR) schedules. Six adult male rhesus monkeys orally self-administered ethanol (8% wt/vol), PCP (0.25 mg/ml), and food (7.0 g/pellet) concurrently with water during daily 3-hr sessions. Response requirements, consisting of lip contacts on the drinking spout, increased from 8 to 4,096 within session under the PR schedule. Completion of each ratio resulted in 40 liquid deliveries (24 ml) under an FR 1 schedule. An open vs closed economy was established by providing the monkeys with 0, 1, 2, or 3 times (X) the mean amount of liquid or pellet deliveries obtained during a 5-session baseline. Monkeys obtained the deliveries under a FR 1 schedule at the beginning of the intersession period, or food was placed in a food hopper. Naltrexone (0.1, 0.3, 1.0 mg/kg) injections were given i.m., in counter-balanced order, 30 min prior to session for 5 days. Results show that NTX decreased responding for drug and food as a function of the economy; that is, as the economy was progressively opened from 0 to 3X the suppressant effects of NTX increased. Food and PCP-maintained responding was not reduced under a closed economy. These results suggest that economic conditions under which drug and non-drug reinforcers are available is an important determinant of the selectivity of medication effects.

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SUBJECTIVE AND OBJECTIVE EFFECTS OF ETHANOL, AND ETHANOL CHOICE, ACROSS THE MENSTRUAL CYCLE IN NORMAL, CYCLING WOMEN

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Ethanol has both stimulant-like and sedative-like subjective effects that might be mediated, at least in part, by the dopamine (DA) and gamma amino-butyric acid (GABA) systems. Ovarian hormones also have actions on these neurotransmitter systems raising the possibility that they may influence subjective, behavioral, and physiological responses to ethanol. One way to investigate the relationship between circulating ovarian hormones and the subjective, behavioral, and physiological effects of ethanol is to administer ethanol to normal, cycling women at hormonally distinct phases of the menstrual cycle. In this study, we administered ethanol during the early follicular, late follicular, mid-luteal and late-luteal phases of the menstrual cycle. Ovulation was confirmed for each subject and hormonal status was assessed in plasma before each session to confirm menstrual cycle phase. During each session, participants first sampled three ethanol-containing beverages (0.2 g/kg each) at half hourly intervals. Subjective, behavioral and physiological measures were obtained before and after each dose. After the third beverage, subjects were allowed to choose up to three additional beverages, one every half hour. The subjective, behavioral, and physiological effects of ethanol, including choice for additional ethanol beverages, did not vary across the menstrual cycle. Ethanol exerted its prototypical effects on breath alcohol levels, heart rate and blood pressure, psychomotor performance, peak saccadic eye velocity, saccadic latency and smooth pursuit gain, and subjective states. These results suggest that the influence of menstrual cycle, if any, on the subjective, reinforcing, behavioral, and physiological effects of ethanol is relatively subtle.

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THE EFFECTS OF ALCOHOL IN FEMALES WITH AND WITHOUT A PATERNAL HISTORY OF ALCOHOLISM

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The present study compared the response to alcohol in females with a confirmed paternal history of alcoholism (FHP), to females without a family history of alcoholism (FHN). Based on previous studies in males, we hypothesized that FHP and FHN females would respond differently to acute doses of alcohol. The two groups were matched on race, age, education, and alcohol use. The acute effects of four doses of alcohol (0 g/kg and approximately 0.25 g/kg, 0.50 g/kg and 0.75 g/kg, based on total body water) were evaluated using a double-blind, placebo-controlled outpatient design. Each session, a 350 ml isocaloric beverage was consumed over 5 min. The effects of alcohol were assessed using blood alcohol concentrations, performance tasks, observer ratings of drug effect and subjective ratings of mood, Drug Strength and Drug Liking. At the highest dose, blood alcohol concentrations were significantly higher in the FHP group than the FHN group, with peak blood alcohol concentrations of 99 mg/dl and 85 mg/dl, respectively. Alcohol produced similar dose-related decreases on most of the performance and memory tasks in both groups. However, alcohol tended to impair DSST performance more in the FHN group compared to the FHP group. Ratings of Drug Liking increased as a function of dose and tended to be higher in the FHP group, although ratings of Drug Strength were similar in both groups. Based on these preliminary analyses, there appear to be limited differences in response to the acute effects of alcohol in FHP and FHN females, which contrasts our previous study showing that FHP females are more sensitive to alprazolam.

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EFFECT OF IFENPRODIL ON EXPRESSION OF ETHANOL WITHDRAWAL SIGNS

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To clarify the role of NMDA receptor in the expression of ethanol withdrawal signs, the present study investigated the effects of non-competitive NMDA receptor antagonist ifenprodil on the appearance of spontaneous ethanol withdrawal signs. Fischer 344 rats were chronically treated with liquid diet containing ethanol for 26 days. The concentration of ethanol in the liquid diet was gradually increased from 2.5 w/v% to 5 w/v%. Withdrawal was induced by substituting normal liquid diet for ethanol-containing liquid diet. Based on motor, emotional and autonomic signs, withdrawal signs were observed at 3-6 hr intervals up to 48 hr after the withdrawal. Ifenprodil (2.5, 5, 10 mg/kg) was injected i.p. 30 min prior to the observation at 3, 6, and 9 hr after the withdrawal. Several withdrawal signs of ethanol, such as seizure, were observed for 48 hr after the withdrawal. The total withdrawal score gradually increased; the maximal score was observed 9 hr after the withdrawal. Ifenprodil drastically suppressed the total, motor and emotional withdrawal scores in ethanol-dependent rats. It is known that ifenprodil is a selective antagonist of NMDA receptors containing NR2B subunits. These findings suggest that NMDA (NR1/NR2B) receptors may play an important role in the expression of the ethanol-withdrawal signs, and ifenprodil may be useful for treatment of alcohol dependence.

INTENSIVE CASE MANAGEMENT FOR HOMELESS SUBSTANCE USERS ON A MOBILE MEDICAL CLINIC

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The benefits of social work services (Intensive Case Management, ICM) on a mobile medical clinic serving homeless people in Manhattan were evaluated in conjunction with an experimental design (N=101). Clients, almost all of whom were found to be substance abusers, were assigned to receive ICM (a detailed social svork assessment; at least four sessions; and the use of incentives to encourage desired behavior) or ‘services as usual, with the two groups evaluated after four months with regard to living arrangements, drug/alcohol treatment, and access to government assistance programs (SSI/SSD, Medicaid, food stamps, home relief, and housing assistance). A process evaluation found greater levels of social worker and agency contacts among JCMs. Percent of clients receiving any government assistance increased from 56% to 72% among the ICMs but decreased from 60% to 50% among the controls (P<= .05; McNemar test). ICMs were less likely to use emergency room (E9) services (a desired outcome) (26% ICM vs. 45% control; P< = .05; chi-square test). Study group differences on other outcomes were not observed. As an adjunct to mobile outreach, ICM holds promise for increasing access of homeless people to government assistance programs, at a time when such services are in flux, and reducing the often misutilized and high cost EM services. Linking homeless substance abusers to appropriate addiction treatment remains problematic.

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THE EFFECTS OF TRIAZOLAM, ALPRAZOLAM, GENDER, AND MENSTRUAL CYCLE ON FOOD INTAKE IN HUMANS

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Previous studies have shown a hyperphagic effect of benzodiazepines (BZPs) on palatable foods across species. In separate studies, the effects of triazolam and alprazolam on food intake were examined in combination with gender, and menstrual cycle phase. Following written consent and both medical and psychological evaluations, 12 female and 13 male healthy adults between the ages of 20-45, blind to the study drug, participated on three consecutive days per week over eight consecutive weeks. Study days coincided with four cycle phases. Each of three doses of either triazolam (0, 0.2, and 0.4 mg/70 kg) or alprazolam (0, 0.4, and 0.8 mg/70 kg) was administered orally 1 day each week in random order. Subjects received a single drug during study participation. On test days, subjects consumed a standard meal at 5:30 p.m., received drug at 6:30 p.m., completed performance tasks and visual-analog ratings of drug effect, and ordered snacks from a computer generated list of assorted food items at 10:45 p.m. Snacks were consumed between 11:00 and 11:30 p.m. Breakfast was ordered from the list shortly upon waking. Consistent with previous studies of the effects of BZPs on food intake in baboons and humans, an inverted U-shaped relationship between dose and food intake was observed following triazolam administration in both males and females. However, following alprazolam administration, food intake increased in a dose-dependent manner. Gender differences in food intake were observed, but dose effects were not different in males and females. A significant dose by menstrual cycle interaction was observed in breakfast protein intake following triazolam administration but no menstrual cycle effects were observed following alprazolam administration. Changes in food intake across the menstrual cycle were prominent in some but not all women. These results indicate that doses of triazolam and alprazolam increase food intake in humans, that BZPs differ in their effects on food intake, and that drug effects vary across the menstrual cycle following triazolam administration but not following alprazolam administration.

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RATE OF ONSET OF EFFECTS AND DOSE ADMINISTERED DETERMINE ALPRAZOLAM ABUSE LIABILITY IN HEALTHY VOLUNTEERS

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Abuse liability is determined in part by intensity and rate of onset of drug effects. Drug abusers prefer benzodiazepines with fast absorption because of rapid and intense obtention of pleasurable feelings. The reinforcing effects of sedatives (diazepam, flunitrazcpam) have been reduced slowing the onset of effects with a specific experimental design (FAST/SLOW administration, Psychopharmacology 1993; 112: 324-30) or administering an slow-release formulation. The effects of two different doses of alprazolam (ALP) (medium [M] and high [H]) given in FAST (single administration) or SLOW (divided administration) schedule were assessed in two groups of twelve healthy male volunteers with two randomized, placebo-controlled, double-blind and double-dummy, cross-over studies. Drugs were administered in 6 capsules over 2.5 h, ingested every 30 min. Conditions were: placebo, ALP SLOW (6 divided doses of 0.27 mg [M] or 0.4 mg [H]), and ALP FAST (5 placebo capsules and a single last dose of 1.35 mg [M] or 2 mg [H]). Variables included: vital signs, subjective effects (VAS, ARCI, POMS), psychomotor performance (reaction time, DSST, Maddox-wing), and ALP plasma concentrations. Both active conditions (FAST and SLOW) induced an impairment of psychomotor performance tasks and sedative effects, with a good dose-effect relationship between M and H doses. No differences appeared between sedative peak effects in SLOW and FAST conditions. At both dose levels, ALP induced pleasurable feelings (VAS-good effects, VAS-high, VAS-liking), which were more intense with the M dose. M dose FAST administration induced more intense pleasurable feelings. At H dose sedation-related unpleasant feelings were evidenced, mostly in SLOW condition. These results provide support to the assumption that the reinforcing effects of drugs are determined by its intensity and rate of onset.

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FLUMAZENIL-PRECIPITATED WITHDRAWAL IN CHRONIC LOW-DOSE BENZODIAZEPINE USERS

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Preclinical studies of the benzodiazepine antagonist flumazenil (FLU; Romazicon™) have contributed to the understanding of the physical dependence associated with chronic benzodiazepine use in that administering FLU to animals chronically pretreated with benzodiazepines precipitates a withdrawal syndrome; however, few controlled clinical studies have been conducted. The present double-blind, placebo-controlled, repeated-measures study evaluated the acute physiological, participant-rated, and observer-rated effects of intravenously administered FLU (1 mg/70 kg) and caffeine (CAF; 300 mg/70 kg; active drug control) in an experimental group of 13 long-term users (mean 4.6 yr) of low therapeutic doses (mean 11.2 diazepam equivalent) relative to a matched group of 13 volunteers without prior exposure to benzodiazepines. Whereas the experimental group did not differ from the control group with respect to the effects of placebo, and both groups showed some changes in response to CAF (e.g., increased blood pressure and anxiety scores), only the experimental group showed considerable changes in physiological measures, participant ratings (e.g., increased ratings of dizzy, blurred vision, heart pounding, feeling of unreality, pins and needles, nausea, sweaty, noises louder than usual, jittery, things moving, sensitive to touch), and observer ratings in response to FLU; in addition, four experimental group participants developed panic attacks in response to FLU. This study clearly demonstrates that flumazenil can precipitate symptoms commonly associated with benzodiazepine withdrawal in chronic low-dose users.

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DISCRIMINATIVE STIMULUS EFFECTS OF ZOLPIDEM IN SQUIRREL MONKEYS

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Zolpidem is an imidazopyridine that exhibits selectivity for benzodiazepine (BZ)/$GABA_A$ receptors containing the *alpha*-l subunit. Previous studies have suggested that zolpidem has a characteristic profile of discriminative stimulus (DS) effects that differ from those of conventional BZ agonists. The present study assessed the ability of BZs and barbiturates, which typically share DS effects with BZs, to reproduce the DS effects of zolpidem in squirrel monkeys. Monkeys were trained to discriminate zolpidem (1.0 mg/kg, i.v.) from vehicle under a 10-response fixed-ratio schedule of food delivery. Under test conditions, zolpidem (0.1-3.0 mg/kg) engendered a dose-dependent increase in drug-lever responding, reaching an average maximum of≥80%. The BZ agonists triazolam and diazepam also engendered 280% zolpidem-lever responding. However, other BZ agonists including chlordiazepoxide and lorazepam, as well as the barbiturates pentobarbital, barbital, and methohexital, engendered maximums of only 20-70% drug-lever responding up to doses that markedly reduced response rate. These results suggest that zolpidem's selectivity for the *alpha*-1 subunit of the BZ/$GABA_A$ receptor complex confers a profile of DS effects that overlaps partially with typical BZs and differs from barbiturates.

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EFFECTS OF ACUTE EXPOSURE TO TOLUENE ON GABA CONCENTRATIONS IN THE BRAIN AND CEREBELLUM OF ADULT RATS

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It has been reported that toluene has anti-convulsant effects in several experimental preparations with Wistar rats. Since GABA is the main inhibitory neurotransmitter in the Central Nervous System, the purpose of this study was to determine the concentration of GABA in the brain and cerebellum of rats exposed to 40 000 ppm of toluene during 15 minutes. Static exposure chambers of 2.7 were used. Two groups (n=8 each) of rats (200-250 g) were exposed to either air or toluene. After the exposure period, each animal was sacrificed, the brain and the cerebellum were obtained and the total GABA concentration was measured by HPLC. A slight decrease in the amount of GABA was observed in both tissues, which, however, was not statistically significant. These results suggest that other neurotransmitter systems are involved in the anticonvulsant effects of toluene.

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ANXIOLYTIC-LIKE EFFECTS OF TOLUENE IN WILD TYPE AND 5-HT1B KNOCKOUT MICE

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Several CNS depressant drugs, such as ethanol and toluene, have anxiolytic-like effects in several experimental models. Since it has been reported that mice lacking the 5-HT1B receptor subtype exhibit differences in ethanol sensitivity, the general purpose of this study was to compare the anxiolytic-like actions of toluene in 129/Sv wild type (WT) and knockout (KO) mice. Two anxiety paradigms were used: the burying behavior test and the elevated plus maze. Static exposures to toluene were conducted in 29-1 gas chromatography jars. Animals were exposed to 0, 1000, 2000 or 4000 ppm of toluene (n=8-12) during 30 min and immediately after, tested for anxiety-like effects. Previously, all mice were trained on two consecutive days by exposing them to air during 30 min in the exposure chambers. In the burying behavior test three parameters were registered: a) cumulative burying behavior that reflects the animal's anxiety levels, b) burying behavior latency that inversely reflects the animal's reactivity, and c) number of shocks. The parameters evaluated in the plus maze were: a) time spent in open arms, b) number of entries into open arms; and c) total number of arm entries. Time in open arms and open arm entries are considered to directly reflect anxiety-like levels. Total arm entries are used to evaluate locomotor activity. Two additional experiments were done to evaluate motor coordination (rota rod test) and nociception (hot plate). Toluene induced anxiolytic-like actions in both strains of mice in the two models of anxiety used. Interestingly, KO animals appeared to be more sensitive to the effects of toluene in comparison with WT type mice. These results cannot be attributed to motor impairment since all animals behaved similarly in the rota rod test, regardless of the treatment. In addition, toluene increased nociception similarly in both strains of mice. Our data suggest differences in sensitivity to toluene such as those reported for ethanol in the 5-HT1B KO mice. These results suggest that the serotonergic system might be involved in the anxiolytic-like actions of toluene.

TOLUENE INDUCES AN INCREASE IN NOCICEPTION IN MICE

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There is recent evidence supporting that toluene is a potent non-competitive inhibitor of NMDA receptors. Since NMDA receptor antagonists have been reported to be analgesics in different experimental paradigms, the present investigation was undertaken to study the effects of toluene on nociception. Swiss-Webster mice (20-30g) were trained on two consecutive days by placing them during 30 min in static exposure chambers inhaling air. On the third day independent groups of animals were exposed to toluene (0, 2000, 4000 or 6000 ppm; n= 10-13) for 30 min. After this period, they were individually tested in the hot plate or in the tail pinch tests. The hot plate was adjusted at 53 ± 0.5 °C. The latencies to the appearance of the spinal reflex, paw-lick, and escape were determined. This experiment was concluded after 30s to prevent tissue damage. The tail pinch test consisted in applying an alligator clip 3 cm from the tip of the mouse tail. The latency to the first tail flick or any active reaction against the clip was recorded. Interestingly, toluene induced a dose-dependent increase in thermo- and mechanociception, as reflected in lower latencies for the parameters evaluated. These effects reached their maximum at 4000 ppm. In order to test if the hyperalgesic effects of toluene were due to an interaction with the endogenous opioid system, two additional experimental series were included. Low doses of toluene (500 or 1000 ppm) were combined with subtreshold doses of the opioid competitive antagonist naloxone (0.1 or 0.2 mg/kg, i.p.) and their effects were evaluated in the hot plate test. Naloxone was injected immediately before exposing each animal to a 30-min period of toluene inhalation. No potentiation was observed when low doses of naloxone and toluene were combined. Our findings suggest that neurotransmitter systems, other than glutamatergic, might be involved in toluene-induced increased nociception The results obtained with naloxone suggest that the opioidergic system is not involved in the effects of toluene in nociception.

EXAMINATION OF THE REINFORCING EFFECTS OF INTRAVENOUS DELIVERY OF PROPOFOL, HALOTHANE AND 1,1,1-TRICHLOROETHANE IN RATS

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Previous reports suggest that propofol (PPF), halothane (HAL), and 1,1,1-trichloroethane (TCE) may have abuse potential in humans. We hypothesized that these drugs might serve as reinforcers in other species. Intravenous propofol self-administration was examined in 12 rats. Six were initially trained to self-administer methohexital (MHX, 2.0 mg/kg/inf) under an FR 1 schedule, while the other six were trained with PPF (1.7 mg/kg/inf). Once stable self-administration was established with the training dose, other doses of PPF (0.56, 1.0, and 1.7 mg/kg/inf) and vehicle (Intralipid) were substituted for MHX or PPF. The number of PPF infusions per session was an inverse function of dose, with 0.56 and 1.0 mg/kg/inf maintaining significantly more infusions per session than vehicle in most rats. For some rats, the number of vehicle infusions per session was greater than the number of PPF infusions, thus obscuring a reinforcement effect in these rats. However, increasing the response requirement to FR 5 decreased the number of vehicle infusions per session, while PPF continued to maintain self-administration at this FR value in six of seven rats. Intravenous HAL (10, 30, 56 mg/kg/inf, N=6) and TCE (10.0, 17.8, and 30.0 mg/kg/inf, N=4) self-administration were examined in rats initially trained to self-administer 1.7 mg/kg/inf PPF. Although considerable levels of responding were maintained in most rats when HAL and TCE were substituted for PPF, no dose of either drug maintained infusion rates significantly greater than those observed with vehicle. Thus, propofol, but not HAL or TCE, served as a reinforcer under FR schedules of intravenous drug delivery in the present study.

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"ACTIVO " INTAKE BY MEXICAN STREET CHILDREN

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Inhalants are the drugs mainly consumed by street children in Mexico. These substances are obtained from commercial products and from drug dealers, and the substance known as "Activo" (active) is one of the most used. The aim of this work was to identify the psychological and social processes of acquisition and consumption of this product among a sample of Mexican street children. Thirty-six kids grouped in four different gangs, ranging between 6 to 23 years of age, were identified and contacted by experienced field researchers through the intensive case finding method. "Active" users were studied during three months. In this time, the distribution places and the process of acquisition were detected. Twenty-five samples of the "Active" were gotten directly from these children and then analyzed by gas chromatography. Chemical analysis revealed that "Active" is almost exclusively made by the organic industrial solvent toluene (99°/O) with small quantities of methanol, ethanol, and acetone. Physiological, psychological and behavioral effects caused by the "Activo" are discussed and field for future research are suggested.

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DSM-IV HALLUCINOGEN USE DISORDERS AMONG ADOLESCENTS

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The DSM-IV criteria for substance use disorders, including hallucinogen use disorders (HUDs), were derived largely from research and clinical experience with adults. We examined DSM-IV HUDs in a sample of 269 male and 169 female adolescent drinkers, age 13-18, drawn from addictions treatment and community sources. After alcohol, nicotine, and cannabis use disorders, HUDs were the most common substance use disorders in this sample. Eighteen and one-half percent of adolescents with an alcohol use disorder, and 6.1% without an alcohol use disorder, received a lifetime HUD diagnosis. The ratio of hallucinogen abuse: dependence diagnoses was 3.3/1 among treatment cases and 10.0/1 among community recruits. The most common HUD symptoms were Failure to Fulfill Role Obligations (occurring in 63% of those with any symptoms) and Legal Problems (47%). The frequency of hallucinogen use differed among those with hallucinogen dependence (12.8 days/month, S.D. = 8.0) hallucinogen abuse (6.5 days/month, S.D. = 6.4), and hallucinogen users with no HUD (3.5 days/month, S.D. = 4.6). Those with hallucinogen dependence used a greater quantity, per occasion, compared to the other groups. HUDs are fairly common among adolescent drinkers and are an important topic for future research.

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NICOTINE USE, COMORBIDITY AND GENDER DIFFERENCES IN QUIT PATTERN AMONG CHILD AND ADOLESCENT PSYCHIATRY INPATIENTS

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The prevalence of nicotine use in children and adolescents is documented but the comorbidity of nicotine use and psychiatric diagnoses is not well documented in this population. We present results of survey of nicotine use and psychiatric comorbidity among child and adolescent psychiatry inpatient admissions at a tertiary hospital. One hundred and twenty-two consecutive inpatients were administered modified Fagerstrom Tolerance questionnaire (mFTQ), Smoking History Questionnaire, Social phobia and Anxiety Inventory (SPAI) and Reasons to Smoke questionnaire. Charts were reviewed for demographic information and DSM-IV (Diagnostic and Statistical Manual-IV) Axis I disorders. Sixty-four (52.5%) patients were either current of past smokers. Only 6 out of 47 current smokers had a chart diagnosis of nicotine use disorder. Twenty-nine smokers wanted to quit and 3 1 had tried to quit in the past but only 4 patients had received any treatment for smoking cessation. We report specific Axis I diagnoses related to nicotine use. mFTQ scores were significantly higher in patients identifying themselves to be addicted ($p=0.0000$, $T=5.37$). mFTQ scores also significantly correlate with cigarettes/day ($r=0.747$, $p=0.000$). We report factors that helped the past smokers quit. SPAI scores did not differentiate smokers from non-smokers, nor did it differentiate addicted from non-addicted smokers. Hence, nicotine use is very common in child and adolescent psychiatric inpatients but is frequently undiagnosed and untreated. Consistent with earlier reports, mFTQ appears to differentiate addicted from non-addicted smokers in this population. More community based studies of psychiatric comorbidity in child and adolescent smokers are needed.

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PATTERNS OF DRUG USE IN YOUNG ADOLESCENT FEMALES: DATA FROM THE GREAT SMOKY MOUNTAINS STUDY

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Data on patterns of drug use are collected prospectively through the Great Smoky Mountains Study, an epidemiologic study, now in the 7th wave of data collection, of white and American Indian youth, aged 9-16, residing in rural Southern Appalachia. Functional impairment was measured as incapacity in the areas of drug use, and relationships with parents, siblings, teachers, and/or peers. It was hypothesized that girls who initiated drug use during early adolescence would be more likely than girls who did not initiate drug use in early adolescence to demonstrate psychiatric comorbidity and higher levels of incapacity in familial and school relationships. Results demonstrated that depression (controlling for comorbidity with other disorders) significantly predicted drug use in adolescent girls. Specifically, alcohol use began 2.5 years earlier in girls who would develop depression by age 16 than in girls who would not develop the disorder. Also, drug use and abuse were significantly higher in girls with disruptive behavior disorders (DBDs) as compared to girls with no psychiatric diagnosis. Moreover, 8-15% of girls reported significantly impaired relationships with respective parental figures. The implications for the implementation of drug use prevention strategies among females
in early adolescence, particularly those with psychiatric disorders, include the involvement of parental figures in treatment interventions.

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PATTERNS OF HEROIN, COCAINE, AND CRACK USE PRIOR TO INITIATION OF INJECTION AMONG ADOLESCENTS AND YOUNG ADULTS

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Objective: To examine patterns of non-injection heroin, crack and cocaine use prior to initiation of an injecting career among young injection drug users (IDU) in Baltimore, MD. Methods: Beginning 7/97, young IDU (15-30 yrs), who recently initiated injection (<=5years) were prospectively studied. Year-by-year non-injection drug use histories were reconstructed over the 5-year period preceding initiation at baseline. Patterns of first use of non-injection heroin, crack and cocaine (5 years prior and continuous to initiation were compared using Chi-square tests by age at initiation (<=21 yrs), gender and ethnicity. Results: To date, of 143 IDU at baseline, 63% were female and 68% African American (AA). Median age and age of initiation of injection were 24 and 22 (range 10-30), respectively. Below are the comparisons of younger initiation vs older, female vs male, and AA vs White. The proportion of IDU's who reported short-term, continuous use of non-injection heroin, crack and/or cocaine are:

1st Use and Continued	Initiation of		Injection Gender		Ethnicity	
<=5 yrs prior to Initiation	**<=21 vs > 21**		**Female vs male**		**AA vs White**	
Heroin snorting (n=134)	81%	57%**	69%	66%	62%	83%*
Crack smoking (n=98)	27%	23%	25%	25%	18%	41%*
Cocaine snorting (n=92)	65%	21%**	35%	47%	23%	9%**

*p<.05, **p<.005

Conclusion: Our preliminary data indicate no difference in non-injection drug use patterns by gender; however, African Americans demonstrated a longer transition from heroin snorting and crack smoking to injection. Younger age of injection initiation was also associated with a higher proportion of a short transition period. These data suggest that timely interventions to prevent initiation of injection drug use among illicit drug using adolescents and young adults may require specific targeting.

ADHD DIAGNOSTIC AGREEMENT AMONG ADOLESCENTS, PARENT, AND CLINICIAN; RELATIONSHIP TO SUBSTANCE USE AND CONDUCT DISORDER

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Introduction: Adolescents with Conduct Disorder (CD) and Substance Use Disorders (SUD) have high rates of Attention Deficit Hyperactivity Disorder (ADHD). Parent and adolescent reports of ADHD often disagree. Aims: I) Assess concordance of ADHD diagnosis and symptom counts by clinician (C-ADHD) and by parent (P-ADHD) and adolescent (A-ADHD) structured interviews (Diagnostic Interview Schedule for Children-DISC) and 2) Assess the relationship of ADHD severity to substance and CD severity. Methods: A clinical interview with both parent and adolescent present assessed DSM-IV ADHD, SUD, and CD (n=52). Adolescents and parents were then separately administered the DISC. Results: Of the 100% with C-ADHD, 88.5% met diagnosis by either parent or adolescent DISC, 76% had P-ADHD, and 60% had A-ADHD. Bivariate ADHD symptom counts from the 3 sources were significantly correlated (1=0.38-0.41), but agreement for individual symptoms of ADHD was mostly poor to fair (kappa: -0.11 to 0.67). Concordance was in the "fair to good" range for the more overt symptoms. ADHD severity was not related significantly to SUD or CD severity. Conclusions: The "either/or" parent-adolescent DISC ADHD diagnosis usually agreed with clinician diagnosis, and total ADHD symptom counts from all three sources correlated well. However, concordances for each individual symptom was generally poor indicating that the parent and adolescent appear to endorse different symptoms of ADHD or aspects of the illness. ADHD severity by all reports does not appear to be related to substance or CD severity in this extreme sample. Results from this study support the importance of utilizing multiple informants, clinician diagnostic assessment, and structured diagnostic instruments in diagnosing ADHD for clinical research in adolescents with CD and SUD.

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ARE CONTROLLED OUTPATIENT PHARMACOLOGICAL TRIALS FEASIBLE IN ADOLESCENTS WITH CONDUCT DISORDER, SUBSTANCE USE DISORDERS AND ADHD?

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Introduction: We find no published outpatient pharmacologic trials in adolescents with conduct disorder (CD), substance use disorder (SUD), and attention deficit hyperactivity disorder (ADHD), despite the high prevalence and public health impact of this clinical population. Psychiatric comorbidity in CD/SUD adolescents (ADHD, affective, anxiety, learning disorders, etc.) may respond to psychopharmacological and/or psychosocial treatment trials. Yet, clinician researchers may be reticent to initiate outpatient trials in this population, thinking it unfeasible. Such trials are necessary to determine treatment effects on comorbid disorders as well as substance and behavioral outcomes in a community setting where these variables are not controlled. Methods: The purpose of the current study is to report the feasibility of conducting an outpatient placebo-controlled trial of pemoline in adolescents (13-18) with DSM IV, CD, SUD, and ADHD. We also report post-hoc analysis of the effectiveness of two different retention strategies (office-based vs. community-based). Results: Findings indicate it is feasible to conduct an outpatient pharmacologic clinical trial in adolescents with CD, SUD and ADHD in that 52 adolescents have been study participants over 2.67 years. Currently, 49 subjects have completed participation in the protocol. Only data from these 49 completers were used in analyses. A retention strategy which utilizes community/home-based follow-up assessments and provides transportation for subjects and their families (n = 44) vs. office-based assessments (n = 5) appears to be more effective in subject retention (mean days in treatment = 71 vs. 54). Moreover, subject/parent compliance with completion of post-assessments appears to be enhanced in the community-based strategy vs. the office-based strategy (59% vs. 20%). Conclusions: It appears feasible to conduct outpatient controlled pharmacologic trials in adolescents with CD, SUD, and ADHD (and likely other comorbidity). Retention and compliance may be enhanced by community-based follow-up assessments.

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SUBSTANCE USE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) SYMPTOMATOLOGY IN COLLEGE STUDENTS

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A number of studies have reported a relation between ADHD and substance use problems, although the nature of this relation has not been clearly specified. Studies supporting this association have used either samples of diagnosed substance abusers or samples of individuals with current or past histories of an ADHD diagnosis. We were interested in determining the nature of the relation between sub-clinical ADHD symptomatology and sub-clinical patterns of substance use. We hypothesized that even among individuals who were not clinic-referred, there would be a significant relation between behaviors associated with a diagnosis of ADHD and those pertaining to substance use. To examine this, we measured ADHD symptomatology using the Wender Utah Rating Scale (WURS) in non-referred, non-diagnosed college students, (N=106) along with self-reported patterns of substance use behavior (both licit and illicit), and several other theoretical measures of impulsivity. Statistical analyses suggest that ADHD symptomatology is significantly associated with a number of substance use variables, including smoker status ($F = 8.3$; $p < 0.01$), cocaine use ($F = 5.2$; $p < 0.03$), and total number of reported illicit drugs used ($r = 0.247$; $p < 0.05$). Further, trends in the hypothesized directions were noted for associations between WURS scores and other substance use variables, such as coffee drinker status ($F = 2.7$; $p < 10$) and marijuana use ($F = 2.6$; $p < 0.08$). Several other measures of impulsivity were also significantly associated with substance use histories, including scores on the Eysenck Personality Inventory and a measure of delay discounting. These preliminary results suggest that there may be common behavioral tendencies that underlie both ADHD and substance use problems.

AGGRESSIVE RESPONDING IN ADOLESCENTS WITH A HISTORY OF HIGH-RISK BEHAVIOR

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As part of a larger, on-going study, aggressive behavior was assessed in adolescents with a history of high-risk behavior and matched controls. Seventeen subjects, ages 1.5-18, were assigned to one of two groups: control or high risk (N=10 high risk, 7 control). All subjects in the high-risk group met criteria for at least 2 of the 5 following high risk factors (all of which are predictive of future substance abuse): conduct disorder, early onset drug use, past substance abuse, school drop-out, and criminal history. Control subjects met none of these criteria. Subjects took part in 6 sessions of the Point Subtraction Aggression Paradigm, an established laboratory measure of aggressive behavior. At the end of the study, subjects completed questionnaires involving psychometric measures of aggression, and risky behavior. Preliminary data point to notable differences in aggressive responding between the two groups, with the high-risk group making, on average, 3x as many aggressive responses. High-risk adolescents also reported more aggressive and risky behaviors on the questionnaires. The data suggests that substance use and other forms of risk taking in adolescents may be concurrent with aggressive behavior.

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AN APPRAISAL OF THE INTEGRATED TREATMENT METHOD FOR DUAL DISORDERS AMONG ADOLESCENTS IN AN INPATIENT PSYCHIATRIC SETTING

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A plethora of literature on the assessment and treatment of substance use disorder, coexisting with mental disorders, has focused on adult population. However, research has suggested that comorbidity of substance- abuse and other psychiatric disorders is as much an area of concern for adolescents as it is for adults. Traditionally, youngsters with a substance use disorder were assessed and treated differently from those who were diagnosed with a mental disorder. Each group was considered mutually exclusive and classified under separate criteria. However, there is a growing need for researchers, practitioners, and programs designed to help those youngsters who suffer from substance use disorders co-occurring with conventional psychopathology. This phenomena is known as dual disorder. According to the Substance Abuse and Mental Health Service of the U.S. Federal Government, there is a consensus from leading experts that an integrated method of assessment and treatment for youngsters with dual disorders is gaining wide acceptance and popularity among professionals in the field. Therefore, the purpose of this study is to appraise the integrated method of assessment and treatment for youngsters in the subacute phase of dual disorder in an inpatient psychiatric setting. Demographic and baseline descriptive data is central to this investigation and serves as the foundation for this study. The data has been systematically collected and used to appraise the type, incidence, rate, and prevalence of the integrated assessment and treatment method for adolescents in the subacute phase of an inpatient psychiatric setting. Special considerations are given to the psychological, sociocultural, and biological factors of the adolescents.

LABORATORY MEASUREMENT OF RISK-TAKING AMONG ADULTS AND ADOLESCENTS WITH A HISTORY OF ANTISOCIAL BEHAVIOR

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Factors associated with substance abuse or dependence include: meeting DSM-IV criteria for conduct disorder; history of criminal activity, past substance abuse, early onset substance use, and dropping out of school. These factors comprise a class of behaviors that can be considered risk-prone. In two experiments, "high-risk" and control subjects were exposed to a laboratory procedure designed to measure risk-taking behavior. Exp 1 included high-risk adults age 19-40, that met at least 2 of the above criteria, and age and gender matched controls. Exp 2 included a group of "high-risk" adolescents, age 15-17, who met at least 2 of the above criteria (60% met at least 3) and matched controls. The procedure involves a computer based two-choice, repeated-trials decision task. Subjects are given an amount of money at the beginning of the session (which increases across experimental days). One option allows subjects to hold current earnings (shown on screen); the other presents a risk of gaining a fixed amount of money or losing a smaller amount. Outcome probabilities are stochastic, and choosing the "risky" option on the majority of trials results in a net loss compared to choosing the "hold" option. For both adults and adolescents, "high-risk" subjects made significantly more risky responses than controls at higher beginning monetary amounts. The probability of consecutive risky responses (resulting in a monetary loss) following a single monetary gain was fit well by an exponential decay function ($r^2 > .98$), and revealed that high-risk subjects were significantly more likely than controls to take consecutive risks resulting in loss. These analyses provide an empirical model for theories of maladaptive behavior focused on hypersensitivity to reward and insensitivity to aversive events.

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BLACK MALE ADOLESCENT REPRODUCTIVE ATTITUDES, POVERTY AND POLICE CONTACTS

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Reproductive values resulting in out of wedlock pregnancy among black male adolescents is a major social problem, yet social scientists have limited conceptual understanding of the imitation of these circumstances. Many black male adolescents are spatially marginalized in poverty enclaves. In addition, many experience repeated police contacts. This article presents data from the National Survey of Adolescent Males and examines reproductive attitudes and behaviors, police contacts, and level of spatial marginalization as an indicator of poverty. Four attitudinal measures arc constructed as dichotomous variables and correlated with race, poverty, and police contacts. The proportional reduction in error statistic is computed for each measure.

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CONTINGENCY MANAGEMENT INTERVENTIONS FOR TREATING THE SUBSTANCE ABUSE OF ADOLESCENTS: A FEASIBILITY STUDY

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Cigarette smoking among adolescents continues as one of the country's foremost public health concerns. While enormous strides have been made in the treatment of adult substance abuse, relatively scant attention has been paid to the development of innovative treatment modalities for adolescents. Consequently, we experimentally assessed the feasibility of utilizing, with adolescents, a contingency management intervention that has proven efticacious in treating the substance abuse of adults. In this study, we used an A (1 week) - B (1 week) - A (1 week) reversal design. During each week of the study, eight adolescent cigarette smokers received monetary reimbursement for participation in the study. During the two baseline phases there were no contingencies placed on cigarette smoking and adolescents received money non-contingently. During the experimental intervention week, however, adolescents received payment contingent on not smoking. This contingent payment escalated in value for each CO reading of <8 ppm (indicating no or very little recent smoking). Results indicated that the contingency management intervention was effective in reducing smoking among the adolescents, both in terms of increasing the total number of abstinences and the number of consecutive abstinences. In addition, significant changes in the adolescent's affective state during smoking cessation were found. These results suggest that contingency management is effective for curtailing cigarette smoking, and possibly other drugs of abuse. In addition, the mood changes following cigarette smoking cessation among the participants suggest the presence of a nicotine withdrawal syndrome in adolescents.

SMOKING CESSATION AND EDUCATION PROGRAMS FOR ADOLESCENTS: A CRITICAL REVIEW

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This paper will present a critical review of the literature pertaining to research on smoking education and smoking cessation programs for adolescents. By linking these two issues, and critically reviewing the research literature on them, it will be possible to provide an overview of the linkages between smoking education and cessation efforts among adolescents. Programs developed around these two issues contain several components in common, including the nature of participation (coercive or voluntary), the important placed on gender in program construction, and of particular importance for adolescents, cultural identity concerns. In this literature review, the emphasis will be directed toward several key issues, including the nature of measures of efficacy in these programs, what forms of cultural knowledge are taken into consideration in the development and implementation of the programs, and the ways in which smoking education and cessation programs are shaped by models and theories from the relevant social science literature. It should also provide some highlights of crossover issues in terms of substance treatment programs for adolescents and the gender and cultural concerns, which emerge within them.

NATIONAL EVALUATION OF DRUG TREATMENT FOR ADOLESCENTS

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This national study examined treatment outcomes of community treatments for marijuana-abusing adolescents. A total of 1,066 adolescents (ages range 11 to 18; 273 females and 793 males) from six U.S. cities were studied using a naturalistic non-experimental evaluation design. Adolescents were consecutive admissions during 1993-1995 to 36 community based treatment programs in the national Drug Abuse Treatment Outcome Study - Adolescents (DATOS-A). Included were 520 admissions to 13 long-term residential (LTR), 219 admissions to 14 outpatient drug-free (ODF), and 327 admissions to 9 short-term inpatient (STI) programs. Almost half (46.3%) of all patients reported weekly marijuana use in the year following treatment (dropping from 96.3% in the year before admission). Similar improvements were observed in heavy drinking (dropping from 32.1% to 18.9%), use of hard drugs (dropping from 58.5% to 36.9%), and criminal involvement (dropping from 76.0% to 51.4%). Additionally, patients reported better psychological adjustment and school performance after treatment. Psychiatric disorder (e.g. conduct disorder) was related to high relapse rate for males. Females in LTR were 3.14 times more likely than those in ODF to be abstinent from hard drugs during the year following treatment. Adolescents in treatment were typically troubled with multiple problems (e.g. 59.9% of them were involved in the legal system and 61.7% met the diagnostic criteria for psychiatric disorder). Polydrug use, psychiatric disorder, criminal involvement, unstable living arrangement, and negative reference group were all correlated with negative outcomes. Counseling that addressed a greater number of problem areas increased the likelihood of marijuana abstinence among these adolescents.

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DIFERENTIAL ASSESSMENT OF TREATMENT EFFECTIVENESS ON PROPERTY CRIME AND DRUG DEALING AMONG ADOLESCENTS

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This study examined the changes in criminal activity among adolescents in the Drug Abuse Treatment Outcome Study (DATOS). The main focus of the study was to examine treatment effects among adolescents by their criminal justice status at intake. Subjects (N=1783) were adolescents admitted into either 13 long-term residential, 9 short-term inpatient, or 14 outpatient drug-free programs. At the time of treatment admission, approximately 54% of the sample reported criminal justice system (CJS) involvement. Adolescents under CJS supervision were more likely to be male, older, African American or Hispanic; to have prior drug treatment; to engage in heavy alcohol use, and were less likely to be enrolled in school at treatment admission. Rates of drug dealing, property crime, and violent crime were reduced from intake to follow-up in all modalities, although adolescents under CJS supervision continued to have higher rates of criminal activity at follow-up. Adolescents in all treatment modalities reduced alcohol and marijuana use from intake to follow-up; rates of use were approximately the same regardless of CJS status. Rates of cocaine use increased slightly in ST1 and ODF among both groups. The findings suggest that adolescents who enter drug treatment through the CJS need additional intervention to reduce criminal involvement.

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FACTORS ASSOCIATED TO ILLEGAL INCOME AMONG YOUNG DRUG USERS IN PUERTO RICO

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Data from our most recent study show that young drug users are more likely to obtain their income from illegal activities than their older counterparts. The objective of this study is to assess the characteristics, life events and risk behaviors of youngsters for whom illegal activities are a source of income. The sample comprises 155 subjects, aged 18 to 24 years, recruited in two communities in Puerto Rico. Interviewers following a structured protocol collected data. Nearly 42% of the subjects had received illegal income; 67.1% had injected drugs and 76.8% had less of high school education. Women reported engaging in illegal activities more than males (5 1.4% vs. 39.0%). Of those receiving illegal income, nearly 50% reported annual income over $40,000; 7 1.4% had been convicted of minor offenses; 49.5% had been incarcerated and 82.6% engaged in exchanges of sex for drugs. Also these subjects reported a high frequency of injections in the last 30 days (108.6 vs. 72.4). Logistic regression analysis shows that prior physical health problems, frequent drug use, absence of drug treatment history, and incarceration experience were associated with procurement of illegal income. These findings suggest the need to develop special programs designed to address the drug treatment needs and the socioeconomic problems of young drug users.

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A DESCRIPTIVE STUDY OF ADJUDICATED ADOLESCENT FEMALES ENTERING RESIDENTIAL SUBSTANCE ABUSE TREATMENT

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Rates of female adolescent drug use and crime in the U.S. have risen steadily in the past decade. Potential risk factors include, a pre-existing psychiatric disorder, history of abuse, family history of a substance use disorder, and delinquent behavior pre-dating the onset of substance use. The intent of this pilot project is to explore the backgrounds of adjudicated female adolescent substance abusers as they enter long-term residential treatment and identify patterns of drug use as associated with pre-adolescent conditions. The sample included 9 female adolescents, 14 to 17 y/o, who had been identified by the courts to have a substance use problem. The data was obtained from the initial psychiatric evaluation and historical materials available from probation, the schools, and previous psychological assessments. A systematic review of this material was performed in an attempt to uncover associations between the pattern of drug use and the characteristics of the subject prior to adolescence. Three observed associations are reported: 1) most irregular drug use, as seen in the number of drugs used and the schedule of use, in those with the earliest onset of delinquency; 2) more consistent use, as seen in the daily pattern and limited number of drugs used, in those young females with early onset of depression or ADHD; and 3) a later onset of a rapidly destructive pattern of drug use, in those with a pattern of early relational problems. This pilot study, by providing detailed descriptions of these young women's backgrounds and psychiatric co-morbidity, will contribute to the limited body of literature focused on this troubled population. It will also be of assistance in the design of a larger study that might result in recommendations for more effective identification, prevention, and treatment of these young women.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON ADOLESCENT AND PEER SUBSTANCE USE

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Previous research has documented strong relationships between peer and adolescent substance use. It is not known whether adolescents use drugs because of the influence of the peer group, or whether drug-using adolescents are attracted to drug-using peers because of personality or other characteristics shared in common. We estimated the relative influence of genes and the environment on experimenting with alcohol, cigarettes, and marijuana, as well as the adolescents' reports of substance use by their three best friends (use ≥ l/month by at least one peer, at least two peers, or all three peers). Information from two waves of interviews was combined. The program Mx was used for structural equation analysis. Subjects were twin participants (aged 13-21) in The National Longitudinal Survey of Adolescent Health (144 monozygotic male; 145 monozygotic female; 131 dizygotic male; 114 dizygotic female; and 204 dizygotic opposite sex pairs). Phenotypic correlations between adolescent and peer use ranged from .56 to .76, and were highest for marijuana. Heritability estimates for adolescent use ranged from .27 (alcohol) to .49 (cigarettes), while those for peer use ranged between .15 (alcohol use by ≥ 1 peers) and .79 (marijuana use by all 3 peers), and tended to be larger for increasing numbers of peer users. In addition, both common environmental influences (which make family members more alike), and unique environmental experiences influenced use of most substances. Phenotypic associations between adolescent use and subjective reports of peer use (which may be influenced by personality) were attributable partly to the same genetic factors influencing both variables, as well as to the effects on both variables of the same environmental factors.

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LOBELINE: A NICOTINIC CHOLINERCIC RECEPTOR STRUCTURE-AFFINITY STUDY

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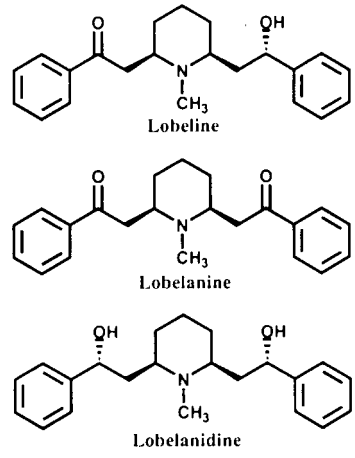
Because nicotinic acetylcholinergic receptors (nAChRs) may be of potential therapeutic importance in the treatment of pain, anxiety, and certain neurological disorders, they recently have become targets for drug development. (-) Lobeline is a structurally unique nAChR ligand that binds at nicotine receptors with an affinity (Ki = 4 nM) comparable to that of (-)nicotine (Ki = 2 nM). Little is known about lobeline analogs. We synthesized a series of such analogs and undertook a structure-affinity study to determine the necessity and contribution of the various structural features of lobeline to $\alpha_4\beta_2$ nAChR binding. Lobelanine (Ki = 7,800 nM) and lobelanidine (Ki = 300 nM) bind with reduced affinity, whereas lobelan (lobeline minus both oxygen functions) does not bind (Ki > 10,000 nM). Also examined: a) removal of the ketone moiety, (b) removal of the hydroxyl group, c) N-methylation to a quaternary lobeline analog, d) ring-opening of the piperidine ring, and d) other changes including abbreviation of the general skeletal structure. Few changes resulted in retention of high affinity. The general conclusion is that an intact lobeline structure, including the presence of both oxygen functions, contri-bute to optimal nACh receptor affinity. However, the presence of both oxygen functions is not an absolute requirement for binding because the –OH group of lobeline can be replaced by a chloro group (i.e., Ki = 5 nM) with retention of affinity.



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NORNICOTINE EVOKES [^{3}H] OVERFLOW FROM RAT NUCLEUS ACCUMBENS SLICES PRELOADED WITH [^{3}H]DOPAMINE

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Previous work from our laboratory has shown that nornicotine, a tobacco alkaloid and the N-demethylated metabolite of nicotine, is active in both neurochemical and behavioral assays. Furthermore, self-administration data from rats suggest that nornicotine has some abuse liability and may play a significant role in nicotine dependence. To further study the abuse liability of nornicotine, these experiments examined the ability of nornicotine to evoke [^{3}H]dopamine overflow from the nucleus accumbens, an area of the brain important for the reinforcing properties of drugs of abuse. Accumbal slices were incubated in the presence of 0.1 µM [^{3}H]dopamine for 30 min and then superfused in the presence of 10 µM pargyline and 10 µM nomifensine. Results demonstrate a concentration-dependent nornicotine evoked [^{3}H]overflow over the 0.1 - 100µM range. This response was inhibited by 10 µM dihydro-β-erythroidine (DHβE), and was calcium dependent, suggesting a nicotinic receptor mediated mechanism. Thus, nornicotine releases dopamine from nucleus accumbens slices in a concentration-dependent, calcium--dependent, and nicotinic receptor-mediated manner. These findings add further support for a role for nornicotine in the pharmacological effect resulting from tobacco use.

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NICOTINE BLOCKS PLASTICITY IN THE BASOLATERAL AMYGDALA

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The basolateral amygdala (BLA) modulates memory storage and plays a major role in the formation of stimulus-reward associations. Furthermore, it appears to regulate the degree of control exerted by these associations on behavior. Nicotinic receptors may mediate some aspects of these functions attributed to the BLA. In the present study, the effects of nicotine on BLA neuronal responsivity have been investigated. Extracellular recordings were made from neurons in halothane-anesthetized young adult male Sprague-Dawley rats. Stimulation (0.05 Hz) of axonal projections from the hippocampal formation elicited reliable neuronal population responses in the BLA; high frequency stimulation (100 Hz) induced significant long-lasting potentiation of neuronal response amplitude. Following acute administration of system nicotine (0.5 - 1.0 mg/kg, i.p.), no significant differences in evoked neuronal response thresholds or maximum response amplitudes were observed. However, a significant blockade of long-term potentiation of BLA synaptic response occurred. Short-term synaptic plasticity, as measured by paired-pulse facilitation, was also reduced. These findings suggest that, in naïve animals, nicotine may significantly alter BLA function.

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EFFECTS OF NICOTINE ON ACOUSTIC STARTLE AND PREPULSE INHIBITION IN HUMANS

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Prepulse inhibition of the acoustic startle response (PPI) is a paradigm in which a startle response to an auditory stimulus is reduced when that stimulus is preceded by a lower intensity, non-startling stimulus (pre-pulse). PPI is used as an operational measure of sensorimotor gating. It can be demonstrated with comparable paradigms in humans and other mammals. It is modulated by brain regions implicated in substance abuse and schizophrenia, and is highly sensitive to pharmacological manipulation. Acute administration of nicotine enhances PPI in rats, an effect which has been recently demonstrated in humans. We compared PPI in 12 male smokers (mean age =37.4 + 13.1) and 14 male normals (mean age = 28.7 + 5.6), tested in 4 repeat startle sessions across 2 test days. In a randomized crossover design, subjects smoked ad lib or abstained from smoking overnight prior to 9 AM testing. On both days, subjects were immediately retested after smoking three cigarettes. Across sessions, the smokers had a modestly reduced startle amplitude in pulse-alone stimuli, as compared to the nonsmokers. The nonsmokers had no change in gating across their four test sessions. During the nicotine abstinence session, smokers had comparable gating to nonsmokers. After nicotine, the smokers had a significant improvement in PPI ($p=.01$) such that their gating exceeded that of the nonsmokers ($p=.02$). This enhancement of gating was not attributable to differences in startle to pulse-alone stimuli. Although the neuroanatomic site of nicotinic modulation of gating is not clear, the effect of nicotine on PPI is consonant with the enhancement of attention and concentration seen after nicotine administration.

NICOTINE DOSE-DEPENDENTLY ACTIVATES THE MESOCORTICOLIMBIC SYSTEM IN THE HUMAN BRAIN

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Nicotine is the most commonly abused psychoactive substance by humans, producing a high level of tolerance and physical dependence. However, the sites and mechanisms within the human CNS responsible for these properties are poorly understood. We have applied fMRI to investigate the dose-dependent effects of nicotine in a population of active cigarette smokers. Fifteen smokers (mean age=26 years, average smoking history 1.1 pack/day for 8.5 years) gave informed consent and received an injection of saline, followed by 3 injections of nicotine (0.75, 1.5 and 2.25 mg/70kg) intravenously in a cumulative dosing paradigm. Inter-injection interval was 30 min. Whole brain fMRI BOLD data were acquired on a 1.5 Tesla GE Signa scanner (TR 6000, TE 40, 64 x 64, 8 mm axial slices) with drug given over a 1 min period, 4 minutes into a 20 min scan. A one way ANOVA was performed on % area under the time effect curve intensity calculated using a non-linear curve fit against a differential exponential pharmacokinetic model. Areas with significant dose effects included the anterior cingulate, right caudate, nucleus accumbens, amygdala and superior frontal gyrus, left orbital frontal and middle frontal gyrus, and bilateral dorsolateral frontal and insular cortex. This dose-dependent regional pattern is consistent with the observed behavioral and physiological effects of the drug. Most of the structures implicated are part of, or receive prominent afferents from, the mesocorticolimbic dopamine system, and provide an anatomical framework to understand nicotine's reinforcing and addictive properties in humans.

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NICOTINE AND D-AMPHETAMINE PRODUCE COMMON DISCRIMINATIVE STIMULUS EFFECTS IN RATS

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The aim of the present study was to investigate further the role of dopamine in mediating the discriminative stimulus effects of nicotine. Male Wistar rats in one group were trained to discriminate nicotine (0.4 mg/kg, ip), and in another group, d-amphetamine (0.5 mg/kg, ip) from saline in a two-lever, food-reinforcement procedure. In rats discriminating nicotine from saline, the nicotinic agonists, epibatidine (0.003 mg/kg) and ABT 594 (0.03 mg/kg), and the indirect dopamine agonist, cocaine (8 mg/kg), produced full substitution for nicotine (>80% substitution). The nicotinic agonists, cytisine (3 mg/kg) and SIB 1553 (30 mg/kg), and the indirect dopamine agonists, d-amphetamine (1 mg/kg) and bupropion (50 mg/kg), produced partial substitution for nicotine (maximum = 50-75% substitution). In rats discriminating d-amphetamine from saline, epibatidine, ABT 594, nicotine, cocaine, and d-amphetamine fully substituted for d-amphetamine at the same doses as those substituting for nicotine. Bupropion substituted for d-amphetamine at a lower dose (10 mg/kg) than that which partially substituted for nicotine (SO mg/kg). In contrast, cytisine and SIB 1553 produced responding, predominantly, on the saline lever. The findings that cytisine, a drug with low intrinsic activity at nicotinic receptors composed of $\alpha4\beta2$ and $\alpha3\beta2$ subunits (Brioni *et al.,* 1997), and SIB 1553, which displays selectivity for the $\beta4$ subtype (Lloyd *et al.,* 1998), partially substituted for nicotine and did not produce d-amphetamine-like discriminative effects are consistent with the finding that mice lacking the $\beta2$ subunit do not discriminate nicotine from saline (Oglesby *et al.,* 1998). In conclusion, the present results indicate that dopamine is involved in the discriminative stimulus effects of nicotine and that nicotinic receptors containing $\beta2$ subunits may be critical for producing the dopaminergic component of the nicotine cue.

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KAPPA-OPIOID RECEPTOR MODULATION OF RESPONSES TO NICOTINE

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Kappa-opioid receptor agonists can modulate the dependence-producing effects of drugs like morphine and cocaine. The present study examined the effects of U50,488, a selective kappa-opioid receptor agonist, on the discriminative stimulus (DS) and locomotor-activating effects of nicotine. Pretreatment with U50,488 (0.625, 1.25, 2.5, and 5.0 mg/kg SC) administered 30 min before nicotine (0.02, 0.06, 0.2, and 0.4 mg/kg SC) failed to modify the DS effects of nicotine (training dose: 0.2 mg/kg SC) measured using a two-lever procedure maintained under a tandem VI60'-FR10 schedule of food reinforcement (n=12). U50,488 in doses above 1.25 mg/kg completely disrupted lever-press responding. Against the chronic locomotor activating effects of nicotine, U50,488 (0.5, 1.5, and 3.0 mg/kg SC) administered 30 min before a nicotine challenge (0.02, 0.06, 0.2, and 0.4 mg/kg SC), dose-dependently attenuated increases in activity at doses that failed to modify baseline levels of activity (n=12). These results provide evidence that kappa receptor activation can modulate behavioural effects of nicotine, which are mediated partly via dopaminergic systems. Evidence in support of the involvement of kappa-opioid receptors in the DS effects could not be obtained because of the marked rate-disrupting effects of the kappa-opioid receptor agonist.

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COGNITIVE DESCRIPTORS PREDICT NICOTINE DEPENDENCE

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Four hundred twelve people, aged 18 to 35, randomly selected to represent the African-American and Caucasian population of a large metropolitan area in terms of sex and educational level, completed surveys of their smoking status (never smoked daily, non-dependent daily smoker, nicotine dependent daily smoker). They rated 134 words, representing 39 categories of outcome effects, associated with smoking to indicated how often (1=never to 7=always) the effects described by the words happen or could happen to them after smoking tobacco cigarettes. Three factors accounted for 74.09% of the variance in the word ratings assigned by the total sample. Factor 1 accounted for 30.9 1% of the variance and included words in 19 categories describing adverse effects of smoking. Factor 2 accounted for 28.08% of the variance and included words in 13 categories that described positive image. Factor 3 accounted for 15.09% of the variance and included words in 7 categories that described positive mood. A multivariate analysis of variance indicated that factors scale scores differed significantly as a function of smoking status (F=20.3, p=.000). Individual comparisons of factor scale scores by smoking status group revealed the following significant differences: Non-dependent smokers rated adverse effects of smoking as significantly **less likely** to happen to them than dependent and never smoked daily groups (mean=2.1 vs. 2.7 and 2.6, respectively, p=.000). Dependent smokers thought it significantly **more likely** that smoking would result in positive mood than non-dependent smokers or the never smoked daily group (mean=2.7 vs. 2.3 and 1.9, p=.003 and .000, respectively). Non-dependent smokers also rated an outcome of positive mood from smoking as significantly more likely than did those who had never smoked daily (p=.003). Factor scale scores and education significantly predicted daily smoking and nicotine dependence in logistic regressions.

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WOMEN TOBACCO SMOKERS ARE MORE SENSITIVE THAN MEN TO THE SUBJECTIVE EFFECTS BUT NOT THE PHYSIOLOGICAL EFFECTS OF TOBACCO CIGARETTE SMOKING

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In regular tobacco smokers, smoking a cigarette typically increases heart rate, decreases skin temperature, and leads to short-term reductions in subject-rated tobacco craving and cigarette withdrawal. If men and women who smoke regularly differ in their sensitivity to these effects, these differences may help to understand why women find quitting smoking more diffficult than men and may help guide gender-specific treatment when planning smoking cessation. This study assessed gender differences in the physiological and subjective effects of tobacco smoking in 38 men and 30 women who were regular cigarette smokers (i.e., smoke > 10 cigarettes/day). During a single laboratory session participants smoked two of their usual brand of cigarettes with an inter-cigarette interval of approximately 15 minutes. Heart rate, blood pressure, and skin temperature were monitored continually throughout the session. Subjective effects, including desire to smoke and a variety of tobacco withdrawal measures, were assessed before and after each cigarette. Because women's body weight, on average, was less than men's ($P < .001$), weight was used as a covariate in all analyses. As expected, cigarette smoking produced typical physiological effects, including increased heart rate and blood pressure and decreased skin temperature (Ps < .05). The magnitude of these effects was nearly identical for men and women. Tobacco smoking also decreased subjectrated cigarette craving and relieved subject-rated withdrawal (Ps < .001). However, women reported greater craving reductions and greater relief from withdrawal after smoking than men (Ps < .05). Thus, women were equally sensitive to the physiological effects but were more sensitive to the subjective effects produced by cigarette smoking. This greater sensitivity to the subjective effects of smoking may indicate that women smokers could benefit from a greater emphasis on craving and withdrawal relief during smoking cessation efforts.

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NICOTINE DECREASES PROSTACYCLIN BUT DOES NOT AFFECT THROMBOSANE OR PGE PRODUCTION FROM PERFUSED HUMAN UMBILICAL VEINS

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Smoking during pregnancy is prevalent, and is associated with a number of maternal and fetal complications. The mechanisms underlying nicotine's negative effects on fetal growth and development are not known, but may involve decreases in umbilical-placental blood flow. Prostaglandins are vasoactive mediators that play major roles in the regulation of umbilical-placental blood flow, and there is evidence that nicotine may alter prostagtandin production in a number of tissues. Thus, alterations in vasoactive prostaglandins from the human umbilical vein may partially explain nicotine-induced decreases in vessel blood flow and may explain some of nicotine's effects on the fetus. This study was designed to determine the relationship between nicotine and human umbilical vein prostaglandin production. Prostacyclin, thromboxane, and prostaglandin E were measured from human umbilical veins which were collected from women at the time of cesarean section. Vessels were perfused in a closed perfusion system with either vehicle (Dulbecco's Modified Eagle's Media), 5mM, 10mM, or 20mM nicotine for 60 minutes. Samples were collected from the perfusate after 5, 15, 30, and 60 minutes of perfusion, and prostaglandins were measured by radioimmunoassay of their stable metabolites. Data were analyzed by ANOVA. Perfusion with 10mM or 20mM significantly reduced prostacyclin production by the human umbilical veins, but nicotine did not affect thromboxane or prostaglandin E. Thus, nicotine-induced decreases in prostacyctin, a vasodilator, may result in contraction of human umbilical veins and a subsequent decrease in blood flow. This mechanism may underlie some of nicotine's negative effects on fetal growth and development.

BIOCHEMICAL AND BEHAVIORAL INDICATORS OF TOBACCO USE IN PREGNANT DRUC-DEPENDENT WOMEN

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Cigarette smoking during pregnancy among drug-dependent women is a serious health concern for both mother and fetus. The present study examined biochemical (i.e. cotinine and carbon monoxide levels) and behavioral indicators of smoking in 77 treatment-seeking opioid and/or cocaine-dependent pregnant women (69 smokers, 8 non-smokers). Participants completed the ASI, self-report smoking measures, and provided breath and urine samples upon admission (baseline), at 7-days, and at 30-day follow-up. The women had a mean age of 29.2 years, 85% were African-American, 82% were unmarried, and average gestational age (EGA) on admission was 20.5 weeks. Women receiving methadone-maintenance (MM, n=46) differed from women ineligible for methadone-maintenance (non-MM, n=23) on EGA and drug severity. Controlling for these differences, 2 x 3 Repeated Measures ANCOVAs, showed that MM had higher cotinine and CO levels at baseline and 7-days than non-MM. Self-reported cigarettes per day prior to treatment was also higher for MM (M=17.1) than non-MM (M=12.3) but Fagerstrom scores did not differ. Cotinine emerged as the most specific (100%) and sensitive (95-95%) indicator of smoking. CO was highly specific (100%) in detecting non-smokers, and its sensitivity (84-88%) was best using a 5 ppm cut-off. Smoking cessation interventions for this population should incorporate biochemical verification, and intensive strategies for MM pregnant women may be warranted.

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SMOKING CESSATION IN METHADONE MAINTENANCE TREATMENT: EVALUATION OF NICOTINE REPLACEMENT AND BEHAVIORAL THERAPIES

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Prevalence of cigarette smoking is extremely high among methadone maintained opiate abusers (85-100%). This study presents the findings from a NIDA-funded effort to evaluate two behavioral methods for optimizing nicotine replacement therapy for this group of tenacious smokers. Participants received 12 weeks of nicotine patch treatment and were randomly assigned to Relapse Prevention (RP; n=42), Contingency Management (CM; n=43), CM+RP (n=47), or no behavioral treatment (n=43). Participants completed a battery of measures at baseline and every four weeks during treatment. Breath and urine samples were collected three times per week. One hundred seventy-five participants completed the trial (Mean age 44 (SD = 7.84); 38.9% Caucasian; 60.6% Male). Analyses show a main effect of CM on the number of clean breath samples provided during the course of treatment (MWU = 3034.0, $p < .05$). There is a marginal trend showing the effectiveness of CM on participants being smoke-free at the end of treatment. The overall quit rate based on breath samples and self-report information provided at the end of treatment is 22.3%. The present study is one of the first systematic evaluations of smoking cessation methods for methadone maintained opiate abusers. These results suggest that participants are able to achieve quit rates comparable with the general population. Findings also demonstrate important associations between tobacco use and illicit substance use in this population.

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FACTORS PREDICTING OVER-THE-COUNTER NICOTINE PATCH UTILIZATION AND SMOKING CESSATION

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Although the nicotine patch has been approved for over-the-counter (OTC) use, there is little information about how the patch is used by smokers in a less intensive environment than a clinical trial. The present study evaluated nicotine patch purchasing, utilization, and treatment response of pack a day smokers to the nicotine patch combined with one of two minimal behavioral interventions. Study participants were randomized to an OTC setting (N=149) or a physician based minimal intervention (N=151). All participants were eligible to purchase patches for 26 weeks and could purchase a maximum of 28 patches per week. Ninety percent of participants made an initial purchase of patches. Non-patch purchasers smoked significantly fewer cigarettes, reported significantly less motivation to quit smoking and significantly more reported past nicotine gum use. Significant predictors of number of patches purchased were baseline CO level, motivation to quit smoking, prior nicotine gum use, prior nicotine patch use, number of adverse events experienced and age (Model R^2=.30). No patient characteristics significantly predicted patch utilization. At each follow-up point abstinent participants had purchased significantly more patches than non-abstinent participants. These results suggest that use of the nicotine patch in a minimal intervention environment is efficacious for certain individuals.

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BRIEF VS. EXTENDED SMOKING TREATMENT: PRELIMINARY FINDINGS

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Cigarette smoking is widely recognized as an addiction. Treatment for most addictions include treatment of extended duration, follow-up support, and, when feasible, easy re-entry into treatment. However, the standard treatment for nicotine dependence uses a brief model of treatment with no or minimal follow-up. Our group is currently conducting a clinical trial examining the efficacy of an extended treatment model with cigarette smokers. The study is a modified 2 X 2 factorial design; brief 12-week treatment vs. extended 52-week treatment by medical management (MM) vs. MM plus group treatment. We have also added a fifth treatment cell, a 52-week simulated over-the-counter (OTC) condition where subjects have access to nicotine gum with no counseling. The quit date for all participants is during Week 2 of treatment. Smoking status is assessed at baseline and at Weeks 12, 24, 36, and 52. Initial analyses have been conducted with the data from the first 139 subjects who have completed treatment through Week 36. Subjects were 56% male, 23% reported a history of major depression (MDD). Mean age = 41.8. Mean daily cigarettes = 24. Mean years smoking = 24.2. Subject's in extended treatments had significantly higher abstinence rates at Weeks 12, 24, and 36 than subjects in the brief treatments ($p < .05$). Closer examination of the extended treatment data indicates that subjects in the 52-week MM condition, and in the OTC condition, maintained higher abstinence rates after Week 12, while abstinence rates of subjects in the 52-week MM plus group counseling condition decreased to a rate comparable to subjects in the brief treatment conditions. No differences were found as a function of MDD history. A significant interaction was found for gender by treatment condition with women doing significantly better in extended treatment than in brief treatment. No differences were found for men.

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THE RELATIONSHIP BETWEEN SMOKING CESSATION TREATMENT RESPONSE AND THE HISTORY OR ABSENCE OF A MENTAL DISORDER

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Smokers (n=208) treated eight weeks with a patch, without lifetime psychiatric diagnoses (n=54; 26%), were compared on during- and post-treatment response (weeks 9, 26, and 52) to smokers with psychiatric diagnoses. Three diagnostic categorizations were evaluated, each including the group without diagnosis, versus: 1), those with a diagnosis (74%); 2). participants with an Axis I diagnosis (58%) or an Axis II diagnosis (16%); and 3). those with a non-nicotine substance dependence diagnosis (52%) or a nonsubstance dependence diagnosis (22%). Smoking determination used both self-report and biological measures. Regression analyses indicated that participants without a psychiatric diagnosis wore the patch more frequently, but there was no indication that having a diagnosis was associated with more smoking during treatment or at follow-up.

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A SMOKING CESSATION TRIAL IN SCHIZOPHRENIC AND SCHIZOAFFECTIVE OUTPATIENTS

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Thirteen patients with schizophrenia or schizoaffective illness received an 8-week, double-blind, placebo-controlled trial of bupropion combined with weekly behavioral therapy. Group therapy sessions offered cognitive and behavioral approaches to achieving abstinence from smoking and relapse prevention. A substantial reduction in mean cotinine level (47.8%) occurred in the active group from Baseline to Week 8, while mean cotinine level in the placebo group increased by 15.5%. Mean Simpson NRS scores increased 59.5% in the active group, whereas the placebo group had a decrease of 10.3%. Mean Hamilton depression (and anxiety) scores decreased 5.2% (22.9%) in the active group but increased 44.2% (41.2%) for the placebo group. Psychotic symptoms were stable over time, in both groups, as measured by PANSS positive and negative syndrome subscales. Pearson correlation between Fagerstrom scores and cigarette count ($r=0.72$) is significant ($P<.01$) at baseline, indicating validity of self-report measures. However, cotinine level is not significantly correlated with either self-report measure, suggesting that cotinine represents an important dimension for randomization in future trials. Preliminary results support the safety and efficacy of bupropion as a pharmacologic therapy for nicotine dependence among patients with chronic psychosis. When such patients attempt to quit smoking, they should be monitored with repeated NRS measures and a decrease in neuroleptic dose considered. Post-study follow-up interviews, at 1 and 6 months, will be conducted to evaluate the efficacy of the maintenance relapse prevention piloted in this study.

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EFFECTS OF CONTINGENT MONETARY REINFORCEMENT AND TRANSDERMAL NICOTINE ON CIGARETTE SMOKING BY SCHIZOPHRENICS

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Smoking and other substance abuse are more prevalent among schizophrenics than the general population. It is unclear why this is so and whether substance abuse by this population can be decreased using methods which affect substance abuse in non-schizophrenics. In a previous study, we found that contingent monetary reinforcement promoted short-term abstinence from smoking among schizophrenics. In the present study, we examined whether transdermal nicotine could increase the effectiveness of contingent monetary reinforcement. Fifteen schizophrenic outpatients participated in the following one-week conditions, with a one-week washout period between each condition: (1) nicotine patch with monetary reinforcement contingent on breath carbon monoxide (CO) levels of 11 ppm or less; (2) placebo patch with the same monetary reinforcement contingency; (3) placebo patch with non-contingent monetary reinforcement. Conditions were presented in counter-balanced order and CO levels were measured 3 times per day. Saliva samples were collected once per day and nicotine withdrawal was assessed once per day using the Minnesota Nicotine Withdrawal Scale. Contingent monetary reinforcement with or without transdermal nicotine decreased average CO levels and increased abstinence, but transdermal nicotine did not increase the effectiveness of contingent monetary reinforcement. Nicotine withdrawal scores were elevated under both conditions in which monetary reinforcement was contingent on smoking abstinence. Analysis of saliva cotinine levels showed that transdermal nicotine provided adequate levels of nicotine replacement. These results indicate that interventions based on contingent positive reinforcement can successfully reduce cigarette smoking in outpatients with schizophrenia, with or without the aid of nicotine replacement.

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SMOKING CESSATION IN AN OUTPATIENT SUBSTANCE DEPENDENCE TREATMENT CLINIC

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An on site smoking cessation clinic for veterans (n=71) participating in an outpatient substance dependence treatment program included weekly group smoking cessation sessions and pharmacotherapy determined by patient and clinician choice. Patients were middle aged (mean=46.8, SD=7.63), 7% female, and 63.4% Caucasian. Alcohol dependence only was present in 46.5%, drug dependence only in 15.5% and alcohol and drug dependence in 38%. All but 3 patients (4.2%) had additional Axis I Psychiatric diagnoses. Mean number of cigarettes smoked per day was 25.81 (SD=12.16). Mean score on the Fagerstrom Test for Nicotine Dependence was 5.85 (SD=2.78). At session 4, 20 patients (28.2%) had breath CO levels <9 PPM indicative of short term smoking abstinence. For those. who reported on number of cigarettes smoked at session 4 (n=27), mean number smoked per day declined from 26.12 (SD=12.86) at baseline to 5.91 (SD=6.88) at visit 4 (t=8.25, p<.001). Patients on a combination of nicotine replacement and bupropion (n=8) attended more sessions (mean=10.75, SD=14.40, mean rank=53.50) than did patients on bupropion only (n=6, mean=4.67, SD=2.25, mean rank=44.08), on transdermal nicotine only (n=40, mean=4.70, SD=4.86, mean rank=36.95) or on no medication (n=17, mean=2.24, SD=1.79, mean rank=22.84; Kruskal Wallis χ^2=14.22, p<.004). With baseline CO as a covariate in the analysis, patients on combined medications also showed greater reductions in CO from baseline to session 4 (mean=-17.86, SD=15.52) than did those on bupropion only (mean=+1.83, SD=5.81), those on nicotine only (mean=-6.30, SD=9.66) or those on no medications (mean=-2.00, SD=8.56; F=8.174, p<.001, R^2=.369). No adverse reactions were noted with the use of combined medications. In conclusion, a smoking cessation program for outpatients in treatment for substance dependence can achieve short term harm reduction or smoking abstinence. Preliminary results indicate that combined pharmacotherapy, with nicotine and bupropion, safely assists in this endeavor.

CHRONIC CAFFEINE EXPOSURE CHANGES THE DISCRIMINATIVE STIMULUS PROPERTIES OF NICOTINE IN RATS

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We previously reported that chronic exposure to high concentrations of caffeine in the drinking water (3 mg/ml) altered the qualitative nature of the nicotine's discriminative stimulus effects (Gasior *et al.,* 1999). The present study involved exposure to very low concentrations of caffeine in the drinking water and assessment of changes in (1) the rate of acquisition of nicotine discrimination and/or (2) the pharmacological characteristics of the nicotine discrimination in male Sprague-Dawley rats. Eight rats maintained continuously on caffeine added to the drinking water (0.25 mg/ml) and eight control rats maintained on tap water were trained to discriminate 0.4 mg/kg nicotine (SC) from saline using a standard two-lever discrimination procedure. Chronic exposure to low levels of caffeine significantly facilitated acquisition of the nicotine discrimination as the caffeine-drinking group required fewer training sessions to reach a criterion level of performance than the water-drinking group ($p<0.05$). Subsequent tests for generalization to different doses of nicotine revealed no significant differences in potency between these groups. In contrast, amphetamine and cocaine, were significantly more potent in generalization tests to the nicotine cue in the caffeine- than the water-drinking group. Daily caffeine intake ranged from 8.8-15.7 mg/kg/day and resulted in an average plasma caffeine concentration of 0.224±0.08 microgram/ml. Thus, chronic caffeine exposure facilitated acquisition of a nicotine discrimination and enhanced the dopaminergic component of the nicotine discriminative cue. Pharmacokinetic factors played a minimal role in the observed effects, since administration of 0.4 mg/kg nicotine (SC) produced comparable plasma levels of nicotine and its metabolite cotinine in water- and caffeine-drinking rats. Plasma levels of caffeine and nicotine in rats in the present study were comparable to those in humans after recreational coffee drinking and cigarette smoking.

THE TASTE OF CAFFEINE IN COLA SOFT DRINKS

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Caffeine is an ingredient in approximately 70% of soft drinks consumed in the United States. The justification provided to the Food and Drug Administration by soft drink manufacturers for adding caffeine to soft drinks is that caffeine is a flavor enhancer. To our knowledge, the effect of caffeine in cola beverages on the threshold for detection of taste differences between cola beverages has not been studied. Subjects were regular consumers of cola beverages who stated they had a preference for a specific brand of cola (e.g. Coca-Cola Classic) based on taste and also had a preference for the caffeine content of soda (i.e. preference for caffeinated over decaffeinated, or vice versa) based on taste. The study used a sensitive taste discrimination procedure which involved a series of trials on which subjects sequentially consumed two 5 ml samples of cola. The first five trials were warm-up trials in which the subject was informed of the content of each of the two samples. These were followed by 20 discrimination trials in which the subject was paid money for correct discriminations and was given feedback after each trial. Based on a screening session, all subjects were able to discriminate Caffeine Free Coca-Cola Classic from Caffeine Free Diet Coke. Over the next 6 sessions, subjects were tested on a series of caffeine vs. no caffeine discriminations in which 6 caffeine concentrations, corresponding to 0.05, 0.1, 0.2, 0.4, 0.8, and 1.6 mg/ml, were presented in mixed order (0.1 mg/ml or 35 mg/12 oz is the approximate concentration in Coca-Cola Classic and Pepsi Cola, the two most widely consumed cola soft drink products). The study is ongoing; of 19 completed subjects, 0, 10, 55, 95, 100 and 100% significantly discriminated 0.05, 0.1, 0.2, 0.4, 0.8, and 1.6 mg/ml, respectively. The results indicate that the taste of caffeine is not readily discriminable in cola soft drinks at the concentration delivered in widely consumed beverages.

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ACUTE CAFFEINE WITHDRAWAL INCREASES CEREBRAL BLOOD FLOW VELOCITY AND ALTERS ELECTROENCEPHALOGRAPHY (EEG) ACTIVITY

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Cessation of daily caffeine consumption produces a withdrawal syndrome comprised of subjective symptoms and functional impairment. Few controlled studies have examined the physiological effects of caffeine withdrawal. The present study examined the effect of caffeine withdrawal on cerebral blood flow velocity and quantitative EEG. Ten volunteers reporting moderate caffeine intake (mean 333 mg/day) participated in this double-blind shady. Subjects completed several tests when maintaining their normal diet (baseline period) and during two 1-day periods during which they consumed caffeine-free diets and received capsules containing placebo (placebo test session) or caffeine (caffeine test session) in amounts equal to their baseline daily caffeine consumption. Blood flow velocity was determined for 4 arteries: right and left middle (MCA), and right and left anterior (ACA) cerebral arteries using pulsed transcranial Doppler sonography. EEG was recorded for 3-minutes from 8 scalp sites while subjects sat, with eyes-closed, in a sound-attenuated electronically-shielded chamber. Subjective effects were assessed with questionnaires. Results showed an effect of placebo (21-hr withdrawal) condition compared to the caffeine condition. Placebo significantly increased the mean velocity, systolic velocity, and diastolic velocily (cm/s) in all four cerebral arteries. In the MCA, the pulsatility index was significantly decreased following placebo. Placebo significantly increased EEG theta power. Placebo also produces subjective effect changes, including increases in heavy feelings in arms and legs, and decreases in ability to concentrate. The caffeine and baseline conditions produced similar results on both the physiologic and subjective measures. Results suggest that cessation of daily caffeine consumption produced changes in cerebral blood flow velocity and quantitative EEG. These changes may be related to classic caffeine withdrawal symptoms of headache, drowsiness and decreased alertness.

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MORPHINE SUPPRESSES EXPRESSION OF COSTIMULATORY MOLECULES B7-1 AND B7-2 AND ENHANCES INTERLEUKIN-12 PRODUCTION

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Our laboratory has shown that morphine suppresses antibody formation in mice, and the depression of macrophagc function is at least partly responsible for reduced immune responses. In this study we investigated the capacity of morphine to modulate expression of costimulatory molecules B7-1 and B7-2 on peritoneal macrophages, and to affect cytokine production. Mice were implanted subcutaneously with a 75 mg morphine slow-release pellet, and 48 hrs later resident peritoneal macrophages were harvested. Cells (0.5x106/ ml) were cultured with IFN-γ and/or LPS. Macrophages were harvested after 48 hrs in culture and stained with Mac-1-PE and with either anti-B7-1-FITC or anti-B7-2-FITC. The results show that morphine treatment suppressed expression of both B7-1 and B7-2 molecules, and naltrexone reversed the suppression. For cytokine expression, RNA was extracted after 24 hrs of stimulation, and RT-PCR was carried out using specific cytokine primers. Morphine enhanced mRNA expression of IL-12 p40 compared with controls. ELISA data showed that both IL-12 p40 and p70 were increased by morphine. The enhancement of IL-12 at both the mRNA level and the protein level was antagonized by naltrexone, indicating that the modulation of this cytokine by morphine is via a classic opioid receptor. Our results suggest that impaired macrophage function in morphine-induced immunosuppression is partly due to the reduced expression of B7 family molecules. The enhancement of IL-12 by morphine might be related to morphine-induced sepsis.

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SUPPRESSION OF MURINE SPLENIC ANTIBODY RESPONSES FOLLOWING ADMINISTRATION OF MU OR KAPPA OPIOIDS IN VIVO USING OSMOTIC MINIPUMPS

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We have previously shown that morphine given by implantation of a 75-mg slow-release pellet suppresses murine splenic antibody responses to sheep red blood cells in a plaque-forming cell (PFC) assay, and a naltrexone (30 mg) pellet blocked the suppression. In the present study, we investigated the feasibility of using Alzet® osmotic minipumps (#1003D) to administer opioids to assess their immunomodulatory effects. In the first study, mice were implanted s.c. with 3-day minipumps administering U50,488H. Control groups received either pumps filled with saline, naloxone, or two pumps, one with U50,488H and one with naloxone. Splenocytes were harvested 48 hrs after implantation of pumps and the number of antibody-forming cells was determined using the PFC assay. The results show that *in vivo* administration of U50,488H (1 mg/kg/day) significantly suppressed the PFC response, and simultaneous implantation of a naloxone (10 mg/kg/day) pump, or a minipump infusing nor-Binaltorphimine (nor-BNI) (5 mg/kg/day), blocked the suppression. In the second study, the mu receptor antagonist, CTAP, administered by minipump, was tested for the ability to block the suppression induced by a 75-mg morphine pellet. Control groups received a placebo pellet, **a** saline pump, a naltrexone pellet, or a morphine pellet plus a naltrexone pellet. Administration of CTAP (1 mg/kg/day) via the minipumps blocked suppression of the PFC response observed with the morphine pellet. These results show that osmotic minipumps are a practical and useful way for administering opioids to study their effects on the immune system, and give further evidence that immunosuppression, induced *in vivo* by opioid agonists, is mediated via both classical mu and kappa opioid receptors.

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DIFFERENTIAL EFFECTS OF BUPRENORPHINE AND MORPHINE ON IMMUNE AND NEUROENDOCRINE FUNCTIONS FOLLOWING ACUTE ADMINISTRATION IN THE RAT PAG

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The effects of the μ-opioid receptor agonists buprenorphine and morphine on immune and neuroendocrine functions, through acute action in the rat mesencephalon periaqueductal gray (PAG), were evaluated. Buprenorphine is an analgesic recently approved for the treatment of drug dependency. In this study, it was shown that injection of an equianalgesic dose of buprenorphine (compared to morphine) into the ventral-caudal PAG, did not alter splenic NK cell, T cell, and macrophage functions, whereas morphine significantly ($p < 0.001$) suppressed splenic NK cell cytotoxic activity (14-50% reduction), splenic and thymic T cell proliferation to concanavalin A (43%-76% reduction), antiTCR (T cell receptor) (85% reduction) and IL-2 (36%-48% reduction), and macrophage functions including nitric oxide (36%-41 % reduction) and TNF-α production (26%), and phagocytosis of *Candida albicans* (39%). In addition, buprenorphine was associated with significant ($p < 0.0001$) reductions in corticotropin (ACTH) and corticosterone (CSO) plasma levels, without altering norepinephrine and serotonin splenic dialysate levels. In contrast, morphine significantly ($p < 0.0001$) increased glucocorticoid and catecholamine levels in plasma and spleen dialysates, respectively. In summary, unlike morphine, buprenorphine did not alter lymphocyte, NK cell, and macrophage functions, which was related to its inability to activate the hypothalamic-pituitary-adrenal axis with glucocorticoid release, or the sympathetic nervous system with bioamine production. Buprenorphine analgesic's and non-immunosuppressive's properties makes it a potential alternative to morphine, heroin, and other opioids in therapy for pain and opioid dependency.

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ACTH, DHEA, AND CORTISOL INCREASES AFTER 0.2 MG/KG COCAINE I.V. ADMINISTRATION

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A statistically significant temporal concordance of intravenous cocaine-induced stimulation of plasma ACTH was observed in men (Sholar, *et al.,* 1998). Cocaine-induced modulation of the HPA axis may result in disruption of normal immune-neuroendocrine interactions, immune function, and enhance risk for AIDS. Ten healthy adult men, who met DSM-IV criteria for cocaine abuse, participated in a double-blind study to assess ACTH, cortisol, and DHEA responses to intravenous cocaine. Placebo or cocaine, 0.2 mg/kg i.v., was infused over 1 min and samples for cocaine, cortisol and ACTH analysis were collected at 2, 4, 8, 12, 16, 20, 30, 40, 60, 80, 120, 180, and 240 min. Samples for DHEA were collected at baseline and 20, 30, 40, 80, 120, 180, and 240 min. ACTH increases were significantly correlated ($P<0.001$) with increases in plasma cocaine levels ($r=0.65$). Cortisol and DHEA increased significantly ($P<0.05$) 15-20 minutes following 0.2 mg/kg cocaine i.v. and persisted until 40-80 minutes post injection. These data will be discussed in relationship to the modulation of immune function.

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HEALTH PROBLEMS AND DRUG USE AMONG CHRONIC DRUG USERS

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With an overall goal of developing information to improve health services for chronic drug abusers, preliminary health problem data were analyzed from a NIDA supported health services project. The purpose of this presentation is (1) to describe the prevalence of self-reported health problems among incarcerated male alcohol and drug users, and (2) to compare self-reported health problems among chronic male drug abusers by type of drug used. Data were collected from 500 male Kentucky prisoners using face-to-face interviews. The average overall age was 31.6. Whites represented 53% of respondents and African Americans 44%; 54.2% were single. The twelve health problems included in this presentation are: male, lung, trauma, bone, liver, circulatory, stomach, nervous, skin, eye, dental, and STD's. The average number of lifetime health problems was higher than expected at 4.96. Comparisons were made between users and non-users across nine drugs for each of the twelve self-reported health problems. Statistically significant differences were found which ranged from: Heroin users and Inhalant users who were significantly more likely to report ever having 7 of the 12 health problems to marijuana users, who were significantly more likely *to* report ever having 2 of the 12 health problems. When the average number of different drugs ever used was examined for those who had specific health problems and those who did not, there were significant differences for 9 of the 12 health problems. Only 3 health problems were not statistically different - Lung problems, Eye problems, and STD's. The highest average number of drugs used (6.77) was found for liver problems. Implications include the need to target specific drugs used and/or specific health problems to tailor prison and aftercare treatment to better manage health care costs in the criminal justice system.

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SOCIODEMOGRAPHIC AND EPIDEMIOLOGICAL FACTORS AFFECTING IMMUNE RESPONSIVENESS AMONG DRUG USERS IN PUERTO RICO

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We have previously reported that drug users in Puerto Rico are less likely to respond to a battery of antigens frequently used in studies of immune responsiveness (tetanus toxoid, mumps, candida and tuberculin). The present study aims to identify factors associated with immune responsiveness among drug users in Puerto Rico. A total of 716 drug users, not in treatment, were recruited in metropolitan San Juan. Participants were skin-tested with tuberculin, tetanus toxoid, mumps, and candida antigens. Delayed type hypersensitivity (DTH) reactions to each antigen was measured in millimeters, and an overall DTH index was calculated for each subject. T-test and one-way analysis of variance were used to examine association of sociodemographic and epidemiological factors with DTH index and reactions to the individual antigens. Overall, mumps (5.14 mm) and tetanus toxoid (5.85 mm) showed the highest reactivity compared to candida (4.94 mm) and tuberculin (1.47 mm). In terms of sociodemographics, males, older individuals, and those without high school education were significantly more reactive to tuberculin compared to their counterparts. Homeless participants and those with a history of incarceration were significantly less reactive to mumps and tetanus toxoid antigens than individuals without those experiences. Also, HIV+ drug users were less reactive to mumps and tetanus toxoid than HIV- drug users. There was no statistically significant difference between DTH reactivity and drug use patterns. The importance of these factors in affecting immune responsiveness will be discussed.

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PREDICTORS OF HEPATITIS C AMONG DRUG USING WOMEN IN EAST HARLEM, NYC

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Objectives: Hepatitis C is a major health problem among drug users. Injection is one route of transmission, but others are more controversial. This study will: 1) document the prevalence of HCV among injecting and non-injecting drug using women; 2) determine lifetime predictors. **Methods:** Data were obtained by structured interviews. HCV testing was offered. Core antibody assays for HCV used Abbott HCV EIA. Women (n=368) were: 55% African American, 39% Latina; 29% IDUs, 71% non-IDUs (crack users/heroin sniffers). Data included: demographic characteristics, self-reported HCV exposure; lifetime use of injection drugs, number of male sex partners and male IDU sex partners; STDs; frequency of oral sores/bleeding gums; blood transfusions. Multiple logistic regression identified significant independent predictors of HCV. **Results:** 1) HCV prevalence-43%, of which 21 % reported no history of injection; self-reported HCV seroaware 7%. 2) Predictors of HCV (p<. 10) were: ever injected (OR=8.85; 95% CL=5.1, 15.3) and HIV seropositivity (OR=2.1; CL=1.1, 4.0). 3) Predictors in non-injectors: HIV seropositivity (OR=4.1; CL=1.6, 10.7) and frequency of bleeding gums (OR=2.47; CL=0.94, 6.5). **Conclusions:** Intravenous drug use and HIV seropositivity are significant predictors of HCV infection among women drug users from East Harlem. Lifetime sexual risk behaviors did not predict HCV serostatus in our sample. Among 'never-injectors,' oral health indicators, such as frequency of bleeding gums, predicted HCV infection. The majority of HCV positive women were unaware of their status, indicating the need for education and testing for HCV antibodies in this population. Further research is needed on HCV, especially among non-injectors.

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TUBERCULOSIS DIRECTLY OBSERVED PREVENTIVE THERAPY FOR ACTIVE DRUG USERS

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Drug users (DUs) have a high prevalence of tuberculosis infection and are at risk of non-adherence to preventive therapy (PT). Efficient means of delivering TB, PT to DUs are needed. Syringe exchange programs (SEP) have the potential to deliver health interventions such as TB screening and PT to this high-risk population. We conducted TB screening at both a NYC SEP and a drug detoxification program. Patients were offered TB screening, were interviewed and received $15.00, with excellent rates of completing TB screening. To date, 94 DUs were approached and agreed to directly observed therapy (DOPT) with twice weekly isoniazid. DOPT was administered at an HIV clinic where a monetary incentive ($12) was provided weekly based on adherence (74 patients) and at a storefront SEP where a modest enabler (but no incentive) was offered (20 patients). The mean age was 40 years, 84% were nonwhite, 16% were homeless/unstably housed, 19% did not have health insurance, 26% were documented HIV+. During the last 6 months, 29% had injected drugs, 74% had inhaled drugs, and 56% used crack. Adherence and retention were examined as dichotomized and continuous outcomes. Seventy-eight (84%) patients were engaged at SEP and 78% (58/74) engaged at the HIV clinic (p=0.02). Of those enrolled through 12/31/97, 26 (35%) have completed ≥ 6 months of INH with ≥ 80% adherence (# doses taken/# doses scheduled): 16 (21 %) transferred their treatment to other settings; 3 (4%) had stopped INH for adverse effects, and 1 (1 %) died during PT. Twenty patients never began DOPT despite initially agreeing, 4 refused to continue, and 19 were lost to follow-up (after a median of 3 months). Even among those lost to follow-up, 27% completed durations of PT known to have clinical benefit (i.e. 20-41 doses). Those at the SEP were less likely to be lost than those at the HIV clinic [0/20 (0%) vs 23/54 (43%), p=0.002]. While measures to improve adherence are needed, syringe exchange may be useful sites to deliver DOPT to active DUs.

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NEONATAL ISOLATION ENHANCES ACQUISITION OF COCAINE SELF-ADMINISTRATION

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In adult rats, stress enhances acquisition of drug self-administration (SA), a model of vulnerability to drug addiction, consistent with findings of common neural effects in the mesolimbic dopamine (DA) system. In neonatal rats, separation from dam and nest is stressful as evidenced by increased ultrasonic vocalizations. Because we find enduring effects of neonatal isolation experience, such as increased amphetamine-induced DA release from N. accumbens and locomotor activity in juvenile and adult rats, we tested whether this experience alters acquisition of Coc SA in adult rats. Pups were isolated from dam, siblings, and nest for 1 hr/day on Postnatal Days 2-9 in a heated (30° C) chamber (ISO; n=6) or left nonhandled (N-ISO; n=6). At about 90 days of age, locomotor activity was assessed over 30 min. There were no group differences in mean (± S.E.M.) horizontal locomotor counts (ISO: 475.2 ± 60.4 vs N-ISO: 474.7 ± 58.6). Next, rats were allowed to lever press for food (FR1; 10" TO; 30 min/day) in standard operant chambers. The groups did not differ in mean (± S.E.M.) trials to acquire this operant (2 days of obtaining all 50 pellets in < 5 min; ISO: 11.2 ± 1.1 vs. N-ISO: 12.8 ± 2.3). Rats were then implanted with indwelling jugular catheters and allowed to lever press for Coc (FRI; 10" TO) for 2 hr/day, 5 day/wk by presenting 4 escalating doses (0.0625-0.5 mg/kg/infusion; 1 dose/5 days) continuing with the highest dose until acquisition occurred (3 days of >20 reinforcers; <10% variance). ISO rats had higher response rates at lower doses and acquired after fewer training trials (17.2 ± 2.8) than N-ISO rats (28.0 ± 2.1). This effect was not due to performance or learning differences since there were no group differences in acquisition of food responding or in locomotor activity. Trials to extinguish operant responding for food or cocaine did not differ between groups indicating that these functioned as reinforcers for both groups. These results demonstrate that neonatal isolation enhances acquisition of Coc SA in adult rats and has important implications for the role of early childhood stress in vulnerability to cocaine addiction in humans.

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STRAIN DIFFERENCES IN THE BEHAVIORAL INTERACTIONS OF STRESS WITH COCAINE

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Cross-sensitization between stress and cocaine (Coc) is well-documented. Both stress and Coc activate the mesolimbic DA and HPA systems which may explain why one can generalize to the other. Further, preclinical and clinical studies suggest that stress increases Coc-seeking behaviors. Two inbred rat strains, Fischer 344 (F344) and Lewis, show differences in effects of stress and Coc but whether stress would alter the behavioral effects of Coc differentially in these two strains is not known. This study examined how stress affected the discriminative stimulus effects of Coc in these two strains. F344 and Lewis rats (n=7 ea) maintained on 85% free-feeding body weight were trained to discriminate Coc (10 mg/kg IP) from vehicle in a 2-lever, food-reinforced (FR 15) discrimination task. Once Coc demonstrated control over behavior, cumulative dose (1, 3, 10 mg/kg) test sessions were performed after presentation of 3 stressors: 15 min restraint; 15 min of random footshock (5 shocks of 5 mA; 100 msec duration) and the visual cues associated with shock (CS+). On separate occasions, corticosterone (CORT) levels were assessed after each stress and after Coc (10 mg/kg IP). Dose-related responding was demonstrated in both strain with higher response rates seen in Lewis rats ($P<0.05$). Restraint stress enhanced the discriminative stimulus effects of Coc in F344, but not in Lewis rats. Footshock stress and the CS+ enhanced response rate in Lewis, but not F344 rats. There were no other effects of stressors on Coc discrimination or rate. Baseline CORT levels were somewhat, but not significantly, higher in F344 rats. Yet, the baseline values were used as the co-variate in ANOCOVA analyses of CORT levels under the stress conditions. Restraint tended to enhance ($P<0.1$) and shock and the CS+ significantly enhanced CORT levels ($P's<0.05$) to a greater extent in Lewis compared to F344 rats, while Coc was not associated with strain differences in CORT levels. Thus, stress exposure enhances CORT levels and the discriminative stimulus and rate effects of Coc in a strain-selective manner.

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STEROID REPLACEMENT AFFECTS COCAINE-INDUCED BEHAVIORS IN OVARIECTOMIZED FISCHER RATS

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To determine whether cocaine-induced behavioral alterations are modulated by ovarian hormones, ovariectomized rats were randomly assigned to one of two drug treatment conditions: "binge" cocaine (15mg/kg, 3 injections, i.p., 1 hour apart) or saline administration; and four hormone pretreatment sub-groups: vehicle control, estrogen, progesterone, or estrogen+progesterone. Ovarian hormones influenced stereotypic behaviors in both saline- and cocaine-treated animals. Saline-treated animals pretreated with estrogen had significantly higher stereotypic activity than animals in the other hormone groups. Cocaine-treated animals displayed significantly higher stereotypic activity than saline-treated animals. Animals pretreated with estrogen+progesterone displayed the greatest increases in scores of stereotypic behavior after the second cocaine injection. Cocaine-treated animals also displayed more locomotor activity than saline-treated animals overall and locomotor activity was higher after the third injection than after the first two injections. When analyzed according to hormone group, the administration of estrogen+progestrone suppressed cocaine-induced locomotion after the first injection; this effect was significant when compared to estrogen-pretreated animals. Interestingly, animals in the estrogen+progesterone group had significantly lower plasma levels of the cocaine metabolite, benzoylecgonine, than animals in the progesterone or estrogen groups. These results confirm our earlier findings in intact female rats, which suggest an interaction between the endocrine environment, cocaine metabolism, and cocaine-induced behaviors.

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THE INFLUENCE OF THE ESTROUS CYCLE ON LOCOMOTOR HYPERACTIVITY EVOKED BY COCAINE

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This study was designed to test the hypothesis that the stage of the estrous cycle in female rats influences the locomotor responsiveness to cocaine and cocaine sensitization. Estrous cycles were monitored cytologically by vaginal lavage in female Sprague-Dawley rats starting 14 days prior to the experimental protocol. Activity was monitored using open field activity chambers. Rats were habituated to the chambers for 3 days prior to a cocaine challenge and 2 hrs of monitoring. Rats received either an acute cocaine challenge (5 mg/kg, i.p; n=24) or a chronic treatment regimen (cocaine 15 mg/kg, i.p; n=8; or saline 1 ml/kg; n=8, BID, 5 days; 72 hrs withdrawal), followed by a cocaine challenge (5 mg/kg). ACUTE: Rats were categorized into stage of estrous according to their lavage result on the day of testing and their 2-wk lavage history. Two-way ANOVA revealed a significant effect of day of estrous for both horizontal (p=0.0081) and vertical (p=0.0235) activity, with higher cocaine-evoked activity levels occurring during proestrus and estrus, the cycle stages during which estrogen and progesterone levels are highest. CHRONIC: A trend toward sensitization was observed. However, since the response to cocaine fluctuates over the estrous cycle, these fluctuations may influence the expression of sensitization in response to a challenge with 5 mg/kg of cocaine.

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EFFECTS OF CHRONIC COCAINE SELF-ADMINISTRATION ON LH AND PRL PULSATILE RELEASE IN FEMALE RHESUS MONKEYS

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Chronic cocaine self-administration can induce anovulation, luteal phase defects, and amenorrhea in otherwise healthy rhesus females studied under controlled conditions (Mello *et al.,* 1997), but the mechanisms underlying cocaine's adverse effects are unknown. LH pulsatile release patterns are one determinant of menstrual cycle adequacy, and we studied the effects of chronic cocaine self-administration and abstinence on LH and PRL pulsatile release patterns in female rhesus monkeys. Thirty-six samples for LH and PRL analysis were collected at 10-min intervals and pulsatile release patterns were quantified by cluster analysis (Veldhuis and Johnson, 1986). The number of LH pulses detected was significantly higher during cocaine self-administration (3.63 ± 0.50 pulses/6 hr) than during drug-free control conditions (2.33 ± 0.33 pulses/6 hrs) ($P < 0.05$). The number of PRL pulses detected during cocaine self-administration (3.13 ± 0.52 pulses/6 hrs) was also significantly higher than during control conditions (1.60 ± 0.24 pulses/6 hrs) ($P < 0.05$). LH and PRL pulse frequency was also higher during cocaine abstinence, but these differences were not statistically significant. These data suggest that chronic cocaine exposure stimulates pulsatile release of LH and PRL which in turn may contribute to the anovulation and luteal phase defects.

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ORAL CONTRACEPTIVES ALTER COCAINE PLASMA LEVELS AND SUBJECTIVE RESPONSES IN FEMALES: A PRELIMINARY REPORT

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Previously, we demonstrated that following the same acute dose of intranasal cocaine, males achieve higher plasma cocaine levels and detect cocaine effects faster than females, and that females in the follicular phase of their menstrual cycle have higher peak plasma cocaine levels and detect cocaine effects faster than females in their luteal phase. To investigate the effects of oral contraceptive use on plasma cocaine levels and subjective responses to cocaine, healthy female recreational cocaine users were challenged with cocaine (0.9 mg/kg i.n.) and responses of subjects on oral contraceptives (OCs) were compared to those not on oral contraceptives (NOCs). Subjects were studied during either the luteal phase or the follicular phase of their menstrual cycle. Subjective responses were collected before and at 15-, 30-, 60-, 120-, and 180-min post-administration, and blood samples were collected before and at 5 minute intervals post-administration. Heart rate was monitored continuously. Results indicated that OC females achieved higher cocaine plasma levels compared to NOC females, with the highest levels observed in OC females in their luteal phase. There were no group differences in heart rate. OC females studied during their follicular phase obtained higher MBG scores, and reported greater "High" at 15-, 30-, and 60-min post-administration. These results indicate that oral contraceptives do not appear to protect against the increased risk of cocaine-induced cardiovascular complications that have been shown to be sex-related. The data also suggest that females on OCs may absorb cocaine more quickly than females not on OCs. A tnore rapid onset of reinforcing effects, secondary to accelerated absorption, may increase the abuse liability of cocaine in females on oral contraceptives.

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ASSESSMENT OF DOPAMINERGIC FUNCTION DURING COCAINE ABSTINENCE

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The prolactin response to oral bromocriptine (BRO) was examined to determine if dopaminergic function was disrupted during cocaine abstinence. Male cocaine abusers resided on a CRC for 20 days. At the beginning of the study, participants had the opportunity to smoke cocaine (12-50 mg) repeatedly (up to 12 doses per day) for 3 consecutive days. After that, no cocaine was available for 2 weeks. We compared the effects of BRO, a D_2 agonist (1.25 mg), and placebo on prolactin (PRL) and growth hormone (GH) at 3 time points: (a) 1-2 days, (b) 7-8 days, and (c) 13-14 days after the last cocaine dose. Basal PRL levels in cocaine abusers were about double those observed in normal controls. BRO significantly decreased PRL levels to about 50% of baseline in both cocaine users and normal controls. BRO-induced decreases in PRL were similar 2, 8, and 14 days after smoking the last cocaine dose. By contrast, BRO increased GH by 300% in controls, but not in cocaine users. Cocaine craving decreased during abstinence and cocaine cue presentation increased cocaine craving. Heart rate, diastolic and systolic pressure were lower on days of a BRO challenge, but the effect of BRO on heart rate and diastolic pressure decreased during abstinence. These data suggest that dopaminergic dysregulation may account for the reported changes in mood and cocaine craving during cocaine abstinence.

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SEROTONIN FUNCTION IN PATIENTS WITH HEROIN DEPENDENCE IN FULL REMISSION

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Obiective: To assess the serotonin function of patients with heroin dependence in full remission. Methods: We compared the serotonin function of 17 patients with heroin dependence in remission who were being treated without medication and 18 healthy controls; we also studied another 9 patients with heroin dependence who were being treated with naltrexone. All participants were men. Serotonin function was assessed by measuring prolactin (PRL) in plasma at baseline and 5 h after the administration of d-fenfluraminc (30 mg) or placebo, on two separate test days. The double-blind neuroendocrine tests were performed in a randomized, balanced order. Placebo-corrected peak PRL values were chosen as an overall mean of neuroendocrine response. Results: The placebo-corrected peak PRL value μg/L) was 4.01 ± 2.57 in the healthy controls, 4.23 ± 2.05 in medication-free patients, and 5.46 ± 3.39 in patients who were taking naltrexone. An ANCOVA to compare PRL response showed a significant group effect (F[2]=8.54, *P* = .0009) after adjusting for age, plasmatic levels of d-fenfluramine and GGT. These same covariants were used to compare the three shady groups among themselves. Statistically significant differences were only found between the healthy controls and the medication-free patients (F[1]= 12.06, P = ,002). Conclusion: Patients with heroin dependence in total remission who were being treated in medication-free programs presented increased serotonin function.

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CHANGES IN PROENKEPHALIN GENE EXPRESSION DURING THE EXTINCTION OF COCAINE SELF-ADMINISTRATION IN SEVERAL RAT BRAIN REGIONS

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Previous works have reported that cocaine administration and its withdrawal affects gene expression regulation of different brain genes. The aim of the present work has been to study the effect of the extinction of cocaine self-administration behavior on proenkephalin (PENK) mRNA content in different cerebral regions using the yoked-box procedure. Seventy two male Lewis rats were randomly assigned in triads to one of three conditions: a) contingent intravenous self-administration of 1 mg/kg/injection of cocaine (CONT) and b) non-contingent injections of either 1 mg/kg/injection of cocaine (NONCONT) or c) saline yoked (SALINE) to the intake of the self-administering subject. The self-administering rats were trained to self-administer cocaine under a FR5 schedule of reinforcement during daily 2 hr sessions for a long period (between 4 and 6 weeks). After stable baseline levels of drug intake had reached, saline was substituted for drug during 5 days at Ieast. Following this first extinction period, cocaine self-administration was reinstated for an additional minimum period of 2 weeks and until stable baseline of cocaine self-administration behavior was again obtained. On the 0, 1, 5, and 10th days after cessation of cocaine self-administration, animal brains in each triad were removed to be processed for in situ hybridization. Frozen serial coronal brain section (20 μm) made at the level of the caudate-putamen nucleus (CPu), nucleus accumbens (NAcc), olfactory tuberculus (Tu), piriform cortex (Pir), ventromedial hypothalamic nucleus (VMH) and central amygdala (CeM) were processed for in situ hybridization histochemistry. The brain sections were hybridized with oligodeoxyribonucleotide probes complementary to PENK gene. Autoradiograms were analyzed with a Macintosh computer using the public domain NIH image program. Optical densities were calculated from the uncalibrated grey scale values. PENK mRNA levels were significantly higher in the cocaine groups when compare with SALINE group in the CPu, NAcc, Pir and Tu regions on days 0, 1, 5, and 10 of the extinction period and lower in the CeM region of CONT group when compared to NONCONT and SALINE groups on days 1, 5, and 10 of the extinction. In the VMH nucleus, PENK mRNA content in CONT was also lower compared with NONCONT and SALINE groups, but there were statistically significant differences only on day 5. These results suggest that changes in the gene expression of PENK might be implicated in the neurobiological processes involved in cocaine withdrawal.

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EXCITOTOXIC LESIONS OF THE NUCLEUS ACCUMBENS: EFFECT ON CARTir VARICOSITIES IN THE MIDBRAIN

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Cocaine and amphetamine related transcript (CART) mRNA levels have been reported to increase in the nucleus accumbens (Acc.) after acute injection of cocaine or amphetamine, thereby suggesting a role of CART in the mechanism of action of psychomotor stimulants. CART peptide immunoreactive (CARTir) neurons are found in both the core and shell regions of the Acc. in rats. Further characterization has identified these neurons as medium spiny projection neurons, which may project to the midbrain. Light microscopic immunohistochemical data have shown a dense CART peptide-immunoreactive innervation of the substantia nigra (SN) and ventral tegmental area (VTA). The goal of the present study was to verify the source of this dense CART peptide innervation of the midbrain through excitotoxic lesions of the Acc.Excitotoxic lesions of the core of the Acc. were achieved with kainic acid. A dramatic loss of CARTir varicosities throughout the rostra1 to caudal extent of the SN resulted from these lesions. However, the CARTir varicosities in the VTA and part of the medial SNc were preserved. Thus, it seems that the CARTir neurons in the core of the Acc. project primarily to the SN, but not the VTA. Future studies will attempt to lesion the shell of the Acc. and observe effects on the CARTir varicosities in the midbrain. These studies further elucidate the role of CART peptides and their circuitry in the nucleus accumbens and midbrain.

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CHARACTERIZATION OF A NOVEL COCAINE BINDING SITE IN BRAIN MEMBRANES PREPARED FROM DOPAMINE TRANSPORTER KNOCKOUT MICE

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Introduction. Previous work suggested that the cocaine analog [^{125}I]RTI-55 labels a novel binding site in rat brain membranes, termed DAT_{site2}, which is not associated with the dopamine (DA), serotonin (5-HT) or norepinephrine (NE) transporters **(***JPET* 274:385-395, 1995). **Methods.** A T-antigen knockin at the DAT gene that results in an effective DAT KO mouse was used. Lack of the DAT gene was confirmed by southern blots. Brain membranes were prepared from frozen whole brain minus caudate of Swiss-Webster (SW) mice, +/+ mice, +/- mice, and -/- mice. KO mice were used at approximately 23 days old. **Results.** Binding surface analysis of [^{125}I]RTI-55 binding to SW membranes, with 100 nM citalopram to block binding to the 5-HT transporter (SERT), revealed two binding sites: DAT (Bmax = 0.63, Kd = 1.8 nM, Ki of RTI- 113 = 18 nM) and DAT_{site2} (Bmax = 1.48, Kd = 28.3 nM, Ki of RTI-113 = 2299 nM), replicating studies conducted with rat brains. [^{125}I]RTI-55 binding blocked with 100 nM citalopram (DAT binding condition) was reduced by 82% in the -/- mice compared to the +/+ mice. Binding surface analysis of this residual [^{125}I]RTI-55 binding under DAT binding conditions in -/- mice resolved two binding sites: the NE transporter (NET) and a second site with IC50 values greater than 10,000 nM for affinity for most agents tested, including procaine, fluoxetine, a variety of tropane analogs, methylphenidate, and mazindol. The Ku values of cocaine and (+)-cocaine for DAT_{site2} were 2.6 µM and 19.6 µM, respectively. **Conclusions.** The previously characterized DAT_{site2} was a composite of two sites: the NET and the "new" DAT_{site2}. The affinity of cocaine for DAT_{site2} is in the physiologically relevant range. Future studies of DAT_{site2} will be require the development of selective higher affinity ligands for this site.

REGULATION OF HYPOTHALMIC POMC MRNA AND BRAIN MU OPIOID RECEPTOR BINDING IN TRANSGENIC MICE WITH SPECIFIC PITUITARY POMC CELL ABLATION

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The role of proopiomelanocortin (POMC)-derived peptides of pituitary origin in the modulation of brain (POMC) mRNA levels and opioid receptor binding was investigated using a line of transgenic mice that express a fusion gene composed of the pituitary expression-specific promoter region of the POMC gene driving the herpes simplex viral- 1 thymidine kinase (TK+) (Allen *et al.,* 1996). Adult male TK+ mice were treated with the antiherpes agent ganciclovir to ablate pituitary POMC cells. One to two weeks later, POMC mRNA levels, measured by quantitative solution hybridization assay, were decreased by 48% in the pituitary of the TK+ mice treated with ganciclovir, which also had lower plama corticosterone levels, reflecting an expected loss of the pituitary POMC cells. Pituitary corticotropin releasing factor receptor CRF_1R mRNA levels were also decreased by 21%. In contrast, hypothalamic POMC mRNA levels were increased by 79% and the increases were negatively correlated with the decreases in putuitary POMC mRNA but not with reduced plasma corticosterone levels. There was no change in POMC or CRF_1R mRNA in the amygdala. Levels of hypothalamic CRF_1R mRNA were 130% higher in mice with pituitary POMC cell ablation, and a significant positive correlation ($r=.96$, $p<0.001$) was found between hypothalamic CRF_1R and POMC mRNA levels in these mice but not in intact controls. Binding of [^{3}H]DAMGO to mu opioid receptors as measured by quantitative autoradiography was significantly reduced in several brain regions with which hypothalamic POMC neurons have efferent connections, including the central grey, median raphe, and superficial grey layer of the superior colliculus. No significant differences were found in the binding to either κ or δ opioid receptors in the brain regions studied. These results indicate that 1) increased hypothalamic POMC expression after targeted ablation of pituitary POMC cells is negatively correlated with reduced pituitary POMC expression, and positively correlated with increased hypothalamic CRF_1R expression, 2) increased hypothalamic CRF_1R expression may result from the presumed increases in hypothalamic CRF, and 3) down-regulation of brain mu opioid receptors may be the result of over-expression of hypothalamic POMC.

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CHRONIC MORPHINE INDUCES LONG-LASTING CHANGES IN ACETYLCHOLINE RELEASE IN RAT AND MICE NUCLEUS ACCUMBENS CORE AND SHELL (IN VIVO MICRODIALYSIS)

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Previously only *in vitro* studies have shown that chronic morphine provokes long-tasting enhanced activity of accumbal cholinergic neurons, which may contribute to behavioural sensitization, positive reinforcement, and aversive effects. The present study was aimed at supporting these adaptive changes, also by *in vivo* microdialysis measurements, in freely moving rats and mice (4-7 in a group), distinguishing the accumbal substructures shell and core (in rats) and observing behavioural changes simultaneusly. In rats, acute administration of morphine dose-dependently decreased acetylcholine (ACh) release in nucleus accumbens (NAc shell also core), with 10 mg/kg s.c. being maximally effective. On the 5th day of spontaneous abstinence from chronic morphine treatment, when withdrawal symptoms were still present, even a lower morphine dose (5 mg/kg) was effective in decreasing ACh release in NAc. During the later phase of abstinence, when no withdrawal symptoms were detectable, the opposite effect - i.e. an increase of ACh release was found (more expressed in NAc shell). Concurrent with changes in ACh release, morphine challenges produced marked stereotypies, possibly indicating behavioral sensitization. These findings may represent a long-lasting neuroadaptive effect of morphine. Similar but less unequivocal results were obtained by microdialysis in mice NAc in a complementary shady.

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ACUTE AND CHRONIC EFFECTS OF HEROIN ON HIPPOCAMPAL SHORT- AND LONG-TERM PLASTICITY IN VIVO

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The hippocampus is one of several brain regions known to participate in learning, and may also regulate opiate seeking behavior. Although behavioral evidence suggests an important role for learning and conditioning processes in opiate reinforcement, the systemic effects of opiates on hippocampal function are still unclear. We sought to characterize the effects of acute and chronic heroin on dentate physiology in halothane-anesthetized Sprague-Dawley rats. Heroin (0.1 and 0.6 mg/kg, s.c.) had little effect on the induction of dentate long-term potentiation (LTP), although both doses markedly suppressed population spike (PS) amplitudes. In contrast, while the 0.1 mg/kg heroin dose had little effect on paired-pulse responses, the 0.6 mg/kg heroin dose markedly reduced paired-pulse inhibition, consistent with local postsynaptic effects of opioids observed in *in vitro* and whole animal hippocampal preparations. In addition, we studied the chronic effects of heroin on acute dentate physiology. Eight days of chronic administration of heroin (0.5 mg/kg/day, s.c.) had little effect on stimulus-response curves, but markedly increased paired-pulse inhibition. Furthermore, the suppression of PS amplitudes and reduction of paired-pulse inhibition in the dentate by a challenge dose of 0.6 mg/kg heroin was markedly attenuated by chronic heroin treatment. We have previously demonstrated that *in situ* application of selective mu-opioid agonists markedly increases PS amplitudes and decreases paired-pulse inhibition in the dentate gyrus. Therefore, the dose-dependent effects of systemic opioids appear to be mediated by extra-hippocampal inputs, as 0.1 and 0.6 mg/kg heroin have differential effects on the induction of theta activity, a prominent hippocampal rhythm implicated in learning and memory and regulated by subcortical projections. These effects of heroin on hippocampal plasticity may be important for understanding the reinforcing and aversive properties of heroin.

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RELATION OF AGE OF COCAINE INITIATION TO DRUG USE SEVERITY AND TREATMENT OUTCOME

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Early initiation of drug use is associated with a number of adverse consequences, including increased risk for drug dependence, increased drug-related problems and an accelerated progression from initiation of drug use to dependence. In this study, we examined relationships between age of initiation of cocaine use, baseline characteristics, and drug use severity among 258 adults enrolled in an outpatient treatment for cocaine dependence. Relation of age of cocaine initiation to treatment outcome was examined in a subset of 123 individuals who received the same treatment (CRA+contingent vouchers) in 4 randomized trials. Subjects were divided into 2 groups according to whether cocaine use began before or after age 18. Individuals who began using cocaine at or before 18 years of age sought drug abuse treatment earlier, engaged in more severe cocaine use, experienced more drug-related problems, and initiated other drug use earlier than those who began cocaine use after age 18. There was a trend towards early-initiators remaining in treatment for a shorter duration than later-initiators (16.4 vs. 18.9 weeks, respectively) and achieving less cocaine abstinence during treatment (7.4 vs. 10.6 weeks, respectively), although that trend was not statistically significant. These results suggest that individuals who begin cocaine use at earlier ages, like others with more severe cocaine-related problems, may need more intense or special interventions to achieve positive treatment outcomes.

CONTINUING CARE FOR COCAINE DEPENDENCE: COMPREHENSIVE TWO-YEAR OUTCOMES

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Virtually all clinicians involved in the outpatient treatment of patients with cocaine dependence believe that some form of continuing care is necessary to solidify and preserve the gains made in the initial phase of rehabilitation. Furthermore, the ASAM patient placement criteria, APA practice guidelines, and noted relapse researchers all stress the importance of continuing care for substance abusers. However, despite wide-spread beliefs concerning the need for continuing care, this phase of treatment has received relatively little study in cocaine-dependent individuals, particularly within the context of outpatient treatment. This report presents two-year outcome data from an outpatient continuing care study in which cocaine-dependent patients (N=132) were randomly assigned to either standard group counseling (STND) or individualized relapse prevention (RP), following the completion of intensive outpatient treatment. Results found little evidence of continuing care condition main effects. However, patients who endorsed a goal of absolute abstinence at entrance to continuing care had better cocaine use outcomes in RP than in STND, whereas the opposite was the case for those with less stringent abstinence goals. In addition, patients who did not achieve remission from cocaine or alcohol dependence prior to continuing care had better outcomes in RP than in STND, although the effect with cocaine use was present only in months 1-6, whereas the effect with alcohol use was present throughout months 13-24. In analyses of posttreatment predictors of cocaine outcomes, greater attendance at self-help and lower employment problem severity consistently predicted less cocaine use in subsequent periods, even when current cocaine use and a number of other factors were controlled.

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TREATMENT CONFIDENCE AT INTAKE IS RELATED TO RETENTION AND ATTENDANCE IN TREATMENT

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Among the factors influencing treatment, retention is the confidence patients have in their treatment. The present study examined the relationship between the Treatment Confidence Scale administered at intake and retention in the study, measured both as number of treatments attended and length of retention in the study, regardless of missed treatments. Subjects (n=158) were participants in an S-week study, examining the efficacy of two kinds of acupuncture and relaxation therapy on cocaine addiction. They comprised the San Francisco cohort of a multi-site study, and were recruited via advertisements in free weekly newspapers and flyers at local food lines. Participants were included only if they demonstrated cocaine dependence as measured by the SCID. Initial treatment confidence was significantly related to both number of treatments attended ($r = .17$, $p<.05$) and length of retention, irrespective of missed treatments ($r = .23$, $p<.01$). The data suggest that treatment confidence may be an important variable to consider in conducting randomized clinical trials.

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BRIEF MOTIVATIONAL ENHANCEMENT THERAPY PRIOR TO RELAPSE PREVENTION FOR COCAINE DEPENDENT PATIENTS

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With the assumption that Relapse Prevention (RP) therapy may be more effective for patients who have initiated a period of abstinence, a brief two-session Motivational Enhancement Therapy (MET) based on Miller and Rollnick's Motivational Interviewing was developed and implemented within the context of an outpatient detoxification program for cocaine dependent patients. Entrance into the 12-week RP treatment was contingent upon the submission of five consecutive cocaine-free urine samples during the 5 to 10-day detoxification program. It was hypothesized that: (1) those receiving MET would be more likely to achieve abstinence and, thus, be eligible for the RP program; and, (2) initial MET would result in improved outcomes throughout the subsequent treatment. To evaluate the efficacy of this component, 105 participants were randomly assigned to MET (n=50) or a detox-only control group (n=55). Results indicated that the addition of MET to the detox program did not produce higher rates of initial abstinence. However, those who achieved abstinence and received MET during detox were more likely to sustain abstinence through the first RP treatment session. Eighty-eight percent of the MET group were cocaine-negative at Session 1, compared to 63% of the detox only group. Also, MET patients significantly increased their behavioral coping strategies relative to the detox-only patients. Based on these results, further study of MET to promote motivation for change prior to cognitive-behavioral treatment is warranted.

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REINFORCEMENT OF STEPWISE DECREASES IN COCAINE USE

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Abstinence reinforcement is effective for treatment of cocaine abuse, but some patients are unable to initiate abstinence and never contact the reinforcement schedule. In this study, we evaluated whether reinforcement of an intermediate step to abstinence (i.e., decreases in urine cocaine metabolite concentration) would improve outcome. Patients who used cocaine during 5 weeks of baseline methadone maintenance (50 mg/day PO) were randomly assigned to two groups receiving: 1) contingent vouchers for cocaine-negative urine specimens for 8 weeks (abstinence group; N=49); or 2) contingent vouchers for each urine specimen with at least a 50% decrease in cocaine metabolite concentration, compared to the previous specimen for 3 weeks, then only for cocaine-negative urine specimens for 5 weeks (stepwise treatment group; N=46). Observed urine specimens were collected MWF; qualitative urinalysis was by EMIT; quantitative urinalysis was by Abbott TDx. Vouchers had monetary value that increased with each consecutive specimen that met criteria. Vouchers were given the day after urine collection and were exchangeable for goods and services. Cocaine abstinence (% cocaine-negative urine specimens) increased during the 8-week intervention in both groups. Qualitative urine data were entered into a generalized linear mixed model, with Contingency as a between-subjects factor with 2 levels, Intervention Day as a repeated factor with 24 levels, and Baseline % Negative as a covariate. Results were: Intervention Day $F(23,1842)=2.73$, $p<.0001$; Baseline % Negative $F(1,92)=32.64$, $p<.0001$; Contingency $F(1,92)=0.50$, $p=.4804$; Contingency x Intervention Day $F(23,1842)=2.10$, $p=.0017$]. While the stepwise schedule was in effect, the reinforcement schedules appeared equally effective in producing cocaine abstinence. At the transition to the abstinence schedule, the stepwise treatment group showed significant additional improvement not seen in the abstinence group. The stepwise schedule may have prepared patients for abstinence.

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TIME TO ABSTINENCE, RELAPSE, AND TERMINATION, IN EFFECTIVE TREATMENT FOR COCAINE DEPENDENCE AMONG HOMELESS PERSONS

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From a randomized controlled study of abstinence contingent housing and work added to behavioral day treatment (DT+) vs. day treatment alone (DT) with homeless cocaine abusers (n=141), this study explored individual responses and times to critical events during treatment and aftercare. Random urine tests, 1-2 per week, in weeks 1-24 at 0, 2, and 6 months respectively, showed DT+=50% vs DT=48% abstinent; DT+ 72% vs. DT 33% (Chi Sq.= 18.71, df=1, p=0.001); DT+=39% vs. DT 16% (Chi Sq.=7.4, df= 1, p=0.007). Numbers of subjects achieving longest consecutive weeks abstinent, and individual subjects' responses to treatment were arrayed in order of longest and earliest established consecutive weeks abstinent. Both showed better DT+ outcomes. Time to event analyses showed superior performance of DT+ in earlier established abstinence of 4 weeks or longer, less time after relapse of 12 weeks to re-establish abstinence, and longer times to treatment termination. Most individuals who established abstinence during day treatment and subsequently relapsed, did so within 4 weeks of day treatment termination. Importance of transition from day treatment to aftercare is implicated to help individuals sustain abstinence. Data support an abstinence-based criterion for transition to aftercare vs. fixed day treatment duration, and continued contingencies to support abstinence.

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SYMPTOMATIC MANAGEMENT OF RESPIRATORY COMPLAINTS IN HOMELESS COCAINE USERS AND ITS RELATIONSHIP TO DRUG USE PATTERNS AND CRAVING

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Homelessness in the US is a growing problem: A known antecedent to homelessness is drug abuse, including cocaine use. In addition to known effects in brain reward pathways, cocaine abuse also results in more systemic effects in the respiratory system, such as cough and rhinitis. As cocaine blocks the reuptake of norepinephrine, it results in vasoconstriction and is the cause of the respiratory complaints in addition to its dopamine depleting effects and is thought to be the cause for drug craving. As homeless persons are often without the resources to deal with the multitude of their problems, they are forced to seek care in many different settings such as missions and shelters where some health care services are provided. Respiratory complaints are one of the most common problems in this population and over-the-counter medications are the most commonly prescribed medication in treating the homeless. Decongestants and antihistamines are some of the medications used. Studies in animals have shown that they can not discriminate between these medications and cocaine. A question arises as to what effect these medications may have on drug use patterns and craving in the homeless. This is an in progress descriptive, correlational study of 100 homeless persons, looking at drug use patterns and craving in patients who receive pseudoephedrine and chlorpheniramine for respiratory symptom treatment in an academic nursing center that serves the homeless. It is based on the biopsychosocial model of addiction as the theoretical framework. Instruments include the Addiction Severity Index (modified), Cocaine Craving Now/General, urine drug screens and physical examination. Data will be collected at baseline and 1 week. Data analyses will consist of ANOVAs, chi squares (x2) and logistic regressions. Demographic information will be reported.

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LAPSE, RELAPSE, AND RECOVERY AFTER ESTABLISHING ABSTINENCE IN A PROGRAM FOR HOMELESS COCAINE ABUSERS

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Patterns of lapse, relapse, and recovery following established abstinence were examined in a sample of 141 homeless cocaine abusers who had been randomly assigned to conditions of day treatment with abstinence-contingent housing and work, or day treatment without housing or work (controls). Established abstinence was operationally defined by four consecutive clean urines, randomly scheduled 2 per week, and achieved by 104 subjects during a 24-week study period. Relapse, which occurred for 76 subjects at least once, was defined as 2 weeks with positive urine at least once each week. "Lapse"-- considered to be less serious than relapses and easier to recover from, were defined as subjects testing dirty for one week or less. Both the initial abstinence period (no relapses or lapses) and the initial partial abstinence period (some lapses, but no relapses) were significantly longer ($p<.01$) for the treatment group (7.00 and 11.53 weeks) than for controls (3.28 and 5.72 weeks). Time from beginning of relapse to establishment of second abstinence period was significantly shorter ($p=.001$) for the treatment group (5.14 weeks) than for the control group (9.2 weeks). Results support notion that sufficient interventions to effectively treat this population must include effective interventions for both substance abuse and homelessness, and the potential therapeutic impact of contingencies on sustaining abstinence.

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FOLLOW-UP RESULTS OF RESIDENTIAL TREATMENT AND SPIRITUALLY-BASED COMMUNITY SUPPORT FOR HOMELESS CRACK-USING WOMEN

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This paper presents the follow-up results on a CSAT-funded demonstration project designed to provide six months of community-based comprehensive residential treatment and community support for homeless women and their pre-school children. Because of capacity limitations, some clients received only the standard residential treatment services, whereas others received these services plus community support. This enhanced condition involved pairing clients with mentors from local African-American churches who maintained daily contact with clients for about one year, as well as spiritually-based group activities. With a six month follow-up rate of 76% for the total sample, 81% of the clients across both groups (n = 72) reported being abstinent from both cocaine and alcohol for the prior 30 days. Significant improvement over time was manifested in terms of cocaine use, depression, self-concept, sexual risk-taking behaviors, and residential stability. Clients who received the standard treatment plus community support (n =35) manifested more positive outcomes in terms of treatment completion (87% vs. 12%) and abstinence from cocaine and alcohol (97% vs. 65%) than those who received the standard treatment only (n = 37). However, these results should be viewed with caution since the study did not employ a randomized design, and outcome assessments were based solely on self-report which were not corroborated with urinalysis. Additional assessment employing a randomized clinical trial with urinalysis verification is recommended to further evaluate this promising intervention.

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COST ANALYSIS OF EFFECTIVE SUBSTANCE ABUSE TREATMENTS FOR HOMELESS PERSONS

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Cost analyses were conducted on two substance abuse treatment programs for homeless persons with crack cocaine dependencies in Birmingham, Alabama. The two treatment programs were compared using a randomized controlled experimental design. They were: Behavioral Day Treatment (DT) vs. Behavioral Day Treatment -plus- Abstinent Contingent Housing and Work Therapy (DT+). Three Phases of treatment were separated by 2, 6, and 12 month assessments points. Subjects (N=141) were primarily male and African American with an average age of 37 years. The following cost figures were calculated: cost of treatment, cost per person, number and percent of abstinent persons, average cost per abstinent person, and marginal cost per marginal abstinent person. Results revealed that 1) cost of effective Behavioral Day Treatment and Contingency Management is reasonable; 2) Behavioral Day Treatment -plus- Contingency Management (DT+) is cost effective; and 3) effective and innovative substance abuse treatments for homeless are worth it. Costs of abstinence resulting from studied treatments are compared to costs of life year saved of various other valued life-saving interventions.

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TIME TO IMPACT: DOES LENGTH OF TREATMENT MAKE A DIFFERENCE?

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We have previously reported that subjects participating in an outpatient intensive treatment program for drug abuse were significantly improved at 6-month followup as measured by the Addiction Severity Index. We were interested in possible differences in outcome related to length of treatment participation. Subjects (N=190) were recruited from patients attending an outpatient intensive program that offered group treatment, including relapse prevention and 12-step instruction. Of 181 subjects with an intake ASI, seventy-three (73) subjects had both baseline and 6 month assessments with the ASI. For this analysis, we divided the sample into two groups: subjects who came to outpatient drug treatment for less than 12 weeks (<3Mos: N=92) vs. subjects attending 12 weeks or more (13Mos.: N=89). Except for 2 drug severity ratings, baseline characteristics did not differentiate those who did and did not return for the six-month followup. Higher baseline drug ratings were found for those without a 6-month followup. The two treatment groups (<3mos. vs. ≥3mos.) were then compared on six-month outcome variables of ASI scores using the ANOVA with repeated measures. A significant tx. Fever group x time interaction ($p<.05$) was found for females on the ASI Drug Composite Score with more improvement over time for the longer tx. group. Similar trends ($p<.10$) were found favoring females in the longer treatment group for patient ratings on the ASI Drug section and Employment Composite Score. A significant interaction favoring the long treatment group was also found for all subjects ($p<.009$) and males ($p<.03$) on the Medical Composite Score. The results suggest the possibility that females may benefit differentially from extended treatment.

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EVALUATION OF CASAWORKS FOR FAMILIES: A NATIONAL INITIATIVE

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States face a special challenge moving women with substance abuse problems from welfare to work under the requirements of the federal Temporary Assistance to Needy Families Program (TANF). This study evaluates a national initiative to refine and pilot test in 11 sites around the nation with at least 1,100 women an integrative intervention strategy designed to support female welfare recipients' efforts to achieve stable employment by overcoming substance abuse and other major barriers to work. Substance abuse treatment is integrated with employment-related services, services for domestic violence, parent and family training, and other needs. The formative and summative study utilizes quantitative data to assess the implementation, feasibility, and outcomes of the intervention strategy. A repeated measures design (with no control group) is employed due to the developmental nature of this first phase of the study, although synthetic comparison groups will be utilized to provide some degree of "conterfactual" evidence. A new version of the ASI and TSR designed to capture more fully the needs and characteristics of low-income women (plus other scales) will be used at baseline, and 6 and 12 months post enrollment; the TSR is repeated at 1, 3, and 9 months. Baseline data from the first 92 women to enroll in CASAWORKS were compared with data from 104 women on TANF who participated in substance abuse treatment as part of the Target Cities Program in Philadelphia. Compared to the Target Cities women, a greater proportion of the women in CASAWORKS were white, never married, and living with their children. The CASAWORKS women also indicated fewer years of substance abuse, and a larger percentage of them had never been in treatment before, and had been emotionally or physically abused during their lifetime.

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EMPLOYABILITY OF METHADONE-MAINTAINED WOMEN

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A significant number of methadone-maintained women suffer from HIV, depression, and post-traumatic stress disorder. It is hypothesized that a combination of medical and psychiatric problems impede the employability of these women. To determine if medical and psychiatric problems are related to employability, a **pilot study** was conducted by interviewing 46 methadone-maintained women. Data were collected and analyzed using the Addiction Severity Index (ASI), the Employee Reliability Inventory (ERI) and the MINI-International Neuropsychiatric Interview (M.I.N.I.). Preliminary results indicated that 24 out of 46 women (52%) have chronic medical problems. Ten women (21%) reported a positive HIV status. Over 30% suffered from psychiatric problems including major depression, social phobia, and general anxiety disorder. On the ERI, the study sample of women compared to a normative sample of 60,000 individuals scored significantly higher on the "likelihood of unreliable behavior" in 6 out 7 areas of employability. Depressed women showed more likelihood of unreliable behavior than those without major depression. The high correlation between major depression and ERI subscales suggest that treating their depression may improve employability.

BARRIERS TO EMPLOYMENT AMONG CHRONIC DRUG USING AND NON-USING FEMALE WELFARE RECIPIENTS

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The Personal Responsibility and Work Opportunity Reconciliation Act of 1996 (PRWORA) imposed new and significant conditions on American welfare recipients. Recipients are now limited in the total number of months they can receive benefits. Recipients must also participate in a work activity in exchange for benefits. The literature has identified potential barriers to employment such as a lack of access to childcare and transportation. Many recipients also suffer from a lack of education and employment skills. Psychological problems also post barriers to joining the work force. In addition, an estimated 10% to 20% of welfare recipients arc believed to have some form of substance use problem. The purpose of this study was to explore the extent of psychological functioning and employability in samples of chronic drug using and non-drug using current and former Temporary Aid to Needy Families (TANF) participants. Drug using recipients were significantly less likely to be employed and reported greater problems with anxiety and self-image. Users also reported lower levels of work related skills and encountered more barriers in seeking employment than non-users.

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EMPLOYMENT OF FORMER SSI DA&A RECIPIENTS

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Supplemental Security Income (SSI) disability benefits for drug addiction or alcoholism (DA&A) was terminated on January 1st, 1997, as part of Congress's Contract with America (Contract with America Act of 1996). Their belief was that many of these people were not really impaired and that they could be self-sufficient. The purpose of this study is to examine the extent to which former SSI DA&A beneficiaries, living in Los Angeles, were able to become employed as well as their overall employability. A sample of 400 was randomly chosen from a list of SSI DA&A recipients. Of the 308 people interviewed, 262 cases were interviewed at 6, 12, and 18-month follow-ups, of those 196 were not receiving SSI benefits. Of those, only 25% found some type of employment with only 8.7% being continually employed since their termination from the program. The most common reasons given for not being employed were: Having a chronic physical illness or injury, having a mental illness, or being in jail. The strongest predictor of employment was having access to a car, while the strongest predictor of continuous employment was having a driver's license. Generally, programs for this population may need to include a component dealing with transportation issues, but additional studies are needed in order to better understand employment issues within this population.

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EMPLOYMENT, SOCIAL CONNECTEDNESS, AND DRUG USE OUTCOMES AMONG RECENTLY DETOXIFIED HEROIN AND COCAINE ADDICTS

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The objective of this presentation is to test the hypotheses that a history of stable employment and the presence of social support from relatives and friends are associated with reduction of drug use 30 days after detoxification. Data presented here were collected from 96 individuals interviewed at entry into hospital-based detoxification and again 30 days later. The data were collected as part of a larger study of patients entering detoxification programs in two hospitals in The Bronx, New York. The dependent variable is number of days of use of the most used of heroin, cocaine, or crack in the 30 days following discharge from the hospital, measured by self-report at the 30 day follow-up interview. Data are analyzed by hierarchical regression analysis. Socio-demographic variables are entered on the first step, drug use intensity and duration variables on the second step, employment variables on the third step, and social support variables on the fourth step. The significance of the contribution of each additional set of variables to the equation is measured by the increment in R^2. Age, gender, education, and homelessness account for a modest 12% of the variance. As predicted, entry into the equation of variables measuring history of drug involvement results in a significant increment in R^2, to 20%. The addition on step three of employment variables results in a further significant increment in R^2, which is now 28%. Supportiveness of friends and relatives, results in a small, and insignificant, increase in variance accounted for. The significance of employment in predicting post-detoxification abstinence has important intervention implications. To the extent that heroin and cocaine dependent individuals are provided with employment training and employment opportunities, the likelihood of future relapse is decreased.

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SUPPRESSION OF OPIOID WITHDRAWAL BY DIAZEPAM IN RATS: A COMPARATIVE EVALUATION AGAINST BUPRENORPHINE

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The study compared the effects of increment doses of diazepam (1.0 - 10 mg/kg) and buprenorphine (0.03-1.0 mg\kg) on the withdrawal syndrome in opiate dependent rats. Dependence was induced by administration of increasing dose of morphine over a period of 5 days (5-25 mg/kg, b.i.d, s.c.). On the sixth day, single dose of morphine injection (25 mg\kg, s.c.) was administered. Withdrawal was precipitated with naloxone (1.0 mg/kg, s.c.) 4 hours after last morphine injection. Test drugs were administered 30 min prior to naloxone-induced withdrawal. Somatic signs of withdrawal were scored by using the global Gellert-Holtzman rating scale and gross activity was monitored simultaneously. Animals pretreated with diazepam (1.0-3.0 mg/kg) and buprenorphine (0.03-0.1 mg/kg) showed 47% and 85% decrease on the global withdrawal scores respectively. This decrease was dose dependent. At higher doses acute effects of diazepam and buprenorphine were seen. There was also an increase in gross activity after administration of both the test drugs. However, motor activities did not correlate well with the dose -related appearance of withdrawal signs. These findings suggest that low doses of diazepam can be used for suppressing the opioid withdrawal syndrome. These results support that benzodiazepines may have potential clinical application for management of acute opioid withdrawal as currently available compounds. Additionally, it appears that low doses of diazepam can very well be used compared to higher doses.

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ACUTE EFFECTS OF TRAMADOL IN METHADONE-MAINTAINED VOLUNTEERS

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Tramadol is a commonly used analgesic characterized as having components of both opioid and non-opioid activity. Previous human laboratory work has shown tramadol does not precipitate withdrawal in subjects with a low level of opioid physical dependence (30 mg p.o. daily methadone). The purpose of this study was to assess tramadol's antagonist potential in subjects with a higher level of physical dependence. Subjects (n=8) were maintained on methadone (60 mg p.o. daily), while living on a residential laboratory and undergoing pharmacologic challenges 2-3 times per week. Challenges were given 20 hours after methadone and consisted of a double-blind i.m. injection of: tramadol (75, 150, 300 mg), naloxone (0.1, 0.2 mg), hydromorphone (5, 10 mg), or saline. Measures included physiologic indices, and self-reports and observer ratings of drug effects. Naloxone produced characteristic antagonist-like effects on subject, observer, and physiologic indices. Hydromorphone produced no significant effects. Tramadol did not produce significant antagonist-like effects on any measures. In addition, tramadol did not produce significant opioid agonist-like effects. These results suggest tramadol does not exert opioid antagonist-like effects in methadone-maintained subjects, and may be safely administered to subjects with levels of physical dependence up to 60 mg of daily oral methadone. These results also show tramadol does not exert strong opioid agonist-like effects. Finally, maintenance on 60 mg of daily methadone results in effective blockade of up to 10 mg of parenteral hydromorphone.

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INPATIENT EVALUATION OF THE TOLERABILITY OF HIGH DOSE DEXTROMETHORPHAN IN METHADONE-MAINTAINED SUBJECTS

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Glutamatergic systems may play a key role in opiate addiction. The low affinity NMDA receptor antagonist, dextromethorphan (DM), inhibits and reverses the tolerance associated with morphine analgesia in rodents. Co-administration of glutamatergic antagonists with low doses of oral methadone may facilitate the dose reduction of methadone and decrease relapse to heroin. The tolerability of high doses of DM (120, 240, 480 mg/day) + methadone (50-70 mg/day) was determined. This 16 day double-blind, placebo (P) controlled, inpatient trial, randomized subjects to a P (N=5) or DM (N=10) group (completers), with three phases: study day (SD) 1-2 (baseline/P), SD3- 14 (P or DM), and SD 15- 16 (P). There were no significant differences between the P and DM for all vital measures obtained with the 120 or 240 mg/day DM groups. However, the highest dose of DM (480 mg/day) vs. P produced statistically significant ($p < 0.05$), although small increases in body temperature (0.4 degrees F), but not in respiration, heart rate, or systolic blood pressure. No dose of DM (vs. P) significantly influenced ARCI scores for euphoria, dysphoria, or sedation. DM did not significantly influence plasma methadone levels. Overall, these results indicate the tolerability of high doses of DM + methadone. Clinical studies evaluating DM + methadone in the treatment of opiate addiction are projected.

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METHADONE PLUS AMANTADINE TO DETOXIFY HEROIN-DEPENDENT PATIENTS WITH OR WITHOUT COCAINE USE DISORDER

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Objectives: To assess whether detoxification treatment for inpatients with both heroin dependence and cocaine use disorder using methadone tapering is more efficacious when complemented with the administration of amantadine (200-300 mg/d). To assess the efficacy of this same combination of drugs for treating opiate withdrawal syndrome in heroin-dependent patients without cocaine use disorder. **Methods:** We conducted two successive double-blind, placebo-controlled, parallel trials, each lasting 14 days, in a closed hospital unit. During the first trial, 40 heroin-dependent inpatients with cocaine use disorder received methadone plus amantadine (n=19) or placebo (n=21). During the second trial, 40 heroin-dependent inpatients without cocaine use disorder received methadone plus amantadine (n= 21) or placebo (n=19). For the statistical analysis, we compared the slope of the principal variables using the Wilcoxon-Mann Whitney Two-Sample Test (Normal Approximation). **Results:** Retention did not differ significantly between amantadine group and placebo group, in both clinical trials. In completers presenting with both heroin and cocaine use disorders, amantadine treatment had no significant effect on scores for Opiate Withdrawal Scale (OWS) (S = 118.0; Z = 0.29; P = 0.76) and craving of heroin (S = 112.0; Z = 0; P = 1.0) or cocaine (S = 124.0; Z = 0.68; P = 0.49). In heroin-dependent completers without cocaine use disorder, anantadine treatment had no significant effect on scores for OWS (S = 188.0; Z = 1.71; P = 0.08) and heroin craving (S= 178.0; Z = 1.17; P = 0.24). **Conclusion:** Complementary administration of amantadine does not enhance the efficacy of detoxification treatment for heroin-dependent patients, regardless of whether they also present with cocaine use disorder.

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TREATMENT OF ACUTE OPIOID WITHDRAWAL WITH IBOGAINE

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Ibogaine is an alkaloid with putative effect in acute opioid withdrawal. Thirty-three cases of treatments for the indication of opioid detoxification performed in non-medical settings under open label conditions are summarized involving an average daily use of heroin of .64 ± .50 grams, primarily by the intravenous route. Resolution of the signs of opioid withdrawal, without further drug seeking behavior, was observed within 24 hours in 25 patients. Other outcomes included drug seeking behavior without withdrawal signs (4 patients), drug abstinence with attenuated withdrawal signs (2 patients), drug seeking behavior with continued withdrawal signs (1 patient), and one fatality possibly involving surreptitious heroin use. The safety concerns raised in this series underscore the need for the security and medical supervision available in a conventional medical setting. Despite methodologic limitations of the informal treatment context, and the need for controlled studies, the reported effectiveness is in agreement with preclinical evidence and other case reports, and suggests the possibility of ibogaine as a novel paradigm for studying the neurobiology of addiction and the development of new treatments.

THE CLINICAL USE OF MEMANTINE IN OPIOID DETOXIFICATION

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Preclinical observations and preliminary clinical findings support the hypothesis that NMDA receptor-mediated glutamatergic neurotransmission is involved in the expression and maintenance of opioid dependence. Therefore, we evaluated whether memantine, a low-affinity noncompetitive NMDA receptor antagonist with an excellent safety and side-effect profile, may be a useful agent in the management of opioid abstinence in humans undergoing detoxification from morphine or heroin. Three male and two female treatment-seekers who were opioid dependent, as confirmed by a naloxone challenge, were admitted to an inpatient unit for the length of the treatment. Memantine, 30-60 mg p.o. daily for 2-3 days, was given in an open-label manner. No other standing medications were offered, except rescue doses of OTC preparations, clonidine, clonazepam, zolpidun, and prochloperazine. Multiple measures of abstinence were used to evaluate the severity of withdrawal signs and symptoms. All patients completed detoxification, confirmed by a negative naloxone challenge. The length of detoxification was 45 days. Most patients experienced mild-moderate symptoms of opioid withdrawal for a duration of 1-2 days and required treatment with additional medications. Patients tolerated memantine well, with minimal side-effects. Our findings provide preliminary suggestion of the safety and feasibility of memantine in detoxification for opioid-dependent individuals. Furthermore, there is some evidence that memantine may be an advantageous alternative to current methods of detoxification as use of it may shorten the duration of detoxification.

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IN-PATIENT SAFETY EVALUATION OF LOFEXIDINE, AN ALPHA-2 ADRENERGIC AGONIST, AS A MEDICATION FOR OPIATE WITHDRAWAL

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Preliminary data have indicated that lofexidine, an alpha-2 adrenergic receptor agonist, may be effective for the clinical management of opiate withdrawal while producing less hypotension than clonidine. The present 20-day inpatient study was conducted to assess the relative safety of lofexidine and to obtain information related to its potential efficacy. Opiate-dependent individuals were stabilized on morphine subcutaneously (25 mg four times daily) for 8 days. On day 9, morphine was discontinued, and lofexidine was administered daily through day 18. No medication was administered on days 19 and 20. Nine subjects took lofexidine in the 1.6 mg/day dosage group (0.8 mg 2x/day), 23 subjects in the 2.4 mg/day dosage group (14 at 1.2 mg 2x/day and 9 at 0.8 mg 3x/day) and 3 subjects in the 4.0 mg/day dosage group (1.0 mg 4x/day). No serious adverse events were observed. One subject displayed transient syncope (1.2 mg 2x/day). There were transient, orthostatic systolic BP changes (sys BP < 85 mmHg): 1.6 mg (n=2), 2.4 mg (n=19), 4.0 mg (n=3). There were also apparent dose-dependent decreases in opiate withdrawal symptoms. Overall, lofexidine appeared to have minimal hypotensive effects up to 4.0 mg/day, although transient orthostatic changes occured.

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COMPARISON OF ABRUPT AND VERY RAPID METHADONE TERMINATION IN LOFEXIDINE-ASSISTED METHADONE WITHDRAWAL

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BACKGROUND: The withdrawal syndrome, following abrupt methadone termination, occurs sooner after a low dose than after a high dose is stopped, probably because of its long half-life. "Very rapid" methadone reduction is a potential method for aligning the peak of withdrawal curves in those terminating both high and low doses of methadone. This may be particularly useful when withdrawal is assisted by alpha-2-adrenergic agonists, such as lofexidine and clonidine, as side effects, effort and expense may be minimized. **HYPOTHESES:** This method will result in **(a)** A more gradual rise in withdrawal symptoms initially (than the method involving abrupt termination of methadone); **(b)** Aligning curves by the day that the methadone is stopped will result in a better defined peak of withdrawal; **(c)** The second (delayed) withdrawal peak seen in some rapid withdrawal studies will disappear if it is due to the time taken for methadone to leave the body in the high dose users. **PROCEDURE:** This method involves reducing the methadone by 15mg per day until 10-20mg is reached, then terminating it and starting the lofexidine. Opiate dependent subjects (N=35) will be compared to the published data of subjects undergoing a similar lofixidine detox where the methadone was stopped abruptly (Beam *et al.* 1996). **RESULTS:** The initial gradient of the withdrawal curve was steeper (not shallower as predicted), but this was found to be due to the group withdrawing from 130mg methadone. Aligning the curves by the day that methadone was stopped resulted in a more distinct peak only for the group withdrawing from 135mg methadone. The second withdrawal peak vanished when aligned by day of methadone termination, but also when those on $\leq$ 30mg and $\geq$ 35mg were looked at separately. **CONCLUSIONS:** During lofexidine-assisted withdrawal those on high and low methadone doses behave like two separate groups. However both dose groups may well benefit from starting the lofexidine 1-3 days before the methadone is stopped in order to try to minimise the initial gradient of the withdrawal symptom curve.

BEHAVIORAL NALTREXONE THERAPY FOR OPIATE DEPENDENCE: PRELIMINARY REPORT

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The aim of this three-year NIDA-funded Stage I Behavioral Therapies development project is to develop and test Behavioral Naltrexone Therapy (BNT), a novel psychotherapy designed to promote abstinence from opiates, adherence to naltrexone maintenance, and lifestyle changes in opiate-dependent individuals. BNT is a six-month therapy approach incorporating components from various empirically tested treatments for drug dependence. These therapies include Network Therapy, in which a significant other is involved to monitor and support medication compliance, the Community Reinforcement Approach (CRA), voucher-based contingency management, cognitive-behavioral Relapse Prevention Therapy, and motivational interviewing techniques. Forty-seven subjects entered the open trial. A BNT psychotherapy manual and treatment adherence measures were developed and continue to be refined. In the second and third years, a small, randomized controlled trial with 40 patients will be conducted to test BNT vs. a standard compliance enhancement approach. Our results from Year 1 demonstrate that nearly half the sample (40%) did not complete beyond the first week of treatment. This is believed to be secondary to the tremendous difficulty transitioning to naltrexone in the context of protracted withdrawal symptoms and high risk of immediate relapse before intensive treatment has begun. Preliminary analyses suggest that important predictors of poor treatment retention include regular methadone use prior to detoxification, severity of current opiate use, and increased depressive symptoms at baseline. A significant positive correlation was found between length of time in treatment and both percentage of opiate-free urines and adherence to naltrexone. Additional independent variables under review include HIV-risk behaviors and personality characteristics. We continue to refine methods for improving retention as we develop Behavioral Naltrexone Therapy (BNT) and examine its efficacy for the treatment of opiate dependence.

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ESEROLINE, A METABOLITE OF PHYSOSTIGMINE, HAS POTENT MU-OPIOID AND WEAK MUSCARINIC ANTINOCICEPTIVE PROPERTIES IN MICE

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(-)-Eseroline-(L)-ascorbate has a profile of activity and potency not unlike that of morphine: it is active in the tail-flick(TF), paraphenyquinone, and hot-plate antinociceptive tests. ED50's ± S.E.M. are: 2.4 (1.2-4.5), 0.3 (0.1-0.7) and 3.0 (1.5-6.0), respectively. However, the antagonist dose(AD50) for naloxone versus the ED the TF test is rather high [0.16(0.05-0.55)], compared to that of morphine [0.04 (0.01-0.09)] suggesting heterogeneous anti-nociceptivc properties. In addition, eseroline substitutes completely for morphine in withdrawn morphine-dependent rhesus monkeys in the range 2.5 to 10 mg/kg, s.c. Also, it is devoid of opioid antagonist properties. Naltrindole, a delta opioid antagonist, nor-binaltorphimine, a kappa-opioid antagonist, and mecamylamine, a non competitive nicotinic-receptor antagonist, were completely inactive versus the ED80 of eseroline-induced antinociception in the TF test. However, beta-funaltrexamine, a mu-opioid receptor blocker, was effective (AD50 = 0.45(0.17-1.18, i.c.v.). Atropine, a muscarinic receptor blocker, was weakly effective as an antagonist (data expressed as 20% at 3, 41% at 10, and 48% at 30, mg/kg, s.c). The results of studies involving physostigmine require careful interpretation. Also, escroline may have advantages over morphine as an analgesic. Finally, its chemical structure may provide new insights regarding mu-opioid receptor sites.

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INFLUENCE OF ENDOMORPHINS ON B-ENDORPHIN-INDUCED ANTINOCICEPTION

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Interaction between endogenous μ-receptor ligands (β-endorphin and endomorphin-1 or -2 in the expression of antinociceptioin remains to be clear. Therefore, the effects of endomorphin-1, endomorphin-2, morphine and DAMGO on β-endorphin-induced antinociception were examined. Antinociceptive effect was evaluated by tail-flick method in mice. Antinociception produced by β-endorphin was significantly increased by combination with morphine or DAMGO but not with endomorphin-1 or -2. Thus, the effect of endomorphin-1 or -2 on the β-endorphin-induced antinociception differed from that of morphine or DAMGO. Antinociceptive effect produced by β-endorphin, combined with endomorphin- 1 or -2 but not with morphine or DAMGO, was significantly increased by i.c.v. or s.c. pretreatment with κ-receptor antagonist nor-BNI. The reason why endomorphin-1 or -2 did not change the β-endorphin-induced antinociception may result from the agonistic action of endomorphin-1 or -2 on κ-receptor. Antinociception produced by β-endorphin was significantly inhibited by $\kappa_{2,3}$-receptor agonist TRK-820, but not by κ_{1}-receptor agonist U-50,488H. These results suggest that endomorphin- 1 and -2 may directly/indirectly activate κ_{2}- and/or κ_{3}-receptors in supraspinal; as a result, they may inhibit antinociception produced by β-endorphin.

EFFECTS OF IFENPRODIL ON PENTAZOCINE-INDUCED ANTINOCICEPTION AND PLACE PREFERENCE

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The present study investigated the influence of non-competitive NMDA receptor antagonist, ifenprodil, on pentazocine-induced antinociceptive and rewarding effects in mice. On the warm plate test, the pentazocine-induced antinociception was a biphasic response and pentazocine produced a significant antinociceptive effect in a dose-dependent manner. The pentazocine-induced immediate and delayed antinociceptions were significantly attenuated by pretreatment with β-FNA and nor-BNI, respectively. Therefore, the immediate and delayed responses may be mainly mediated by μ and κ receptors, respectively. Moreover, ifenprodil significantly enhanced both phases the pentazocine-induced antinociception. Effect of ifenprodil on the rewarding effect in a dose-dependent manner. The pentazocine-induced place preference was significantly antagonized by ifenprodil and ketamine. It is well known that ketamine produces psychotomimetic action and psychological dependence. However, we found that ifenprodil potentiates the pentazocine-induced antinociception and blocks the pentazocine-induced rewarding effect. These results suggest that ifenprodil may be useful for adjunctive medication.

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NALTREXONE PRODUCES HYPERALGESIA IN THE RAT AFTER A SINGLE DOSE OF MORPHINE

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Several hours after the administration of a single dose of morphine to otherwise drug-free rats (and humans), opioid antagonists elicit behavioral changes indicative of a withdrawal syndrome and acute physical dependence. Hyperalgesia is a characteristic of the withdrawal syndrome in chronic opioid dependence. The objective of the present study was to determine if the opioid antagonist naltrexone (NTX) or naloxone (NLX) precipitate hyperalgesia (*i.e.,* decreased response latency in the hot-plate test) in adult male rats that were injected with only a single dose of morphine. Following two base-line measures of response latency, rats (n=62) received a single injection of either morphine (1.0, 3.0, or 10 mg/kg, SC) or saline. Four hours later, rats received an injection of saline, SC, followed at 20-min intervals by tests on the hot plate and injections of either NTX or NLX in cumulative doses (0.01, 0.1, 1.0, and 10 mg/kg). NTX produced hyperalgesia in rats that had received 3.0 or 10 mg/ not 1.0 mg/kg morphine. In contrast, the highest doses of NLX (1.0, 10 mg/kg) produced analgesia in animals pretreated with morphine (10 mg/kg) compared to saline-pretreated animals. To determine the time course of the effect, additional rats (n=8/group) received either 3.0 or 10 mg/kg morphine and 2 or 6 hr later were tested on the hot plate after an injection of saline and cumulative doses of NTX. NTX did not induce hyperalgesia either 2 or 6 hr after pretreatment with morphine. These results add hyperalgesia to the cluster of signs and symptoms elicited by an antagonist in subjects treated with morphine acutely, they provide further evidence that a single dose of morphine induces a state of acute physical dependence that has many of the same characteristics as chronic dependence. It is unclear why the effects of NLX were different from those of NTX.

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LACK OF OPIOIDERGIC INVOLVEMENT IN BEHAVIORAL EFFECTS OF NITROUS OXIDE IN HEALTHY VOLUNTEERS

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A number of studies have suggested that the analgesic effects of nitrous oxide are mediated by the opioidergic system. We have not been able to demonstrate that other behavioral effects of nitrous oxide (e.g., subjective effects) are affected by an opiate antagonist, naloxone. In the present study, the effects of a relatively high dose of naloxone was examined to determine its effects on nitrous oxide-induced analgesia, as well as on the subjective and psychomotor effects of nitrous oxide. Fourteen subjects participated in a four-session crossover trial in which they received intravenous injections of either saline or 30 mg/70 kg naloxone, 10 minutes into a 35-min period, in which they were inhaling either 100% oxygen or 30% nitrous oxide in oxygen. Eight minutes after the naloxone administration, subjects were tested on the cold pressor test. Mood and psychomotor performance were also assessed before, during, and after the inhalation period. Subjects reported higher pain ratings after the naloxone injection than the saline injection, but there was no evidence of naloxone reversing the analgesic effects of nitrous oxide. Similarly, while naloxone also affected mood and impaired psychomotor performance, there was no evidence of naloxone reversing nitrous oxide's effects on these measures. The results of this study call into question the role of the opioidergic system in mediating various effects of nitrous oxide in humans.

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DEXTROMETHORPHAN (DM) EFFECT ON MORPHINE (MS) EUPHORIA, DEPENDENCE AND RESPIRATORY DEPRESSION

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DM in equal amounts potentiates morphine analgesia possibly as an NMDA antagonist. To determine if this potentiation is selective for analgesia, three placebo (P) controlled crossover studies were done. Twenty opiate abusers were given P/P; MS 180 mg/P; P/DM 180 mg; and MS 180 mg/DM 180 mg orally at 48-hour intervals according to 4x4 balanced Latin squares. DM had no effect on the liking, MBG or miotic response of MS. Eight subjects were pretreated with MS 60 mg at 6 AM, 12 Noon, 6 PM, and 12 Midnight, accompanied by DM 0 mg, or DM 30 mg, or DM 60 mg, or DM 120 mg. The next day, the DM or P dose was repeated at 6 AM. At 6:30 AM, MS 30 mg was given IM. At 8:30 AM, naloxone (Nx) 2.5 mg was given IM. There was no effect of DM and any sign of Nx induced withdrawal. In the third study, 12 normal subjects were given P/P; MS 60 mg/P; P/DM 60 mg; and MS 60 mg/DM 60 mg orally at 48-hour intervals. Prior to and 2, 4, and 6 hours after dosing, subjects breathed from compressed gas tanks containing 2%, 4%, 6%, and 8% CO_2 with 21%, O_2, and the balance N_2 to obtain a minute volume CO_2 response curve. MS but not DM depressed the slope. DM had no effect on action of MS. These results support the concept that DM selectively potentiates the analgesic action of MS and does not alter the abuse potential of MS.

EFFECTS OF DIFFERENCES IN INSTRUCTION, DRUG HISTORY, AND STIMULUS INTENSITY ON PAIN SENSITIVITY

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The purpose of this study was to determine whether radiant heat intensity, instruction (response threshold), and drug history influence pain sensitivity to radiant heat. Drug history groups consisted of healthy nonsmokers (n=10), healthy smokers (n=6), and methadone-maintained volunteers (n=9, eight of whom smoked). Each volunteer was exposed to seven different radiant heat intensities and instructed to remove their finger either when they first felt the heat (sensory threshold), when the stimulus first felt unpleasant (affective threshold), when they first felt pain (pain threshold), and when they could no longer tolerate the pain (pain intolerance). Mean finger withdrawal latency significantly decreased as heat intensity increased and there were predictable differences by instruction. At higher heat intensities, the methadone group exhibited greater antinociceptive effects relative to the non-smoking control group but not the smoking control group. This trend would suggest that tobacco dependence status is associated with increased antinociceptive effects. The lack of a predicted difference between methadone and smoking groups is most likely due to tolerance to the analgesic effects of methadone.

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PAIN RESPONSES IN METHADONE-MAINTAINED PATIENTS

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Providing pain management for the opioid abusing patient is a challenging clinical task, in part because little is known about the pain experience and analgesic requirements of individuals chronically using opioids. This study describes pain tolerance and pharmacological analgesic response in a sample of opioid addicts stabilized in methadone-maintenance (MM) treatment (n = 60) in comparison to non-dependent controls (n = 60) matched on gender and ethnicity. Using a placebo-controlled, two-way factorial Latin square design, tolerance to cold-pressor (CP) pain was examined, both before and after administration of therapeutic doses of common opioid (hydromorphone 2mg PO) and non-steroidal anti-inflammatory (ketolorac 10mg PO) analgesic agents. MM subjects were stable in treatment (in program 130 days, consistently dosed at same dose x 14 days) and tested within 125" of morning methadone dose (mean 66.2mg/d). Urine toxicology (opioid, cocaine, and benzodiazepine) and menstrual cycle phase were collected on all subjects, to examine the effects of these intervening variables on pain tolerance. Replicating previous work, MM individuals were significantly less tolerant of CP pain than controls ($t = 3.24$, $p = .002$), related to neither absolute methadone dose nor time since dosing, suggesting opioid-induced hyperalgesia or baseline pain intolerance in this population. The effects of the analgesics were significant neither for medication nor group, thus not ruling out differential effects at higher doses. These data provide evidence that MM patients represent a relatively pain intolerant group of patients, and thus their complaints of pain and requests for pain medication should be evaluated seriously rather than interpreted as drug-seeking behavior

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PAIN DETECTION AND TOLERANCE IN METHADONE MAINTENANCE TREATMENT

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Background: There are increasing numbers of people chronically maintained on opioids, including methadone maintenance (MM). Long term maintenance may have important effects on these patients' acute pain threshold and tolerance. **Methods:** Sixteen patients (MM) on stable doses of methadone (mean 62mg ± 5.8 SEM) were recruited from a public methadone program. Sixteen controls were age and sex matched with the MM group. We used two types of pain induction: (1) electric stimulation (ES) via the ear lobe, (2) cold-pressor test (CP) using the non-dominant forearm. Two parameters were used to measure response to pain: detection for onset of pain, and pain tolerance levels. MM patients were tested twice over an inter-dosing period: 23 hours after the previous dose (trough), and again 3 hours after their daily dose (peak). Blood samples were collected concurrently with pain induction (MM only) to determine plasma methadone concentration. Control subjects were tested over exactly the same duration. **Results:** Within group comparison (MM): for ES, increases in methadone concentration (trough to peak) resulted in significant increases in voltage for detection and tolerance ($p< 0.0001$, paired t-test); for CP, there were also significant increases for detection and tolerance ($p<0.0001$, paired t-test). Between group comparisons: for ES, MM patients voltage levels for pain tolerance were lower than controls at trough ($p = 0.013$, t-test) but higher than controls at peak $p=0.015$). There were no significant differences in detection levels between groups; for CP, MM patients detected pain significantly earlier than controls ($p = 0.019$) and were also significantly less pain tolerant than controls ($p < 0.0001$) at trough, and were also significantly less pain tolerant ($p <0.0001$) at peak. There were no significant differences in pain detection levels between groups. **Conclusions:** Pain sensitivity of MM patients is determined by the nature of the stimulus, methadone concentration, and by whether thresholds are determined for pain detection or tolerance. Results suggest that MM patients are relatively intolerant of CP pain.

FENTANYL IN AGED GROUP

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Fentanyl is a potent synthetic opioid often used in anesthetic management but the influence of age on fentanyl dosage requirement in this context has never been reported. This retrospective study used ophthalmological patient data. Fentanyl was administered with the goal of preventing pain during retro- or peribulbar block (RBB or PBB), along with hypnotics midazolam and propofol for amnesia and sedation. Consecutive charts beginning in 1995 through the first quarter of 1997 were reviewed. The dosage data were collected for fentanyl, the sole analgesic. Patients were divided into six age groups, ranging from <40 to >81. Group data were analyzed by ANOVA followed by Tukey's test for multiple comparisons. As expected, age 8 1 or above took the lowest dosage to reach an endpoint (no pain during a RBB or PBB): 0.76 mcg/kg vs. 1.38 mcg/kg in <40 age group in ASA Class I-II patients ($p<0.0001$), 0.71 mcg/kg vs. 0.93 mcg/kg in ASA Class III-IV patients ($p<0.0001$). The correlation between increasing age and decreasing dosage was $r = -0.9449$ ($P<0.01$)

Comparison of Target Analgesic Dosage of Fentanyl by ASA Class within Same Age Group
Mean Dosage (ug/kg)

Age Range (Years)	<40	41-50	51-60	61-70	71-80	>81
ASA Class						
I & II	1.53	1.15	1.08	0.89	0.79	0.77
III & IV	0.94	0.58	0.63	0.68	0.68	0.69
Student t Test P =	0.13	0.02	0.0001	0.0001	0.0002	0.027

POSTER SESSION III

MODULATION OF THE DISCRIMINATIVE-STIMULUS EFFECTS OF METHAMPHETAMINE BY 5-HT1A AND 5-HT2A/2C RECEPTORS IN RATS

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Involvement of serotonergic 5-HT1A and 5-HT2A/2C receptors in the discriminative-stimulus effects of methamphetamine (METH) was analyzed in rats discriminating 1.0 mg/kg METH, i.p., from saline under a fixed-ratio schedule of food presentation. 5-HT1A agonists, 8-OH-DPAT (0.03 - 0.56 mg/kg), and buspirone (1.0 mg/kg - 10.0 mg/kg), partially generalized to METH at doses that decreased rates of responding. This generalization was antagonized by co-administration of WAY- 100635 (1.0 mg/kg), a 5-HT1A antagonist. Although WAY-100635 (0.1 - 3.0 mg/kg) did not attenuate the discriminative-stimulus effects of METH, it partially reversed the leftward shift of the METH dose-response curve produced by 5.6 mg/kg of fluoxetine, 5-HT uptake inhibitor. The 5-HT2A/2C agonist, DOI (0.1 - 1.0 mg/kg), partially generalized to METH (the effect was more prominent with a long pretreatment time). A 0.3 mg/kg dose of DOI shifted the METH dose-response curve markedly to the left and this effect was antagonized by co-administration of 3.0 mg/kg of ketanserin, a 5-HT2A/2C antagonist. Ketanserin also produced a shift to the right in the METH dose-response curve and completely reversed the leftward shift of the METH dose-response curve produced by 5.6 mg/kg of fluoxetine. These data suggest that 5-HT modulation of METH's discriminative-stimulus actions involves stimulation at 5-HT2A/2C and, to a lesser extent, 5-HT1A receptors. This stimulation might play a direct role in mediating the discriminative-stimulus effects of METH or a secondary, modulatory role through influences on dopaminergic neurotransmission.

STEREOCHEMICALLY-DEFINED LOBELINE ANALOGUES: INHIBITION OF [^{3}H]-DOPAMINE UPTAKE AND [^{3}H]-NICOTINE BINDING IN RAT STRIATUM

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Recent neurochemical evidence suggests that lobeline (LOB) may be useful as a therapeutic agent in the treatment of stimulant abuse. Although previous reports have indicated that LOB primarily acts at nicotinic receptors, we have recently demonstrated that LOB redistributes presynaptic dopamine (DA) storage and appears to reduce the pool accessible to amphetamine for reverse transport (Teng *et al.,* 1998). LOB has been shown to bind (Ki = 6 nM) to nicotinic receptors (Jones *et al.,* 1998). Thus, LOB interacts with both nicotinic receptors and inhibits DA transport at the plasma membrane (DAT; IC50 = 80 μM) and the vesicle (VMAT; IC50 = 0.88 μM). In the present study, LOB (0.1-1.0 μM) was found to inhibit nicotine (0.1-10 μM)-evoked [^{3}H]overflow from [^{3}H]DA-preloaded rat striatal slices, shifting the nicotine concentration response curve to the right, which suggests competitive antagonism at nicotinic receptors. Removal of both functionalities from the LOB molecule (transdiene) resulted not only in complete loss of affinity (Ki = 1000 nM) for the nicotinic receptor, but in a 80-fold more potent inhibition of DAT (IC50 = 1 μM), compared with LOB. Removal of the hydroxyl group (ketoalkene) resulted in a 16-fold loss of affinity (Ki = 100 nM) for the nicotinic receptor, but interestingly, the ketoalkene inhibited DAT (IC50 = 6 μM) 13-fold more potently than LOB. Removal of the keto group (lobelanidine) resulted in a complete loss of nicotinic receptor affinity (Ki = 1000 nM); however, lobelanidine inhibited DAT (IC50 = 110 μM) equipotently with LOB. Conversion of the hydroxyl group of LOB to a bulky tosyloxy group (LOB-O-tosylate) reduced the affinity (Ki = 25 nM) for the nicotinic receptor by only 4-fold, but did not alter (IC50 = 80 μM) the interaction with DAT. The results suggest that appropriate structural modification of the LOB molecule affords a compound (transdiene) in which nicotinic receptor interaction has been eliminated, and the interaction with DAT enhanced.

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CORTISOL RESPONSE TO QUITTING METHAMPHETAMINE USE

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Glucocorticoids have been linked to self-administration of drugs of abuse in animals, and their role in human drug abuse is a topic of increasing interest and research. Glucocorticoid levels are increased by both stress and administration of many drugs of abuse, and there is evidence that individual differences in the profile of this glucocorticoid response may be linked to likelihood of problems with drug and alcohol abuse. Attempts to quit using drugs might be expected to increase this activity due to stress, but abstinence might also result in rebound reductions in glucocorticoid activity due to physiological withdrawal from a glucocorticoid-stimulating drug of abuse. In previous work with smokers, we found that early reductions in cortisol levels were associated with post-quit distress and were marginally predictive of abstinence. In an ongoing methamphetamine treatment study, we collected saliva samples on subjects whose visits occurred between 4 and 6 p.m. with the intent of replicating previous analyses with smokers. However, due to the small number of baseline cortisol samples collected, change from baseline in salivary cortisol could not be used as a predictor. With the current analyses, we examine cortisol levels as a function of duration of abstinence from methamphetamine, and also the relation of cortisol to depression and craving. In the sample of 13 subjects for whom cortisol data were available, cortisol levels were not related to either depression or craving. However, though there did appear to be a small initial increase in cortisol levels early in the treatment period, as would be predicted by the association of stress with attempting to quit, cortisol levels were significantly and negatively related to self-reported days since last use over time, consistent with a rebound effect.

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FLUOXETINE IN METHAMPHETAMINE DEPENDENCE -- A CONTROLLED TRIAL: PRELIMINARY ANALYSIS

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Objective: A controlled trial to test the efficacy of fluoxetine (FLX) in the outpatient treatment of methamphetamine (MA) dependence. In animal studies, FLX reduces MA self-administration. **Method:** Eight wk randomized controlled parallel group design with a 1 wk single-blind placebo lead-in, followed by 7 wks of double-blind FLX 40 mg QD or placebo (PLA). Results are reported on the first 60 of the 64 Ss. All were DSM-IV primary MA dependent, stratified by presence or absence of current major depressive disorder (MDD). Mean age was 35, 42 (70%) were male and 44 (73%) white. Of males, 2 I (50%) were gay/bisexual. Of all Ss, 9 (I 5%) were HIV seropositive, 8 (13.5%) met criteria for current MDD. Mean years of MA use was 7.4. At study intake, mean days/wk of MA use was 2.6; mean times/wk of MA use was 6.9; mean amount of MA use/wk was 2.4 grams, and median total quantitative urine MA + Amphetamine concentration was 4594 ng/ml. **Results:** MA use declined for both groups over the study. While craving was lower in the FLX group, no other significant differences emerged between the 2 groups either in reported use or in quantitative MA plus Amphetamine urine concentrations (available at this time only for Ss 1-30). **Conclusion:** Preliminary data do not support the efficacy of fluoxetine as a treatment for methamphetamine dependence. Further analysis is needed of the remaining urine MA levels and of urine MA/Amphetamine ratios in order to assess the pharmacokinetic impact, if any, of FLX on MA metabolism.

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A RISK ASSESSMENT AND CHARACTERISTIC PROFILE OF INJECTING VERSUS NON-INJECTING METHAMPHETAMINE USERS

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Methamphetamine has quickly made its way to becoming one of the nation's leading drugs of abuse. Initially "speed" was injected taken orally or used intranasal. In the early 1990's, a new smokeable form of methamphetamine hydrochloride became available. Almost a decade later, we are finally studying the effects of various routes, as well as, characteristics indicative of the users. What are the characteristics that define injecting and non-injecting users? What are the potential risk factors associated with different routes of administration of methamphetamine? To address these questions, 493 methamphetamine abusers were questioned about their preferred route of administration and asked multiple demographic and psychosocial questions. These participants were moderate to heavy users interviewed in a clinic in Rancho Cucamonga, California. Sixty percent of those sampled were males, 77% of the sample were Caucasian. The average education level was high school graduate or equivalent. Eighteen (4%) reported only injecting MA and not using any other route. This subset had significantly more individuals seroconvert to HIV+, have been using longer, spend more money, and more of them are on parole than users of other routes. Forty-one (8%) reported injecting MA at some point in their lifetime but preferred another route. This subset has more sexual problems, psychological problems and had committed more felonies than either of the other groups. These findings illustrate characteristic differences, which may provide useful information to clinicians in regards to applying different treatment strategies to injecting versus non-injecting MA abusers.

LIFE IN THE FAST LANE: QUALITATIVE FINDINGS ON THE METHAMPHETAMINE USER CAREER

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Amphetamine/Methamphetamine (A/M) abuse is a complex bio-psychosocial problem whose progression (natural history) is poorly understood. What is the context and nature of A/M use? What characterizes the addiction careers of A/M users? How do users relate their struggles with addiction to choices (or default choices) made about employment, crime, health, relationships, and risk-taking? As part of larger parent study "Methamphetamine Abuse: Natural History and Treatment Effects", focus groups on these questions were conducted in 1998 with 20 African-American, Latina/o and white Euro-American men and women treated for A/M use by Los Angeles County treatment facilities in 1996. Content analysis of focus group transcripts revealed that even though routes of administration, context of use, and social significance of use varied among individuals, all participants had nevertheless engaged in similar addiction career patterns. All had first been given A/M by a friend or acquaintance and had chosen to try it either as a substitute for cocaine, because it was readily available, to feel "super-human", to enhance sexuality, to lose weight, and/or to counteract the effects of alcohol. When they first transitioned to regular use, participants felt that they needed A/M to "stay focused" and to "stay sexually productive", often in sex work. Transition from regular to problem use was characterized by out of control, long binge periods, unfocused daily routines, and loss of jobs, relationships, and resources. Participants reported having "maintained" their use for several years before recognizing their problems. In "hitting bottom", these users experienced paranoia and hallucinations, low self-esteem, fatigue, legal problems, and serious health problems, including HIV/AIDS. Findings suggest that earlier intervention may help reduce the degree of HIV-risk taking behavior implicated in A/M abuse, and that chronic A/M users would benefit from ongoing personal contact with outreach workers much earlier in their addiction careers.

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CEREBRAL PERFUSION ABNORMALITIES AND GENDER EFFECTS IN ABSTINENT METHAMPHETAMINE USERS

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Methamphetamine (METH) is a popular drug of abuse. However, little biological data arc available on the potential toxic effects of METH on the human brain. We performed perfusion MRI and neuropsychological (NP) tests in 19 previously METH-dependent, abstinent subjects (lifetime exposure 9234±3568 grams, last METH use 7.8±2.1 months) and in 14 control subjects without a history of drug abuse. Compared to the control subjects, METH users showed decreased regional cerebral blood flow (rCBF) in both lateral frontal and subcortical brain regions, significantly more in the male than the female subjects. Although the METH users appear asymptomatic on neurological examination, they performed less accurately and slower on various NP tasks which measured psychomotor speed and attention. In contrast to the pMRI, we did not observe a gender effect with the NP tests. Our findings show that persistent blood flow and cognitive abnormalities are present in these abstinent users. These findings may reflect the underlying neuronal damage associated with prior METH exposure, which appears to affect the male users more extensively than the female users.

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GENDER DIFFERENCES OF PSYCHOPATHOLOGY IN METHAMPHETAMINE USERS

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Levels of psychopathology and problem behaviors were examined among male (n=64) and female (n=44) methamphetamine abusers who entered a NIDA-funded treatment program in San Bernardino County, California. Symptoms of psychopathology were assessed based on nine dimensions of the Symptoms Checklist-90 Revised (SCL-90-R). The severity of drug use, the incidence of violence, and difficulty in interpersonal relationships were measured by the Addiction Severity Index (ASI). At treatment admission, females reported higher levels of psychopathology and problems across the nine sub-scales of the SCL-90-R than males. All of the females in our sample reported symptoms of depression, obsessive-compulsive tendencies, and interpersonal distress. Females (25.8%) experienced moderate to high levels of depressive symptoms, obsessive-compulsive tendencies (19.4%), and interpersonal distress (9.7%). Results indicate that 41.9% of females and 31.0% of males scored moderate to high across the nine sub-scales on the SCL-90-R upon admission to the program. Female addicts, in addition to the impairments in psychological functioning, had significantly longer history of methamphetamine use prior to entering treatment (females reported 9 years of lifetime methamphetamine use versus 7 years for males). There was also a significant relationship ($p<.05$) between violence and gender, where 64.9% of males reported trouble controlling violent behavior versus 35.1% of the females. The higher incidence of psychopathology found in women is concerning in that psychopathology is often correlated with poorer treatment outcomes. Overall, the average Global Severity Index (GSI) score for females (M=.87, SD=.58) and males (M=.78, SD=.61) indicates a high level of psychopathology among methamphetamine users at the intake period. Results will be discussed in terms of implications for treatment interventions that will be sensitive to issues specific to women.

PATTERNS OF METHAMPHETAMINE USE AND TREATMENT UTILIZATION

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Amphetamine and methamphetamine (A/M) use and consequences have increased dramatically in the past few years. However, despite the currently increasing legislative interest and research in developing specific treatment protocols, little information exists on the natural history of users of the drug or outcomes of in-place treatment. This study is based on a sample of over 400 A/M users admitted to treatment programs in Los Angeles in 1996, random sampling was used within gender-by-ethnicity (African-American, Hispanic, and non-Hispanic whites)-by-treatment modality (outpatient or residential) categories to obtain approximately equal numbers within each category. This analysis describes A/M use and treatment histories and explores predictors of time to relapse. Based on data from the state treatment admission record database, this sample had an average of 2.2 treatment episodes and 154 days of treatment during the 6-year period, 1992-1997, no significant ethnic differences were found in total treatment days, but women averaged more total days than men. More detailed analysis of substance use and treatment utilization were compiled using data from the natural history interviews conducted with the first 100 subjects (the study is on-going and interviewing has not yet been completed). A/M use began for this subsample at an average age of 18.8 years, with regular use following at an average age of 20.9 years. The average age at entry to first treatment for A/M was 29.3 years. For 29% of all treatment episodes for this subsample, at least some A/M use was reported within one month following treatment discharge, relapse within 1 years was reported for 54% of the episodes. Survival analysis using Cox proportional hazards showed that Hispanic ethnicity and younger age at first A/M use were associated with shorter relapse times.

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COMBINING CRACK WITH RISKY SEX

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The state of our current knowledge about HIV prevention for African American communities, like this report, is in many ways still exploratory. That is, the disproportionate increase in HIV seroprevalence among persons of African descent indicates that current prevention messages have not been effective for this population. A great deal of HIV transmission is attributable to the role substance use plays in unsafe sexual behavior and raises concern for public health and policy officials. Several attributes of crack use, for example, including its potential to enhance sex and impair judgment may increase sexual risk-taking and the transmission of the HIV virus among persons of African descent. Understanding and ultimately changing the social and psychological processes that determine this pattern of behavior must inform public health policy. Such policy is urgently needed to direct the next set of prevention interventions for this population. Although isolated efforts to explain the presence of elevated HIV risk behavior have been put forth; a need exists to conceptualize the psychosocial mechanisms that underlie this phenomenon within an integrated theoretical framework. The basis of this report rests on using the AIDS Risk Reduction Model (AARM) for that purpose.

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TREATMENT EFFICACY FOR METHAMPHETAMINE-USING GAY AND BISEXUAL MALES IN LOS ANGELES, CALIFORNIA

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Methamphetamine use is widespread among gay and bisexual males in Los Angeles and is associated with high-risk behaviors for HIV transmission. The present study examines preliminary outcome data on a gay-specific behavioral treatment/research program. Clients are randomly assigned to one of four behavioral treatment conditions and participate in treatment for 16 weeks. The treatment conditions are Contingency Management (CM), Relapse Prevention (RP), Contingency Management and Relapse Prevention combined (CM + RP), and Relapse Prevention combined with gay-specific HIV Risk Reduction (RP + HRR). All clients are active methamphetamine users when they enter treatment. A total of 68 men have completed treatment. Their mean age was 35.63 years (s.d. = 6.07); 61.7% were HIV positive, and most were Caucasian/white (77.9%), with 17.6% Hispanic/Latino and 4.5% Other. The treatment effectiveness score (TES), which counts the number of urine samples negative for metabolite, is used as the primary measure of drug use and can range from 0 to 48. Clients in the CM + RP (mean 29.81) and CM (mean 28.89) conditions averaged higher TES; clients in RP + HRR (mean 21.50) and RP (mean 16.76) scored lower. Preliminary findings from 43 clients indicate a reduction in HIV risk behaviors as a result of drug treatment. At baseline, 25 (58%) clients reported receptive anal sex without a condom in the previous 30 days. By the fourth week of treatment, 19 (44%) and by 16 weeks, 15 (35%) clients reported receptive anal sex without a condom ($p<.10$). Number of sexual partners in the previous 30 days was also reduced from 15.8 partners at baseline to 6.1 partners at 4 weeks and 5.8 partners at 16 weeks ($p<.0001$). At baseline, 39 (91%) clients reported engaging in sex while high, at 4 weeks 26 (61%), and at 16 weeks 22 (51%) reported sex while high ($p<.001$). Preliminary findings indicate that drug treatment is an effective HIV risk-reduction strategy.

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DOSE-DEPENDENT EFFECTS BUT NOT SENSITIZATION OF DRL 45-SEC PERFORMANCE BY ORAL D-AMPHETAMINE WITH CUMULATIVE AND REPEATED DOSING REGIMENS

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The effects of d-amphetamine (AMPH) were evaluated using a cumulative- and repeated-dosing regimen on a food-reinforced 45-sec DRL schedule. Daily 190-min sessions were composed of five 35-min subsessions, separated by 3-min time out periods. Cumulative and repeated oral doses of AMPH were administered during the time out period prior to the start of each of the five daily subsessions for selected sessions. Drug sessions were separated by intervals of at least ten days of non-drug sessions. Four cumulative dose-effect functions for AMPH 0.5, 1, 2,4, 8 mg/kg were determined. This was followed by four dose-effect functions of repetitive 0.5 mg/kg AMPH and four dose functions of repetitive 1 mg/kg AMPH. Cumulative doses resulted in a leftward shift in the IRT distribution as well as dose-dependent increases in sub-criterion responses (<45 sec.) termed shorts and decreases in reinforced responses. The effects of repeated doses of 0.5 mg/kg were less dramatic and lower in amplitude than either cumulative or repeated 1 mg/kg AMPH dosing. Doses of repeated 1 mg/kg resulted in earlier leftward shifts in the IRT distribution than either cumulative or repetitive 0.5 mg/kg dosing. Although dose-dependent effects were evident and statistically significant, no clear trend towards or statistical significance in support of sensitization of the DRL response was found with either cumulative or repeated dosing regimens, unlike a previous similar study in which oral cocaine was administered.

OLANZAPINE PRETREATMENT MASKS THE AMPHETAMINE DISCRIMINATION CUE

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Research has suggested that the atypical antipsychotic olanzapine (LY170053) may possess stimulant craving attenuation properties. This study examined olanzapine's potential using a two-lever, food reinforced, drug discrimination paradigm. Eight experimentally naïve male Sprague-Dawley rats were first randomly assigned into two groups and then trained to discriminate amphetamine injections (1.0 mg/kg ip, 15 min. pretreatment) from saline/sham injections (FR10). Once established, a baseline dose-effect curve (No Treatment condition) was generated using various doses of amphetamine (0.0, 0.25, 0.32, 0.56, 1.0, 1.8, 2.2, and 3.2 mg/kg ip). A second dose-effect curve (Treatment condition) was generated using these same doses of amphetamine after olanzapine pretreatment (1.5 mg/kg sc, 60 min. pretreatment). Additionally, longer pretreatment intervals (120 min. and 240 min.) and lower doses of olanzapine (0.56 and 1.0 mg/kg) were tested against select amphetamine doses (0.56, 1.0, and 1.8 mg/kg ip) to determine, respectively, the time dependence and dose dependence of the treatment effect. In both conditions, responding was recorded as percent correct lever responding and rate of responding. Olanzapine pre-treatment (1.5 mg/kg sc) at one hour successfully interfered with animals' ability to discriminate amphetamine injections across doses. Percent correct responding on the amphetamine lever, and rate of responding on the amphetamine lever, were both significantly attenuated. Additionally, the lower doses of olanzapine (0.56 and 1.0 mg/kg sc) did not appear to possess the same ability to interfere with the amphetamine discrimination to the extent that a dose of 1.5 mg/kg (sc) did. Therefore, we believe that this preliminary investigation has successfully shown that olanzapine pretreatment using 1.5 mg/kg (sc) can interfere with an animal's ability to sense some subjective cue(s) associated with amphetamine administration. These cues may be related to the human phenomena of craving. We believe that this animal model has supported the hypothesis that olanzapine has some utility as a pharmacological adjunct to traditional therapeutic interventions for stimulant abuse/dependence.

DISCRIMINATIVE STIMULUS EFFECTS OF (-)EPHEDRINE IN RHESUS MONKEYS: PHARMACOKINETIC ISSUES

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There is public health concern over the abuse potential of ephedrine and its isomers. Recently, we reported that (-)ephedrine can serve as a positive reinforcer (Winger *et al.* CPDD Proceedings, 1998). However, we obtained mixed results regarding the generalization of (-)ephedrine (1.0 - 30.0 mg/kg, i.g.) to a d-amphetamine discriminative stimulus (1.0 mg/kg, i.g.). One possible account of these mixed results is pharmacokinetic variability associated with the i.g. route of administration. Thus, the present study was designed to evaluate the influence of route of administration and pretreatment time on the ability of (-)ephedrine to substitute for *d*-amphetamine. Three rhesus monkeys trained to discriminate 1.0 mg/kg, i.g. *d*-amphetamine from saline in a two-lever, fixed-ratio 5, shock-avoidance discrimination paradigm were given (-)ephedrine (1.0 - 30.0 mg/kg, i.m.). The (-)ephedrine stimulus substituted for *d*-amphetamine in a dose-dependent manner and relatively less variability was observed when compared to results obtained with the i.g. route of administration. Full substitution (greater than 80% drug-lever responding) of (-)ephedrine occurred for all of the monkeys at one or more doses, an effect not observed following i.g. administration. These data suggest that route of administration may affect the extent to which ephedrine and its isomers exhibit amphetamine-like effects. Comparative data over the i.g., i.m., and i.v. routes of administration and various pretreatment times were presented.

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ESTIMATION OF THE METABOLIC DISPOSITION OF MDMA AND MDA ENANTIOMERS IN HUMANS

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This study measured the metabolic disposition of MDMA (3,4-methylenedioxymethamphetamine) enantiomers in humans. A new gas chromatography-mass spectrometry assay, performed using a bonded-phase capillary column coated with a chiral, derivatizedβ-cyclodextrin, has been developed for the measurement of the *S*-(+)- and *R*-(-)-enantiomers of MDMA and its dealkylated metabolite MDA (3,4-methylenedioxyamphetamine) in human plasma and urine. Eight MDMA users, all CYP2D6 extensive metabolizers (determined by dextromethorphan to dextrorphan metabolic ratios), were administered oral racemic MDMA (or placebo) in doses of 0.5 or 1.5 mg/kg. Plasma and urine samples were obtained at regular intervals for 48 hours after dosing. Results indicate that stereoselective metabolism of the enantiomers occurs with plasma concentration ratios of approximately 2:3 for *S-(+)-/R*-(-)-MDMA. Concentration ratios for *S*-(+)-/*R*-(-)-MDA exhibited a high degree of intersubject variability. The concentration ratio of total MDMA/MDA was approximately 10-15:1.

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ALTERATION OF G PROTEIN BETA GAMMA SUBUNIT EXPRESSION IN BEHAVIORAL SENSITIZATION TO METHAMPHETAMINE

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Chronic abuse of methamphetamine(MAP) leads to MAP-induced psychosis. The vulnerability to relapse in the psychosis shares a common property in behavioral sensitization observed in chronically MAP-treated rodents. It has been indicated that the pathway via G protein play a crucial role in behavioral sensitization to MAP, but little is known about the contribution of the pathway via G protein beta-gamma subunits and their effectors. To clarify the intracellular signaling via G protein beta-gamma subunit in behavioral sensitization to MAP, we examined expression of G protein beta 1,2, gamma 1-3 and Ras protein, a candidate effector beta gamma subunits, using immunohistochemistry. The results are as follows; 1) Beta1 and gamma3 expression increased in nucleus accumbens (NA) and ventral tegmental area (VTA) in rats with MAP challenge injection (M-I group) after chronic saline treatment. 2) Gamma3 expression increased after the MAP challenge injection at 8 weeks after 14-day MAP treatment (M-II group), but beta1 expression in VTA unaltered in M-II group. 3) Ras expression decreased in NA and prefrontal cortex in the M-I and M-II groups. These results indicate that subtype-specific regulation of G protein bg subunit expression play an essential role in the behavioral sensitization to MAP. It is suggested that the different expression of Gbl between in single and chronic administration of MAP in VTA is a persistent change of response to MAP administration, possibly correlating to vulnerability to relapse in MAP-induced psychosis.

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NEUROTOXIC EFFECTS OF MDMA AS DETECTED BY 1H MRS

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The severity of the neurotoxic effects of 3,4-methylene-dioxymethamphetamine (MDMA), also called "ecstasy", on serotonergic (5-HT) neurons has been the subject of controversy for many years. In this study, the potential neurotoxic effects of MDMA were assessed by *ex vivo* proton (^{1}H) magnetic resonance spectroscopy (MRS) and compared to the neurotoxic effects of p-chloroamphetamine (PCA), a known potent 5-HT neurotoxin. Male Sprague-Dawley rats (200-240g) were randomly assigned to treatment with MDMA (20 mg/kg, bid, 4 days, sc, n=8), a single dose of PCA (10 mg/kg once followed by saline bid, sc, n=9), or saline (bid, sc, n=7), and were sacrificed by decapitation two weeks later. Analysis of the frontal cortex and hippocampus by ^{1}H MRS was performed and N-acetylaspartate (NAA) concentrations, a measure which reflects neuronal integrity (Chang *et al.,* in press), was determined. Animals exposed to PCA or MDMA showed no significant changes in NAA concentrations in the frontal cortex as compared to saline controls. Animals exposed to PCA showed a 12% decrease (a trend at p=0.12) in NAA concentrations in the left hippocampus. There was also a non-significant 7% decrease in NAA concentrations in the MDMA treated animals in the left hippocampus. No significant effects were found in the right hippocampus. Since ^{1}H MRS can be performed on human brain in vivo, results from this animal study can be related to studies of humans exposed to MDMA and other drugs of abuse with neurotoxic capabilities. One such study by Chang *et al.* (in press) also found no significant effects on NAA levels in the frontal cortex.

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[^{123}I]β–CIT SPECT IMAGING IN COCAINE DEPENDENCE WITH AND WITHOUT ATTENTION DEFICIT-HYPERACTIVITY DISORDER

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Attention Deficit-Hyperactivity Disorder (ADHD) is a syndrome consisting of severe inattention and/or locomotor hyperactivity with impulsivity. Knockout of the dopamine transporter (DAT) in mice produces spontaneous locomotor hyperactivity and a decreased locomotor response to psychostimulants which is mediated by serotonergic neurotransmission (Gainetidinov *et al.,* 1999). Recent work has also highlighted the role of serotonergic mechanisms in modulating the reinforcing properties of cocaine (Walsh and Cunningham, 1997; Sora *et al.,* 1998). In this study, [^{123}I] β-CIT binding was assessed in acutely abstinent adults with cocaine dependence with and without ADHD and healthy controls using single photon emission computed tomography (SPECT). Subjects were scanned 22.1±1.3 hours after injection with β-CIT under equilibrium conditions. MR co-registration was used to more accurately define brainstem and reference regions. Group comparisons were performed using a ratio of specific to nonspecific brain uptake (V3" = (striatum-cerebellum/cerebellum)), a measure proportional to the binding potential (Bmax/Kd). To date, 24 healthy controls, 9 cocaine dependent subjects without ADHD, and 5 cocaine dependent subjects with ADHD have been studied. At this point, superior and inferior brainstem β-CIT binding, chiefly reflecting serotonin transporter availability, is significantly increased in both cocaine dependent groups. These data suggest that brainstem serotonin transporter availability may be increased in acutely abstinent cocaine dependent humans.

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DOSE-DEPENDENT LIMBIC ACTIVATION IN THE HUMAN BRAIN FOLLOWING IV COCAINE

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Cocaine is a powerful psychostimulant agent with high abuse potential. While considerable progress has been made in understanding cocaine's mechanisms of action using animal models, limited information is available on the pharmacokinetics and localization of action of cocaine in the human brain, and no neuroanatomical data have appeared using multiple doses. We have utilized fMRI to examine brain activation patterns following 3 doses of cocaine given in a cumulative dosing paradigm. Nine experienced crack cocaine users (mean 35 years old, average drug use 8 years; recent drug use=$990/month) gave informed consent and received an injection of saline followed by 3 IV injections of cocaine (10, 20 and 40 mg/70kg), delivered with an inter-injection interval of 30 min. Whole brain fMRI BOLD data were acquired on a 1.5 Tesla GE Signa scanner (TR 6000, TE 40, 64 x 64, 8 mm axial slices) with drug given over a 1 min period, 4 minutes into a 20 min scan. A one way ANOVA was performed on % area under the time-effect curve intensity calculated using a non-linear curve fit against a differential exponential pharmacokinetic model. Significant activations were determined for each dose using a t-tested against the null hypothesis of no activation. Regions showing significant dose effects include the insula, orbitalfrontal and medial frontal gyri, and the nucleus accumbens on the right side. Bilateral activation was seen in the anterior cingulate, superior frontal gyrus, caudate and hippocampus. These data are consistent with the behavioral properties produced by cocaine in humans and suggests possible future target sites for pharmacotherapy.

ACKNOWLEDGEMENTS: Supported by USPHS grant DA09465.

NORMAL CARDIAC TROPONIN SUBUNITS T AND I AFTER INTRAVENOUS COCAINE IN HUMAN SUBJECTS: BIOCHEMICAL EVIDENCE AGAINST SILENT MYOCARDIAL INJURY

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Recent evidence indicates that an increase in vonWillebrand Factor (vWF) predicts adverse outcome in patients with unstable angina and that elevation of cardiac troponin subunits in serum provides improved detection of minor ischemic myocardial injury. We, therefore, measured cardiac troponin T (cTnT) and troponin I (cTnI) concentrations using the Elecsys 1010 Analyzer (Roche-Boehringer Mannheim) and the Stratus II Analyzer (Dade Behring), respectively in human subjects (n=12) who met DSM-IV criteria for cocaine abuse before and sequentially after receiving 0.4 mg/kg of cocaine intravenously. All subjects remained asymptomatic without electrocardiographic changes of ischemia after this dosage, which resulted in statistically significant ($p<0.05$) increases in cardiovascular parameters and in vWF from 10 to 30 and 30 to 240 minutes post-cocaine, respectively. Cardiac TnT remained within normal limits (<0.1ng/L) and cTnI undetectable (<0.35ng/L) up to 4 hours after intravenous cocaine administration. Normal post-cocaine values for cTnT and cTnI provide biochemical evidence against silent injury to the myocardium, extending prior observations on the safety of using moderate doses of cocaine intravenously in human subjects.

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SUSTAINED COCAINE EXPOSURE OF 12 OR 24 HOURS PRODUCES CARDIOVASCULAR TOLERANCE BUT INCREASES PLASMA ENDOTHELIN

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Although a substitution pharmacotherapy using cocaine may decrease self-administration or desire for cocaine, cardiovascular toxicity may occur at doses needed to achieve these effects. Endothelin-1 is an endogenous vasoconstrictor peptide, synthesized in vascular endothelial cells, and may be a key mediator in cardiovascular disease. The cardiovascular and endothelin-1 effects of smoked (two 100 mg pipeloads available 1 hour before and 25 hours after starting infusions) and sustained 12 or 24 hour infusions (6 mg/kg) of cocaine or placebo were assessed in 7 non-dependent cocaine abusers (6 subjects completed study, 1 discharged prior to completion). The infusions produced steady state plasma cocaine concentrations of ~200 (24 hours) to ~600 (12 hours) ng/ml and, except for one episode of atrial tachycardia (with the 12 our infusion), were generally well tolerated. Heart rate and blood pressure were increased with the 12 but not the 24 hour infusion compared with placebo. Endothelin-1 increased with plasma cocaine concentration to clinically significant levels, suggesting that cocaine (or cocaine metabolites) has direct peripheral vascular vasoconstrictor effects in humans.

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CARDIOVASCULAR EFFECTS OF PROPOSED COCAINE TREATMENT AGENTS IN SQUIRREL MONKEYS

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A number of pharmacological agents have been proposed for use in the treatment of cocaine abuse. While it is hoped that these agents will not be used concurrently with cocaine, there will undoubtedly be times when individuals relapse to cocaine use while still on a treatment medication. From a drug safety standpoint, it is therefore important to determine whether these agents might have adverse effects when combined with cocaine. In particular, because of cocaine's potent cardiovascular effects, we have studied three potential treatment agents alone and in combination with cocaine in squirrel monkeys. In conscious squirrel monkeys, cocaine, in doses up to 3 mg/kg IV, produced clear increases in both blood pressure and heart rate, but few prominent effects on ECG. The partial D1 agonist SKF 77434, in doses up to 3 mg/kg IV, produced a brief increase in blood pressure followed by more prolonged, dose-dependent decreases in both blood pressure and heart rate. When given in combination with cocaine, SKF 77434 tended to reduce cocaine's effects. In contrast, the dopamine uptake inhibitor GBR 12909, in doses up to 3 mg/kg IV, increased both blood pressure and heart rate. When given in combination with cocaine, neither potentiation of cocaine's effects nor additive effects on blood pressure and heart rate were seen. As with cocaine, GBR 12909 did not produce significant effects on the ECG. The MAO-B inhibitor Selegiline (*l*-deprenyl), in doses up to 0.3 mg/kg IV, had little effect on either blood pressure or heart rate. When given in combination with cocaine, no change in the cocaine response was observed.

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EFFECTS OF LABETALOL TREATMENT ON THE PHYSIOLOGICAL AND SUBJECTIVE RESPONSE TO SMOKED COCAINE IN HUMANS

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Noradrenergic system is implicated in mediating some of the physiological effects of cocaine. The purpose of this study was to investigate whether treatment with an alpha- and beta-adrenergic blocker, labetalol, which would be expected to attenuate the physiological effects of cocaine would also attenuate the subjective response to cocaine. In this double-blind, placebo-controlled, crossover study, 12 cocaine users were treated with a single 100 or 200 mg dose of labetalol, or placebo in each of 3 experimental sessions. Starting 2 hours after the medication treatment, subjects received 3 doses of 0.4 mg/kg smoked cocaine, 30 min apart. Labetalol treatment significantly attenuated the cocaine-induced increases in heart rate and systolic blood pressure. This attenuating effect of labetalol on the cardiovascular response did not decrease with repeated cocaine deliveries. The subjective response to smoked cocaine deliveries was not affected by labetalol treatment. These results suggest that labetalol effectively attenuates the systolic blood pressure and heart rate increases induced by repeated doses of smoked cocaine, but does not alter subjective effects.

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CARDIOVASCULAR EFFECTS OF KAPPA AGONISTS IN THE SPINAL RAT

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The spinal rat, made dependent to morphine, is a useful preparation for evaluating the cardiovascular effects of opioids. A single administration of morphine (30 mg/kg) induces a state of physical dependence that can be unmasked by naloxone (Nlx, 0. 1 to 10 mg/kg). Since several kappa agonists are also mu partial antagonists, the purpose of this work was to test the agonistic and/or antagonistic effects of kappa compounds on the cardiovascular system of the spinal rat. The following drugs were tested: bremazocine (0.3, 1 and 3.1 mg/kg), U-50488 (0.3, 1 and 3.1 mg/kg) and xorphanol (3.1 mg/kg). All drugs were i.v. administered. Three groups were established: a) kappa compounds + Nlx; b) morphine + kappa; and c) morphine + kappa + Nlx. Acutely, kappa agonists produced a long-lasting and dose-dependent decrease in heart rate with mild and transient changes in blood pressure. When these drugs were administered for 2 h at 3.1 mg/kg, they produced a state of dependence that was unmasked only with high concentrations of Nlx. Kappa compounds administered to rats exposed to morphine (30 mg/kg) for 2 h elicited a mild abstinence response. Interestingly, when these drugs were given 5 min before a challenge dose of Nlx (3.1 mg/kg), they were able to partially block the precipitated abstinence response. These results suggest that kappa compounds are agonists with low dependence liability and neutral partial antagonist activity for mu receptors.

A STUDY ON MECHANISM OF SKIN SCRATCHING INDUCED BY INTRAVENOUS MORPHINE IN CYNOMOLGUS MONKEYS

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It has been known that epidural or spinal administration of morphine causes pruritus in humans. In some diseases, in which pruritus is a prominent symptom, it has been suggested that endogenous opioids are involved in mechanisms of the pruritus. In this study, systemic skin scratching, induced by opioids, was investigated in four cynomolgus monkeys. Morphine and methadone, at 0.25 and 1 mg/kg i.v, produced systemic skin scratching in a dose-dependent manner, while U-50,488 did not. Skin scratching induced by morphine 1 mg/kg, i.v. was completely abolished by pretreatment with naloxone and significantly suppressed with either of histamine H_1 antagonist, pyrilamine or U-50,488, while not affected with histamine H_2 antagonist, ranitidine (paired *t* tests). These results suggest that the mechanism of systemic skin scratching, induced by intravenous morphine, includes opioid mu and histamine H_1 receptors but not opioid kappa receptors. However, administration of morphine, in combination with pyrilamine, caused CNS depressing signs such as eye-closing and decreased spontaneous motor activity. Therefore, the decrease of skin scratching by pyrilamine pretreatment may be attributable to the behavioral depression due to the combination effects.

ANTINOCICEPTIVE AND ANTIPRURITIC POTENCIES OF PERIPHERALLY SELECTIVE KAPPA AGONISTS IN MICE

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A number of arylacetamides have been synthesized that bind to the cloned human kappa opioid receptor and exhibit low CNS penetration. Several of these agonists are antinociceptive in rodent pain models, for example, the standard compounds ICI 204448 and asimadoline. We have reported recently that ICI 204448 and asimadoline are antipruritic in the mouse model of itch described by Kuraishi *et al.* (Eur. J. Pharmacol. 275:229, 1995). In the present work, we compared the s.c. antinociceptive and antipruritic potencies of six novel arylacetamides designed for peripheral selectivity. Asimadoline served as the reference compound. Antinociception was measured in the (0.6%) acetic acid writhing test using male ICR mice (~ 25 g; n=8-12). Antipruritic activity was measured using male Swiss mice (~ 25 g; n=8-12) and compound 48/80 (50 micrograms in 100 microliters, s.c.) as the scratch-inducing agent.

	A_{50} (mg/kg s.c.)	
Compound	Writhing test	Compound 48/80 test
ADL 10-0102	0.005	0.005
ADL 10-0116	0.018	0.19
ADL 10-0110	0.20	4.0
ADL 10-0111	0.66	1.7
Asimadoline	0.72	0.51
ADL 10-0108	0.78	7.7
ADL 10-0101	3.3	13.6

A comparison of relative potencies in the two tests gave a Spearman rank order coefficient of 0.86 ($p<0.01$). Our study suggests that pruritus may be added to pain as a therapeutic target for peripherally selective kappa agonists.

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DIFFERENTIAL EFFECTS OF PERIPHERAL KAPPA OPIATE AGONISTS IN THE ROTAROD AND DIURESIS ASSAYS

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The use of kappa opiate agonists as analgesics has been hindered by CNS side effects. The development of kappa agonists that have poor CNS penetration is a strategy that may provide novel analgesics. We compared the antinociceptive potencies of four kappa agonists designed for peripheral selectivity to their potencies in producing motor impairment and diuresis in male rats following s.c. administration. All of the kappa agonists produced a dose-dependent inhibition of late phase formalin-induced flinching, with a rank order of potency and ED_{50} values (mg/kg) of ADL 10-0116 (1.1) < ADL 10-0110 (7.6)≤ ADL-10-0101 (8.8) ≤ EMD 61753 (11). The ratio of the ED_{50} values for impairment of rotarod performance and inhibition of late phase formalin-induced flinching may reflect the relative degree of CNS penetration by these kappa agonists. The rank order for the rotarod:formalin ED_{50} ratios (in parentheses) was EMD 61753 (est. 5) < ADL 10-0116 (11.8) < ADL 10-0110 (est. 25.1) < ADL 10-0101 (> 34). Kappa opiates produce diuresis; however, the degree to which central kappa receptor activation is involved is unclear. All four kappa agonists were diuretic in normally hydrated rats with similar maximal effects. The rank order for the diuretic:formalin ED_{50} ratios (in parentheses) was ADL 10-0110 (0.03) < ADL 10-0116 (0.09) < EMD 61753 (0.6) < ADL 10-0101 (4.6). These findings suggest that if both diuretic activity and impairment of rotarod performance are indices of activation of central kappa receptors, ADL 10-0101 was the most peripherally selective of the compounds tested. Additionally, the potency of ADL 10-0110 and ADL 10-0116 in the diurecsis assay suggests that kappa agonists that have poor CNS penetration could be useful as diuretics.

THERMOREGULATORY BALANCE BETWEEN MU AND KAPPA OPIOID RECEPTORS IN RATS

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Our studies have shown that intracerebroventricular (icv) injection of the mu antagonist CTAP (1.0 nmol, icv) can significantly block the body temperature (Tb) increase induced by icv injection of a high dose (25 nmol) of the kappa antagonist nor-BNI during the first 45 minutes of measurement. This finding suggests that nor-BNI may block kappa opioid receptors, allowing endogenous mu opioid receptor activity to be seen. To further determine whether a high dose of CTAP can decrease Tb, and whether it is a kappa-receptor-mediated effect, we administered the selective mu antagonist CTAP (10 nmol, icv) 30 min after nor-BNI (1.25 nmol, icv) and measured rectal Tb for 3 hours using a digital thermometer in unrestrained SD rats. Tb measurements and cannulae implantation into the lateral ventricle were carried out according to standard procedures in our laboratory. Statistical analysis of difference between groups was assessed with a two-way analysis of variance (ANOVA) followed by Duncan's test. The dose-response curve of CTAP (0.1 to 10 nmol) showed that icv injection of 5 or 10 nmol can significantly decrease the Tb ($p<0.05$). Icv injection of 1.25 nmol of nor-BNI can block the Tb decrease induced by icv injection of 10 nmol CTAP ($p<0.05$). The findings suggest that mu antagonists, in blocking the endogenously mu-receptor-mediated hyperthermia, can unmask the endogenously kappa-receptor-mediated hypothermia. These results strongly support our hypothesis that there is a tonic balance between mu and kappa opioid receptors that serves as the homeostatic mechanism for maintaining body temperature.

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MORPHINE AND NALOXONE DISCRIMINATIVE CONTROL IS MEDIATED BY THE MU OPIOID RECEPTOR SUBTYPE: ASSESSMENT OF SNC 80 AND NALTRINDOLE SUBSTITUTION

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Both morphine and naloxone are effective training drugs in drug discrimination procedures. In subsequent generalization tests in which other opioids are administered, mu opioid agonists and antagonists, respectively, selectively substitute for the training drugs. Given the relative selectivity of morphine and naloxone for the mu receptor, such substitution patterns suggest that the mu opioid receptor subtype is mediating the discriminative control of these two compounds. The present study further assessed this selective mediation by examining the ability of the delta opioid agonist SNC 80 and antagonist naltrindole to substitute for morphine and naloxone in rats trained to discriminate these latter compounds from vehicle within the conditioned taste aversion baseline of drug discrimination learning. Following acquisition of discriminative control to 10 mg/kg morphine (Experiment 1), various doses of morphine (1.8, 3.2, 5.6, and 10 mg/kg) or SNC 80 (3.2, 5.6, 10, and 18 mg/kg) were given in generalization assessments. While morphine displayed dose-related substitution, there was no evidence of substitution by SNC 80 at any dose administered (1-18 mg/kg). Following acquisition of discriminative control to 1 mg/kg naloxone (Experiment 2), various doses of naloxone (.18, .32, .56, and 1 mg/kg) and naltrindole (1, 3.2, 5.6, 10, and 18 mg/kg) were given in generalization assessments. While naloxone displayed dose-related substitution, there was no evidence of substitution by naltrindole at any dose tested (1-18 mg/kg). These data suggest that at these training doses, the discriminative control established to morphine and naloxone are mediated selectively by their activity at the mu opioid receptor subtype.

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ASSESSMENT OF DELTA-OPIOID COMPOUNDS WITHIN A CONDITIONED TASTE AVERSION DESIGN

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Selective mu and kappa agonists and antagonists differ in their abilities to condition taste aversions. Given that assessments of opioids within the conditioned taste aversion design have focused primarily on compounds that have activity at the mu and kappa receptor subtypes, little is known about the ability of systemically administered delta compounds to produce such aversions. Thus, following water deprivation, 63 female Long-Evans rats (Experiment 1) were given pairings of a novel saccharin solution and various doses (0.32, 1, 3.2 and 10 mg/kg, s.c.) of the selective delta agonist, SNC 80. In a second experiment, 88 female Long-Evans rats, also adapted to water deprivation, were given pairings of a novel saccharin solution and various doses (1, 3.2, 5.6, 10 and 18 mg/kg, s.c.) of the selective delta antagonist, naltrindole. For comparison, the mu agonist, morphine (Experiment 1), and the mu antagonist, naloxone (Experiment 2), were assessed under identical conditions. In Experiment 1, although both morphine and SNC 80 induced aversions at the two highest doses administered, aversions induced by SNC 80 were greater than those induced by morphine and were acquired at a faster rate. The pattern was opposite in Experiment 2. Specifically, aversions induced by naloxone were evident at lower doses than those induced by naltrindole. Further, at doses at which aversions were induced by both compounds, the aversions induced by naloxone were greater and were more rapidly acquired than those induced by naltrindole. These differential abilities of mu and delta opioid agonists and antagonists to induce taste aversions may be related to the differential role mu and delta subtypes play in the rewarding effects of the opioids. That is, if the mu receptor subtype mediates reward, mu agonists may be less aversive (while mu antagonists may be more aversive) than delta agonists and antagonists as a result of their selective activity at the mu subtype.

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(±)-4-[(N-ALLYL-CIS-3-METHYL-4-PIPERIDINYL)PHENYLAMINO]-N,N-DIETHYLBENZ-AMIDES ARE SELECTIVE FOR THE DELTA OPIOID RECEPTOR

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In search of analgesics possessing a reduced side-effect profile relative to morphine, much effort has been expended towards finding opioids which operate via delta or kappa opioid receptors as opposed to the mu opioid receptor which meditates the actions of morphine and its congeners. BW373U86 and SNC-80 represent one class of opioid agonists discovered to be selective for the delta opioid receptor. The piperazine subunit found in these compounds is not commonly found in typical opioid ligands. Racemic 4-[(N-allyl-*cis*-3-methyl-4-piperidinyl)phenylamino]-N,N-diethylbenzamide, which is as an analog of BW373U86 or SNC-80 where the internal piperazine nitrogen has been transposed with the adjacent benzylic carbon, was synthesized and found to have good affinity and selectivity for the delta receptor in radioligand binding studies. The significant change in basicity associated with this structural change (tertiary amine to diarylamino) supports the notion that the internal nitrogen atom in SNC-80 or BW373U86 is not protonated when interacting with the delta opioid receptor.

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A NOVEL BUPRENORPHINE ANALOGUE, BU48, CAUSES DELTA OPIOID-MEDIATED CONVULSIONS BUT NOT ANTINOCICEPTION IN MICE

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BU48 is a novel, ring constrained, analogue of buprenorphine. In mouse brain homogenates the compound had good binding affinity for all three opioid receptors in the order $\mu > \delta = \kappa$. *In vitro,* the compound displayed κ-opioid agonist properties in the guinea pig ileum, potent δ-opioid agonist properties in the mouse vas deferens and was a partial agonist at the rat cloned δ- and human cloned κ-opioid receptors with very low efficacy at the rat cloned μ-opioid receptor. *In vivo,* BU48 produced brief, non-lethal convulsions in mice followed by brief Straub tail and a short period of catalepsy characteristic of BW373U86 and other non-peptidic delta receptor agonists. Naltrindole-sensitive convulsions were seen in all animals at a BU48 dose of 10 mg/kg (s.c.). In the mouse abdominal stretch assay, low efficacy antinociceptive activity was seen which was not prevented by the δ-opioid antagonist naltrindole. BU48 is the first compound described which produces δ-opioid mediated convulsions without any evidence of δ-opioid mediated antinociception and may prove a useful tool in the pharmacological investigation of the δ-opioid receptor.

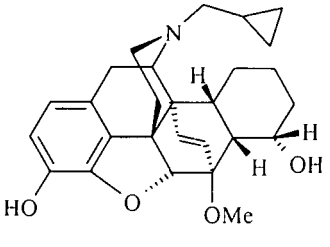

Figure 1: Structure of BU48

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SYNTHESIS AND PHARMACOLOGY OF OPTICALLY PURE N-SUBSTITUTED PHENYLMORPHANS AS OPIOID RECEPTOR ANTAGONISTS

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The phenylmorphans are an intriguing and extremely unusual class of synthetic opioids. For example, both (-)-(NIH 8508) and (+)-2-methyl-5-(3-hydroxyphenyl)morphan (NIH 8509) display opioid actions in the mouse. Both optical isomers were shown to have potent antinociceptive activity in vivo, but the (-)-isomer, was also found to be a nalorphine-like antagonist, indicating that opioid antagonist activity could be obtained in the phenylmorphan series, even with those phenylmorphans which bore an N-methyl substituent. It was formerly noted that substitution of N-phenethyl for N-methyl in the benzomorphans and morphinans increases antinociceptive potency. However, racemic N-phenethylphenylmorphan (**1**), was only about one-half to one-third as potent in the hot plate assay as the racemic N-methylphenylmorphan. Thus, the phenylmorphans appeared to be different than the other classes of opioids. We considered the possibility that an enantiomer of **1** , like an enantiomer in the N-methyl series, might have opioid antagonist activity. Racemic **1** might be ineffective because the enantiomer of **1**, with opioid antagonist activity, blocked the agonist effects of its optical antipode. We have, then, synthesized and evaluated the opioid receptor binding affinity and efficacy (GTPgammaS assay) of the N-phenethylphenylmorphans and found that both enantioners were opioid antagonists.

AUTORADIOGRAPHIC DETERMINATION OF REGIONAL DIFFERENCES IN 5-HT TRANSPORTER (SERT) INACTIVATION BY RTI-76

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The serotonin (5-HT) transporter (SERT) serves as an important target for cocaine and some antidepressants. We have shown that the irreversible cocaine analogue, RTI-76, {3b-(3-*p*-chlorophenyl) tropan-2b-carboxylic acid *p*-isothiocyanato-phenylethyl ester hydrochloride} can inactivate SERT in homogenates of gross brain regions (Soc. Nsci. vol 24:pg 1115, 98). The purpose of this study was to determine the extent of RTI-76 induced inactivation of SERT in discrete brain regions, in order to provide a neuroanatomical map of regions amenable to investigation of SERT turnover. Adult male, Sprague-Dawley rats, received bilateral injections of 100 nmol RTI-76 (i.c.v.) and were sacrificed at 24 hr post-treatment. RTI-76 markedly reduced (80-90 %) SERT densities in regions, such as nucleus accumbens, septal nuclei, paraventricular and other hypothalamic nuclei, hippocampus (CA1-CA3), prefrontal cortex and ventral pallidurn. In midbrain, comparable and marked reductions (-85%) in SERT densities were observed in 5-HT perikarya regions such as dorsal and median raphe. In contrast, SERT reductions in regions containing DA perikarya such as ventral tegmentum (-85 %) and substantia nigra (-45 %) were notably different. Smaller reductions, (-45 %) in SERT densities were also noted in parietal, entorhinal and occipital cortex and basolateral amygdala. These data demonstrate extensive reduction in SERT densities in regions containing 5-HT perikarya as well as in regions innervated by 5-HT neurons. Differences in the magnitude of SERT inactivation may be due to the differential regional distribution of RTI-76 from the lateral ventricles. These data demonstrate the feasibility of using RTI-76 as a tool to investigate SERT turnover in various discrete neuroanatomical regions of brain and to study the effects of drugs of abuse on the kinetics of SERT turnover.

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CHARACTERIZATION OF THE BEHAVIORAL EFFECTS OF AMI-193, A $5HT_{2A}$ RECEPTOR ANTAGONIST, IN THE SQUIRREL MONKEY

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The ability of brain serotonin (5HT) systems to modulate the behavioral effects of cocaine has been well documented, and evidence implicates $5HT_2$ receptors in these behavioral effects. In the present studies, AMI-193, a compound with high affinity at $5HT_{2A}$ receptors and greater than 2,000-fold selectivity for $5HT_{2A}$ versus $5HT_{2C}$ receptors, was examined for its ability to modulate the behavioral effects of cocaine. In squirrel monkeys trained under a 300-sec fixed-interval schedule of stimulus termination, AMI-(0.003-0.01 mg/kg) dose-dependently decreased response rate. AMI-193 (0.01 mg/kg) attenuated the behavioral-stimulant effects of low doses of cocaine (0.03-0.3 mg/kg) and the selective dopamine uptake inhibitor GBR 12909 (0.03-1.0 mg/kg), as well as the rate-decreasing effects of higher doses of cocaine (1.0 and 3.0 mg/kg) and the highest dose of GBR 12909 (3.0 mg/kg). In drug-discrimination experiments, AMI-193 (0.003 and 0.01 mg/kg) also attenuated the subjective effects of cocaine. In monkeys trained to self-administer 0.1 mg/infusion cocaine i.v., AMI-193 dose-dependently reduced response rate. The profile of behavioral effects and drug interactions obtained in conjunction with the relatively high affinity of AMI-193 for D_2 receptors suggests that AMI-193 alters the behavioral effects of cocaine via direct dopaminergic effects rather than through serotonergic mechanisms.

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DEVELOPMENT OF A HIGH-THROUHGPUT ASSAY FOR BIOGENIC AMINE TRANSPORTER SUBSTRATES

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INTRODUCTION. Stimulant withdrawal is characterized by low extracellular levels of DA and 5-HT. Clinical and preclinical data indicate that substrates (SBSTs) of the DA and 5-HT transporters (DAT and SERT) may be useful as treatments for stimulant dependence. SBSTs, such as amphetamine, increase extracellular neurotransmitter (NT) by a combination of carrier-mediated exchange and increased release of NT from vesicular stores. Uptake inhibitors (UI) bind to the transporter, block the transport process and increase extracellular NT. UIs and SBSTs have different neurochemical actions: the ability of the UIs, but not SBSTs, to elevate extracellular NT is nerve impulse dependent and subject to feedback inhibition. The major goal of this study was to establish a high-throughput assay to detect SBSTs for use in a project to develop new drugs with dual activity as SBSTs of DAT and SERT. METHODS. Using minor modifications of published procedures, rat brain synaptosomes were preloaded with either [^{3}H]DA, [^{3}H]NE or [^{3}H]5-HT. Test drugs were added and the reaction terminated by rapid filtration over Whatman GF/B filters. Release was quantified by counting how much tritium was retained on the filters. RESULTS. Using optimized conditions known SBSTs potently decreased retained tritium in a dose-dependent manner whereas known UIs were weak or ineffective. UIs shifted SBST inhibition curves to the right, consistent with antagonist-like activity. CONCLUSION. We have developed high throughput assays which detect SBSTs for the DA, 5-HT and NE transporters.

PROFILING CNS STIMULANTS WITH A HIGH-THROUGHPUT ASSAY FOR BIOGENIC AMINE TRANSPORTER SUBSTRATES

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INTRODUCTION. CNS stimulants increase mesolimbic DA and produce anorexia, locomotor stimulation and self-administration behavior. They increase extracellular neurotransmitter (NT) by a combination of carrier-mediated exchange and increased release of NT from vesicular stores. Most amphetamine-type stimulants were introduced in the 1960s and have not been studied with modern neurochemical methods. This study examined the interaction of selected stimulants at the DA, NE and 5-HT transporters. METHODS. Compounds were characterized with uptake inhibition assays and release assays. [^{3}H]DA, [^{3}H]5-HT and [^{3}H]NE uptake assays were conducted using published methods. The in vitro release assay was conducted using methods described at this meeting (Rothman et al.). RESULTS. Methamphetamine and amphetamine potently released NE (IC50s = 14.3 and 7.0 nM) and DA (IC50s = 40.4 nM and 24.8 nM), and were much less potent releasers of 5-HT (IC50s = 740 nM and 1765 nM). Phentermine released all three biogenic amines with an order of potency NE (IC50 = 28.8 nM)> DA (IC50 = 262 nM)> 5-HT (IC50 = 2575 nM). Aminorex released NE (IC50 = 26.4 nM), DA (IC50 = 44.8 nM) and 5-HT (IC50 = 193 nM). Chlorphentermine was a very potent 5-HT releaser (IC50 = 18.2 nM), a weaker DA releaser (IC50 = 935 nM) and inactive in the NE release assay. Chlorphentermine was a moderate potency inhibitor of [^{3}H]NE uptake (Ki = 451 nM). Diethylpropion, which is self-administered, was a weak DA uptake inhibitor (Ki = 15 μM) and NE uptake inhibitor (Ki = 18.1 μM) and essentially inactive in the other assays. Phendimetrazine, which is self-administered, was a weak DA uptake inhibitor (IC50 = 19 μM), a weak NE uptake inhibitor (8.3 μM) and essentially inactive in the other assays. CONCLUSIONS. 1) Stimulants can be a substrate at one transporter and an uptake inhibitor at another, i.e. chlorphentermine. 2) "Old" drugs classified as amphetamine-type stimulants do not have an amphetamine-type neurochemical profile.

ELICITATION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE BY COMBINATIONS OF INDIRECT DOPAMINE AND SEROTONIN AGONISTS

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Pretreatment with selective serotonin (5-HT) reuptake inhibitors (SSRIs) has previously been shown to produce a leftward shift of the cocaine dose-effect curve in the drug discrimination assay. The present study investigated the conditions under which co-administration of indirect dopamine (DA) and 5-HT agonists would mimic the discriminative stimulus effects of cocaine. Male Sprague-Dawley rats (N=23) were trained to discriminate cocaine (10 mg/kg, IP) from saline (1 ml/kg, IP) in a two-lever, water-reinforced drug discrimination task and were tested with combinations of 5-HT and DA reuptake inhibitors or the 5-HT releaser fenfluramine in substitution tests. The DA reuptake inhibitors mazindol (0.156-2.5 mg/kg, IP) and nomifensine (0.5-2 mg/kg, IP) engendered a dose-dependent increase in cocaine-lever responding and resulted in a full substitution at the highest doses tested. The DA reuptake inhibitor GBR 12909 (4-16 mg/kg, IP) partially substituted for cocaine. The SSRIs fluvoxamine (5-20 mg/kg, IP) and sertraline (5-10 mg/kg, IP) did not substitute for the training dose of cocaine, while the 5-HT releaser fenfluramine (0.5-2 mg/kg, JP) partially substituted (maximum 67% cocaine-lever responding). Administration of fluvoxamine (20 mg/kg) in combination with a dose of mazindol (0.313 mg/kg), nomifensine (0.5 mg/kg) or GBR 12909 (4 mg/kg), which elicited less than 30% cocaine-lever responding, resulted in a full substitution. Administration of sertraline (5 or 10 mg/kg) or fenfluramine (1 mg/kg) in combination with mazindol (0.313 mg/kg), nomifensine (0.5 mg/kg) or GBR 12909 (4 mg/kg) resulted in partial to full substitutions. Thus, the full interoceptive effects of cocaine can be generated in the absence of cocaine administration by a combination of an indirect 5-HT agonist and a sub-threshold dose of a DA reuptake inhibitor. These data support the involvement of serotonergic processes in the overall stimulus effects of cocaine.

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DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE COMBINED WITH DOPAMINE D_1 AND D_2 ANTAGONISTS IN RATS

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It is generally accepted that the discriminative stimulus effects of cocaine are primarily mediated by an increase in dopamine (DA) neurotransmission. However, there is suggestive evidence that other neurotransmitter systems, specifically serotonin (5HT) and norepinephrine (NE), might also be involved in mediating the discriminative stimulus effects of cocaine. In the present study, two groups of rats were trained to discriminate 10 mg/kg of cocaine alone from saline and 10 mg/kg of cocaine following pretreatment with 0.003 mg/kg of the D1 DA antagonist SCH 23390 plus 0.01 mg/kg of the D2 DA antagonist eticlopride from saline. In rats trained on the drug combination, d-amphetamine and GBR 12909 produced partial substitution, whereas fluoxetine and nisoxetine produced responding primarily on the saline-appropriate lever. The D2 DA receptor agonist NPA showed greater efficacy and potency in rats trained on the drug combination than in rats trained on cocaine alone. d-Amphetamine and the D3 DA receptor agonist 7-OH-DPAT produced partial substitution for the training stimulus in rats trained on the drug combination and full substitution for the training stimulus in rats trained on cocaine alone. GBR 12909, the D1 DA receptor agonist SKF 8 1297, the D2 receptor agonists quinpirole and quinelorane and the D4 DA receptor antagonist L745,870 all produced either partial or no substitution and did not show different effects between the two groups of rats. However, when L745,870 was combined with the training drug(s) in each group, the training stimulus was significantly attenuated in rats trained on the drug combination compared to rats trained on cocaine alone. These results suggest that blockade of D1 and D2 DA receptors does not enhance serotonergic or noradrenergic mediation of the cocaine discriminative stimulus; however, it may change the nature of the involvement of D2, D3 and D4 receptors.

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INTRA-ACCUMBENS MICROINFUSION OF AN ANTISENSE OLIGONUCLEOTIDE FOR D5 (BUT NOT D_1) BLOCKS THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE

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Microinfusion of the dopamine (DA) D_1-like receptor antagonist SCH 23390 into the nucleus accumbens (NAc) attenuates the behavioral effects of cocaine, although the non-selectivity of SCH 23390 does not allow attribution of observed effects to either D_1 or D_5 receptors. In the present experiment, we analyzed the relative contribution of NAc D_1 and D_5 receptors to the discriminative stimulus properties of cocaine. Rats trained to discriminate cocaine (10 mg/kg, IP) from saline were surgically implanted with bilateral cannulae aimed at the NAc shell (bregma: AP=+ 1.7, ML=0.75, DV=8). Antisense oligonucleotides (ASN) targeted to either DA D_1 or D_5 receptors or a scrambled oligonucleotide (SCR) were injected (0.75 nmol/0.3 ul/side) twice daily for three days at a rate of 0.1 ul/min. Twelve hrs after the last injection of the DA D_5 ASN, the cocaine dose-effect curve was shifted to the right and the ED_{50} for cocaine (3.72 mg/kg) was significantly increased compared to baseline (ED_{50}= 1.2 mg/kg) or after 7 days recovery (ED_{50}=1.38 mg/kg). The D_l ASN and SCR did not alter the stimulus effects of cocaine. The results suggest that contribution of D_5 receptors in the NAc to the stimulus effects of cocaine is greater than that of the D1 receptor and suggests the potential utility of developing new pharmacotherapeutic approaches for the treatment of cocaine dependence.

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DISCRIMINATIVE EFFECTS OF COCAINE ALONE AND IN COMBINATION WITH SIGMA RECEPTOR LIGANDS THAT ALSO HAVE AFFINITY FOR THE DOPAMINE TRANSPORTER

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Several sigma receptor ligands have recently been reported to also have affinity for the dopamine transporter. In fact, rimcazole showed slightly higher affinity for the dopamine transporter than sigma sites. However, rimcazole lacks a pharmacological profile of behavioral effects similar to other drugs, such as cocaine, that inhibit the uptake of dopamine. Because of this profile of activity, the interactions with cocaine of rimcazole and novel analogs (Newman *et al.,* CPDD, 1999) were assessed. The compounds studied were rimcazole, its N-methylated (SH 1-73) and carbozole-substituted (SH 1-76) analogs, and the N-propylphenyl analogs, SH 3-24 and SH 3-28. The latter compound has a diphenyl-amine group in place of the carbazole moiety of rimcazole, giving the compound structural similarities to the dopamine uptake inhibitor, GBR 12909. In mice, the rimcazole analogs decreased cocaine-induced locomotor activity at doses lower than those that decreased activity when administered alone. In rats trained to discriminate 10 mg/kg cocaine (i.p.) from saline injections, cocaine produced a dose-related increase in cocaine-appropriate responding, with virtually exclusive saline-appropriate responding at 1 mg/kg and virtually exclusive cocaine-appropriate responding at 10 mg/kg. The two propylphenyl analogs of rimcazole decreased cocaine-appropriate responding at the cocaine training dose to about 73% (SH 3-24) to 58% (SH 3-28) with four of six or two of five subjects, respectively, selecting the cocaine response key. In contrast, GBR 12909 potentiated the discriminative-stimulus effects of cocaine. These results indicate that analogs of rimcazole can attenuate the behavioral effects of cocaine. Though the mechanism is not clear, it is possible that the attenuation was mediated by actions of the rimcazole analogs at the dopamine transporter.

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STRUCTURE-ACTIVITY RELATIONSHIPS AT THE MONOAMINE TRANSPORTERS AND SIGMA RECEPTORS FOR A NOVEL SERIES OF RIMCAZOLE ANALOGS

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In the search for a pharmacological intervention for cocaine abuse, compounds that are not selective for the dopamine transporter (DAT) and demonstrate attenuating effects on cocaine-induced behavior have been discovered. Among these are a variety of sigma ligands, including rimcazole. We have previously reported that rimcazole binds with higher affinity to DAT (Ki=103 nM) than to sigma sites. Yet, despite inhibiting dopamine uptake *in vitro,* rimcazole attenuates the locomotor stimulation produced by cocaine in mice. Binding to a low affinity component of DAT or interaction at sigma sites or the other monoamine transporters may be involved in the behavioral actions of this drug. A series of rimcazole analogs have been synthesized and evaluated for binding at sigma, and $sigma_2$-sites, DAT, and serotonin (5HTT) and norepinephrine transporters (NET). Binding studies revealed that aromatic substitutions on rimcazole are not tolerated at DAT. N-Alkylations generally decreased DAT binding affinity, although an improvement was achieved with longer chain alkyl groups (i.e. propylphenyl > methyl). One analog in which the phenyl rings of rimcazole were free to rotate with a propylphenyl group on the terminal nitrogen, was found to have higher affinity for DAT (Ki=61 nM) than the parent drug. Comparison of binding affinities at sigma sites as well as at the 5HTT and NET demonstrated a unique structure-activity relationship profile for this class of ligands. The discovery of neurochemical mechanisms involved with the attenuation of cocaine's behavioral effects will prove useful in the search for a cocaine-abuse pharmacotherapeutic.

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TETHERED BIPHENYL WIN 35,065-2 ANALOGS: EVIDENCE OF A REMOTE LIPOPHILLIC BINDING SITE ON THE DOPAMINE TRANSPORTER

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A series of 3-substituted WIN 35,06.5-2 analogs were synthesized and studied which contain two phenyl rings tethered by a chain of 1 to 5 carbons. These analogs were made as part of our research into the reinforcing and behavioral effects of cocaine, which are thought to be modulated by binding to the dopamine, serotonin, and norepinephrine transporters (DAT, 5-HTT, and NET). Earlier evidence indicated that large groups on the phenyl ring of WIN 35,06.5-2 would cause a dramatic loss of binding to these sites. Surprisingly, some of these biphenyl analogs retained high affinity binding to the DAT and lost binding to the 5-HTT and NET. These results suggest that the second phenyl ring could be associated with a remote lipophillic pocket on the DAT. This remote site is not evident on the 5-HTT or NET. Also, the area between the known site and the remote site contains some sort of steric barrier. Rings tethered by alkynes bound roughly an order of magnitude better than those tethered via a saturated linker.

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COCAINE BINDING TO THE DOPAMINE TRANSPORTER INVOLVES UNIQUE DOMAINS

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Attempts at developing a cocaine antagonist at the level of the dopamine (DA) transporter (DAT) are based on the hypothesis that there are, in addition to likely shared domains, also separate regions on the DAT for cocaine and DA binding. Evidence in support of this comes from previous studies with the sulfhydryl reagent N-ethylmaleimide including our own. In the present experiments, cysteine residues arc alkylated more selectively by methane-thiosulfonate-ethyltrimethylammonium (MTSET), which is positively charged and attacks only residues facing the external medium or the inside of a binding pocket in contact with the medium. Membrane preparations of HEK-293 cells expressing the human (h) DAT were pretreated at 21°C for 5 min with various compounds (protectors) before addition of MTSET (10 mM) or vehicle; 15 min later, reagents were removed in three centrifugation steps, and residual binding of the cocaine analog [^{3}H]WIN 35,428 was determined. High concentrations of some protectors by themselves caused a reduction in binding in vehicle-treated membranes. and such an incomplete wash-out was taken into account in the calculation. The ratio of the PC50 (concentration needed for half-maximal protection) over IC50 (concentration causing 50% inhibition determined separately under conditions identical to those during the MTS/vehicle treatment) were for cocaine, 0.7 ± 0.2; WIN 35,428, 0.2 ± 0.04; benztropine, 2,322 ± 918; mazindol, 19 ± 5, BTCP, 128 ± 30, DA, 132 ± 36, and d-amphetamine, 314 ± 98 (mean ± S.E. for 3 - 5 determinations; $P < 0.05$, one-way Analysis of Variance). Thus, only cocaine and the cocaine analog, WIN 35,428, protected potently with a PC50 close to or smaller than their IC50 value, whereas structurally different blockers and substrates were very weak protectors, suggesting the involvement of unique binding domains involved in the interaction between cocaine-related compounds and the hDAT, or, alternatively, a selective potentiation of binding by cocaine-like compounds that has the appearance of protection.

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DOPAMINE TRANSPORTER SYNTHESIS AND DEGRADATION RATE IN RAT STRIATUM AND NUCLEUS ACCUMBENS AFTER WITHDRAWAL FROM COCAINE

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The dopamine transporter protein (DAT) is a substrate for many drugs of abuse, including cocaine and amphetamine. Cocaine administration and withdrawal has been found to alter levels of DAT in the brain, and these changes in DAT levels may play a role in craving and other effects of withdrawal. Changes in DAT levels may be due to changes in the synthesis and/or degradation rates/ of the protein. To determine the synthesis rate and degradation rate constant of DAT in the rat, ICV administration of the irreversible DAT inhibitor RTI-76 was used to. inhibit [^{3}H]GBR12935 binding of DAT. Measurement of the recovery of binding following RTI-76 administration determined that the half-life of DAT in the striatum and nucleus accumbens of normal untreated rats was 2-3 days. To determine the effects of repeated intermittent cocaine and withdrawal upon the kinetic parameters of DAT, rats received 20 mg/kg cocaine every day for 10 days (days 1 - 10), then were withdrawn from cocaine for another 10 days (days 11-20). Animals received ICV RTI-76 on day 21, then DAT binding was used to determine DAT turnover kinetics in the striatum and nucleus accumbens.

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EVALUATION OF THE REINFORCING EFFECTS OF TWO NOVEL TROPANE ANALOGS IN COCAINE-NAIVE RHESUS MONKEYS

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Previous studies with the novel cocaine analog 2β-propanoyl-3β-(4-tolyl)-tropane (PTT), a compound with high affinity at the dopamine transporter (DAT), have shown that it maintains low rates of self-administration when substituted for cocaine in rhesus monkeys. One purpose of the present study was to examine the reinforcing effects of PTT in cocaine-naive monkeys. A second goal was to evaluate another novel cocaine analog with high affinity at the DAT and serotonin transporter (SERT), 2β-propanoyl-3β-(4-naphthyl)-tropane (WF-23), in cocaine-naive animals. Monkeys (n=4) were initially trained to respond under a fixed-ratio 30 schedule of food reinforcement. Next, saline, PTT (0.0010-03 mg/kg/inj, i.v.) and WF-23 (0.0003-0.0056 mg/kg/inj, i.v.) were male available for self-administration for 5-7 sessions. Neither drug maintained responding significantly higher than saline during 3 hour OTTT and WF-23) nor 22 hour PTT) sessions. After cocaine self-administration was established and a cocaine defect function (0.0003-0.3 mg/kg/inj, i.v.) determined, PTT and WF-23 dose-effect curves were re-determined. PTT functioned as a reinforcer in 3 of the 4 monkeys tested, while WF-23 did not maintain responding above saline levels. These results indicate that the effects of PTT can be modified by exposure to cocaine.

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INHIBITION OF DOPAMINE UPTAKE BY LOCAL ANESTHETICS IN RHESUS MONKEYS: RELATIONSHIP TO REINFORCING EFFECTS

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We have previously reported that some local anesthetics function as positive reinforcers under progressive-ratio schedules of reinforcement in monkeys, Local anesthetics have also been found to bind to dopamine (DA) transporters and inhibit the uptake of DA in rats. The goal of the present study was to determine the relationship between reinforcing potency and efficacy and DA uptake inhibition in a single species. Accordingly, we examined the effects of cocaine (C) and the local anesthetics dimethocaine (D), procaine (P), chloroprocaine (CP), tetracaine (T) and lidocaine (L) on inhibition of [^{3}H]DA uptake into slices of caudate nucleus from rhesus monkeys. At sufficiently high concentrations local anesthetics blocked DA uptake to the same extent as cocaine with a potency order of C≥ D>T≥CP≥ P>L, which was consistent with the potency order for their reinforcing effects. With regard to their relative reinforcing efficacies, the compounds could be rank ordered with C>D>P>CP>T. This was identical to the relative magnitude of DA uptake inhibition for these compounds over a concentration range of 10^{-6} to 10^{-4} M. These data suggest that inhibition of DA uptake is involved in the reinforcing effects of local anesthetics in rhesus monkeys. Differences in the extent of DA uptake blockade over concentrations that are likely to be relevant *in vivo* may account for differences in relative reinforcing efficacy.

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GBR 12909 DECANOATE CAN PRODUCE LONG-LASTING DECREASES IN COCAINE-REINFORCED PROGRESSIVE-RATIO RESPONDING

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In a previous report from our laboratory, pretreatment with GBR 12909 decanoate decreased rates of responding maintained by a fixed-ratio schedule of cocaine delivery for up to 28 days but had little or no effect on food-maintained responding. The present experiment was designed to assess the effects of GBR 12909 decanoate on progressive-ratio (PR) responding maintained by cocaine and by food, because performance on this schedule is thought to provide a clear index of the relative effectiveness of the reinforcing event. Six rhesus monkeys (8.2-10.0 kg) were trained on an alternating PR schedule, in which cocaine was available on Mondays, Wednesdays, and Fridays, and food was available on Tuesdays and Thursdays each week. Unit doses of cocaine (5.6 or 10.0 µg/kg/inj) were chosen separately for each subject, such that, the number of cocaine or food reinforcers earned were as similar as possible. GBR 12909 decanoate was dissolved in sesame-seed oil and was administered i.m. in a volume of 1-6 mL. In three of six monkeys, this treatment produced substantial decreases in the number of cocaine infusions earned without marked effects on food-maintained performance. Doubly determined probes with different unit doses of cocaine (3.0-56.0 µg/kg/inj) in two monkeys revealed a downward-shifted unit-dose-effect function. In three other subjects, GBR 12909 decanoate had minor or transient effects on cocaine-maintained responding. These data (a) demonstrate that there are individual differences in response to GBR 12909 decanoate and (b) suggest that schedule of reinforcement variables may influence effects of GBR 12909 decanoate. Whether this drug has potential as a pharmacotherapeutic component in the treatment of cocaine abuse requires more investigation.

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EFFECT OF COCAINE AND OTHER LOCAL ANESTHETICS ON RESPONDING FOR ELECTRICAL BRAIN STIMULATION ON A PROGRESSIVE RATIO SCHEDULE

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Some local anesthetics are self-administered by experimental animals and have effects on dopamine metabolism, yet do not consistently stimulate locomotor activity. It was of interest to determine if effects of cocaine, dimethocaine, procaine and chloroprocaine on self-stimulation correspond to reinforcement efficacy (all are self-administered) or to locomotor activity (which only cocaine and dimethocaine stimulate). Rats with an electrode aimed at the medial forebrain bundle at the level of the lateral hypothalamus responded for 200 msec of constant current 60 cycle stimulation. Each brain stimulation reinforcer was accompanied by a 200 msec tone and house light "off." In preliminary sessions, current was individually adjusted for each animal to maintain a steady but less than maximal rate of responding on a continuous reinforcement schedule. Rats were then given experience with a fixed ratio 2 (FR-2) schedule. In subsequent sessions, the schedule began at FR-2 and the ratio requirement doubled after every 80th reinforcement. The session ended when the animal went 90 seconds without earning a reinforcer. After experience with this schedule, rats were injected (i.p.) one minute prior to initiation of sessions with saline or one of the local anesthetics. Cocaine and dimethocaine resulted in total responses > 2SD above their individual saline mean in 8 of 8 rats. Procaine similarly increased responding at one or more doses in only 3 of 8 rats. Chloroprocaine increased responding > 2SD above their saline mean in the same 3 rats as did procaine. At the doses tested, procaine and chloroprocaine often decreased responding > 2 SD below saline mean, whereas cocaine and dimethocaine did not. Thus individual differences in responding were greater after procaine and chloroprocaine than after cocaine and dimethocaine. Overall, the effects of local anesthetics on brain stimulation reinforced progressive ratio performance more closely parallel effects on locomotor stimulation than self-administration.

CHARACTERIZATION OF PROGRESSIVE RATIO INTRACRANIAL SELF-STIMULATION IN RATS

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This study was undertaken in order to characterize a progressive ratio (PR) schedule of intracranial self-stimulation (ICSS) as a baseline for testing drugs of abuse. Adults rats (N= *6-8*) were trained on a PR schedule of ICSS, where trains of biphasic square-wave pulses (250 msec, 100 Hz) of variable intensity were delivered to the lateral hypothalamus, contingent on pressing a lever. This free-operant procedure generated stable baseline response rates (1.52 + 0.08 responses/sec), and a behavioral measure of "reward": breakpoint. Parametric increases in the magnitude of the reinforcing stimulation (i.e., stimulation amplitude, frequency, and train duration) produced significant positively-correlated changes in both response rates and breakpoints. In contrast, three different PR schedule changes that simply altered reinforcement density within the test session (e.g., the number of reinforcers obtainable at each response requirement), produced significant, but negatively correlated, changes in response rate and breakpoint. Cocaine (3.0 - 10 mg/kg) or amphetamine (0.3-1.0 mg/kg) increased both response rates and breakpoints; doses of these drugs 0.5 log-unit higher decreased them. Both measures were decreased concurrently by a variety of drugs: morphine (3.0 - 5.6 mg/kg), naltrexone (10 - 5.6 mg/kg), haloperidol (0.1 - 1.0 mg/kg), caffeine (30 - 56 mg/kg), tubocurarine (0.1 - 0.3 mg/kg), and chlordiazepoxide (10 - 30 mg/kg). Phencyclidine (3.0 mg/kg) increased breakpoint, without significantly affecting response rates. Overall, the nine drugs tested under the PR ICSS schedule produced response rate changes that correlated well with those seen under food-reinforced operant schedules and, except for phencyclidine, breakpoint changes were always positively correlated with rates. These data suggest that positively correlated rate and breakpoint changes may predict alterations in reinforcer magnitude, but do not indicate that such correlation is specific to this effect.

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EFFECTS OF KETOCONAZOLE ON ACQUISITION OF COCAINE SELF-ADMINISTRATION IN RATS UNDER FOOD RESTRICTION AND SATIATION

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Ketoconazole, an inhibitor of corticosterone synthesis, has been reported to decrease the self-administration of low doses of cocaine (Goeders *et al.* 1998) and prevent stress-induced reinstatement of cocaine-reinforced behavior in rats (Mantsch and Goeders 1999). In the present experiment, the effects of ketoconazole were extended to the acquisition of cocaine self-administration during food restriction. Food restriction accelerates the acquisition of cocaine self-administration (Carroll and Lac, 1993); and the goal of this experiment was to determine whether ketoconazole would block the food deprivation effect. The effects of ketoconazole on acquisition of cocaine self-administration in food satiated rats is currently being evaluated and results will be compared to the food restricted groups. Using an autoshaping procedure, two groups of rats were trained to self-administer i.v. cocaine (0.2 mg/kg/inf) under a fixed-ratio 1 (FR 1) schedule. In both groups, food availability was restricted to 20 g per day. Daily sessions included a 6-h autoshaping component followed by a 6-h self-administration component. During the autoshaping component, 60 infusions were delivered under a random interval schedule after extension and retraction of a lever. During the self-administration component, the lever remained extended and cocaine infusions were available under an FR 1 schedule. The acquisition criterion was an average of 100 infusions over 5 consecutive days during the self-administration component, Rats were given 30 days to reach this criterion. Ketoconazole (25 mg/kg, i.p.) or vehicle (i.p.) was administered 30-min prior to the autoshaping and self-administration components to Groups 1 and 2, respectively. Results showed that pretreatment with ketoconazole decreased both the rate of acquisition of cocaine self-administration and the percentage of rats meeting the acquisition criterion. These findings indicate that ketoconazole delayed or blocked the acquisition of cocaine-reinforced behavior during food restriction.

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COMPARISON OF THE EFFECTS OF THE COCAINE VACCINE IPC-14,551 ON RESPONDING MAINTAINED BY COCAINE AND FOOD DELIVERY

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Immunization with IPC-14,551 has been shown to reduce drug-seeking behavior and drug intake in rats self-administering cocaine under a second-order schedule of drug delivery. These effects were evident in rats whose serum antibody levels exceeded approximately 65 µg/ml. To determine the behavioral specificity of this action, the vaccine (n=6) and alum control (n=3) were examined in rats maintained under an identical schedule of food delivery. In another group of rats, the vaccine (n=7) and alum control (n=4) were re-examined for their effects on cocaine self-administration behavior, but this time, the rats had daily access to cocaine during the 6-week immunization period. IPC-14,55 1 did not alter responding maintained by food throughout the immunization period. In contrast, the vaccine produced changes in cocaine self-administration behavior that emerged gradually over time. By the last 2 weeks of the immunization period, drug-seeking behavior and drug intake were significantly reduced in vaccinated rats whose serum antibody levels exceeded 65 µg/ml (N=3, range 122 to 498 µg/ml). In the two subjects with the highest antibody levels, responding was extinguished to saline substitution levels, and in the third subject, responding was reduced by approximately 50%. In rats with antibody levels less than 65 µg/ml (N=4, range 11 to 64 µg/ml), cocaine intakes were significantly elevated by the last 2 weeks. For the group of 11 subjects there was a significant negative correlation between serum antibody level and drug-seeking behavior ($r = -0.82$, $p<0.001$) and between serum antibody level and drug intake ($r = -0.65$, $p<0.03$). These findings suggest that the reductions in drug-seeking behavior and drug intake after immunization with IPC-14,551 did not result from a reduced ability of the rats to respond on the lever. Furthermore, daily exposure to cocaine during the immunization period did not influence the efficacy of the vaccine for reducing cocaine self-administration behavior. These findings also confirm the need for a sufficiently high antibody level to blunt the reinforcing effects of cocaine and reduce its intake.

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COCAINE-INDUCED REINSTATEMENT OF RESPONDING FOR BOTH COCAINE AND FOOD

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Priming injections with CNS stimulants have been reported to reinstate extinguished responding previously maintained by cocaine, but not by food when reinstatement testing was conducted in separate groups of rats. The purpose of the present experiment was to establish a procedure with which to examine the reinstatement of responding for both cocaine and food in the same rats within the same test session. This procedure should also allow for repeated reinstatement testing. Fourteen male Wistar rats were implanted with intravenous jugular catheters and trained to self-administer cocaine (0.25 mg/kg/infusion; FR 4) and food (45 mg pellets; FR 10) under a multiple, alternating schedule. This schedule alternated between food and cocaine reinforcement every 15 minutes. When behavior stabilized, a 45-min time-out period and a second 1-hr component (i.e., extinction) were added to the multiple schedule. During the extinction component, rats were trained under the same alternating schedule described above, but no reinforcers were delivered. When rats were responding at levels that were less than 20% of baseline (i.e., during the first hour) during extinction, reinstatement testing began. During reinstatement tests, rats were injected with 10 mg/kg cocaine or saline 15 min before the beginning of the extinction component of the schedule, and all responses during the extinction component were recorded. When rats were injected with saline, responding on the cocaine lever dropped to 10% of baseline, and responding on the food lever dropped to 2% of baseline. In contrast, when the rats were pretreated with cocaine, responding for cocaine increased to 89% of baseline, and responding for food increased to 32% of baseline. In conclusion, 10 mg/kg cocaine fully reinstated responding for cocaine and partially reinstated responding for food in this multiple, alternating schedule of food and cocaine reinforcement. In addition, pretreatment with 25 mg/kg of ketoconizole, an adrenocorticosteroid synthesis inhibitor as well as a glucocorticoid receptor antagonist, resulted in a blockade of the ability of cocaine to reinstate responding for both cocaine and food.

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DOPAMINERGIC MECHANISMS IN RELAPSE TO COCAINE-SEEKING BEHAVIOR: RECEPTOR SUBTYPE SELECTIVITY AND EFFICACY

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Understanding the pharmacological mechanisms of relapse to cocaine-seeking behavior may facilitate the development of effective medications for cocaine abuse. The present study investigated the role of D1- and D2-like dopamine (DA) receptor agonists using a non-human primate model of relapse. Squirrel monkeys were trained to self-administer cocaine under a second-order fixed-interval (FI) fixed-ratio (FR) schedule. Completion of each FR produced a brief visual stimulus, and the first FR completed after expiration of the Fl produced an intravenous injection of cocaine paired with the stimulus. Subsequently, animals underwent a period of extinction during which saline was substituted for cocaine and the cocaine-paired stimulus was omitted. Following extinction, priming injections of cocaine and DA agonists, accompanied by restoration of the cocaine-paired stimulus, were assessed for their ability to reinstate extinguished cocaine-seeking behavior. Cocaine-induced reinstatement was dose-dependent, approaching levels of responding similar to those maintained by cocaine self-administration. Comparable to cocaine, the D2-like full agonists R(-)-propylnorapomorphine and quinpirole but not the D2-like partial agonists SDZ 208-911 and terguride induced robust reinstatement of drug-seeking behavior. The D3-preferring agonist PD 128,907 was ineffective in reinstating cocaine-seeking behavior, and 7-OH-DPAT did so only in half of the subjects at the highest dose tested. The D1-like full agonists SKF 81297 and SKF 82958 and partial agonists SKF 83959 and SKF 38393 did not mimic the priming effects of cocaine in any subject. These results suggest that both receptor selectivity and intrinsic efficacy are relevant factors determining the ability of DA agonists to reinstate cocaine-seeking behavior, and that D1 - and D2-like receptor mechanisms play distinct roles in the relapse process.

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PREPULSE INHIBITION OF STARTLE WAS NOT ALTERED IN COCAINE-WITHDRAWN RATS

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Chronic cocaine administration has been shown to induce long-term alterations in dopaminergic function. The present study used prepulse inhibition (PPI) of the acoustic startle reflex to assess the effects of withdrawal from chronic cocaine in rats. PPI of startle is a sensorimotor gating task in which a startle response to an auditory stimulus is reduced when the stimulus is preceded by a subthreshold pulse (prepulse). In the present study, male Sprague-Dawley rats received daily injections of either saline (n=10) or cocaine (n=9, 30 mg/kg, ip) for two or eight weeks. Acoustic startle and PPI were measured prior to and at 1, 3, and 14 days withdrawal from, the chronic cocaine regimen. No significant differences in startle amplitudes or PPI were observed between cocaine-treated and saline-treated rats. These results support work indicating that withdrawal from chronic cocaine administration does not alter PPI of startle. A previous study by this group found no differences in prepulse inhibition or startle amplitudes between cocaine-treated (30 mg/kg, ip) and saline-treated rats tested after 14 days of treatment. These findings were surprising, given that PPI of startle is sensitive to alterarions in DA neurotransmission (both pharmacological and pathological). In a parallel clinical study (see Duncan *et al.,* CPDD 1998), altered startle responses were observed in withdrawn cocaine addicts.

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EFFECTS OF COCAINE ON SOCIAL BEHAVIOR IN GROUP-HOUSED, MALE CYNOMOLGUS MONKEYS

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Cocaine is a drug of abuse that is often taken in social situations; however most animal studies examine the effects of cocaine administered to individually-housed subjects, thus precluding assessment of social consequences. In the present study, the effects of several doses of cocaine (0.1-1.0 mg/kg, i.v.) were examined in group-housed cynomolgus monkeys (n=4 per pen). On a particular test session, one of the four animals was pretreated with a dose of cocaine, and all other animals were administered saline. The animals were immediately placed into the pen and agonistic and affiliative behaviors were measured over a 45-minute period. When saline was administered to all animals, there were orderly relationships between social rank and rates of particular behaviors. When cocaine was administered, there were dose-related changes in aggression and submission that were dependent on social rank. Dominant monkeys receiving cocaine became more aggressive; however, dominants also became more aggressive when subordinates received cocaine. This is possibly because subordinates receiving cocaine inappropriately increased their rate of submissions. Cocaine produced different effects on affiliation measures (e.g. time spent alone, grooming) depending on whether dominant or subordinate animals were treated. Cocaine generally produced increases in sexual activity. These data suggest that in group-housed monkeys, social rank is the most important determinant of cocaine-induced changes in behavior, including aggression. Furthermore, untreated, as well as treated, monkeys changed their behavior demonstrating that cocaine can have indirect as well as direct social consequences.

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RELATIONSHIP BETWEEN THE COCAINE WITHDRAWAL SYNDROME AND HISTORY OF MOOD DISORDER

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This study examines the relationship between cocaine withdrawal and lifetime history of mood disturbance. Participants were 146 individuals with a history of regular cocaine use. All individuals were administered the SCID (DSM-IV) and were asked to recall whether they experienced any of the six DSM-IV cocaine withdrawal symptoms. All individuals with substance induced mood disorder and lifetime anxiety and psychotic disorders were excluded from the present analysis. Of the 146 participants, 24% (n=35) had a lifetime diagnosis of major depression, dysthymia or bipolar disorder (DEP group), while 76% (n=111) had no history of a mood disturbance (N-DEP group). Of the DEP group 9 1.2% reported the withdrawal symptom of "dysphoria" versus 53.2% of the N-DEP group ($p<.001$). The DEP group was also significantly more likely than the N-DEP group to self report "insomnia/hypersomnia" (68.6% vs 49.5%; $p<.05$), "vivid, unpleasant dreams" (57.1% vs 27.9%; $p<.01$) and "psychomotor agitation/retardation" (80.0% vs 50.5%; $p<.01$). No differences were found for "fatigue" and "increased appetite". The DEP versus N-DEP group was also more likely to have the cocaine withdrawal syndrome (dysphoria + 2 other symptoms; 85.3% vs 46.2%; $p<.001$). The above relationships remained after controlling for demographics, severity of addiction and the presence of opiate, alcohol and cannabis dependence or abuse. Results suggest that lifetime history of mood disorder is strongly related to whether or not a cocaine abuser self reports withdrawal symptoms.

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TREATMENT CONCERNS OF WOMEN WITH DUAL DIAGNOSIS

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Although some research exists concerning the needs of women in substance abuse treatment, little is available on the issues of women with dual diagnosis. Standard structured focus group methodology was used to explore treatment issues specific to women with dual diagnosis. The participants (n=7) were recruited from a larger research project, comparing two different intensive day treatment modalities for dual diagnosis. The coeducational, multicultural treatment groups were integrated into the continuum of care in a large community mental health center. The women each had several diagnoses of serious and persistent mental illness and chemical dependency (actually poly-diagnosed). Participants had moderate to severe impairment in multiple areas on the ASI. Length of time in the public mental health system averaged 11.5 years. Most were mothers (ages 22-55). The participants responded as follows to three main questions regarding their treatment experiences: (1) What works: empathetic, encouraging staff with good listening skills; staff who can teach skills and give simple, honest responses; client-directed treatment goals; welcoming, informal treatment environments; drug-free living sites and daytime activities; effective but minimal medications; availability of female primary care physicians. (2) What does not work: judging, blaming staff with their own agendas; focusing only on substance abuse issues; high staff turnover; losing benefits when they get better. (3) What needs to be added: client advocates, specialists in the areas of Child Protective Services issues, legal issues, and mental health system resources; availability of groups for women only (e.g., parenting, domestic violence, sexual abuse); extra monetary assistance for people trying to improve.

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OUTCOMES OF COCAINE-INDUCED VERSUS MAJOR DEPRESSION IN OUTPATIENTS

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Cocaine-Induced Depression is presumed to have a different course than primary Major Depression. Forty-seven depressed Cocaine Dependent outpatients were assessed for diagnosis with a SCID at intake to outpatient treatment. The naturalistic course of depression was followed for eight weeks with repeated Hamilton Depression Rating Scale (HAM-D) measurements. Ongoing cocaine use was assessed with urine drug screens. There was no difference by diagnosis of Cocaine-Induced Depression versus Major Depression in eight-week HAM-D scores by mixed effects modeling, and most subjects remained mildly depressed. Compared with a matched group of non-depressed Cocaine Dependent outpatients, the subjects were using significantly more cocaine in treatment. Depressed cocaine users who enter outpatient treatment may have difficulty with achieving enough abstinence for the depressogenic effects of cocaine to abate, and treatment of the depression may be warranted whether the diagnosis is of primary or substance-induced depression.

DEPRESSIVE SYMPTOMS AMONG AMPHETAMINE AND COCAINE USERS IN TREATMENT

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This national study examined the prevalence of depression among amphetamine and cocaine users before and after treatment. Data were collected from 1991-1993 in the Drug Abuse Treatment Outcome Study (DATOS). The sample includes 2,952 adult men and women admitted into either long-term residential, outpatient drug-free, short-term inpatient, or outpatient methadone programs, and who completed the intake and 12-month post-treatment follow-up instruments. Controlling for demographics, polydrug use, and lifetime major depressive episode, weekly cocaine users who also used amphetamine at least monthly were 1.5 times more likely to report depressive symptoms in the year prior to intake compared to cocaine users who did not use amphetamine. Weekly amphetamine users who used cocaine only monthly, or not at all, were no more likely to have depressive symptoms than cocaine only users. Those who continued amphetamine use and those who initiated amphetamine use after treatment were 3 and 3.6 times more likely, respectively, to have depressive symptoms in the year following treatment than those who did not use amphetamine at either time. However, amphetamine users who ceased use were no more likely to report current depressive symptoms at follow-up, and did not report a greater number of 2-week depressive periods than those who did not use amphetamine at intake or follow-up.

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PERSISTENT DEPRESSIVE SYMPTOMS AFFECT OPIOID MAINTENANCE TREATMENT OUTCOME

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The prognostic significance of depressive symptoms at treatment entry and at week four in opioid agonist maintained patients was evaluated by analyzing differences in retention, rates of opioid-positive and cocaine-positive urine samples, and rates of abstinence achievement associated with depressive symptoms in two completed clinical trials. In Study 1, 159 patients with concurrent heroin and cocaine dependence were maintained for 22 weeks on either daily methadone (65-85 mg) or buprenorphine (12-16 mg) and treated with CRA. In Study 2, 92 patients with heroin but not cocaine dependence were treated with drug counseling and maintained for 12 weeks on either daily or thrice weekly buprenorphine (112 mg/70 kg per week). Patients with current major depression were excluded from both studies. In Study 1, 76/159 patients (48%) were never symptomatic (BDI<16 at baseline and week 4), 34/159 (21%) resolved depressive symptoms (baseline BDI≥16 and ≤10 week 4), and 49/159 (31%) had persistent depressive symptoms (baseline BDI ≥16 and >10 week 4). In Study 2, 36/90 patients (40%) were never symptomatic (CES-D≤16 at baseline and week 4); 29/92 (32%) had resolved depressive symptoms (baseline CES-D>16 and ≤16 at week 4), and 26/92 (29%) had persistent depressive symptoms (CES-D>l6 baseline and week 4). In Studies 1 and 2 respectively, patients with persistent depressive symptoms had significantly lower rates of treatment completion compared to those never symptomatic or with resolved symptoms (Wilcoxon χ^2=10.8, p<0.01 and Wilcoxon χ^2=7.3, p<.0.05), higher rates of opioid-positive urine samples (Study 1: 67% vs. 58% and 52%; p<.05; Study 2: 73% vs. 64% and 60%, p=.05), and lower rates of ≥ 3 consecutive weeks abstinence from illicit opioids (Study 1: 31% vs. 50% and 62%; p<.05; Study 2: 19% vs. 44% and 55%, p<.05) and cocaine (Study 1: 20% vs. 34%, 47%; p<.05; Study 2: 39% vs. 58%, 59%; p=0.22). Adverse outcomes associated with persistent depressive symptoms point to the importance of developing interventions targeted at demoralization and depressive symptoms.

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COMPARISON OF NEFAZODONE VS. CITALOPRAM FOR DEPRESSION IN METHADONE-MAINTAINED SUBJECTS

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Eight subjects participated in this open label, randomly assigned study. Methadone-maintained subjects with more than 4 weeks in the program and Beck Depression Inventory (BDI) score >20 and diagnosis of Depressive Disorder(s) on SCID for DSM IV were included in the study. Subjects received screening and weekly BDI, Hamilton Depressive (HAM-D) Rating Scale, General Symptom Checklist, Urine Toxicology and Breathalyzer. During the first week one subject on citalopram developed skin rash and was discontinued from the study and one subject on nefazodone discontinued for personal reasons. Two subjects in each group C/O mild gastric irritation during the first two weeks of treatment. Two subjects on citalopram C/O loose bowel movement during the first week of treatment. All the subjects on nefazodone reported improved sleep during first two weeks of treatment. One subject on citalopram during sixth week of treatment reported decreased sexual desire and penile erection dysfunction and was discontinued from the study. BDI scores and HAM-D scores for individual subjects and mean scores indicated reduction of depressive symptoms by 4–5 weeks and remained low through out the study. Nefazodone and citalopram have shown efficacy in the treatment of depressive in Depressive Disorder(s) in Methadone-Maintained depressed subjects. Nefazodone has a favorable side effect profile in comparison to citalopram. Larger scale studies are needed for the better understanding of the efficacy of both the medications.

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CLINICAL AND PSYCHOSOCIAL CHARACTERISTICS OF SUBSTANCE DEPENDENT PREGNANT WOMEN WITH AND WITHOUT PTSD

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The present study compared psychiatric and psychosocial functioning in pregnant drug-dependent women with and without a comorbid DSM-IV diagnosis of Posttraumatic Stress Disorder (PTSD). Subjects were 123 pregnant opioid and/or cocaine dependent women enrolled in a comprehensive perinatal drug treatment program. All subjects completed the Addiction Severity Index (ASI) and Structured Clinical Interview for DSM-IV Axes I and II (SCID) within 7 days post-admission. The sample had a mean age of 30.2 years, mean education of 11 years, 87% were African American, 95% were single, and 93% were unemployed. Lifetime prevalence of DSM-IV PTSD was 19%. Subjects with PTSD reported more drug treatment episodes (2.3 vs. 1.4, $p<.05$), greater need for psychiatric treatment (2.7 vs. 1.1, $p<.01$), and were more likely to report a previous suicide attempt (33% vs. 13%, $p<.05$) than subjects without PTSD. Women with PTSD were twice as likely to have a comorbid Axis II personality disorder (38% vs. 18%, $p<.05$) and Axis I mood disorder (50% vs. 27%, $p<.05$) than women without PTSD. Criterion validity of the SCID-I PTSD module was supported by higher ASI composite and interviewer severity ratings for the family/social and psychiatric domains (all $p<.01$). Furthermore, women with PTSD reported higher rates of recent emotional abuse (46% vs. 24%, $p<.05$) as well as lifetime physical (50% vs. 24%, $p<.05$) and sexual abuse (46% vs. 13%, $p<.01$) than women without PTSD. Findings suggest that pregnant drug-dependent women with comorbid PTSD may benefit from specialized treatment services for trauma and/or abuse issues.

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PROBLEM SEVERITY IN TREATMENT SEEKING PATIENTS WITH AND WITHOUT PTSD

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This project examined the multidimensional problem severity and history of four diagnostic groups of Veterans (n=466) entering outpatient substance abuse treatment. Those with: substance dependence only (SU only) (n=222); substance dependence and additional Axis I disorders excluding PTSD (Axis I) (n = 162); substance dependence and PTSD (PTSD) (n=21); and substance dependence, PTSD, and additional Axis I disorders (PTSD+) (n=61). All four groups were compared on medical, employment, drug, alcohol, legal, family, and psychiatric problem status using the Composite Scores (CS) and Clinical Factor scores (CF) of the Addiction Severity Index (ASI). Results for both the medical and psychiatric CS and CF revealed the PTSD+ group was significantly worse than the Axis I and SU only groups. The four groups did not differ significantly on the drug, alcohol, employment, or legal CS and CF of the ASI. When the groups were compared on individual ASI items, the PTSD+ group had the most extensive psychiatric treatment and problem history, importantly more suicide attempts. These results emphasize the importance of thorough diagnostic assessment for treatment seeking substance abusers, and subsequent treatment planning for the dually diagnosed - especially those with PTSD and an additional Axis I disorder.

ATTENTIONAL BIAS AND COCAINE CRAVING IN ACUTELY ABSTINENT PRIMARY AND COMORBID SCHIZOPHRENIC ABUSERS

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Recent studies have shown that cocaine-relevant stimuli can trigger memories of previous drug use and elicit cravings. These cravings typically reflect positive expectancies. However, the cocaine high and other positive subjective effects are transient and quickly lead to more prolonged negative consequences. It is unclear, consequently, why positive expectancies persist. Within a decision-making theory framework, it has been postulated that attentional bias (AB) fosters persistent and erroneous inferences. Primary abusers appear to be particularly vulnerable to AB because the highly pleasurable subjective effects of cocaine early in the course of addiction are likely to be preferentially encoded, while negative experiences are not fully processed. In contrast, comorbid schizophrenic abusers (CS) manifest intrinsic deficits in selective attention and contextual memory which may limit, or preclude, AB. The present study investigates this proposed association between AB (measured as a difference score between cocaine-related and neutral Stroop distracter words) and craving (measured with the CCQ-GEN: Tiffany, et al., 1993). Preliminary results indicate that primary abusers (n=14) manifest greater attentional bias ($p<.05$) and report greater craving ($p<.01$) than CS (n=14). In comparison to non-abusing controls (n=17), CS demonstrate no differences in AB. The regression of predicted CCQ-GEN score with AB by diagnostic group accounted for a significant proportion of variance ($R^2 = .40$) in the criterion variable, F (3,24) 5.25, $p<.01$, and yielded different prediction equations for primary abusers and CS. These preliminary results provide evidence that CS do not selectively encode their drug-use experience, which may limit their reporting of cocaine craving.

VALIDITY OF THE TRANSTHEORETICAL MODEL OF CHANGE FOR SCHIZOPHRENIA

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Drug abuse by people with schizophrenia is a major public health problem, with a pronounced negative impact on community functioning and response to treatment. While some patients are able to reduce their drug use, little is known about the process of change in this population. One of the most widely accepted models of change in less impaired populations is the Transtheoretical Model (TTM), which places a premium on the role of self-control and decision-making. Given the pronounced deficits in higher level cognitive processing in schizophrenia, the TTM may not be a viable model of change for this population. The purpose of this investigation was to test the validity of the TTM for people with schizophrenia. Two standard TTM measures (URICA and Decisional Balance) were administered to 21 schizophrenia patients who met DSM-IV criteria for drug dependence and 24 matched patients with Major Affective Disorder (MAD). The scores for the schizophrenia sample on both tests showed good internal consistency and the overall pattern of results was comparable to the MAD group, supporting the psychometric adequacy of the instruments for this population. Twelve of the schizophrenia patients subsequently participated in a manualized, 6-month treatment program. Six subjects had very good outcomes (assessed by twice per week urinalysis), and 6 did poorly. There were highly significant differences in baseline TTM scores between the two groups: good outcome patients exhibited greater readiness to change on the URICA and endorsed more cons for drug use on the Decisional Balance scale. These findings support the validity of the model for the population.

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CONTINGENCY MANAGEMENT OF COCAINE ABUSE AMONG INDIVIDUALS WITH SCHIZOPHRENIA

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Individuals who suffer from schizophrenia and abuse cocaine represent a significant cost to the health care system. This, added to the cost in terms of the suffering of the afflicted individual and their family suggests that there is an urgent need for the development of a successful, yet cost-effective, treatment for cocaine abuse among schizophrenics that can be easily implemented in community treatment centers. Toward that end, we are currently studying the efficacy of a contingency-management intervention in which cocaine abusing schizophrenics receive vouchers for providing urine specimens which indicate no recent cocaine use. Importantly, we are providing this treatment in an out-patient setting without any psychosocial treatment for substance abuse. Thus, we are able to attribute any decreases in cocaine use we observe to the contingency-management intervention alone. Using an A (2-wk)-B (4-wk)-A (2-wk) reversal design, we have studied the cocaine use of two individuals in this ongoing study. Both individuals exhibited a 20% decrease in their cocaine use during the intervention phase of the experiment. While we would not argue that this program should serve as a stand-alone treatment, we do believe that the experimental strategy of studying the different components of a potential treatment program in isolation will eventually allow us to develop a comprehensive and cost effective treatment program.

DUAL RECOVERY IN SELF-HELP

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***National Development and Research Institutes, Inc., New York City, NY and **Mental Health Empowerment Project, Inc., Albany, NY**

Presents baseline data (N = 310) from an ongoing longitudinal study of the effectiveness of self-help for dually-diagnosed persons. Ss are members of Double Trouble in Recovery (DTR), a self-help group designed to meet dual recovery needs. Ss are mostly members of underserved minority groups with long histories of substance abuse (SA) and mental health (MH) disorders. Both MH symptoms and SA usually began in adolescence. Over one-third of Ss (38%) experienced MH symptoms before onset of SA; 50% showed a reversed pattern, 12% started experiencing both at the same age. Crack/cocaine has been the primary substance for 42% of Ss. Almost all (96%) have been diagnosed with a MH disorder: schizophrenia (43%), bipolar (25%), and major depression (26%) are most frequent. Two-thirds (70%) experienced symptoms in the past year, 38% were "very" or "moderately troubled" by MH in the past month. Recent substance use is limited - 47% the past year, 9% the past month. Data suggest a strong connection between the two disorders: 69% reported that their MH symptoms get worse when they are using drugs/alcohol, and 44% feel like using drugs/alcohol "very much" when they experience symptoms. Ss have extensive experience with formal treatment in both areas, starting in early adulthood. Currently, 91% are enrolled in outpatient treatment for SA or MH; 75% also attend AA/NA; 91% are on psychiatric medication. Overall, Ss struggle most with emotional and socioeconomic issues, areas with far-reaching consequences for recovery. Preliminary one-yr. follow-up data will be available in mid- 1999.

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NEUROPSYCHOLOGICAL ABILITIES AT ADDICTIONS TREATMENT ENTRY

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The latent structure of neuropsychological abilities in persons with alcohol and other drug use disorders was examined. We hypothesized that persons with an alcohol-only or dual diagnosis would show more neurocognitive impairment than those with a drug use disorder only, taking into account the effects of risk factors such as age, education, medical status, and psychopathology. Participants were 128 men and women with an alcohol use disorder only, 32 with a drug use disorder diagnosis only, and 37 with co-occurring alcohol and drug use disorders entering addictions treatment. Fifteen neuropsychological performance scores gave rise to four latent constructs: fluid cognitive abilities/ executive functions, speed of complex verbal information processing, memory, and verbal ability. The measurement model provided a good fit to the data (x^2=83.04, df=70, p>.10; RMSEA=.03; Bentler & Bonett's Non-normed index=.99, NFI=.96, GFI=.95). In the structural model, gender did not explain significant variance in any of the latent factors. In partial support of the hypothesis, dual alcohol and other drug diagnoses predicted significantly lower verbal ability and slower complex processing speed. Frequency of drug use was a significant predictor of poorer memory. The data indicated that co-occurring alcohol and drug use disorders were associated with lower neuropsychological abilities in selective areas of functioning. Men and women appeared to be similar in ability levels.

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SOCIAL RELATIONSHIPS, GENDER, AND ABSTINENCE IN OPIOID MAINTENANCE PATIENTS

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Abstinence from opiates and cocaine remains elusive for many methadone and LAAM maintenance patients. In this prospective study, we explored whether differences in social relationships might help to explain why some patients achieve abstinence while others do not. Social variables studied were structural support, general functional support, drug use in the social network, and behavioral support for abstinence and drug use. The latter was measured with a multidimensional scale developed for this study. Ss were 139 patients (58% male, 42% female) from three methadone/LAAM maintenance programs. At study baseline and at 3 months, Ss completed face-to-face interviews and paper-and-pencil questionnaires. Abstinence was measured via self-report and confirmed by urine toxicology. Statistical associations between support and abstinence at 3 months, adjusting for baseline abstinence, were found to vary by type of support and by drug. Neither structural support nor general functional support predicted abstinence. Having a social network consisting entirely of non-cocaine users predicted cocaine abstinetice. Decreases in several types of behavioral support from baseline to follow-up also predicted cocaine abstinence, including complaints about drug use, drug exposure, and demoralization. Women, compared to men, reported greater availability of functional support, but associations between support and abstinence were not conditional on gender. Methadone/LAAM programs should actively help patients develop social networks of nonusers and encourage them to spend time in settings where they will not be exposed to drug use or discouraged from abstinence.

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GENDER DIFFERENCES IN TREATMENT SEEKING COCAINE ABUSERS-IMPLICATIONS FOR TREATMENT AND PROGNOSIS

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This study examined gender differences in demographics, psychosocial functioning, substance abuse severity, psychopathology, and 1 year outcome in cocaine-dependent patients with the goal of identifying factors important to improving treatment and identifying prognostic indicators. Standardized assessments and self-reports were administered at least 5 days after last reported cocaine use. Differences by gender were identified using X^2 or t-tests with $p<.05$ considered significant. The sample included 298 cocaine-dependent adults (92 women). Ninety-four patients (29 women) provided 1-year follow-up assessments. Women were more often primary caretakers of children, unemployed, and on public assistance. Compared to men, women consumed similar quantities of cocaine by more addictive routes and experienced somewhat more rapid progression of drug dependence. Alcohol consumption was greater in men, but women showed significant impairment from alcohol. Women had more depressive symptoms and anxiety disorders, similar rates of conduct disorder and antisocial personality disorder, and less attention deficit hyperactivity disorder. At follow-up, 49% of men and 41 % of women no longer met dependence criteria. Cocaine dependence may progress more rapidly in women, highlighting the need to facilitate treatment entry. High rates of psychiatric disorders and alcohol abuse in those receiving drug abuse treatment underscores the need for evaluation and treatment of comorbid disorders in the context of substance abuse treatment programs. The substantial rates of positive treatment outcomes emphasizes the effectiveness of treatment for cocaine-dependent individuals.

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LOOKING FOR POPPA: A DEVELOPMENTAL-ECOLOGICAL PERSPECTIVE ON FATHERS ENROLLED IN METHADONE MAINTENANCE TREATMENT

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Despite longstanding concern about the impact of parental substance abuse on child development, very little is known about the adjustment of drug-dependent men as parents. In this pilot study, 50 opioid-dependent fathers completed a structured interview designed to explore issues relevant to their status as parents. Descriptive analysis of these data highlighted a number of trends that were at odds with popular stereotypes. Rather than confirming patterns of indiscriminate reproduction, woeful neglect of children, and fiscal irresponsibility, the data indicated that, while struggling with their addiction, these men had 1) made some effort to father children in a socially responsible manner, 2) made some effort to maintain a presence in the lives of their children, and 3) made some effort to contribute to the financial support of their children. The data also suggested that, like their alcohol-abusing fathers, these men tended to be most involved early in the lives of their children. Consistent with a developmental-ecological perspective on parenting, the findings raise questions about ways historical and situational influences might interact within this population to compromise socially responsible efforts to function as a father. The results also raise questions about ways the substance abuse treatment system and other human service systems might better support drug-dependent men interested in being a more effective parent.

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LOOKING FOR POPPA: PARENTING RESPONSIBILITIES OF MEN SEEKING METHADONE MAINTENANCE TREATMENT

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Despite longstanding concern about the impact of parental substance abuse on child development, very little is known about the status of drug-dependent men as parents. For this survey, data concerning parenting responsibilities were collected from the records of 362 men and 162 women seeking methadone maintenance treatment over a 12-month period. As a group, this ethnically diverse cohort averaged 36.3 (SD = 8.2) years of age and 12.9 (SD = 9.4) years of opioid-dependence. All were living in southern Connecticut. As expected, a greater proportion of women (84%) versus men (60%) were biological parents. However, because men outnumbered women more than 2:1, men with children comprised the largest subgroup (37%) seeking treatment, and fathers accounted for a disproportionate number (60%) of the 328 parents. A greater proportion of mothers (45%) versus fathers (20%) were also living with at least one child, and even though fathers outnumbered mothers, there were actually more mothers (n = 60) than fathers (n = 40) living with children. Nonresident fathers (n = 156) comprised the largest subgroup (48%) of parents seeking treatment. In addition, when fathers were compared with mothers, there were no significant differences in either the average number of children (M [*SD*] = 2.1 [1.1]) or the average age of their children (M [*SD*] = 12.6[7.7]). Although always considered a critical issue in the treatment of drug-dependent women, the results of this survey raise questions about need to identify parenting as an equally important, but largely neglected issue in the treatment of drug-dependent men.

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THE WOMEN'S ISSUES QUESTIONNAIRE: ADDRESSING GENDER SPECIFIC FACTORS IN SUBSTANCE ABUSE

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Some factors that contribute to, coincide with, or are consequences of substance abuse are likely to be gender specific. In order to elucidate factors that are specific to women, we designed and are currently piloting the Women's Issues Questionnaire (WIQ). In addition to collecting factual information in several areas, women are asked to report the effects that certain conditions and events have had on their alcohol and/or cocaine use. Thus far, we have data from 20 alcohol and/or cocaine dependent women. Preliminary findings show differences between women with or without cocaine dependence: The dually addicted women are younger (35.0 yrs for cocaine, vs 27.5 yrs for alcohol), and began menstruating 1 year earlier than the alcohol dependent women (11.8 yrs vs 12.8 yrs). In both groups, there were incedences of serious gynecological problems (e.g., 10% endometriosis, 30% PID). While many alcohol dependent women reported being physically (58%) but not sexually (8%) abused, the majority of the alcohol and cocaine dependent women reported being both physically (75%) and sexually (75%) abused.

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GENDER DIFFERENCES AMONG IMPAIRED HEALTH CARE PROFESSIONALS

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Few investigations of impaired professionals have evaluated gender differences and the limited information available has been based upon very small female sample sizes. With the increasing percentage of female physicians, it is important to identify unique risk factors that may influence treatment needs and outcome. The purpose of the present study was to compare substance use patterns and psychosocial characteristics of female and male drug impaired health care professionals. One hundred and twenty-six female and 896 male health care professionals were interviewed at time of intake to one of four state monitoring programs during a 3-year period. Women were significantly younger than men; $p<.03$) and both groups were primarily Caucasian. There was a significant difference between groups regarding marital status ($p<.001$); women were more likely to be single (divorced or never married) compared to men. Although there were no gender differences in type of specialty, several were over-represented in both groups including family practice, anesthesiology, and emergency medicine. Gender differences were observed regarding type of practice and employment status. Fewer women were in group and solo office practice and more were working in a hospital setting. Also, women were less likely to be employed full time ($p<.001$). No gender differences were found regarding pattern of substance use including primary substance of abuse, polysubstance use, age of first use, etc. Significant group differences were found for several psychosocial variables including motivation for seeking treatment, presenting problems, childhood living situation, religious background, quality of relationship with mother, father and significant other, incidence of childhood sexual abuse, and suicide behavior. Significantly more women reported physical and emotional problems ($p<.01$) and less social support both in childhood and as an adult. The rate of childhood sexual abuse was more than four times greater for women compared with men ($p<.001$). Suicide ideation was four times higher and suicide attempts were six times higher for women ($p<.001$). Similar to research on women in general and substance abuse, female impaired physicians appear to have particular risk factors that may have treatment implications.

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RATES AND PATTERNS OF SUBSTANCE ABUSE IN FAMILIES OF PREGNANT DRUG-DEPENDENT WOMEN

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This study investigated the rates and patterns of drug and alcohol problems in the families of pregnant drug-dependent women. Women (N=279) from a comprehensive drug treatment program were interviewed upon admission for treatment using the Family Alcohol and Drug Survey. This survey asked study participants to report on parental and sibling alcohol and drug use histories. Family members were categorized as having alcohol or drug (cocaine, heroin, or marijuana) problems if they met Family History Research Diagnostic Criteria (FHRDC) separately for alcohol abuse and drug abuse. Data were analyzed only for study participants who had at least one sibling and who could report on the drug use history of at least one parent (N=195). Large percentages of participants had siblings, mothers and fathers with alcohol (29%, 16% and 47%, respectively) and drug (56%, 14% and 14%, respectively) problems. Probands with an alcohol-abusing mother or father were 2-3 times as likely to report at least one alcohol-abusing sibling than probands whose parents did not have alcohol problems. The proportion of siblings with alcohol problems was 2-3 times higher for the siblings of probands who had an alcohol-abusing mother or father. Also, the proportion of siblings with drug problems was significantly higher for probands who had an alcohol and/or drug-abusing mother, than those who did not. Substance abuse appears common in families of pregnant drug-dependent women, and is concentrated in selected families.

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LONG-TERM DRUG TREATMENT OUTCOMES OF WOMEN WITH HISTORIES OF SEXUAL AND PHYSICAL ABUSE

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High levels of past sexual and physical abuse have been found in women seeking substance abuse treatment. Although such abuse histories are associated with numerous psychological and social problems, research has not supported the assumption that having been a victim of abuse decreases the likelihood of a positive short-term drug treatment outcome. Studies to date, however, have only examined the effect of such histories on short-term treatment outcome. Presented here is an examination of the effects of sexual and physical abuse on a number of behavioral measures over a two-year post-treatment period. No differences were seen between women with and without an abuse history on measures such as drug treatment participation, criminality, intimate relationships, family functioning, and psychiatric symptoms. The findings indicate that the impact of sexual and physical abuse histories on relatively long-term treatment outcomes is minimal. Overall, the findings suggest that addressing the sexual and physical abuse histories of women seeking treatment for drug abuse will not significantly improve the long-term effectiveness of drug treatment.

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SEXUAL ABUSE AND HIV RISK BEHAVIORS IN INCARCERATED WOMEN

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Previous research has shown high rates of drug use among women who were sexually abused as children. Studies have also found high rates of drug use among jailed women. Less well known is the association between childhood sexual abuse and future drug use among jailed women. This is the first study using California Drug Use Forecasting Data (CAL-DUF) to assess these factors in a sample of women arrestees. Women who reported a history of childhood sexual abuse were compared to non-abused women. Hypothesis: women arrestees with a stated history of sexual abuse will differ in drug-using behavior from women who do not report a history of abuse. Methods: Structured interviews were conducted with 391 women arrestees in jails located in 13 counties throughout California. Urinalysis was also performed to validate self-reported drug use. Results: Bivariate analyses and multiple linear regression show that women with a stated history of sexual abuse (21%) were more likely to report that they used heroin, had a history of sexually transmitted diseases, and had higher rates of somatic and mental health problems. Conclusions: Women arrestees would benefit from receiving community referrals to sexual abuse counseling, drug treatment programs and health care services upon their release.

THE MEANING OF AND PATHWAYS INTO SUBSTANCE USE AMONG INCARCERATED WOMEN

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The proposed presentation will have the results of an investigation into the meaning of and pathways into drug use by women incarcerated in jails. Such an exploration seemed imperative as the numbers of women in jail has been increasing steeply since the 1980's, and a majority of them admit to regular drug use. The research was completed among convicted women in a New York City jail. The participants stated that they started using drugs either on their own or in the company of friends, mostly female. Furthermore, the participants earned the necessary funds to purchase drugs, and procured them themselves from the drug dealers. These results indicate that the relationship between gender and substance use/abuse has changed over time because previous studies reported that women were initiated into drugs mostly by their male partners, and depended on these partners for further use.

FACTORS THAT PREDICT TREATMENT OUTCOMES AND LIFE OUTCOMES OF WOMEN ENROLLED IN OUTPATIENT AND RESIDENTIAL SUBSTANCE ABUSE TREATMENT

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The purpose of this study was to identify client factors that predict treatment and life outcomes of women enrolled in outpatient (OP) and residential (R) substance abuse treatment. Subjects were 95 women who enrolled in (OP) or (R) from 9/94-2/97; remained in treatment a minimum of 3 months; and completed a 12 month assessment protocol. Measures included Psychosocial History (PSH), PSH update; Beck Depression Inventory; Urine Drug Screens; Everyday Stressors Index; Social Network Interview; Life Satisfaction Ratings; MCMI-III; Client and Staff View of Engagement Questionnaires; Program Satisfaction Interview; and service utilization and retention data. Data analysis included factor analyses to identify predictors and a series of multiple regression procedures to examine whether biopsychosocial characteristics at intake predicted treatment outcomes and life outcomes; and whether intermediate treatment outcomes mediate life outcomes. Intake predictors explained 27-34% of the variance in OP treatment outcomes and 40-56% of the variance for women in R. The strongest predictors of life outcomes for women in OP were for the Biopsychosocial Well-Being domain (38% of the variance) and Family/Social domain (26% of the variance). For women in R, the strongest predictors were found for the Substance Use and Treatment Involvement domain (43% of the variance), Family/Social domain (39%) of the variance), Personal Resources and Responsibilities domain (33% of the variance), and Biopsychosocial Well-Being domain (24% of the variance). For both outpatient and residential clients, intermediate treatment outcomes were found to enhance, rather than to mediate life outcomes. The results suggest that prediction of women's life outcomes is complex, differs for women in residential and outpatient treatment, and is related to a number of factors including social support, daily stressors, partner abuse, substance abuse by self and significant others, psychiatric history, chronic medical conditions, childcare responsibilities and treatment engagement.

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DRUG TREATMENT OUTCOMES FOR WOMEN WITH CHILDREN: OLIVIA'S HOUSE

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Olivia's House was a demonstration project designed to develop, implement, and evaluate an innovative substance abuse treatment program for drug-dependent women with children. The gender specific program provided six months residential followed by six months outpatient substance abuse treatment. The present study will outline key outcome findings on drug and alcohol usage, depressive symptoms, parental distress, and child development. Participants were 88 women and their children, 76% African American, 23% Caucasian, and 1% Hispanic. Follow-up rates were 47% at exit. Results from the Addiction Severity Index Composite Scores revealed significant decreases from Baseline to Exit in: Drug Use ($\underline{X}$ =. 12, SD =. 12 to $\underline{X}$ =.01, SD=.01); Family/Social ($\underline{X}$ =.31, SD = .25 to $\underline{X}$ = .11, SD=.15); and Alcohol Use ($\underline{X}$ =.16, SD =.22 to $\underline{X}$ =.01, SD=.01). On the SCL-90-R, there were significant decreases in Depression ($\underline{X}$ = 61, SD = 9.3 to $\underline{X}$ = 55, SD = 9.0); Paranoia ($\underline{X}$ = 65, SD = 9.2 to $\underline{X}$ = 59, SD = 10.1); and Global Severity of Problems ($\underline{X}$ = 64, SD = 9.9 to $\underline{X}$ =58, SD = 9.0). The Parenting Stress Index showed significant decreases in Parental Distress from baseline ($\underline{X}$ = 77.0, SD= 23.0) to exit ($\underline{X}$ = 58.0, SD = 33). On the Child Development Review/Infant Development Inventory, the children were delayed by an average of 7.7 months at baseline, which improved significantly to an average delay at exit of 4.1 months. The CDR/IDI also revealed that children had fewer problems in Unhappiness. In conclusion, women who completed treatment demonstrated significant improvements in functioning, including decreases in substance use, parental distress, and depressive symptoms and their children exhibited less delay at exit. These findings have implications for further development of gender specific drug treatment programs for women, their children, and families.

TREATMENT OUTCOMES AMONG WOMEN IN THE DRUG ABUSE TREATMENT OUTCOME STUDY: EFFECTS OF CLIENT AND PROGRAM CHARACTERISTICS

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Specialized services for women within drug treatment programs have increased because of policy attention directed to reducing the problems associated with maternal substance abuse. This study examined treatment outcomes for women (N=638) in residential drug treatment programs (N=16) in the national, multi-site Drug Abuse Treatment Outcome Studies (DATOS). Multi-level modeling was used to assess the program characteristics associated with treatment outcomes after controlling for client characteristics. The finds show that women treated in residential programs where there was a higher percentage of women who were pregnant or had dependent children (<18 years) had higher rates of retention and post-treatment abstinence. Further, age was positively associated with retention; having prior drug treatment and being married were negatively associated with retention. Longer retention was positively associated with abstinence. Programs with a higher percentage of women who were pregnant or had dependent children were more likely to provide specialized services for these women, including prenatal, postnatal, and pediatric care; pre-school programming for children; and educational, family, psychological, financial, and legal services. These programs also had smaller clients/counselor ratios and longer planned treatment durations. Women in these programs were more likely to report that they had a good relationship with their counselors and that they received mental health services while in treatment. The findings suggest that providing specialized services for pregnant women and women with children is beneficial in terms of enhanced treatment retention and posttreatment abstinence.

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TOWARD A GENDER-SPECIFIC TREATMENT APPROACH FOR FEMALE OPIATE ADDICTS

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Alcohol and drug treatment programs have been traditionally set up for adult men and these programs generally fail to take into account the specific needs of drug dependent women. This may be partly due to the fact that women are in the minority within treatment clinics and treatment providers often erroneously presume that data on men's substance use are generalizable to women. Fortunately, there is a small but growing literature in addiction research that describes how and why the treatment needs of chemically dependent women differ from chemically dependent men. This report discusses the literature on gender differences in substance abuse and illustrates these differences with some data from our opiate treatment studies and outcomes of focus group discussions from women who participated in these studies. Focus groups were conducted with women at two study sites, the Washington clinic and the Pizarro clinic. The average age of women at the Washington clinic was 44 years, with an average of 25 years drug use. The average age of women at the Pizarro clinic was 22 years, with an average length of 7 years of drug use. A range of topics was discussed, such as the reasons for starting drug use, the role of counseling in getting clean, issues of self-esteem, relationships with domestic partners, children and other family members. The focus group data suggest that women need different kinds of psychosocial support than men; women have lower self-esteem and more self-blame, women have different medical needs and often need help with child-care services and parenting skills training. In this report, the need for a gender specific treatment approach, specifically targeted to female opiate addicts is proposed.

THE EPIDEMIOLOGY OF INHALANT USE DISORDERS IN THE INTERNATIONAL CONSORTIUM FOR PSYCHIATRIC EPIDEMIOLOGY

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The aim of this study was to report basic data on the epidemiology of inhalant use disorders from the International Consortium for Psychiatric Epidemiology, a cross-national investigation that encompasses surveys in the U.S. (the National Comorbidity Survey [NCS] and in Fresno, CA), Mexico (Mexico City), Canada (Ontario), Brazil (Sao Paulo), Germany (Munich), and the Netherlands (national). DSM-III-R inhalant use, abuse and dependence were assessed with data collected by lay interviewers using the Composite International Diagnostic Interview in all study sites. The lifetime prevalence of ever using any inhalant ranged from 7.0% in the NCS to 1.3% in Germany. Prevalence of inhalant use 5 or more times ranged from 3.5% in Brazil to 0.3% in Mexico and in the Netherlands. Prevalence of inhalant abuse or dependence ranged from 0.5% in the NCS to 0.0% in the Netherlands and Brazil. Prevalence of inhalant use was higher among males in all sites. Mean age at onset was 17 years. Discrete-time survival models suggested that early age of first inhalant use is a predictor of subsequent abuse-dependence.

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CLUSTERS OF DRUG USE AMONG YOUTHS IN PANAMA

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The purpose of this epidemiological study is to investigate clustering of tobacco, alcohol, inhalant, and other drug involvement among school students in Panama, using data from Panama's 1996 National Youth Survey on Alcohol and Drug Use. This is a school survey of 6,477 youths with self-administered questionnaire assessments of drug use. Pair-Wise Cross-Product Ratios (PWCPR), a measure of clustering, is estimated via the recently developed Alternating Logistic Regression (ALR) method. Results indicate greater clustering of tobacco (1.41; 95%CI=1.22-1.64) and alcohol (1.33; (95%CI=1.22-1.45) use at the school level as compared to clustering of inhalants (1.35; 95%CI=1.07-1.69) and other drug (1.38; 95%CI = 1.14-1.68) use. These PWCPR estimates were consistent with values observed in the United States. The findings of this study are discussed in relation to the epidemiology and prevention of drug use among Panama's youths as well as among youths in the U.S. These findings suggest that Panama's drug prevention efforts can be more focused on schools where clusters of drug use occur.

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LIFETIME PREVALENCE OF DRUG USE IN GENERAL POPULATION OF JAPAN

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Stimulants and inhalants have been the most common illicit drug of use in Japan for a couple of decades. In 1995, the first national household survey on legal and illegal drug use in Japan was conducted to clarify the lifetime prevalence of use of alcohol, tobacco, legally prescribed drugs and OTC drugs, and a variety of illicit drugs, and to ascertain the related lifestyles and attitudes towards illicit drug use. The survey was based on a noninstitutional general population aged 15 and older, using stratified multi-stage area probability sampling. Of the five thousand persons randomly selected, 3,946 persons (79.8%) were interviewed for the survey; 1,289 persons (32.7%) reported to have smoking habits, and 2,700 persons (68.4%), drinking habits. Approximately 6% of the survey population reported using tranquilizers, and 4.7% reported using sleeping pills within one year prior to the survey. The rate of lifetime use of inhalants was 1.4%, of marijuana, 0.4%, and of stimulants, 0.3%. The rate of past year use of inhalants was 0.08%, of marijuana, 0.05%, and of stimulants, 0.05%. The rate of experiences of being tempted to use inhalants was 1.7%, of marijuana, 1.0%, and of stimulants, 0.6%. These results suggest that, in Japan also, more attention should be focused on marijuana use.

THE EPIDEMIOLOGY OF DRUG DEPENDENCE IN AUSTRALIA: FINDINGS FROM THE NATIONAL SURVEY OF MENTAL HEALTH AND WELLBEING

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The National Survey of Mental Health and Well-Being (NSMHWB) is the first stratified household survey of the prevalence of common mental disorders in the Australian adult population. The survey interviewed a representative sample of 10,641 adult Australians and assessed symptoms of the affective, anxiety, and alcohol and drug use disorders. In the past 12 months, 12.5% of males and 6.9% of females reported the use of at least one of the drug classes assessed (cannabis. stimulants, sedatives, and opioids). The most commonly used drug was cannabis (10.3% males; 4.3% females). In the past 12 months, 6.5% of Australians had an alcohol use disorder, and 2.2% had another drug use disorder. More males than females had alcohol and other drug use disorders. The prevalence of drug and alcohol use disorders decreased with increasing age: 10.6% of respondents aged 18-34 years met criteria for an alcohol use disorder and 4.9% met criteria for a drug use disorder. The rates of these disorders among those aged 55 years or older were 4.4% and 0.8%, respectively. Alcohol was the most widely used of any drug but more users of other drugs had a use disorder in the past year. Specifically, only 8.9% of those who used alcohol in the previous 12 months had an alcohol use disorder, while 22.7% of those who used other drugs had another drug use disorder. There was a moderate degree of comorbidity between drug and alcohol use disorders and other mental health disorders and they were also associated with a moderate degree of disability. Relatively few people (29%) with a drug and alcohol use disorders had sought treatment. The results of the NSMHWB indicate that drug and alcohol use disorders are relatively common among the Australian population. Their prevalence in Australia is reasonably comparable to that in surveys conducted in the United States using similar diagnostic interviews.

THE PREVALENCE AND EXTENT OF ILLICIT DRUG USE IN AUSTRALIA

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This paper details the major methods used to assess the extent of illicit drug use in Australia, describes recent findings regarding the prevalence of illicit drug use and drug use disorders in Australia and compares these findings with comparable data sources from the United States. Data presented are from three sources: the most recent National Drug Strategy Household Survey (1998), the Australian School Students' Drug and Alcohol Survey (1996), and the National Survey of Mental Health and Well-Being (NSMHWB, 1997). The National Household Survey obtained information from a stratified random sample of 10,000 adults (14 years +), the School Students = Survey collected information from 30,000 school students aged 12-17 years and the NSMHWB conducted standardised diagnostic interviews with 10,641 adults. Findings from these surveys indicate that illicit drugs are widely used in Australia, with the most commonly used drug being cannabis: 39% of the adult population and 36% of students aged 12-17 years reported ever having used cannabis. The NSMHWB indicated that 2.9% of the adult population met criteria for a DSM-IV drug use disorder within the past 12 months. Comparison of these results with comparable data from the U.S indicates that cocaine use may be more prevalent in the U.S while both cannabis and heroin use may be more common in Australia.

PROTECTIVE FACTORS AGAINST DRUG ABUSE AMONG ASIAN AMERICANS

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This study described protective factors against drug abuse among Chinese and Filipino non-drug users by comparison with drug users who were not currently enrolled in drug treatment programs. This study first conducted qualitative interviews, and later survey interviews. Drug users were recruited based on targeted sampling methods. Non-drug users were matched by ethnicity, gender, immigrant status, and age groups. A total of 59 Chinese (30 heavy drug users and 29 non-drug users) and 70 Filipinos (37 heavy drug users and 33 non-drug users) were interviewed using a questionnaire with structured open-ended questions. A total of 190 Chinese (94 drug users and 96 non-drug users) and 189 Filipinos (87 drug users and 102 non-drug users) were interviewed using a structured survey questionnaire. Both qualitative and survey data revealed that non-drug users and light drug users had received social support from family members. Heavy drug users had received the lowest levels of support from family members; however, some of them received financial support from family members who knew about their drug use. Religiosity had influenced those who had never used drugs and those who had recovered from drug abuse. Filipino drug users were less likely to practice their religion (mostly Catholicism) than Chinese drug users (mostly Buddhism). More Filipino drug users than Chinese drug users expressed shame or guilt about their drug use and tried to hide their drug use from their family members. This study indicated that the influence of protective factors, such as social support and religiosity, on drug use or non-drug use behaviors differs depending on levels of current and past drug use, ethnicity, gender, and immigrant status.

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ACCULTURATION AND TOBACCO USE AMONG HISPANIC WOMEN OF CHILDBEARING AGE IN NEW MEXICO

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Data were obtained from a small sample of women (N=159) who sought pregnancy testing in maternal and infant care clinics throughout the state of New Mexico. These women anonymously provided information on their use of tobacco, alcohol, and other illicit substances during the last 30 days, last three months, and lifetime. Questions also explored each woman's cultural roots. Data from Hispanic women were scored to determine an acculturation level. Analyses then tested the hypothesis that tobacco use by Hispanic women would increase as acculturation level increased. Statistical analyses included descriptive statistics, chi-squares, t-tests, partial correlations, linear and logistic regressions. Analyses revealed that there was a positive relationship between acculturation level and lifetime and 30 day use of tobacco by Hispanic women. Other results supported the literature which posit that as Hispanic women acculturate into the dominant society, they tend to abandon their norms and values of no use or moderate use, and adopt the tobacco using patterns typical of Anglo women. New Mexico has the highest percentage of Hispanic population of any state in the U.S. The percentage of babies born in New Mexico who have low birth weight is slightly higher than the national average. Results will help health planners and health care providers to develop prevention strategies to reduce smoking during pregnancy and thereby improve newborns' birth weights.

ACKNOWLEDGEMENTS: This research was conducted with the help of the Substance Abuse Epidemiology Unit of the New Mexico Department of Health.

ACCULTURATION AND ALCOHOL USE AMONG HISPANIC WOMEN OF CHILDBEARING AGE IN NEW MEXICO

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Data were obtained from a small sample of women (N=159) who sought pregnancy testing in maternal and infant care clinics throughout the state of New Mexico. These women anonymously provided information on their use of tobacco, alcohol, and other illicit substances during the last 30 days, last three months, and lifetime. Questions also explored each woman's cultural roots. Data from Hispanic women were scored to determine an acculturation level. Analyses then tested the hypothesis that alcohol use by Hispanic women would increase as acculturation level increased. Statistical analyses included descriptive statistics, chi-squares, t-tests, partial correlations, linear and logistic regressions. Analyses revealed that there was a positive relationship between acculturation scores and lifetime alcohol use by Hispanic women, when controlling for pregnancy status, lifetime tobacco use, and husband/boyfriend's use of any drug in the 30 days preceding the pregnancy test. Other results supported the literature which posit that as Hispanic women acculturate into the dominant society. they tend to abandon their norms and values of no use or moderate use, and adopt the alcohol using patterns typical of Anglo women. New Mexico has the highest percentage of Hispanic population of any state in the U.S. The percentage of babies born in New Mexico who have low birth weight is slightly higher than the national average. Results will help health planners and health care providers to develop prevention strategies to reduce alcohol use during pregnancy and thereby improve newborns' birth weights.

ACKNOWLEDGEMENTS: This research was conducted with the help of the Substance Abuse Epidemiology Unit of the New Mexico Department of Health.

MALE-FEMALE DIFFERENCES ASSOCIATED WITH PARENTAL MONITORING AND THE OPPORTUNITY TO USE ALCOHOL

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The aim of this epidemiologicat study is to increase understanding about the determinants of youth alcohol use by focusing on how parental monitoring and supervision might account for earlier opportunities to use alcohol. This study tests hypotheses that boys have earlier opportunities to use alcohol as compared to girls, and that lower levels of monitoring and supervision by parents might account for any such observed male-female difference. Focus on youthful drinking opportunities represents an effort to build from prior evidence that parental monitoring might reduce early-onset illicit drug use. The mainly African-American sample originated in 19 primary schools within a single urban school system. The analyses were based on 1,273 youths whose parental monitoring levels had been measured in 1989, who had not had a prior drinking opportunity, and who were followed up and assessed through early adolescence. As hypothesized, survival analyses disclosed that boys had earlier drinking opportunities than girls ($p<0.001$). However, contrary to our hypothesis, sex-related differences in monitoring did not account for the observed male-female difference in age at first drinking opportunity. As we continue this line of research, we will examine other possible mechanisms for the observed male-female difference in age first offered alcohol, including the possible rote of alcohol use by parents and peers, which might promote early drinking opportunity. Findings from this research might provide direction for the development of prevention strategies to delay the opportunity to use alcohol.

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MULTI-LEVEL EPIDEMIOLOGICAL ANALYSIS OF DRUG USE AMONG U.S. MOTHERS

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Perinatal drug use has been identified as a major public health problem; however, additional research needs to focus beyond the postpartum years.[1] In addition, it is important to explore individual characteristics, as well as group characteristics, that may be related to variation in drug use. The purpose of this multi-level epidemiological study was to compare drug use (cigarettes, alcohol, marijuana, and cocaine) at the individual and group level for mothers in the U.S. using data from the 1994B through I996 National Household Survey on Drug Abuse (NHSDA). The sample consists of 12,874 mothers of minor children (<18 years of age). The data were analyzed using hierarchical linear modeling (HLM) which permits the modeling of individual variation while at the same time providing optimal group estimates. The HLM analyses examined differences in drug use based on client characteristics (income, depression, race/ethnicity) and community characteristics (geographic area). The results showed that after controlling for income, mothers who reported depression were more likely to use cigarettes, alcohol, marijuana, and cocaine than those who were not depressed. The proportion of drug use and depression did not vary by geographic area, but there were geographic differences in use based on race/ethnicity. The findings suggest the need to investigate specific geographic characteristics that are related to use of drugs and the interaction with mental health and client variables.

REFERENCES: [1]Rahdert, E.R. (Ed.), 1996. Treatment for drug-exposed women and their children: Advances in research methodology. NIDA Monograph No. 166. Rockville, MD: U.S. DHHS, NIH.

DRUG USE AMONG MIDDLE-AGED AND ELDERLY PERSONS: FINDINGS FROM CALIFORNIA

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Elderly people (age 65 and over) report lower rates of alcohol and other drug (AOD) use than their younger counterparts. However, when AODs are used, use may be heavy and lead to significant personal and social consequences. We analyzed several archival databases, containing information on a diverse sampling of elderly people (e.g., households, criminal justice). We found that: (1) alcohol is the most commonly implicated substance among elderly AOD users, although for African-Americans, cocaine and heroin are also reported at non-trivial rates, (2) there were ethnic group differences (e.g., Latinos reported high rates of endorsing CAGE items, an alcohol abuse screening measure), (3) injection drug use of illicit drugs does occur in older groups, (4) cigarette smoking occurs at significant levels in older age, (5) men are over-represented in drug-use specific and outcome or consequence databases (e.g., hospitalizations, arrests). Research gaps include: (1) under-representation of minority groups and females, especially in outcome/consequence databases, and (2) information on frequency or level of use-smaller doses may lead to significant physical and psychological effects. Implications and future directions for research are discussed.

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DIMETHYLHEPTYL METHYL ARACHIDONYLFLUOROPHOSPHONATE (DMH-MAFP) SHOWS SPECIFIC INHIBITION OF FAAH VERSUS ITS ACTION AT THE CB1 RECEPTOR

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Fatty acid amide hydrolase (FAAH) is the enzyme that is responsible for the hydrolysis of anandamide and 2-arachidonyl glycerol, endogenous agonists of the central cannabinoid receptor (CBI). Compounds that inhibit FAAH but which do not act at CBI would be useful as pharmacological and potential therapeutic agents. While MAFP has been shown to be a potent irreversible inhibitor of FAAH, it also binds strongly to the CBI receptor and is a potent antagonist in the guinea pig ileum preparation (GPI). In this paper, we report that DMH-MAFP is a potent inhibitor of FAAH, yet elicits only a weak response in animal tissue tests. DMH-MAFP is a hybrid of MAFP and DMH--arachidonylethanolamide, the latter being an anandamide analog with increased *in vivo* activity and affinity for the CBI receptor. The results of DMH-MAFP testing were as follows: 1) it is a potent inhibitor of FAAH with an IC_{50}=1.3 nM; 2) has moderate affinity for the CBI in guinea pig forebrain of 95-128 nM versus CP 55,940 and WIN 55,2 12-2; 3) is a weak antagonist in the GPI at 60 μM; 4) is a weak agonist in the mouse vas deferens (MVD) with an EC50 ~ 1 μM; 5) is a potent partial agonist in hCBI/CHO transfects with an EC50 ~ 0.1 nM and Emax=40%; and 6) is a weak inhibitor of acetylcholinesterase with an IC_{50}>10 uM. Thus, DMH-MAFP exhibits selectivity for FAAH relative to CBI receptor mediated effects at similar concentrations. The apparent dichotomy between antagonism in the GPI and agonism in the MVD and hCB_1/CHO cells reflects the different receptor populations in the three systems. As the receptor density drops from high Ievels in hCB_1/CHO to moderate levels in MVD to lower levels in the GPI, partial agonists (such as DMH-MAFP in hCB_1/CHO) find fewer and fewer receptors to the point where insufficient receptors arc occupied to elicit an agonist effect. If the intrinsic affinity of the receptor does not change, then binding with low efficacy results, which is effectively antagonism.

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DISRUPTION OF NEURONAL SYNCHRONIZATION IN THE MESOCORTICOLIMBIC SYSTEM DURING DELAYED MATCH TO SAMPLE TASK BY DELTA-9 THC

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Mesocorticolimbic (MCL) network plays an important role in cognitive function and is considered to be a potential neuronal substrate for marihuana action. To test the hypothesis that marihuana may interrupt MCL network processing and thus impairs cognitive function, a 64 channel, single-unit recording technique was used to record the neuronal activities in multiple regions of the MCL system during delayed (non-) match to sample task (DMTS). Seven rats were trained to perform DMTS with a 5 to 30 second random delay. The neuronal activity in the medial prefrontal cortex, nucleus accumbens, hippocampus, and substantia nigra pars reticulata were simultaneous recorded using chronically implanted stainless steel microwires. Delay-dependent decreases in performance accuracy were found when the delay exceeded 20 seconds. Synchronized neuronal activity was analyzed using normalized joint pre-stimulus histogram. Spikes from two neurons were computed using the sample lever press as a reference event. The neuronal activity before sample lever press may represent encoding processes to register the space information and the activity after sample lever press (up to 30 seconds) may reflect short term memory process. Synchronized activities were detected in pair of neurons within the same region and across different regions of MCL system. More pronounced synchronization was observed during the delay period suggesting a functional significance of synchronization in short-term memory. The active component of marihuana, Delta-9-THC (0.5-1 mg/kg i.p., 15 min before session), altered delay period neuronal activity, decreased neuronal synchronization, and behavioral performance accuracy. This result suggests that the interference within the MCL network properties may account for the adverse effects of marihuana on learning and memory process.

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EFFECTS OF DELTA^9-TETRAHYDROCANNABINOL (THC) ON BRAIN ACTIVITY AND COGNITIVE TASK-INDUCED BRAIN ACTIVATION: A fMRI STUDY

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Marijuana and its principal psychoactive component, THC, produce a broad spectrum of physiological and behavioral effects, which in part are predictable from the distribution of cannabinoid receptors in the brain. However, THC's sites of action in the human brain and their involvement in THC's behavioral effects are not yet well understood. In order to better determine the functional consequences of marijuana use, we have studied the effects of THC on brain activity and the ability of a concept formation (CF) task to produce brain activation using functional magnetic resonance imaging (fMRI). Frequent marijuana users were injected iv with THC (3 mg over 1 min) while undergoing fMRI scanning. THC produced a time related decrease in fMRI signal (suggesting neuronal activity reduction) in the cerebellum including the region of the dentate nucleus, as well as the middle temporal and medial orbital gyri. Increases in FMRI signal (activation) were seen in the cingulate, globus pallidus and areas of parietal cortex. THC also affected brain activation by the CF task. Forty minutes after THC administration, CF task activation was decreased in the dorsolateral frontal (DLF), primary motor, premotor, cingulate and SMA cortex and the posterior parietal and occipital lobes. In contrast, THC induced an increased extent of cerebellar activation, particularly in the left hemisphere. This may be due to the need for more cerebellar activation as a result of THC induced impairment of this structure's basal function. These studies demonstrate that THC alters brain activity in humans in regions such as the cerebellum and DLF that are involved in its behavioral actions.

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SPONTANEOUS AND PRECIPITATED WITHDRAWAL OBSERVED IN THE RAT AFTER THE CONTINUOUS INFUSION OF A SYNTHETIC CANNABINOID, WIN 55212-2

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Physical dependence on WIN 55212-2 or R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]-pyrrolo[1,2,3-de]-1,4-benzoxazin-yl]-(1-napthalenyl) methanone mesylate, was demonstrated by either abruptly withdrawing this high-affinity cannabinoid receptor agonist or after challenge with 10 mg/kg, s.c. of SR141716A, (N-(piperidin-1-yl)-5-(4-chloro-phenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide·HCl). In both instances, a dose regimen of 2, 4, 8 and 16 mg/kg, i.p. / 24 hr, on days 1 through 4, respectively, was sufficient to evoke a typical withdrawal syndrome characterized by the signs wet-dog shakes and facial rubs. In a previous study, physical dependence on delta-9-tetrahydrocannabinol (THC), the major psychoactive substance in marihuana, was demonstrated only after challenge with the cannabinoid receptor antagonist SR141716A, (Aceto *et al.,* J. Pharmacol Exp Ther., 1996). In contrast, in another preceding study, neither anandamide, an endogenous cannabinoid, nor a metabolically stable analog, produced overt signs of physical dependence by either procedure (Aceto *et al.,* J. Pharmacol. Exp. Ther., 1998). We tentatively conclude that pharmacokinetic properties most likely account for the different results obtained with THC and WIN55212. On the other hand, anandamide's actions appear to be atypical. Finally, the results with WIN55212 provide additional evidence regarding the dependence liability of cannabinoids.

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A COMPARISON OF THE SUBJECTIVE EFFECTS OF ORAL DELTA-9-TETRA-HYDROCANNABINOL AND MARIJUANA IN HUMANS

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Although the primary active ingredient in marijuana, delta-9-tetrahydrocannabinol (THC), is available in an oral formulation, patients have argued that smoked marijuana is more effective. The hypothesis of the present study was that differences between pure THC and marijuana might be attributed to other active constituents of the marijuana plant. Thus, the present study compared the subjective effects of pure THC to the effects of an equivalent dose of THC in whole plant marijuana when both were administered through the oral route. Twelve regular marijuana users (7 male, 5 female) participated in a double-blind, placebo-controlled, crossover design in which they ingested a chocolate brownie on each session that contained either pure THC only, whole plant marijuana, or placebo marijuana. The THC content of the THC only and whole plant marijuana conditions was matched. Dependent measures were analyzed using ANOVA for repeated measures. Pure THC and whole plant marijuana elicited similar subjective effects. However, pure THC induced greater self-reported drug high and marijuana-like effects than whole plant marijuana. In contrast, whole plant marijuana elicited greater sedative-like effects than pure THC. These results indicate that there are subtle differences in the subjective effects of pure THC and whole plant marijuana; and hence, there may also be differences in the therapeutic effects of these two treatments.

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THE INFLUENCE OF GENDER AND ETHNICITY ON THE EXPRESSION OF CANNABINOID RECEPTORS AND THEIR GENE TRANSCRIPTS

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There is overwhelming experimental evidence for an endogenous marijuana (cannabinoid) system in the brain and peripheral organ systems in humans. This previously unrecognized elaborate network provides a new means for systematically studying the biology of marijuana use/abuse/dependence and the role of the cannabinoid system(s) in normal physiology. Previous studies in women (Kendler and Prescott: Am. J. Psy., 155: 1016-1022, 1998) and in men (Tsuang *et al.,* Am. J. Med. Gen. 67: 473-477, 1996) report that heavy cannabis use and dependency are highly heritable (with genetic basis) and that women have similar rates as men in the use of cannabis. Blood samples (6ml) were obtained from 23 adult male and female subjects who did not meet DSM-IV criteria for alcohol or marijuana dependence. The samples were analyzed for CB1 and CB2 cannabinoid receptor **(***Cnr***)** gene expression using PCR and blot hybridization. Western blotting analysis was performed on the samples using *Cnr* CB1 polyclonal antibody. The results obtained show that the human *Cnrs* and their gene transcripts can be analyzed in blood samples when combined with PCR. Primer pairs from CB1 and CB2 cDNA coding region sequences showed identical amplified DNA bands sizes in both DNA-PCR and reverse PCR, with human templates, suggesting that these genes are intronless at least in their coding regions. The advantage of being intronless in the coding region may have implications related to the biological functions of these proteins. The, expression of *Cnrs* appears to vary according to racial background with Caucasians>Blacks>Asians. While the implication of these findings is subject to a variety of speculations, the data suggest the existence of an elaborate human cannabinoid system that can be exploited therapeutically.

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EMERGING DRUGS OF ABUSE IN CALIFORNIA

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Previous investigations in Texas and Florida by our group focused on Rohypnol use among youth and concluded that Rohypnol abuse was usually part of a pattern of polydrug abuse. In, through youth outreach programs and methadone programs, via posted flyers and Internet postings, by approaching concert and rave attendees in parking lots and in waiting areas, and by word of mouth. Subjects had a mean age of 25 years. The interviews were transcribed, and analyzed using grounded theory with the aid of Nudist. Of nine subjects who reported having voluntarily used "roofies" or "rochas," none was able to accurately describe Rohypnol. These same street names are also used for Rivotril and for Klonopin, the Mexican and US brand names for clonazepam. Confusion among these three preparations may be responsible for some reports that Rohypnol is still easily available. Fifteen subjects reported using ketamine, and fifteen reported using GHB. Other new substances such as "illusion," "molecule," and "KGB," were used or discussed each by five or fewer subjects. Some subjects credibly reported familiarity with or actual experience of an event involving surreptitious administration of drugs, although this was not always for the purpose of sexual assault. Some subjects reported that the association of a drug with sexual assault was a factor preventing initiation of use of a particular drug. From the information given by subjects, definitions of four patterns of drug use are proposed. Focusing on patterns of drug abuse rather than individual drugs may allow better understanding and prevention of the propagation of drug abuse.

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CURRENT DRUG SCHEDULING REVIEWS REPORTED BY THE DRUG ENFORCEMENT ADMINISTRATION

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DEA is engaged in comprehensive reviews of a number of abused substances and in each case are collecting data regarding the abuse and dependence liability, pattern, history and significance of its actual abuse, pharmacology, chemistry, and legitimate medical use. These reviews are conducted to determine the appropriate control status under federal law. Several ongoing projects are summarized below and these and others will be discussed more fully. Two substances abused by high school and college students, and rave party attendees are gamma hydroxybutyrate (GHB) and ketamine. GHB is a CNS depressant that is not approved for medical use in the US, but is abused to produce euphoric and hallucinatory states, and for its alleged role as a growth hormone releasing agent to stimulate muscle growth. Recently, the abuse of GHB (liquid X, goop) has increased substantially due to its ease of clandestine synthesis and availability of information on the Internet. GHB dose-dependently produces drowsiness, dizziness, unconsciousness, seizures, respiratory depression and coma. DEA has documented over 3,500 overdoses (OD) and law enforcement encounters with GHB and 32 GHB-related deaths. Ketamine is marketed as a dissociative general anesthetic for human and veterinary use and reports of abuse are increasing. Ketamine ("Special K") produces effects similar to those of phencyclidine (PCP) with the visual effects of LSD. "Special K" trips are touted as better than that produced by PCP or LSD, because it lasts only an hour or less. Diversion of the legitimate supplies is the only known source on the street. Ketamine is found in powder and liquid forms. Other substances that will be discussed include carisoprodol, an analgesic and muscle relaxant, and dextromethorphan, a commonly used OTC cough suppressant. There have been reports of abuse of both carisoprodol and dextromethorphan ("DXM").

ABUSE LIABILITY ASSESSMENT OF NEUROPROTECTANTS

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There has been considerable interest in the potential of N-methyl-D-aspartate (NMDA) antagonists in the treatment of a diverse group of neurological disorders including cerebral ischemia and neurodegeneration. The amino acids L-glutamate and L-aspartate might mediate excitatory synaptic transmission in the CNS via selective excitatory amino acid receptors. Competitive and noncompetitive antagonists, acting at the NMDA receptors, have been shown to possess relevant activity. However, NMDA antagonists produce a variety of adverse neurobehavioral effects. These adverse effects are particularly pronounced with NMDA antagonists (phencyclidine (PCP), ketamine and MK801), which have dissociative anesthetic properties and block NMDA receptor-mediated responses by binding to the cation channel of the NMDA receptor complex. When a new pharmaceutical product demonstrates structural similarity and/or a similar pharmacological profile with a known drug of abuse, sponsors are required to thoroughly characterize its abuse potential and submit study results for scientific review. A complete and comprehensive evaluation of the relative abuse potential of the drug substance and/or product is required. Within the FDA/Center for Drug Evaluation and Research, issues relating to drug abuse and the appropriate scheduling of a drug under the U. S. Controlled Substances Act are the responsibilities of the Division of Anesthetic, Critical Care and Addiction Drug Products, Controlled Substance Evaluation Team. A drug's abuse potential is determined relative to the < pharmacologically similar comparator drug. The abuse liability assessment is based upon a comprehensive evaluation of available data on the chemistry, pharmacology (preclinical and clinical), pharmacokinetics, and pharmacodynamic profiles of the drug, and the adverse events/effects reported in clinical trials.

EFFECTS OF SITE SELECTIVE N-METHYL-D-ASPARTATE (NMDA) ANTAGONISTS ON DELAYED DISCRIMINATION: ASSESSMENT OF TASK ACCURACY AND SIGNAL DETECTION ANALYSIS TO EVALUATE DISCRIMINABILITY AND BIAS

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The NMDA receptor has been implicated as a mediator of short-term memory but research to date has not determined its functional importance in component memory processes. A central goal for this research was to further delineate the effects of NMDA antagonists on the persistence of working memory (retention). A rodent modeled delayed non-match to position (DNMP) task was used to examine the effects of site selective NMDA antagonists on accuracy of lever choice at varying delay intervals. Accuracy by interval performance curves were analyzed for delay dependent performance changes (retention effects). A signal detection analysis of the data provided independent measures for stimulus discriminability [d'] and subject responsivity (response bias [β′"]) and rate of trial completion [total trials]). Compounds tested included three compounds acting at a site within the NMDA receptor ion channel; two compounds that bind at the transmitter recognition site (competitive NMDA antagonists); an antagonist at the glycine recognition site; and an NR2B selective antagonist. The profile of behavioral effects produced by these ligands differed with dependence upon the modulatory site of action. MK 801 disrupted retention while PCP produced accuracy effects in the absence of a retention effect. Competitive NMDA antagonists did not affect retention or accuracy, but did markedly affect the rate of trial completion. Glycine and polyamine site antagonists did not remarkably change performance relative to control sessions, but modestly reduced the rate of trial completion. PCP and MK 801 each produced a significant decrease in stimulus discriminability but failed to affect response bias. These findings emphasize the importance of separately considering drug effects on detection of stimuli, on retention of stimulus information, and on non-cognitive performance variables (motor and motivational), when elaborating the pharmacology of site-selective NMDA antagonists.

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HARMALINE AND RELATED β-CARBOLINES: STRUCTURE-AFFINITY STUDIES

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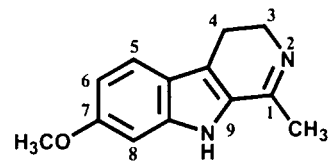
Harmaline is a hallucinogenic agent and, structurally, is a member of a large class of 1-methyl-β-carbolines. These structures vary in their degree of unsaturation in the pyridyl ring: harman derivatives (fully aromatic), harmalan derivatives (3,4-dihydro ring), and tetrahydroharmans. Harmaline, then, is 7-methoxyharmalan. Due to their limited availability, few such agents have been previously investigated. We prepared a series of (>30) carbolines to investigate their structure-affinity relationships; features examined included: a) relocation of the -OCH_3 group to the C_5-C_8 positions, b) replacement of the 7-OCH_3 with –H or –OH, c) degree of saturation of the pyridyl ring, d) C_1-demethylation, e) N_2-methylation, f) N_9-methylation, and g) other changes. Hallucinogens typically bind at 5-HT_{2A} serotonin receptors. 5-HT_{2C}, 5-HT_{1A} and dopamine D_2 receptors have also been previously implicated in the actions of certain hallucinogens (notably LSD). Some, especially 3-substituted, β-carbolines bind at benzodiazepine (BZ) receptors. Hence, these were primary receptor targets for investigation. Five hallucinogen-related indolealkylamines (i.e., DMT, 4-OMe DMT, 5-OMe DMT, 6-OMe DMT, 7-OMe DMT) and twelve phenylalkylamines (e.g. DOM, DOI, DOB, DOET, DOPR, 2,5-DMA, 2,4,5-TMA, 2,4,6-TMA) were examined for purpose of comparison. Although none of the examined compounds displayed affinity for D_2 or BZ receptors, many displayed affinity for cloned rat [^{3}H]DOB-labeled 5-HT_{2A}, [^{3}H]mesulergine-labeled 5-HT_{2C}, and/or (for certain β-carbolines and DMT derivatives) [^{3}H]8-OH DPAT-labeled 5-HT_{1A} receptors.



Harmaline

ACKNOWLEDGEMENTS: Supported by NIDA grants DA 09153 and DA 01642.

NEUROBIOLOGICAL EFFECTS OF IBOGAINE, NORIBOGAINE, AND HARMALINE, IN MICE

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Ibogaine is an indole alkaloid with "anti-addiction" properties. It is known that systemically injected ibogaine is converted to an *o*-demethylated metabolite, 12-hydroxyibogamine (noribogaine). However, the pharmacology of noribogaine is largely unexplored. In this study, we compared neurobiological effects of ibogaine, noribogaine, and the related drug, harmaline, in mice. Adult male C57 mice received ip injections of saline, ibogaine (30, 100 mg/kg), noribogaine (30, 100 mg/kg) or harmaline (30, 100 mg/kg), and were sacrificed 30 or 60 min later. Trunk blood was collected for analysis of plasma corticosterone and prolactin whereas brains were harvested for analysis of dopamine (DA) and the metabolites DOPAC and HVA. All drugs evoked tremors and were potent stimulators of hormone release. Ibogaine and noribogaine caused dramatic decreases in tissue DA, with concomitant increases in DOPAC and HVA; these effects occurred in nigrostriatal (caudate/putamen) and mesolimbic (accumbens/olfactory tubercle) nerve terminals. Harmaline, in contrast, caused small reductions in tissue DA, DOPAC, and HVA. Our data demonstrate that ibogaine and noribogaine have analogous effects on behavior, stress hormone secretion, and central DA metabolism. Harmaline shares some actions with iboga alkaloids, but has different effects on DA neurons. The fact that ibogaine and noribogaine suppress drug-seeking behavior, while harmaline does not, suggests that dopaminergic effects of iboga alkaloids might be involved in the therapeutic potential of these drugs.

ACKNOWLEDGEMENT: This work was generously supported by NIDA IRP.

IBOGA ALKALOIDS AND OTHER SIGMA LIGANDS MODULATE CALCIUM AND INDUCE CYTOTOXICITY BY ACTING ON INTRACELLULAR SIGMA-2 RECEPTORS

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We have previously shown that activation of sigma-2 receptors by ibogaine and other ligands induces a rise in intracellular calcium levels ([Ca++]i), causes changes in cellular morphology, and ultimately induces apoptotic cell death. Sigma receptors are localized mainly in subcellular organcelles, particularly endoplasmic reticulum. Here we investigate the possibility that sigma-2 ligands must cross the cell membrane in order to be active. Human SK-N-SH neuroblastoma cells were used to measure rapid changes in [Ca++]i (indo-1) or cyrotoxicity after a 24 hr treatment (LDH release). Two approaches were taken: 1) comparison of potency of compounds within a structural class with similar sigma-2 affinity, but with different lipophilicities and 2) comparison of potency of an individual compound under different pH conditions. The LgP (lipophilicity) and pKa values for various sigma ligands were predicted using the ACD/ILab Web service, v. 2.6 and 2.7, respectively, at www.acdlabs.com/ilab. Compounds examined were: iboga alkaloids (ibogaine, ibogamine), phenylmorphans, butyrophenones, arylethylenediamines. In both assays, the potency within a given structural class increased as the lipophilicity (LgP) values increased. Based on pKa values, all compounds examined are >90% protonated at pH 7.2. Raising medium pH leads to increased deprotonation, and thus increasing lipophilicity. Raising the pH from 7.2 to 8.2 increased the activity of compounds in both assays, whereas lowering the pH to 6.5 decreased the activity. This included the antagonists BD1047 and BD1063, which were ineffective in the calcium assay at pH 7.2, but which effectively attenuated agonist activity at pH 8.2. Cytotoxicity ED_{50} values were up to 20-fold lower at pH 8.2 compared to pH 7.2. Correcting the ED_{50} values at each pH for the fraction of deprotonated ligand present led to normalization to a much lower value which was similar at each pH. Changing pH had no effect on ligand binding. The dependency of activity on lipophilicity supports a requirement for ligands to cross the membrane to act at intracellular receptors.

GENDER DIFFERENCES IN THE METABOLISM OF IBOGAINE TO NORIBOGAINE IN RATS

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Ibogaine is a plant-derived compound that interrupts drug-seeking behavior. *In vivo,* ibogaine is rapidly converted to its *o*-demethylated metabolite, 12-hydroxyibogamine (noribogaine), and evidence suggests gender can affect this transformation. In the present work, we assessed the role of gender and gonadal steroids on the metabolism of ibogaine in rats. Males were castrated or sham-operated, whereas females were ovariectomized or sham-operated. All rats were fitted with indwelling jugular catheters. Rats received ibogaine (40 mg/kg, ip), and serial blood samples (0.4 ml) were collected over the next 48 h. Whole blood levels of ibogaine and noribogaine were determined using GC/MS methods. After ip injection, ibogaine levels in blood quickly reached maximum (Cmax at 10 min), then gradually declined; noribogaine levels increased to Cmax by 1-3 h and remained elevated for at least 24 h. In males, castration reduced ibogaine Cmax and decreased metabolic conversion to noribogaine. In females, ovariectomy reduced ibogaine Cmax when compared to control males, and also decreased conversion to noribogaine. Interestingly, females in late diestrus (i.e. increased plasma estrogen levels) exhibited 2-fold greater levels of ibogaine, as measured by Cmax and area-under-the-curve (AUC), compared to all other groups. Our data show that gonadectomy impairs the metabolism of ibogaine to noribogaine. Furthermore, female sex steroids can increase blood levels of ibogaine, and such sex differences should be considered when administering ibogaine to animals and humans.

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COMPARISON OF 18-METHOXYCORONARIDINE (18-MC) AND IBOCAINE: INDICES OF ANTI-ADDICTIVE EFFICACY, TOXICITY AND MECHANISM

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18-MC is a novel *iboga* alkaloid congener that may be an effective and safe treatment for multiple forms of drug abuse. Like ibogaine (40 mg/kg), 18-MC (40 mg/kg) decreases the self-administration of morphine, cocaine, ethanol, and nicotine in rats; unlike ibogaine, 18-MC does not affect responding for a non-drug reinforcer (water). Both ibogaine and 18-MC decrease extracellular levels of dopamine (DA) in the nucleus accumbens (NAC) but only ibogaine increases serotonin (SHT) in the NAC. Both ibogaine and 18-MC block morphine-induced and nicotine-induced DA release in the NAC; only ibogaine enhances cocaine-induced increases in NAC DA. Ibogaine produces whole body tremors and, at high doses (≥100 mg/kg), cerebellar damage; 18-MC does not produce these effects. Ibogaine, but not 18-MC, causes bradycardia at high doses. While 18-MC and ibogaine have similar affinities for kappa opioid and possibly nicotinic receptors, 18-MC has much lower affinities than ibogaine for NMDA and sigma-2 receptors, sodium channels, and the 5HT transporter. Both 18-MC and ibogaine are sequestered in fat and, like ibogaine, 18-MC probably has an active metabolite. The data suggest that 18-MC has a narrower spectrum of actions and will have a substantially greater therapeutic index than ibogaine.

ACKNOWLEDGEMENT: Supported by DA03817 and Albany Molecular Research, Inc.

PRETREATMENT WITH THE PUTATIVE ANTI-ADDICTIVE DRUG, IBOGAINE, INCREASES SENSITIVITY TO THE PSYCHOMOTOR STIMULANT EFFECTS OF COCAINE

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Previous studies demonstrated that pretreatment (19 hrs) with the putative anti-addictive agent, ibogaine, potentiates cocaine-induced locomotion in rats. In an initial study, it was found that the magnitude of this effect depends on the previous cocaine history of the animal. Compared to rats with no previous cocaine experience, ibogaine pretreatment (40 mg/kg, IP, 19 hrs earlier) markedly enhanced the expression of locomotor sensitization in response to a cocaine challenge injection (7.5 mg/kg, IP) in rats that were chronically treated with cocaine (15 mg/kg, IP, daily for 5 days). To assess whether or not the observed ibogaine effect reflected a shift to the left in the dose-locomotor response function for cocaine, a second study determined the effects of ibogaine pretreatment on locomotion induced by a range of cocaine doses (0, 5, 10, 20, and 40 mg/kg, IP) in chronic cocaine- and saline-treated rats. Ibogaine pretreatment shifted the inverted U-shaped dose-response function to the left in both chronic and acute cocaine groups, indicating that ibogaine augments a rat's sensitivity to the psychomotor stimulant effects of cocaine, an effect which may underlie this compound's anti-addictive efficacy.

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PHARMACOLOGICAL AND BEHAVIORAL CHARACTERIZATION OF COCAINE-KINDLED SEIZURES IN MICE

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Seizures can result from a single high dose of cocaine (COC) and evidence is accumulating that correlates repetitive administration of sub-convulsive doses of COC with decreased seizure threshold, a phenomenon known as pharmacological kindling. Daily administration of 60 mg/kg COC (i.p.) produced robust seizure kindling; significant left shifts in the dose-response curves for seizures and lethality were observed in COC-kindled mice. The lethal potency of methamphetamine was significantly lowered in COC-kindled mice. COC kindling was enduring as these left shifts persisted for at least twenty days, indicating possible permanent synaptic changes. Induction of convulsions *per* se utilizing 75 mg/kg COC was not sufficient to engender kindling with a nonoptimal dose (40 mg/kg). However, administration of non-kindling doses of COC (40 mg/kg) on as little as four occasions produced increased seizure sensitivity to a 60 mg/kg COC challenge. The ongoing behavior of kindled mice was not affected even though seizure threshold was reduced. However, challenge doses of COC (30 mg/kg) produced significant differences in the vertical activity of kindled vs. non-kindled mice. Overall, this study provides a description of important parameters for a model of COC kindling that may be useful for the elucidation of the mechanisms responsible for the long-term changes in sensitivity to COC and the discovery of novel pharmacological treatments.

PRECLINICAL EVALUATION OF NEW ANTI-EPILEPTIC DRUGS AGAINST COCAINE-INDUCED CONVULSIONS

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Seizures and status epilepticus are among the neurological complications of cocaine overdose in humans. The protective efficacy and therapeutic index (separation between anti-convulsive and side-effect profiles) of 14 new antiepileptic drugs were assessed. Conventional antiepileptic drugs have been reported to be either ineffective or only effective at doses producing significant sedative/ataxic effects in mice (Witkin *et al.,* this meeting). Felbamate, gabapentin, loreclezole, losigamone, progabide, remacemide, stiripentol, tiagabine and vigabatrin produced dose-dependent protection against cocaine-induced (75 mg/kg, i.p.) convulsions with varied separations between their anticonvulsant and side-effect profiles: the PI values (toxic TD_{50} protective ED_{50} values) ranged from 1.26 (felbamate) to 7.68 (loreclezole), to PI > 152 for gabapentin. In contrast, clobazam, flunarizine, lamotrigine, topiramate, and zonisamide were ineffective against seizures up to doses producing significant motor impairment. Drugs which increase levels of endogenous GABA offer better protective/behavioral profiles relative to those directly acting at the $GABA_A$ or NMDA receptor complex whereas functional antagonists of Na^+ and Ca^{2+} channels are generally ineffective. Overall, this study provides the first description of the effectiveness of new antiepileptic drugs against experimentally induced cocaine seizures and points to several drugs that deserve clinical scrutiny for this indication.

COMPARATIVE EFFICACY OF CLINICALLY-USED ANTICONVULSANTS AND NMDA ANTAGONISTS IN THE CONTROL OF COCAINE-INDUCED CONVULSIONS

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Convulsions associated with cocaine (COC) abuse can be life-threatening and resistant to standard emergency treatment. COC (75 mg/kg, i.p.) produced clonic convulsions in ~90% of male, Swiss-Webster mice. A variety of clinically used antiepileptic agents either did not significantly protect against COC convulsions or did so only at doses with significant sedative/ataxic effects. In contrast, functional NMDA antagonists all produced dose-dependent and significant protection against the convulsant effects of COC. Competitive antagonists, ion-channel blockers, polyamine antagonists, and functional blockers of the strychnine-insensitive glycine modulatory site all prevented COC seizures. There was a positive correlation between the potencies of noncompetitive antagonists or competitive antagonists to block convulsions and their respective affinities for their specific binding sites on the NMDA receptor complex. Although some NMDA blockers produced profound behavioral side-effects at efficacious doses (e.g., non-competitive antagonists), others (e.g., some low-affinity channel blockers, some competitive antagonists, glycine antagonists) demonstrated significant and favorable separation between their anticonvulsant and side-effect profiles. The present results provide the most extensive evidence to date identifying NMDA receptor blockade as a potential strategy for the discovery of agents for clinical use in averting toxic sequella from COC overdose.

MODULATION OF COCAINE-CONDITIONED LOCOMOTION BY SITE-SELECTIVE NMDA RECEPTOR ANTAGONISTS IN RATS

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A growing body of evidence suggests that NMDA receptor antagonists may affect expression of behaviors conditioned with abused drugs. The outcome of drug-conditioning experiments appears to be dependent at least in part on the type of NMDA receptor antagonist used. The present study tested the ability of various site-selective NMDA receptor antagonists to modify cocaine-conditioned increases in locomotion. Rats were administered intraperitoneal injections of cocaine (30 mg/kg) or saline paired with distinctive environments. Following five drug-environment pairings, subjects displayed significant increases in locomotion when exposed to the cocaine-paired environment. The following antagonists were administered prior to the test: dizocilpine (MK-801; 0.03-0.1 mg/kg), D-CPPene (0.3-3 mg/kg), ACEA-1021 (3-10 mg/kg), eliprodil (1-10 mg/kg) and memantine (0.3-10 mg/kg). To help interpret the results, the same drugs were evaluated for their direct effects on locomotion, alone and in combination with cocaine. Dizocilpine and D-CPPene eliminated differences in locomotor responses in cocaine- vs. saline-paired environments that was, at least, in part due to their own stimulator-y effects. Memantine, eliprodil and ACEA-1021 attenuated expression of cocaine-conditioned locomotion at doses that did not significantly suppress spontaneous locomotion or block cocaine's unconditioned effects on locomotion. Spontaneous locomotor activity was dose-dependently enhanced by pre-treatment with dizocilpine (0.03-0.3 mg/kg) and memantine (1-30 mg/kg), but not D-CPPene (1-10 mg/kg), eliprodil (3-30 mg/kg) or ACEA 1021 (3-56 mg/kg). It can be concluded that NMDA receptors are involved in the expression of cocaine-conditioned locomotion.

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BRAIN σ_1 RECEPTORS ARE INVOLVED IN THE BEHAVIORAL EFFECTS OF COCAINE

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In previous studies, BD1008, a novel sigma ligand, and several structural analogs attenuated the behavioral toxic effects of cocaine. In this study, structural analogs of BD1008 with aryl-substitutions were tested for their ability to reduce the toxic and locomotor stimulatory effects of cocaine. Male, Swiss Webster mice were pretreated (0-30 mg/kg, i.p.) for 15 min with saline, high (YZ-011, YZ-016, YZ-018, YZ-027, YZ-028, YZ-029; 4-30 nM), moderate (YZ-030, YZ-032, YZ-033; 276-579 nM) or low (YZ-005, YZ-007, YZ-008; 2223-5457 nM) affinity sigma ligands followed by a convulsive ED_{97} (60 mg/kg, i.p.) or lethal LD_{97} (125 mg/kg, i.p.) dose of cocaine. Pretreatment with the high affinity ligands prevented cocaine-induced convulsions and lethality ($P<0.05$), while the low affinity ligands failed to block the convulsive and lethal effects of cocaine. Representative high and moderate affinity sigma ligands (YZ-029, 5 mg/kg; YZ-011, 0.1 mg/kg; YZ-032, 15 mg/kg), at a dose that alone was behaviorally inactive, were also tested for their ability to antagonize the locomotor stimulatory effects of cocaine. After a 15-min pretreatment period, the mice were injected with cocaine (10 mg/kg, i.p.) and horizontal locomotor activity was quantified for 30 min. YZ-011, YZ-029, and YZ-032 significantly reduced the locomotor activity induced by cocaine. To further verify that the sigma receptors were involved in cocaine's toxic and locomotor effects, mice were injected i.c.v. on days 1, 2, and 4 with either 10 µg/5 µl of a σ_1 receptor antisense or mismatch oligodeoxynucleotide or saline. On day 5, the animals were challenged with either the convulsive or locomotor stimulatory dose of cocaine used in the above experiments. There was a significant reduction in the response of antisense-treated animals to the convulsive and locomotor stimulatory doses of cocaine as compared to mismatch and saline-treated animals. The data suggests that sigma receptors play a significant role in the behavioral effects of cocaine.

ANTAGONISM OF SIGMA RECEPTORS ATTENUATE THE LOCOMOTOR STIMULATORY EFFECTS OF COCAINE

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The ability of cocaine to interact with sigma receptors provides a logical target for the development of anticocaine agents. We have previously shown that BD 1008 and related analogs attenuate the behavioral toxic effects of cocaine through antagonism of sigma receptors. In the present study, BD1008, two conformationally-restricted analogs (BD1018, BD1063), and two pyrrolidinyl ring-altered analogs (BD1047, LR172) that were previously shown to possess anti-cocaine actions in the toxicity studies were tested for their ability to attenuate the locomotor stimulatory actions of cocaine. Male, Swiss Webster mice who were acclimated to an automated activity monitor were pre-treated with saline or one of the sigma ligands (0-30 mg/kg, i.p.), followed 15 min later with a dose of cocaine (0-20 mg/kg, i.p.). Analyses of variance demonstrated that the sigma ligands significantly attenuated the locomotor stimulatory effects of cocaine. A separate group of mice were treated intracerebroventricularly with controls or an antisense oligodeoxynucleotide for sigma, receptors under conditions reported to knock down the levels of the receptor. Upon subsequent challenge with cocaine, the antisense-treated animals exhibited a significantly lower level of cocaine-induced locomotor activity as compared to sense- and saline-treated animals. Together, the data demonstrate that strategies that impede cocaine's access to sigma receptors can reduce the psychomotor effects of the drug.

STEROTYPY AND LOCOMOTOR RESPONSE TO CHRONIC "BINGE" PATTERN COCAINE ADMINISTRATION IN MALE C57BL/6J AND 129/J MICE

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The C57BL and 129 strains of mice are common host strains for many transgenic animals. We have previously demonstrated that mice of the C57BL/6J and 129/J strains differ significantly in their behavioral response to acute "binge" pattern cocaine administration. In the present study, we examined the behavioral responses to chronic "binge" pattern cocaine administration. Methods: Male C57BL/6J and 129/J mice were randomly assigned to either control or experimental groups and individually housed in a standard cage within a behavioral monitoring frame in a stress-attenuated facility. Following acclimation, animals received "binge" pattern cocaine (15 mg/kg/day x 3 commencing ½ hour following the start of the daily light cycle and separated by one hour) or saline administration. Twenty minutes following each injection, animals were videotaped for 30 seconds and the tapes were later scored for the presence of stereotypy. The amount of time each animal spent engaged in sniffing, rearing or grooming behaviors (common components of stereotype rating scales) was also determined. Results: There was a significant increase in locomotor activity in C57BL/6J mice in response to chronic "binge" pattern cocaine ($p < 0.0005$) but not in 129/J mice, extending our earlier finding following acute "binge" cocaine administration. Tolerance to cocaine-induced locomotor activity was observed in C57BL/6J mice, confirming a previous report from our laboratory. The stereotypic response to chronic "binge" cocaine was significantly greater in C57BL/6J mice than in 129/J mice ($p < 0.001$), again confirming and extending our earlier finding following acute "binge" cocaine administration. Neither tolerance nor sensitization of the expression of behavioral stereotypy was observed in either mouse strain. Of the individual behaviors examined (locomotion, sniffing, rearing, and grooming), only locomotion and sniffing were significantly effected by drug treatment. There were no strain differences in the expression of these behaviors.

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CART PEPTIDE 55-102 INDUCES PSYCHOSTIMULANT-LIKE BEHAVIORAL EFFECTS

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CART is a novel mRNA that is increased by acute psychostimulant drug administration. The aim of this study was to examine the effect of centrally injected CART peptide on psychostimulant-related behaviors in male Sprague-Dawley rats. CART fragments were bilaterally injected into the ventral tegmental area in the volume of 0.5 µ1 through pre-implanted cannulae. CART 55-102 (0.2-5 µ g) dose-dependently increased locomotor activity and stereotyped activity, while CART 1-26 (0.1-2.5 µg) had no significant effect. Four injections of 1 µg of CART 55-102 induced a significant conditioned place preference for the environment associated with CART injections. Ten days after the place preference test, the CART 55-102 pretreated rats showed a sensitized locomotor response to IP injection of cocaine (10 mg/kg). When CART 55-102 was injected into the nearby substantia nigra, no change in motor activity was seen up to the dose of 1 µg. Injection of 5 µg of CART 55-102 into the substantia nigra induced an increase in motor activity with a delayed onset, suggesting possible diffusion into the ventral tegmental area. Our findings suggest that CART peptides in the ventral tegmental area are involved in psychostimulant activity and that CART 55-102 is an active fragment. While the involvement of CART in psychostimulant's action has been suspected since its identification, this is its first demonstration.

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INTRA-MEDIAL PREFRONTAL CORTEX INJECTIONS OF QUINPIROLE BLOCK THE ACUTE MOTOR-STIMULANT RESPONSE TO COCAINE

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Considerable evidence suggests that dopamine (DA) in the medial prefrontal cortex (mPFC) has an integral role in mediating the behavioral responses to cocaine in the rat. However, distinct cortical DA receptors contributing to the effects of cocaine-induced DA transmission in this region have yet to be determined. Since DA in the mPFC has been reported to have an inhibitory influence in this region and on subcortical structures, including the nucleus accumbens (NAC), the effect of intra-mPFC microinjections of DA agonists were determined on the acute locomotor response to cocaine. One week following bilateral cannulae implantation, male Sprague-Dawley rats received intra-mPFC injections of either saline, the D2-like agonist quinpirole (0.015, 0.05, 0.15, 0.5, 1.5 or 5 nmol/side) or the D1-like agonist SKF 38393 (0.5, 1.5 or 5.0 nmol/side) 5 min prior to systemic saline or cocaine (15 mg/kg) administration. Quinpirole pretreatment resulted in a dose-dependent decrease in cocaine-induced motor activity, with high dose quinpirole (3.0 and 10.0 nmol) administration producing a complete abolition of the acute motor-stimulant response to cocaine. In contrast, intra-mPFC injections of SKF 38393, at the doses tested, did not alter cocaine-induced motor activity. As well, intracortical quinpirole (5 nmol/side) significantly inhibited cocaine-induced DA transmission in the NAC. It was also found that neither quinpirole nor SKF 38393 pretreatment, at any dose, significantly altered basal motor activity. These results suggest the potential involvement of DA D2-like receptors in the mPFC in mediating cocaine-induced DA transmission in this region, and elucidate potential cellular processes in the mPFC that may contribute to the behavioral and neurochemical responses to cocaine.

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CONDITIONED LOCOMOTOR STIMULANT EFFECTS OF COCAINE IN RATS: A RESULT OF ASSOCIATIVE PROCESSES OR INTERFERENCE WITH HABITUATION?

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Many studies have demonstrated hyperactivity in drug-free rats placed in an environment previously paired with cocaine or amphetamine. Classical conditioning has been proposed to account for this phenomenon. However, an alternative explanation is that hyperactivity results from an inability of rats to habituate to the environment under the influence of cocaine. In the present study, rats were habituated to the test environment (activity boxes) prior to drug-environment pairings; 7-8 saline sessions were run over 15-17 days. Mean locomotor activity decreased by 31% (n=44) between the first and last habituation days. Six 60-min conditioning sessions followed over a 13-day period. Habituated rats were assigned to one of three groups: Paired, Unpaired and Time Off. Paired rats received 10 mg/kg cocaine ip prior to activity sessions and saline ip upon return to the colony room. Unpaired rats received saline prior and cocaine after. Time Off rats were withheld from the activity boxes, but were subject to all other procedures during conditioning. On the test day, all rats received saline prior to 30-min activity sessions. The Paired group exhibited a 66% greater mean activity than the Unpaired group on the test day suggesting that conditioned stimulant effects developed in habituated rats, The mean activity of the Time Off group was not significantly different from that of the Unpaired group demonstrating that habituation had not decayed over this time period even though this group had no additional exposure to the test environment. These results support the conclusion that associative processes (classical conditioning), rather than antihabituation effects of cocaine, mediated the hyperactivity observed in the test environment.

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EFFECT OF PERINATAL OPIOID EXPOSURE ON NEUROTROPHIN MRNAS IN RAT STRIATUM

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Previously, this laboratory has demonstrated that perinatal exposure to the opioid methadone (m) or buprenorphine (b) disrupts the development of striatal cholinergic neurons and significantly reduces striatal nerve growth factor (NGF) content in the rat. To determine whether the reduction in NGF levels results from a decrease in NGF mRNA, and whether the effect is restricted to NGF mRNA, mRNAs for NGF and several other neurotrophins were quantitated by RNAse protection assay (RPA) after perinatal exposure to m or b. On day 7 of gestation, pregnant Sprague Dawley CD rats under methoxyflurane anesthesia were implanted subcutaneously with 28 day osmotic minipumps which delivered sterile water (w), methadone HCl (9 mg/kg/day) or buprenorphine HCl (1.5 mg/kg/day). Within 24 hr of parturition, litters were culled to 10, with equal numbers of males and females, and cross-fostered, resulting in the following prenatal/postnatal exposure groups: w/w, m/w, w/m, m/m, b/w, w/b, and b/b. On postnatal day 10, pups were decapitated, and striata were dissected and pooled for the RPA. No statistically significant changes were observed in the content of mRNA for NGF, brain-derived neurotrophic factor (BDNF), or glial-derived neurotrophic factor (GDNF). However, there was a significant treatment effect for ciliary neurotrophic factor (CNTF) mRNA, $p=0.05$, with a significant increase in CNTF mRNA in the m/w group as compared to w/w control ($p < 0.05$). These results indicate that perinatal opioid exposure may not reduce the expression of NGF protein by reducing mRNA levels. The change in CNTF mRNA needs to be further investigated.

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THE EFFECTS OF PRENATAL EXPOSURE TO ALCOHOL AND NICOTINE ON S100B EXPRESSION

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The adverse effects of alcohol and/or nicotine on CNS development and underlying mechanisms have been the subject of numerous studies (reviewed by Randall *et al.,* 1990 and Lambers and Clark, 1996). Some proposed mechanisms to account for these effects include altered placental transport, diminished neurotransmitter function, hypoxia, and disruption of neurotransmitter-gated ion channels. Another possible mechanism that has received limited focus is the effect of alcohol and nicotine on the synthesis, functioning, and/or expression of proteins associated with neuronal growth and survival. To begin to address this possibility, expression of the Ca^{2+}-binding protein S100B was examined in the molecular layer of the hippocampal dentate gyrus of the mouse (C57BL/6J). This protein was chosen because of its dual role as a neurotrophic and neurotropic molecule. Brain tissue was collected from adult offspring of dams either 1) exposed prenatally to ethanol and/or nicotine, 2) pair-fed to the alcohol/nicotine group, or 3) allowed free access to Lab Chow and water. The tissue was fixed in 10% buffered formalin and processed for immunocytochemistry. Preliminary data revealed that S100B expression was less prominent in cells in the molecular layer of the dentate gyrus in animals prenatally exposed to ethanol and nicotine compared to controls. These data provide evidence to suggest that changes in protein expression may be a mechanism through which alcohol and nicotine exert their effects on the developing CNS.

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CHANGE IN ACOUSTIC STARTLE RESPONSE AND LOCOMOTOR ACTIVITIES IN RATS PRENATALLY EXPOSED TO HEROIN

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Prenatal heroin exposure results in the developmental symptoms like tremulousness and irritability, impaired cognitive and psychomotor functions. The present study examines the effects of prenatal heroin esposure on postnatal (PN) behavioral development in rats. Pregnant Sprague-Dawley rats were administered with heroin (10mg/kg/day, s.c.) from gestational day 8 to 20. Acoustic prepulse inhibition (PPI) and habituation were parameters measured in male and female pups at PN 3 weeks. PPI is an operational measure of sensorimotor gating when an abrupt startling stimulus is preceded 100 msec by a barely detectable prepulse, and habituation, a simple form of learning, is the decrement in responding to repeated presentations of an initially novel and intense stimulus. Locomotor activity and rearing was assessed using the photobeam activity system of a figure-8 configuration. Results showed that although both the heroin-exposed and pair-fed groups showed a marked reduction in birth weight in both male and female pups when compared with their controls, by PN 3 weeks, the female heroin-exposed pups failed to regain their weight to that of the controls and pair-feds. These female pups also showed a significant increase in locomotor activities when compared to the pair-fed and control groups. These pups also showed impairment in learning as evident by the decrease in habituation observed. It therefore can be concluded that prenatal heroin-exposure can result in a marked retardation of postnatal development and learning. This effect is more pronounced in female pups than in male pups.

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THE NATURE OF RESPONSE DISINHIBITION IN INDIVIDUALS PRENATALLY EXPOSED TO ALCOHOL

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Deficient response inhibition is considered one of primary behavioral manifestations of Fetal Alcohol Syndrome. Neurobehavioral research on response inhibition in alcohol-exposed children has, however, produced equivocal results. We conducted two studies to elucidate the processes underlying response inhibition in alcohol-exposed individuals. In the first study, we tested the hypothesis that children with prenatal alcohol exposure would exhibit more deficits than controls in response inhibition in both verbal and non-verbal domains. Forty-four children, 22 alcohol-exposed and 22 normal controls, participated. A battery of tests measuring vocabulary, auditory comprehension, and response inhibition in verbal and non-verbal domains was administered to the two groups. Group mean comparisons did not reveal statistically significant differences in vocabulary, auditory comprehension and response inhibition. Therefore, we conducted a second study to determine if the apparent behavioral disinhibition in alcohol-exposed children results from a processing problem rather than impulsive responding. Thirteen subjects with prenatal alcohol exposure and 13 normal controls participated in the second study. The Matching Familiar Figures Test, which allows differentiating between fast-inaccurate responding and slow-inaccurate responding, was utilized to measure response inhibition. Results showed that, despite taking as long as the control group to make the first response, the alcohol-exposed group made more errors, a pattern suggesting slow-inaccurate responding. This finding may prove useful in making a differential diagnosis between response disinhibition associated with alcohol exposure and that associated with other neurodevelopmental disorders such as Attention Deficit Disorder.

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PRENATAL DRUG EXPOSURE AND NEONATAL OUTCOME IN HUMAN INFANTS

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The purpose of this study is to determine the effects of cocaine and/or opiate exposure on neurobehavioral outcome during the neonatal period. The outcome of infants prenatally exposed to drugs remains a serious public health problem with as many as 220,000 exposed infants born each year. Research results are inconsistent due in part to methodological flaws and confounding factors. This study tests the hypothesis that cocaine/opiate exposed infants show less optimal neurodevelopment at 40 and 44 weeks after accounting for polydrug use, social risk and medical risk. One hundred subjects completed the study, 85% were term infants, 25% were exposed to cocaine and/or opiates, 70% were exposed to alcohol, 62% were exposed to nicotine, 23% were exposed to marijuana. Overall, the mothers were 67% white, 61% unmarried, and middle to low SES. Mean age was 25 years. At 40 weeks, mothers reported demographic information and prenatal drug use. Infants were evaluated with the NICU Network Neurobehavioral Scale (NNNS) developed for use with drug-exposed infants. The examiner was masked to exposure status. At the 44 week home visit, the Time Line Follow-back Interview, an extensive structured interview of all drug use during pregnancy, was administered to the mother. The NNNS exam was repeated with the infant. Hierarchical regression was used to analyze each of 10 NNNS summary scores. With other drugs, gestational age and SES controlled, cocaine exposure was associated with lower arousal ($P<.01$) at 40 weeks and with poor orientation ($P<.01$, more stress signs ($P<.01$ and greater excitability ($P<.05$) at one month. Opiate exposure was associated with poor movement ($P<.01$), less optimal reflexes ($P<.01$), and greater arousal ($P<.01$) at 40 weeks but no significant behaviors at 44 weeks. All effects were small, $R^2<15\%$. In sum, exposed infants show neurobehavioral deficits that change from 40 to 44 weeks and may be drug specific. Concern for drug exposed infants is warranted, but findings suggest subtle deficits amenable to intervention.

PREDICTORS OF BEHAVIORAL AND EMOTIONAL ADAPTATION AT THREE YEARS OF AGE IN CHILDREN WITH *IN UTERO* COCAINE/POLYDRUG EXPOSURE

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The objective of this study was to assess significant predictors of behavioral and emotional competence at three years of age in children with prenatal cocaine/polydrug exposure. It was hypothesized that children's externalizing and internalizing behavior problems would be predicted by factors such as maternal psychopathology and mother-child affective/behavioral interactions. Study participants were .156 full-term, inner-city, African-American children, enrolled prospectively at birth and categorized as cocaine/polydrug-exposed. Prenatal cocaine exposure was defined by a combination of maternal self-report and/or positive urine or meconium assays. Mothers completed the Symptom Checklist-90R (SCL-90R) and the Child Behavior Checklist 2/3 (CBCL). Mother-child pairs completed a 15-minute, free-play interaction which was later coded for maternal supportiveness, hostility and other behavioral qualities. Only children in the care of their biological mothers were included in the analyses. Stepwise multiple regression analyses indicated a significant linear relationship between mothers' global psychological distress and children's externalizing (Adj. $R^2=.116$, $p<0.0001$) and internalizing ($R^2=.146$, $p<0.0001$) behavior problems. Maternal psychopathology continued to significantly predict children's behavior problems when models were analyzed by gender. In addition, maternal hostility during free play predicted externalizing (Adj. $R^2=.197$, $p<0.001$ and internalizing (Adj. $R^2=.233$, $p<0.001$) behavior problems, for boys only, when both variables were entered. Overall, results suggest that within families where children have been exposed to cocaine/polydrugs prenatally, high levels of maternal psychological distress are associated with increased rates of both externalizing and internalizing behavior problems. For boys, maternal hostility during free play also was associated with increased externalizing and internalizing behavioral symptoms.

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THE RELATIONSHIP BETWEEN NEONATAL HAIR BENZOYLECGONINE LEVELS AND NEURODEVELOPMENT AT THREE YEARS

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Sixty-two children exposed to cocaine prenatally were evaluated for developmental status by a multidisciplinary team at one and three years. Degree of exposure was measured by neonatal hair benzoylecgonine (BZE, a major metabolite of cocaine) in ng/g hair as well as BZE in ng/g hair per meter^2 of body surface area (BZS). Neurodevelopment (ND) was assessed by number of domains affected (motor, cognitive, language, behavior) and the severity of deficits, as determined by developmental quotient (DQ) percentiles (<75, 75-85, >85) utilizing standardized developmental tests. Mean BZE and BZS levels were 3,420 and 19,605, respectively. The incidence of abnormal behavior and multiple area deficits ($\geq$2) was 34% and 27%, respectively, after controlling for maternal alcohol and tobacco use and SES. In children exposed to > 18,000 BZS, 54%, had persistent multiple area deficits at one and three years. They also had significant relative risk of severe motor deficits (10-fold), language deficits (12-fold), and moderate cognitive deficits (7-fold) compared to those with < 18,000 BZS. Children with abnormal behavior had significantly higher BZS ($\underline{M}$=21,508) compared to those who were normal ($\underline{M}$= 17,975), $p<0.05$. ND at three years seems to be reliably predicted by prenatal exposure to cocaine as indicated by neonatal hair BZS.

ATTENTIONAL PROCESSING AND BEHAVIORAL REGULATION IN S-YEAR-OLD AFRICAN-AMERICAN CHILDREN WITH PRENATAL COCAINE/POLYDRUG EXPOSURE

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The objective of this longitudinal study is to determine the long-term effects on *in utero* cocaine exposure on neuro-cognitive and behavioral functioning in children. Study participants were 476 full-term, inner-city, African-American children, enrolled prospectively at birth and categorized into cocaine-exposed (COC) and comparison (COMP) groups. Cocaine exposure was defined by maternal report and/or positive urine or meconium assays. The COMP group included children who were drug-free (n=147) or with some degree of prenatal alcohol, marijuana or tobacco exposure (n=76). Attentional processing was measured with the Test of Variables of Attention (TOVA®), a computerized continuous performance task. The Achenbach Child Behavior Checklist and tester behavioral observation ratings were used to assess child behavioral regulation. Four hundred and eight children (86% of the total) were seen for evaluation at 5 years, 6 months of age. Of these, 50 were unable to complete the TOVA®: 41 due to developmental delay and/or behavioral problems; 8 due to computer malfunction; 1 due to early clinic departure. Attrition did not differ between groups. A general linear model, controlling for prenatal tobacco, alcohol, and marijuana, was used in the analyses. COC children had significantly more omission (inattention) errors as reflected by lower TOVAB® omission error standard scores (COC 79.44 vs. COMP 88.03; $p=0.0048$). TOVA® standard scores<85 are more than 1 S.D. (15) below the mean (100). The COC group also showed significantly poorer scores ($p<0.05$) on tester behavioral observational ratings of impulsivity, aggressiveness, cooperativeness, difficulty in testing, and interest in testing tasks. There were no significant group mean differences in CBCL caregiver reports of child behavior. In summary, these data suggest that prenatal cocaine exposure contributes to poorer attention at age 5 years as measured by TOVA® omission error scores and worse behavioral ratings by testers but not primary caregivers.

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POSTNATAL CAREGIVER COCAINE USE, NOT IN UTERO COCAINE (COC) EXPOSURE ALONE, IS A MARKER FOR LANGUAGE PROBLEMS IN CHILDREN AT SCHOOL AGE.

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OBJECTIVE: To assess whether *in utero* COC exposure affects language development. **STUDY DESIGN:** In a longitudinal study,of inner-city COC and control (CON) children enrolled at birth, language is assessed at four time points: (1) Preschool Language Scale (PLS) age 2.5 yrs; (2)&(3) Verbal Scale of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) ages 4 and 6 yrs; (4) Assessing Semantic Skills Through Everyday Themes (ASSET), age 7 yrs. So far, 42 COC (median *in utero* COC exposure 99 days) and 37 CON have completed all 4 evaluations. **RESULTS:** COC and CON did not differ on PLS (all $p \geq .2.66$) or on Verbal IQ Scores at age 4 yrs, or 6 yrs (all $p \geq 2.39$). COC and CON were also similar on ASSET (standard score 100±115) in Receptive Total, Expressive Total, and Total Test Score (all $p \geq .2.72$). Language ages (LA) for Total Test, however, showed 67% COC and 73% CON with LA>12M below chronologic age. Although we detected no effect of *in utero* COC on language outcome, there was an association of postnatal caregiver COC use and outcome. Of the 79 children assessed at age 7 yrs, 76 of their caregivers had at least 1 urine screen for COC use since screen at study entry. Nineteen caregivers had positive screens: 16 used COC during pregnancy, whereas 3 were previous controls. Children of the 19 postnatal caregiver users (values shown first) scored lower on Expressive (79.7±14.6 vs 88.4±13.9[p=.023]) and Total ASSET (75.7±15.8 vs 84.5±14.0 [p=.024]) than the 57 children of caregivers who did not use COC postnatally; Total ASSET scores of these 19 children were also lower than scores of children with *in utero* exposure only (75.7±15.8 vs 85.0±12.9 [p=.04]). **CONCLUSIONS:** (1) Inner-city children demonstrate poor language development at age 7 yrs. (2) Postnatal caregiver COC use is a marker for poor language outcome whereas *in utero* exposure alone is not. In our cohort, the postnatal environment may be more influential than *in utero* environment on language development.

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WHAT HAPPENS WHEN THE CHILD WITH *IN UTERO* COCAINE-EXPOSURE (COC) GOES TO SCHOOL?

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There is much speculation regarding school performance of COC. We report outcome of 49 COC (median *in utero* COC 99 da) and 52 control children (CON) followed since birth who have now completed Grade 1. **METHODS:** COC and CON were evaluated on: (1) School Performance: grades, grade retention/special education placement(Ret./S.Ed.), and absences; and (2) Behavior: Teacher Report Form of the Child Behavior Checklist (CBCL-TRF). **RESULTS:** Grade Point Average (CPA [scale of A=5, C=3, F=0]) was similar for COC (3.1±1.1) and CON (3.4±0.9) (p=.19) as were absences, COC (16.4±16.4 days) vs CON (14.0±11.1) (p=.42). 8 COC vs 4 CON were Ret. (p=.23); 5 COC vs 4 CON were placed in S.Ed. (p=.74). Taken together, nearly twice as many COC (27%) as CON (15%), were Ret./S.Ed. but this did not reach statistical significance (p=.22). CBCL-TRF scores were similar in COC and CON (all $p \geq 2.09$). Given cohort poor Grade 1 outcome (20% Ret./S.Ed regardless of COC), we compared children passing Grade 1 (PASS) (n=80) vs. those Ret/S.Ed. (n=21). Of the 101 children evaluated, 58 of their caregivers have been screened for postnatal COC use (urine screen); 20 (34%) had positive screens. Of those with positive postnatal screens, 18 caregivers were previous COC users and 2 were previous CON. Children of postnatal COC users (values presented first) vs children of non-users were compared as follows: CPA (2.9±1.2 vs 3.5±1.0 [p=.04]); Ret./S.Ed. (35% vs 15% [p=.10]); and days absent (17.9±12.0 vs 15.4±14.5 [p=.53]). PASS had higher total scores than did those Ret./S.Ed. on Home Observation for Measurement of the Environment (45.8±4.4 vs 40.4±7.2 [p=.014]) and on 5 of its 8 subscales (all $p \leq 2.032$). PASS had higher Full Scale IQ scores than Ret./S.Ed (87.2±12.1 vs 67.0±13.4) (p<.001). **CONCLUSIONS:** (1) When children with *in utero* COC exposure go to school their outcome is similar to CON although their higher rate of Ret./S.Ed. remains a concern. (2) Lower IQ and the environmental factors of postnatal caregiver cocaine use and less stimulating homes are associated with poor school outcome regardless of COC or CON status.

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EFFECTS OF PRENATAL SUBSTANCE USE ON GROWTH OF SIX-YEAR-OLD OFFSPRING OF ADOLESCENT MOTHERS

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In an ongoing study, teenage mothers were interviewed about their drug use during pregnancy. Their offspring were examined at birth and at six years. These preliminary analyses represent data on the first 144 of 415 offspring who have been followed. During pregnancy, the average age of the mothers was 16(13-18); 73% were African-American. During the first trimester, 49% were smokers, 49.3% were drinkers, and 15.3% used marijuana. These rates changed to 60.4%, 11.1%, and 4.2%, respectively, by the third trimester. Six years later, when their children were examined, 58.5%, 87.3%, and 31.7% of their mothers used these substances, respectively. The long-term effects of prenatal substance exposure on offspring growth were examined for the following outcomes: height, weight, head circumference, skinfold, body mass index (BMI), and weight-forheight z score (WHZ). Regression analyses controlled for current maternal substance use, growth measures at birth, and covariates of substance use and growth. Second trimester alcohol use, third trimester marijuana use, and mother's current smoking significantly predicted reduced height in the offspring at age 6. Prenatal alcohol exposure from the third trimester predicted reduced skinfold thickness. However, prenatal tobacco exposure from each trimester predicted increased skinfold thickness, BMI, and WHZ, all indices of adiposity. No prenatal substance use predicted weight or head circumference at age six.

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ATTACHMENT AT 18 MONTHS: PRENATAL PSYCHOLOGICAL SYMPTOMS IN COCAINE-USING WOMEN

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The purpose of this study was to identify the characteristics of low-income, cocaine-using mothers who were able to establish secure attachments to their 18-month old toddlers. During the third trimester of pregnancy, 35 women were interviewed about their history of drug use and were administered a standardized measure of psychopathology, the Millon Clinical Multiaxial Inventory-I. When the children were 18-months of age, they and their mothers were brought to the laboratory and adminstered the Ainsworth Strange Situation, the standard measure of mother-child attachment. While a wide range of significant prenatal psychological problems were identified, this study focuses primarily on paranoia and dysthymia. Of the 35 toddlers, 11 were classified as securely attached and 24 were classified as insecurely attached. This distribution of attachment classifications was found to vary significantly from that found in the normative population. Securely attached toddlers did not differ from insecurely attached toddlers in their mothers' history of drug use. However, the pattern of maternal psychopathology differed significantly between mothers of the two groups of toddlers, with mothers of insecurely attached toddlers expressing clinical levels of paranoid symptoms and/or narcissistic and antisocial symptoms. Toddlers who were securely attached were more likely to have mothers who expressed only prenatal dysthymic symptoms in the clinical range. Within this population, paranoia may be a greater risk for children's development than maternal depression.

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MICRONUTRIENT INTAKE IN A POPULATION OF COCAINE-DEPENDENT PREGNANT WOMEN

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The focus of this study was to assess the nutritional status and intake of micronutrients in cocaine-dependent pregnant women who were participating in a comprehensive treatment program. Subjects were pregnant women who were 28 weeks gestation or less, with a primary diagnosis of cocaine dependence, or opiate dependence with secondary cocaine dependence. They were randomly assigned to one of three treatment groups and were subjected to a baseline treatment that included a combination of behavioral and group therapy sessions. Patients were also required to attend the Substance Abuse Prenatal Clinic once a week and the Treatment Research Clinic twice a week, providing a urine sample at each of these visits. All subjects were weighed at each visit. Additional nutrition information was also obtained. Analyses of results indicates a significantly low consumption of fruits and vegetables (average 1.25-3.49 servings per day). This translates to a suboptimal intake of several micronutrients (vitamins and minerals). These include vitamins A, D, K, folacin, calcium, iron, iodine, and zinc. Nutritional deficits of these micronutrients may have serious implications for maternal and infant health.

FAMILY AND COGNITIVE STRUCTURE PREDICTS TREATMENT RETENTION AND SATISFACTION AMONG DRUG DEPENDENT PREGNANT WOMEN

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Retention of patients in treatment is a challenge faced by drug treatment programs. Anecdotally, many drug abusers report a lack of structure and consistency in their lives, which contrasts with the structured nature of drug treatment. This study examined the relationship between the structure within a patient's family of origin and their cognitive structuring ability and drug treatment outcomes (retention and satisfaction). Participants were 118 opioid and/or cocaine dependent pregnant women enrolled in a comprehensive drug treatment program. Patients were 87% African American with a mean age of 30 and education of 11 years. Assessments included the Family Unpredictability Scale (FUS), a neuropsychological Cancellation Task, the Addiction Severity Index (ASI), the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), and a patient satisfaction survey. Greater structure and predictability within patients' family of origin was associated with greater treatment attendance (r=.15, p<.05), program satisfaction (r=.33, p<.001), education (r=.20, p<.05), and fewer employment difficulties (r=-.24, p<.01). Better cognitive structuring ability was associated with greater treatment satisfaction and attendance for some but not all measures of cognitive structuring. Information on patients' family structure during childhood may assist drug treatment staff in their efforts to help patients adjust to the more organized nature of drug treatment.

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DRUG USE PATTERNS OF ADOLESCENT MOTHERS: PRE PREGNANCY TO 24 MONTHS POST PARTUM

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Despite their presumed high risk status, little is known about postpartum drug use patterns of adolescent mothers. This study provides descriptive, longitudinal data on substance use within a large cohort (n=931) of adolescent mothers. Three hundred and forty-nine Mexican American, 301 African American, and 281 Caucasian adolescents ≤ 18 years of age were recruited on a postpartum unit to participate in a study of drug use during the first 2 years following delivery; 86% of the subjects completed at least 3 follow-up surveys mailed 3, 6, 12, 18, and 24 months post partum. Outcome variables included the use of tobacco, alcohol, or marijuana during the 3 months prior to conception, the last 30 days of pregnancy, and within 2 years of delivery. Several important patterns were identified within this cohort. First, Caucasian adolescents reported the highest rates of tobacco and alcohol use at each time period. Second, the use of most substances decreased dramatically during pregnancy. Third, greater than 75% of the adolescents who stopped smoking during pregnancy resumed their nicotine use within 24 months of delivery. Moreover, almost half of the adolescent mothers who smoked following delivery were new starters in that they denied using tobacco during pregnancy or prior to conception. Fourth, almost 80% of those who had drank alcohol before conception but not during pregnancy resumed this behavior by 12 months postpartum; 27% of the sample reported alcohol use following delivery but not during pregnancy or before conception. Fifth, about half of those who used marijuana before conception but not during pregnancy resumed its use after delivery. Most importantly, an additional 12% used marijuana for the first time in the post partum period. These data suggest that while pregnancy itself may help motivate some adolescents to reduce or eliminate their use of harmful substances, the onset of parenthood is not sufficient to maintain these healthy behaviors. Moreover, at least one in ten adolescent mothers appears to initiate the use of illicit substances after delivery and may be at risk for progressing toward harder drugs. The special needs of adolescent mothers must be carefully considered when planning interventions.

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THE EFFECTIVENESS OF INTENSIVE CASE MANAGEMENT SERVICES FOR DRUG DEPENDENT WOMEN AND THEIR CHILDREN

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Children of drug dependent women are at increased risk for a variety of medical and developmental difficulties. Those children at highest risk are children whose mothers drop out of substance abuse treatment in the perinatal period. Outreach services have been found to be a successful public health measure in the treatment of high-risk populations of women and children. This study evaluated the effects of routine vs. intensified case management services for a group of women in a comprehensive drug treatment facility. Women receiving intensified case management services in the 4 months following the birth of their child remained in substance abuse treatment for a longer period of time, received a wider variety of services, and perceived that their infants status would be significantly worse without those services. Women in the control group were more likely to have positive urine toxicology for cocaine at 4-month follow-up assessment. Number of case management visits was positively correlated with total time in treatment across both intervention groups. Although outcome data must be interpreted with caution due to relatively small group sizes, this study supports the efficacy of intensified case management services for drug dependent women and their children.

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SEX FOR CRACK EXCHANGE, POOR BLACK WOMEN AND PREGNANCY: EPIDEMIOLOGY AND ETHNOGRAPHY

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Having few economic resources, poor black female crack users are disproportionately at risk for exchanging sex for the drug. The men on the street often demand unprotected, vaginal sex and the women comply. The connection between STD'S and HIV transmission and exchanging sex for crack is well documented. Pregnancy is also a consequence of this behavior. In a sample of 34 poor black women who exchanged sex for crack, an epidemiology of sex for crack conceived pregnancies was conducted. Ethnographic interviews with women who became pregnant were conducted and analyzed using a Grounded Theory variant. Eighteen out of thirty-four women reported sex for crack pregnancies and over half that number became pregnant this way more than once. Twenty-nine pregnancies were reported and only six were terminated by abortions. (1) Severity of crack use, (2) religious beliefs, and (3) social organization patterns within poor black communities influenced the women to carry these pregnancies to term. The findings have implications for drug treatment and child welfare policy.

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PHYSICAL, SEXUAL, AND EMOTIONAL ABUSE IN PREGNANT AND POST-PARTUM SUBSTANCE ABUSING WOMEN AND THEIR CHILDREN

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The purpose of this study was to determine the characteristics of violent episodes experienced by a group of drug dependent women and their children, and their consequent need for services. Participants were women attending a specialized pediatric clinic at The Center for Addiction and Pregnancy of the Johns Hopkins Bayview Medical Center. A semi-structured anonymous questionnaire was developed and administered to 72 substance-abusing mothers when they came for routine pediatric care for their children. Subjects were predominantly African American (71.4%), mean (SD) years of age 30 (4.26), and mean (SD) number of children 3.12 (1.5). There were high rates of various types of abuse reported by the women ranging from 41.8% (sexual abuse) to 66.2% (emotional abuse) to 66.7% (physical abuse). The participants reported that their children frequently experienced and/or witnessed violent episodes at home, at school and on the street. Mothers with a history of abuse and mothers of children who witnessed violence reported more current domestic violence and street fights, and greater need for help due to problems related with exposure to violence. The results of this study underscore the importance of screening substance abusers and their children for exposure to violence. Facilities treating substance abusing pregnant and post-partum women should address the needs of the patients exposed to violence.

ASSESMENT OF DRUG ABUSE USING A POSTMARKETING SURVEILLANCE PROCEDURE

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The FDA, in conjunction with the DEA, schedules medications based upon their chemical structure, pharmacological effects, and therapeutic indication. Medications may be scheduled on the basis of the similarity of their chemical structure and therapeutic indication to an already scheduled medication. Strategies for collecting evidence that might be used to request de-scheduling of such a substance are presently being developed. We will report on one strategy that might prove useful. Our ongoing national postmarketing surveillance study is examining reports of street-use of a newly marketed, scheduled, psychoactive agent that appears without abuse potential in both animal and human clinical tests. Treatment centers arc adding a one-page questionnaire to their intake procedure to screen for street-use of the medication and other similar medications. Importantly, the questionnaire assures consistent methods across centers by standardizing the questions posed. Clients are questioned about the medication, other chemically similar medications and a false medication. In addition the clients are queried about what these medications are being sold for on the street and whether use is repeated. Follow-up on potential repeated abuse will use more detailed ethnographic investigations involving the CEWG. This study builds upon other postmarketing studies and will provide important information with which to compare the pre-marketing abuse potential studies and to inform policy decisions about possible de-scheduling.

ASSESSING "DEPENDENCE LIABILITY" OF NEW MEDICATIONS USING THE DRUG EVALUATION NETWORK SYSTEM

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It is not uncommon for the FDA or the DEA to receive reports suggesting that a new medication is being abused on the street. This in turn, leads to the question of whether that medication should be rescheduled for more restrictive prescription practices. Not surprisingly, the manufacturers are reluctant to have their medications "scheduled" since it could restrict sales. The question of abuse liability for a particular drug has typically been decided through formal and informal surveys of addiction treatment professionals to determine if any "cases" of dependence on the drug in question have been seen during a reference period (typically past three to six months). While reasonable, this procedure is slow, inefficient and open to question on sampling grounds. With funding from the ONDCP, we have developed a Drug Evaluation Network System (DENS) that has placed portable computers loaded with patient interviewing software (primarily the ASI) in a developing national sample of 250 treatment programs. These programs administer the interview to all clients who apply for treatment and this information is reported by modem to a single server on a bi-weekly basis. An attractive feature of this software is its ability to insert new questions and instructions into the interview at the point of each modem transfer. Using this system, we asked patients from 41 providers in 5 cities "how many days in the past 30 have you taken XXXXXXX (a new medication)" This system provided us with a sample of 6,500 patients in just 6 months and offered clear indication of the prevalence of use of the new medication. The presentation will discuss the methodological features of the DENS system, its limitations and some suggested procedures for using it to test new drugs for abuse liability.

THE BRIEF SUBSTANCE CRAVING SCALE - MEASURING CRAVING IN A CLINICAL TRIAL

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In an effort to develop a Brief Substance Craving Scale (BSCS) for use in multi-center cocaine clinical trials, a committee of staff from NIDA Medication Development Research Units adapted a previous measure and added new items. The core of the measure consists of 3 questions concerning the "Intensity," "Frequency" and "Length" of craving during the past 24 hours. Each of the 3 questions is answered on a 0-4 Scale, which can be summed to yield a "Total Score" ranging from 0-12. The questions are asked three times, once for cocaine, and twice more for other drugs of abuse. Several additional questions include asking about craving during the "worst" day in the past week. Preliminary data was collected from 124 subjects participating in cocaine clinical trials at three sites. These subjects completed up to three craving ratings per week, yielding 1,451 individual rating sheets for this data set. The following data is, therefore, a summary not for subjects but for ratings sheets. The results indicate that cocaine craving decreased across the course of the 8-10 week clinical trials. In addition to craving for cocaine, the ratings also listed the following second drugs of choice: Nicotine (41%), None (20%), Alcohol (19%), Left Blank (12%) and Marijuana (7%). Contrary to predictions, craving was not worse on weekends. The BSCS was cross validated by correlating the total cocaine craving score with four factors of the Cocaine Craving Questionnaire - General, yielding correlations ranging from .57 to .20. Furthermore, "Total" cocaine craving on the BSCS was related to qualitative cocaine urine results (positive or negative; $r = .25$, $p<.0001$), and quantitative urine BE levels ($r = .28$, $p<.0001$). Conclusion: the BSCS appears to be a valid measure of craving, correlates with actual cocaine use, and allows for the measurement of craving for at least two drugs other than cocaine.

A BRIEF VERSION OF THE ALCOHOL CRAVING QUESTIONNAIRE (ACQ-NOW)?

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A major challenge facing researchers and practitioners is the fact that craving has multiple meanings, thus craving measures should include a number of items covering a broad range of content. On the other hand, clinical utility demands that measures be easy to administer and score, so the development of valid and reliable, brief versions of craving assessments could fulfill both requirements. Secondary data analyses from a preliminary study of the relationship between craving and neurological deficits were conducted to compare the performance of the original Alcohol Craving Questionnaire (47-item, ACQ-NOW-Long Form) with a brief version (12-item, ACQ-NOW-Short Form). Mean scores on the subscales (four factors) were similar in magnitude for both versions, and no differential effects of race/ethnicity, gender, age, or level of education were noted. Regardless of instrument, the most prominent finding was a significant relationship between frequency of daily drinking in the last month with craving and stated intention to drink ("Purposefulness" factor). However, reducing the number of items decreased reliability and adversely influenced validity such that the magnitude of the frequently cited inverse relationship between craving and drinking latency was substantially diminished using the brief version, but not using the long form. Internal consistency reliability on the short form could be enhanced by the addition of one or two items on each of the four factors that would increase the number of questions from 12 to 15-16. The brief form is not recommended for use until these deficiencies are corrected.

MARIJUANA CRAVING QUESTIONNAIRE: DEVELOPMENT OF A NEW CRAVING SCALE

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The Marijuana Craving Questionnaire (MCQ-Now) was developed to measure marijuana craving at the time the questionnaire is completed. The MCQ-Now was constructed based on the premise that drug craving represents a complex set of behavioral and physiological responses controlled by environmental and cognitive processes such that craving is multiply determined and manifested in different ways at different times. The MCQ-Now contains items from the following categories: 1) urges and desires to use drugs, 2) intent and planning to use, 3) anticipation of positive outcomes from using drugs, 4) anticipation of relief from withdrawal or negative mood states, and 5) lack of control over drug use. The MCQ-Now was administered to 217 subjects who reported use of marijuana at least once during the past month. Factor analysis yielded four unique dimensions of craving, similar to questionnaires measuring alcohol, heroin, and cocaine craving. Subjects did not endorse a distinction between craving as a "strong urge only" versus "any urge." Craving scores increased as the frequency and duration of reported craving episodes increased. To our knowledge, this is the first attempt to assess marijuana craving using a multidimensional instrument.

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NEW APPLICATIONS OF STATISTICAL TECHNIQUES TO RELATE SUBSTANCE DEPENDENCE TO CIRCADIAN ACTIVITY RHYTHM IN ADOLESCENTS

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Circadian activity rhythms may reflect aspects of the underlying biology of substance dependence. Body movement counts (activity) in substance using adolescents may differ from controls' activity and may differ by gender. AIMS: We demonstrate how new statistical techniques provide a means of accounting for the often ignored, complicated covariance structures characteristic of longitudinal data, thereby improving precision and power for detecting relationships with other variables and group differences. METHODS: We completed psychiatric assessments and automatically recorded body movement counts from adolescent patients (n=67) in treatment for substance dependence and controls (n=65) during a 28-hour period of controlled activities. Statistical models varying the number of harmonics and covariance structures were compared prior to examining group differences and the relationship of activity to other dichotomous and continuous variables. RESULTS: Using a two-harmonic model accounting for the serial correlation characteristic of longitudinal data, patients have significantly lower activity levels than controls and females have lower activity levels than males. Once the appropriate model for activity data is established, we will examine its relationship to other dichotomous (e.g. presence of withdrawal symptoms) and continuous (e.g. substance dependence severity) variables and illustrate the value of these procedures in substance use research. CONCLUSIONS: We expect to demonstrate with activity data that analytic techniques allowing for modeling of the mean and correlational structure of longitudinal data improve the ability to assess relationships with other variables and group differences.

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ASSESSING MATERNAL PERCEPTIONS OF HARMFUL EFFECTS OF DRUG USE DURING PREGNANCY

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Research has shown that perceived risk is a critical predictor of health behavioral change (e.g., Weinstein, 1988). Drug use risk education is a vital component in many substance abuse prevention and early intervention programs. In pregnant women, perceived risk studies have focused on alcohol and tobacco use. Much less is known about the perceived risk associated with prenatal exposure to illicit drugs and no studies have systematically examined perceived risk in pregnant women who are seeking and not seeking treatment for illicit drug use compared to pregnant women who do not use drugs. The present study administered the Perceived Risk Questionnaire (PRQ), a 17-item tool assessing perceptions of prenatal effects of illicit drug use, to 74 pregnant women seeking prenatal care in urban hospital OB/Gyn clinics. Three groups pregnant women including non-treatment-seeking illicit drug abusing pregnant women, treatment-seeking illicit drug abusing pregnant women and pregnant women not using drugs provided informed consent and completed the PRQ. Results indicated that non-treatment-seeking drug abusing women were less knowledgeable about the risks of low birth weight and believed it was better to have a smaller baby as compared to pregnant non-drug using and treatment-seeking drug abusing women. These results suggest that drug using pregnant women may be less knowledgeable about the potential risks of substance use during pregnancy and that such women may benefit from additional education about the harmful effects of drug use on both mother and child.

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THE FAMILY IMPACT SURVEY: DEVELOPMENT OF A MULTIDIMENSIONAL INSTRUMENT TO MEASURE THE IMPACT OF DRUG ABUSE ON FAMILY MEMBERS

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Existing family assessment tools measure family relationships and functioning. They do not address the variety of special problems faced by family members and significant others (FSOs) of drug users. A comprehensive instrument is needed to objectively assess a wider variety of problems. We have been developing the Family Impact Survey (FIS), a multidimensional instrument that collects standard, comprehensive, clinically-pertinent information about drug and alcohol use of family members and seven problem areas: Emotional, Relationship, Lifestyle, Legal, Financial, Health, and Physical Abuse. We interviewed FSOs and clinical professionals and generated 70 items addressing problems in the seven areas. One hundred and eleven FSOs of a drug or alcohol abuser examined the 70 items and indicated which problems they had experienced. Fifty-four participants provided lifetime information and 57 provided current information (i.e., past 30 days). Almost all FSOs (90 - 100%) reported experiencing lifetime and current problems in emotional, relationship, lifestyle, financial, and health areas. Over half reported lifetime and current problems in the legal and physical abuse areas. FSOs. who were partners or spouses of the drug abuser, reported more current financial problems ($F(2,54) = 5.0$, $p = .01$) and more lifetime relationship ($F(2,43) = 4.4$, $p = .02$) and social problems ($F(2,43) = 4.4$, $p = .02$) than parents. FSOs of male drug abusers reported more financial problems than FSOs of female drug abusers ($F(1,49) = 9.9$, $p > .01$). While the FIS requires further development, early versions of the instrument appear to provide interesting information about the impact of drug abuse on the family members of the drug abuser. The instrument has potential clinical, research, and health policy uses. Test-retest reliability, inter-rater reliability, and validity studies are needed to further develop this instrument and explore its utility.

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EXTENDING THE TIMELINE FOLLOW-BACK INTERVIEW TO ASSESS POLYSUBSTANCE USE AMONG ALCOHOLICS

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An extended Timeline Follow-Back (TLFB) calendar for the previous 90 days was administered to 89 alcohol-dependent clients entering treatment at Smithers Alcohol Treatment and Training Center. Male (75%); African-American (39%); non-Hispanic white (33%); education beyond a high school diploma (44%); government-related insurance (66%). Almost three-quarters (72%) were polysubstance users who used cocaine powder (34%), crack (38%), heroin (11%) and cannabis (26%). One in 5 clients used 2+ illicit drugs in addition to alcohol. Clients drank on over half the days (mean=56%) on which they were not in a controlled environment such as a treatment facility or hospital. For drugs, the mean proportion of exposed days on which users consumed a substance were 25% for powder cocaine, 39% for crack cocaine, 44% for heroin, and 26% for cannabis. The mean number of standard drinks consumed on a drinking day was 13. The mean dollar value of drugs consumed on a using day was $64 for powder cocaine, $86 for crack cocaine, $27 for heroin, and $4 for cannabis. Virtually all polysubstance users (97%) reported sometimes using multiple substances sequentially or simultaneously, rather than on different occasions; but sequential patterns were nine times as common as simultaneous use. Data from biological measures indicated that 23% of detected cocaine users did not report using cocaine. These data suggest that the contemporary polysubstance user poses a major clinical challenge, and that the extended TLFB can be an effective tool for distinguishing types and patterns of polysubstance use to help inform treatment planning.

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SUBSTANCE USE AND OTHER BEHAVIORAL HEALTH CONCERNS IN CHRONIC PAIN PATIENTS: PRELIMINARY REPORT ON THE BEHAVIORAL HEALTH INVENTORY (BHI)

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Many patients adopt lifestyles that cause/exacerbate chronic illness. Screening tools are needed to assist providers in identifying behavioral health problems. The BHI is an 88-item questionnaire designed to assess problem severity in 9 domains: diet, exercise, sleep, smoking, ETOH, drug (RX, OTC & illicit), prevention, adherence, and motivation to change health habits. To validate the BHI, it was administered to 263 chronic pain patients who were 45 years of age, 62% female, 60% white (29% black) with back pain (40%), MDPS (10%), and neuropathic pain (8%). Overall Quality of Life (QOL) was poor (4/5) with exercise, sleep, smoking, and diet/weight control showing the greatest problem severity. Scale reliability (ALPHA) ranged from .7713 (Diet) to .9932 (Smoking) for scales with homogeneous content and from .502 (Drug) to .652 (Adherence) for scales with heterogenous content. Factor analysis yielded 3 components accounting for 61% of the variance. Using stepwise regression smoking, drug problems, and poor motivation predicted ETOH abuse whereas poor adherence and sleep disturbance predicted drug problems. Nicotine dependence was predicted by health risk-taking and ethnicity (non-black). Cluster Analysis generated 3 groups. Group 1 had multiple health concerns, moderate drug (but no ETOH or nicotine problems), poor adherence, but willingness to change. Group 2 was comprised of substance abusers with high smoking and drug severity, moderate adherence severity and willingness to change. Group 3 had low behavioral health severity, low nicotine and drug severity (but moderate ETOH severity), minimal adherence problems and little willingness to change. These findings demonstrate the potential utility of the BHI in medical settings as a screening tool for substance abuse and other behavioral health problems.

NEUROPSYCHOLOGICAL ASSESSMENT OF AIDS PATIENTS WHO ARE CHEMICALLY DEPENDENT: THE NATIONAL NEUROAIDS TISSUE CONSORTIUM BATTERY

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We present a battery developed by a consensus committee of the National NeuroAIDS Tissue Consortium for evaluating cognitive changes associated with HIV infection. In contrast to many earlier batteries, which focus on detecting early and frequently subclinical impairments in patients without substance use issues, the present battery is designed for patients with AIDS and is suitable for patients with or without chemical dependency issues across a broad range of impairments. Other characteristics are: brevity of administration, usefulness for serial administration, and incorporation of instruments not previously available. There is a core component, taking about 40 minutes and an optional component taking an additional 15 minutes.

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SUBSTANCE ABUSE AND PERSONALITY DISORDERS: A META-ANALYSIS

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Personality disorders (PDs) among substance abusers have received attention for methodological reasons and as treatment prognosticators. Meta-analysis is a quantitative tool for examining hypotheses across studies and populations. This paper reviews the literature to test moderator variables in PD rates in studies from 1980-97. Inclusion criteria: use of a DSM-based categorical diagnostic system and publication in English. Exclusion criteria: Use of the MCMI or an incarcerated population. Partitioning of chi-squares (Hedges&Olkin 1985) was used to test hypotheses about moderator variables.Results:85 studies of substance abusers and 12 studies using general community samples were identified. Rates of PDs were 2.4-13 times higher among treatment-seeking substance abusers than in general community samples. The mean prevalence rate of ASPD in community-based samples of substance abusers (16.4%) was significantly different from treatment-entering samples (26.2%; χ^2=340.35, p<.0001). Gender-related differences in PDs followed expected lines. Samples of opiate abusing subjects were associated with lower rates of PDs than cocaine or alcohol using subjects with the exception of ASPD. Chart review resulted in lower rates than interview-based methods. Clinical applications will be discussed.

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SUBSTANCE DEPENDENCE SEVERITY SCALE (SDSS): RELIABILITY AND VALIDITY OF A CLINICIAN-ADMINISTERED INTERVIEW FOR DSM-IV SUBSTANCE USE DISORDERS

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To demonstrate the effectiveness of treatments for drug dependence and abuse, reliable and sensitive measures of change and outcome must be used. Without such measures, even a good treatment cannot be shown to be effective, since measurement problems may obscure the occurrence of true change. While a DSM-IV diagnosis of substance dependence is a consistent way of conceptualizing patient status, no diagnostic interview assesses severity of dependence based on the common language of DSM-IV criteria across a range of substances. The Substance Dependence Severity Scale (SDSS) was designed to serve this purpose, consisting of substance-specific scales of both severity and frequency of DSM-IV criteria. This study investigated the reliability and concurrent validity of the SDSS. The test-retest reliability of the SDSS in 175 (112 male and 63 female) treated substance users ranged from good to excellent for alcohol, cocaine, heroin and sedatives (ICC's = .75-.88 for severity, .67-.85 for frequency). Results for cannabis were lower, ranging from fair to good (ICC's =.50-.62). The joint rating reliability of SDSS audio taped interviews was excellent for all substances (ICC's ranging from .92-.99). The internal consistency reliabilities of severity and frequency variables were good to excellent for alcohol, cocaine and sedatives (alphas ranging from .85-.91) and fair to good for heroin and cannabis (alphas ranging from .75-.87). Concurrent validity data will also be presented and scale applications, particularly involving the use of the SDSS in treatment outcome studies, will be discussed.

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STANDARDIZING DATA DICTIONARY, DOCUMENTING SUBSTANCE ABUSE STUDIES AND FACILITATING THE RESEARCH ACTIVITIES

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Over the years, the Treatment Research Institute at the University of Pennsylvania and DeltaMetrics, Inc. have successfully implemented a large number of studies of substance abuse treatment outcome evaluation using the Addiction Severity Index and the Treatment Services Review. To facilitate data analysis and dissemination of the research findings, efforts have been made to create central data registries, and to document the studies. The first issue that had to be tackled was the heterogeneity of the database management systems developed over the years by different designers and developers in different software packages. As a solution, standard dictionaries were created and applied to the central data registries which combine the data from all of the studies. To facilitate the data analysis and project management, documentation of the projects and data has been created in two versions: a paper version and an electronic version. The electronic version was created in HTML so that it can be accessed using the internet browsers. The documentation consists of six sections: 1. Overview of the projects, which includes the information about the principal investigators and key personnel, purpose of, methodology and types of instruments used in each of the studies, and projected and actual number of clients enrolled; 2. Data usage policies; 3. Procedures for safeguarding data; 4. Central data registry dictionaries; 5. Code list for the identifier variables in the Central Data Registries and; 6. Appendices that include all the instruments used in each of the studies. The central data registries and the dictionaries now serve as a template such that data collected by other organizations as well as by TRI can be merged together. They will continuously be updated to reflect the progress of the data collection and research activities.

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TECHNOLOGY TRANSFER: USE OF AN EXCEL SPREADSHEET FOR CALCULATING ASI COMPOSITE SCORES

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The Addiction Severity Index (ASI) is an instrument utilized clinically by practitioners throughout the drug and alcohol treatment field for purposes of detecting and measuring the severity of clients' problems in seven areas: medical, employment, alcohol, drug, legal, family/social and psychiatric. The ASI is also utilized for research purposes to measure change or evaluate treatment outcomes. One way of evaluating treatment outcomes with the ASI is through the calculation and analysis of composite scores. These Scores were empirically developed and mathematically derived by combining items in each of the seven ASI problem areas to achieve a single score for each area *in* a range from 0 to 1. The composite scores are generally utilized by scientists and researchers using statistical programs to analyze ASI data for research purposes. The presentation will demonstrate an easy to use, clinically relevant, Microsoft® Excel-based program for use by counselors and practitioners to calculate ASI composite scores. In addition, normative data will be incorporated into the program to allow for interpretation of scores for clinical use. The presentation will also provide information to guide practitioners in understanding and utilizing individual client and program-level ASI data.

INVESTING TREATMENT PROGRAMS IN RESEARCH: A SURVEY OF PROGRAM DIRECTORS IN THE DRUG EVALUATION NETWORK SYSTEM

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Treatment Research Institute at the University of Pennsylvania, Philadelphia, PA and *the National Center for Addiction and Substance Abuse at Columbia University (CASA), New York, NY

In an effort to identify factors which motivate substance abuse treatment programs to participate and remain invested in research and study protocols, a survey was conducted with directors in 25 programs participating in the Drug Evaluation Network System (DENS) study. The program directors responded to questions regarding the benefits of their participation in the study, as well as providing feedback on the usefulness of the DENS ASI software and the quarterly reports they receive. This presentation will review results of the survey, highlighting factors which directors identified as having motivated them to become involved in the research study. In addition, the presentation will review the incentives incorporated into the study design which we believe are related to high agreement rates from programs approached to participate. DENS is an ongoing, nationwide electronic system providing standardized, timely, clinical and administration information on treatment programs and their patients. The primary source of data collection of DENS is the Addiction Severity Index (ASI). Forty treatment programs throughout the country have completed participation in piloting the system. DENS will be expanding to include a nationally representative random sample. During expansion, the study design and procedures will include those factors identified by the survey as motivating programs to continue participation.

DEVELOPING A "UNIVERSE" OF TREATMENT PROGRAMS TO PROVIDE A NATIONAL RANDOM SAMPLE FOR DRUG ABUSE RESEARCH: AN EXAMPLE FROM THE NATIONAL DRUG EVALUATION NETWORK SYSTEM-DENS

C. Royer-Malvestuto, D. Carise, A. T. McLellan, M. Love, and M. Edwards

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This presentation will provide a useful illustration for health services researchers who want to sample treatment programs in major metropolitan areas. The Drug Evaluation Network System (DENS) is an ongoing, nationwide electronic system in substance abuse treatment programs in five major metropolitan areas. Currently in 40 treatment programs, representing four modalities, (methadone maintenance, inpatient/residential, outpatient and intensive outpatient abstinence oriented), DENS is planning an expansion to include a nationally representative sample, as well as representative samples of 10 major cities. To select a representative sample, the "universe" of treatment programs must be defined. Currently, there is no single source providing this "universe" of treatment programs. Our development of this "universe" began with SAMHSA's National Directory of Drug Abuse and Alcoholism Treatment and Prevention Programs; however, this was not a complete listing of all available treatment programs. Sources such as the traditional Yellow Pages, Infospace, the internet Business Directory Yellow Pages, the National Clearing House for Alcohol and Drug Information, lists from other large scale studies, and listings available for some states from NASADAD state directors were also reviewed. This presentation will review the procedures for developing this "universe" of treatment programs and will illustrate how easily different studies can produce very different estimates of the "universe" of treatment programs. We wilt also provide an example of this procedure in a specific city.

VARIATIONS IN STRUCTURE, ORGANIZATION, STAFFING PATTERNS, AND FINANCING IN A SAMPLE OF TREATMENT PROGRAMS USING THE ADDICTION TREATMENT INVENTORY

L. Nickell, D. Carise, A.T. McLellan, M. Love, T. Coyne, and M. Edwards

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Substance abuse treatment programs differ greatly in terms of their organizational structure, staffing mix, financing, and services delivered. The Drug Evaluation Network System (DENS) is a nationwide electronic tracking system that provides standardized, timely information on patients entering into substance abuse treatment. One of the objectives of DENS is to collect information about the structure, organization, and function of participating treatment programs to allow comparison between treatment programs, and to monitor the development and adaptability of substance abuse treatment programs in this changing world of health care. Last year, researchers from TRI developed and piloted a questionnaire based on aspects of treatment programs including IRS status and affiliation, capacity, intensity, and length of the program, types of treatment, patient demographics, staff demographics, activities and services offered, and sources of payment. Since then, the survey has been revised to incorporate feedback from researchers and end-users. This presentation will discuss the feedback from other researchers and end-users as well as resulting changes 'made in the instrument now called "The Addiction Treatment Inventory." The revised instrument and data from over 40 SDU's will be presented.

INCREASING THE EFFICIENCY OF CLINICAL TRIALS: A SOFTWARE PACKAGE FOR EXPEDIENT DATA MANAGEMENT

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Inefficient data management practices can significantly increase the time and financial costs associated with clinical trials. Two years devoted to evaluating the practices of a data management center has yielded a software program, the Cincinnati Teledata Manager (CTM-2.0), that optimizes the speed and accuracy of data processing. Based on an evaluation of data management practices, as well as experience with prototypes of the CTM program, CTM-2.0 was designed to automate many tasks that were traditionally completed by data staff, resulting in a more expedient data management process. Moreover, CTM-2.0 was designed for maximal versatility so that computer programming is not required to customize the program for a particular setting or study. This versatility was accomplished by providing a window-driven process by which the user can define the essential components of a study (e.g., study phases, CRFs, collection schedules, participant identifying information) as they pertain to a particular center or study. Additional features of CTM-2.0 include a sophisticated data tracking system, automatic checks of CRF and data entry errors, and automatic generation of data management aids and summary reports. With the use of CTM-2.0, a data staff consisting of three full-time-equivalent personnel should be able to manage data, including double data entry, from multiple moderately sized (i.e., around 20,000 CRFs expected per trial) clinical trials and should be able to provide analysis-ready databases approximately one month after the final data are collected.

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DIFFERENCES IN LIFETIME PREVALENCES OF DRUG DEPENDENCY DISORDERS IN FIRST-DEGREE RELATIVES OF DRUG-DEPENDENT PATIENTS

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Increasing evidence of a genetic basis underlying the chemical dependency disorders has included demonstrations of family clusters of affected individuals for specific drug types. However, the prevalence of chemical dependencies and the inheritance pattern in individual family members has not been ascertained. We interviewed and administered detailed questionnaires to 311 consecutive human volunteers. Using the Addiction Severity Index (ASI) as well as DSM-IIIR and DSM-IV criteria to establish past or current diagnoses of drug dependence, patients were categorized into groups based on predominant drug preference. The final groups were defined as *O*, or primarily chronic opiate addiction with or without other drug use (n=103); *DA*, or non-opiate drug abuse or dependence (n=73); or *Normals,* a control group for subjects with no drug history (n=114). There were no significant demographic differences among the three groups. Detailed and standardized family histories were taken, obtaining such information as geographical origins, medical background, and drug histories for individual family members. Family tobacco use histories were also taken, in order to compare family reports of drug use with a less stigmatized addictive substance. Results suggest that siblings of affected patients are three to five times more likely to be reported as having chemical dependence disorders than siblings of normal controls ($p < 0.0001$ by Chi-square analysis). Fathers and mothers of affected patients are at least one and a half times more likely to be reported as having drug abuse and dependency disorders than fathers and mothers of controls; however, this finding did nor reach statistical significance. Similar results were found for tobacco use in family members. All of these findings appear most strongly in the opiate-addicted group. These results should help shed light on family patterns of drug dependence disorders, and suggest that psychoeducation and/or early intervention in siblings of patients with known drug dependency disorders may be clinically beneficial. Future work will focus on the validity of using individual family member histories to identify family phenotypes in studies of heritable factors that contribute to drug dependence.

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EFFECTS OF PARENTAL HISTORY ON DRUG ABUSE SEVERITY AND TREATMENT OUTCOME

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Influence of parental substance abuse was examined on severity of drug use and methadone maintenance therapy (MMT) outcome in 234 probands meeting DSM-IIIR criteria for opioid dependence (mean age 37.2, 64% male, 53% Caucasian) and having no other current DSM Axis I psychiatric disorders. Parental problems were identified from Addiction Severity Index items that inquire about need for treatment in biological relatives. High sensitivity and specificity were found between parent diagnoses based on ASI items and DSM-IV alcohol and drug dependence criteria. No effect of having a mother or father with alcohol or drug problems was found on any sociodemographic measure except race, which was adjusted for in subsequent severity and outcome analyses. Parental history positive (PHP) probands had an earlier age of first heroin use and more DSM-IIIR opioid dependence symptoms but otherwise did not differ from parental history negative (PHN) probands on other drug severity measures (including number of treatment episodes). Interestingly, PHP probands had significantly more total DSM-IIIR diagnoses ($p=.003$) and symptoms not attributed to substance abuse ($p<.001$) than PHN probands. Generalized estimating equations (GEE) were used to examine family history influences on illicit drug use (determined by urinalysis) during the first 5 weeks of MMT (50 mg/day). Although PHP probands had higher scores at admission on several opioid severity measures, PHP probands had significantly lower rates of illicit opioid use during MMT than PHN probands ($p=.007$). In contrast, while PHP and PHN probands did not differ on any cocaine severity measure at admission, PHP probands had higher rates of illicit cocaine use during MMT than PHN probands ($p=.03$). These different results of family history on illicit opioid and cocaine use during MMT may be related to the specificity of methadone in the treatment of heroin dependence and to the interaction of methadone with genetic factors that underlie susceptibility to heroin dependence.

TREATMENT ENTRY UNDER CONDITIONS OF TREATMENT ON DEMAND: PRELIMINARY RESULTS

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San Francisco has dramatically expanded substance abuse treatment services. Since 1998, an 800 additional treatment slots have been made available on a monthly basis. The present study attempts to determine the factors associated with treatment entry among long-term injection drug users (IDUs) in San Francisco during this period. In the first half of 1998, IDUs (n=594) were recruited and interviewed regarding drug preference, frequency of use, drug treatment history, and health status, among others. Booth and colleagues (1998) modified Motivation Scale was used to measure readiness to change drug use (reference available from first author). Sixty respondents were randomly selected and the CSAS data was searched to determine preliminary rate of treatment entry. Multivariate analysis of factors associated with readiness to change drug use were conducted on overall sample (n=594). Bivariate analysis was conducted to determine variables associated with treatment entry among a random sample of 60 respondents. Socio-demographic characteristics of the total sample were as follows: 48% African American, 37% white, and 9% Hispanic; 29% female; 9% HIV positive; and 47% homeless. Half reported using heroin most frequently, followed by crack (20%), speedball or cocaine (10%), and amphetamines (6%). Only IDUs who had a drug injecting steady sex partner (AOR=4.08; 95% CI=1.3, 12.8) and who would accept a drug treatment slot if it were available the next day (AOR=15.0; 95% CI=4.85, 46.6) were found to be ready to change drug use. No variables were associated with treatment entry among the random sample, although 76% had entered drug treatment by the end of 1998. The treatment entry rate was high in the random sample. The complete data set is required to determine treatment entry rates and assess factors associated with treatment entry in this sample.

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FREE TREATMENT OUTCOMES FOR OPIATE USERS: A SUMMARY OF FOCUS GROUPS

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This qualitative study was designed to examine the reasons why opiate users who are offered free treatment have different outcomes regarding treatment entry and retention. Previous research shows that some opiate users stay in methadone maintenance programs beyond a free 90-day time period, while others either drop out before 90 days or fail to begin treatment altogether. Variables that predict these differences include stage of change to quit drugs, previous treatment experience, desire for treatment, and ASI scores on drug, alcohol, legal, medical, social and family problems. In order to further investigate these findings, six focus groups were conducted among the following groups, separated by gender: opiate users offered free treatment for 90 days who remain beyond 90 days, opiate users offered free treatment who drop out before 90 days, and opiate users offered free treatment who fail to enter. All subjects (n=23) were recruited for an ongoing study and all were offered free methadone maintenance for 90 days. Recruitment took place through street and community outreach in Denver, Colorado. Subjects were pre-screened for eligibility and then asked to participate in a paid, hour-long focus group. Results complement quantitative data currently being collected by this same research group. Focus groups are a useful tool to examine the opiate user's in-depth perspective on treatment decision-making. The personal opinions and comments provided by these participants give answers to questions that are not readily answered through quantitative means. The results of these focus groups have generated hypotheses for further studies: do family and other support systems facilitate treatment entry for addicts and if so, how can researchers access them? What is the profile of the "junkie mentality", and how can treatment address that in counseling? In what way can barriers to treatment, such as *side effects, withdrawal,* and *lifetime addiction to methadone,* be addressed to make treatment more attractive for opiate users?

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NOVELTY-SEEKING PREDICTS DIFFERENTIALLY EARLY VERSUS LATE DROP-OUT IN A HEROIN-DEPENDENT POLY-SUBSTANCE ABUSE POPULATION

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The role of novelty-seeking (NS) in predicting drop-out was examined in a heroin dependent poly-substance use population. Sixty-eight participants were enrolled in a 6-month contingency management study and received buprenorphine and cognitive-behavioral treatment. Early unexpected findings (Helmus *et al.,* 1998) suggested that those high on NS were more likely to stay in treatment than those low on this measure in the first five weeks of the study. All participants filled out the Tridimensional Personality questionnaire at the beginning of the study and the total score for the NS subscales was used for the analysis. Participants also had urine drug screens three times per week. Results indicated that those high on NS had lower retention rates (22%) than those low on NS (50%), $X^2(1)=5.76$, $p<.05$. However, a proportional hazards model with time dependent covariates resulted in a significant NS and NS by Time interaction ((-2LL=316.38; overall $X^2(2)=12.53$, $p<.01$)), indicating that those high on NS show greater retention early in treatment but this effect reverses over time. In the first eight weeks of treatment, those with some poly-drug negative screens had higher NS scores than those with all positive drug screens, $F(1,39)=4.80$, $p<.05$. There were no significant urine drug screen differences on NS later in treatment. These findings suggest differential treatment approaches such as incorporating novel components throughout the program to engage the novelty-seeking individual.

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SEXUAL ACTIVITY UNDER THE INFLUENCE OF DRUGS IS COMMON AMONG METHADONE CLIENTS

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Despite a recent increase in research concerning the sexual behavior of injection drug users (IDU), the relationship between sexual behaviors and drug use is poorly understood. Eighteen male and 13 female IDU in methadone maintenance for over 12 months were administered a newly developed structured interview concerning drug use and sex. Use of heroin, cocaine, and cannabis in the prior 6 months was common ranging from 77.8% for cannabis use by men to 33.3% for cocaine use by men. Of the men reporting heroin use, 30% indicated they combined heroin use and sex in the prior 6 months, and for all these men the use represented a relapse from a period of non-use. Of the men reporting cannabis use, 57.1% indicated they combined cannabis use and sex in the prior 6 months, and for 37.5% of these men the use represented a relapse. The women combined sex and drugs infrequently in the prior 6 months. For 14 (77.8%) men and 10 (76.9%) women their most recent sexual experience included substance use by them or their partner. For 5 (27.8%) men and 5 (38.5%) women, the most recent sexual experience had been over one year ago. Three (16.7%) men and 2 (15.4%) women indicated the combining of sex and drugs during their most recent sexual experience represented a relapse to drug use. Nine (50%) men and 12 (92.3%) women indicated an enhanced sexual experience associated with the use of drugs during their most recent sexual experience in which drugs were used. Only 4 men (22.2%) and 6 women (46.2%) indicated sexual impairment associated with the use of drugs during the most recent sexual experience in which drugs were used. Only 8 (44.4%) men and 3 (23.1%) women indicated they had had at least one sexual experience in the past year without being under the influence of drugs. Three (60%) of five men who had sexual experiences in the past year both under and not under the influences of drugs rated the experience under the influence of drugs more pleasurable. In the prior 6 months, 5 men (27.8%) and 4 (30.8%) women said they were tempted to use drugs to enhance sexual experiences or increase the likelihood that a sexual encounter would occur. These findings suggest that even for clients maintained for over a year on methadone, sex and drug use are often still intertwined, and may contribute to relapses and drug use urges.

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COSTS AND BENEFITS OF METHADONE TREATMENT FOR WOMEN AND MEN WHO LEFT BEFORE OR WERE STILL IN TREATMENT AT FOLLOW-UP

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Longer lengths of stay in methadone treatment have been associated with greater treatment benefits and reductions in heroin use. As a companion study to a cocaine treatment, cost-benefit analysis conducted for NIDA's Drug Abuse Treatment Outcome Study (DATOS), this cost-benefit analysis has been conducted to determine returns from investments in methadone treatment for opioid users. It was hypothesized that methadone treatment benefits regarding costs of crime to society before, during, and after treatment would differ by gender, and crime cost savings would be greater for those who were still in treatment at follow-up. Subjects were 394 methadone patients from 8 cities and 16 programs; overall 37% were women, 33% African American, with an average age of 37.2. Women had greater reductions in crime costs than men, and net social benefits were greater for women. Longer retention or greater lengths of stay in treatment were associated with greater percent reductions and greater crime cost savings. It was concluded that methadone treatment provides significant returns on treatment investments.

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ENHANCED OUTREACH COUNSELING: AN INTERVENTION TO RE-ENROLL DISCHARGED METHADONE PATIENTS INTO TREATMENT

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Within a few months following discharge from methadone maintenance treatment (MMT), the majority of ex-patients resume opiate use and many engage in risk activities such as needle sharing and crime. In a pilot study with discharged opiate dependent male veterans, we were able to re-enroll 44% in a MMT program by actively helping ex-patients to re-enter treatment. The current replication study is designed to track and intervene with patients discharged from both a VA and a community-based MMT program. To date, we have obtained consent from 733 active patients enrolled in MMT permitting a free, confidential 3-month post-discharge check-up. Overall 14% (N=105) of patients have been discharged and 49 received a 3-month post-discharge baseline assessment. Following the baseline assessment, ex-patients who reported drug use (N=28) were randomly assigned to receive either a passive referral (PR, n=9) to drug treatment services or enhanced outreach counseling (EOC, n=19) provided by a case manager who helps the person access treatment services. The case manager assists clients in overcoming both internal (i.e., lack of motivation) and external (i.e., funding) barriers associated with treatment entry. At baseline, 68% of ex-patients were using IV drugs and they reported an average of 4 days of illegal activity in the last month. Six-week post-baseline data show that approximately one-third of the EOC patients returned to treatment compared to none of the PR patients, indicating at least preliminarily, that EOC may be an effective intervention strategy for discharged methadone patients. Six-month data will allow a comparison of patient functioning across the two conditions and assess any residual effect of the intervention.

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PARTICIPATION IN A PROGRAM FOR MMTP DROP-OUTS AND PRELIMINARY OUTCOMES

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Hvpothesis: A program for MMTP drop-outs was implemented to help them reduce their drug use, reenter drug treatment, and reduce HIV risk behaviors. It was hypothesized that the program's 3 components (street outreach, cognitive behavioral group counseling sessions, and individual counseling sessions) would achieve high participation levels and be effective in accomplishing these goals. Methods: *Subjects:* Thus far, 250 MMTP dropouts have been recruited: subjects are 70% male, 49% Hispanic, 32% African -American and mean age is 40. *Procedures:* Drop-outs (who left MMTP within the prior year) are recruited through MMTP clinics and the streets and randomly assigned to the intervention or comparison condition. Six- and 12-month follow-up interviews are conducted. *Statistical Analysis:* Repeated measures analysis of variance. Results. *Participation:* Almost all subjects (88%) had at least one post-recruitment outreach contact, 60% attended at least one group and 29% had at least one individual session; 96% were exposed to at least one component of the intervention and 26% were exposed to all components. Outcomes: Preliminary outcomes of six-month follow-up data indicated there was a significant group X time interaction for 30-day mean frequency of heroin injection, with a significant decline for the intervention group (13.9 to 5.5 compared to a change from 2.8 to 10.3 for the comparison group, $p<.05$). Importance of Findings: MMTP drop-outs can be engaged in this intervention. Preliminary data show promising results in terms of frequency of injection, an important HIV risk behavior.

METHADONE TREATMENT OUTCOMES IN THE NATIONAL TREATMENT IMPROVEMENT EVALUATION STUDY (NTIES)

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Hypothesis: The benefits of outpatient methadone treatment (OMT) for discharged clients with less than one year of treatment may be of relatively short duration. Procedures: In a re-analysis of data from the National Treatment Improvement Evaluation Study (NTIES), N=422 OMT clients were assessed for drug use, HIV/AIDS risk behaviors, criminality and employment/support over the 12 months prior to admission and 5 to 20 months prior to follow-up (FU). Four groups were assessed: I. Maintenance/Short FU (Maintenance/Short) - Continued in treatment till FU (Median stay =16.4 months, Median number of months assessed at FU=6.0 months, N=144); 2. 3-12 Month Stay/Short FU (3-12/Short) - (Median Stay=6.6 months median FU=6.2 months, N=98); 3. 3-12 Month Stay/Long FU (3-12/Long) - (Median stay=5.1 months, Median FU= 11 months, N=85); 4. <3 Month Stay/Long FU (<3/Lang) - (Median stay=1 month, Median FU= 11 months). Reported drug use and other behaviors over time were compared for these groups using Cochran Q. Logistic regression (LR) was also used to assess the likelihood of each behavior at follow-up for the Maintenance/Short, 3-12/Short and 3-12/Lang relative to <3/Lang. Controlled were admission characteristics e.g., age gender, education, race and prior alcohol/drug treatment, in addition to the respective behavior at admission. Results: Relative to the <3/Lang, reductions in drug use, HIV risk, and criminality were consistently found for Maintenance/Short clients and to a lesser extent 3-12/Short, but not the 3-12/Lang. For example, Maintenance/Short clients were more likely to report no heroin use at FU (OR=6.7, p<.001), as were 3-12/Short clients (OR=3.1, p<.01), but not 3-12/Lang. Maintenance/Short only were more likely to report no cocaine use(OR=2.3, p<.05). In direct comparisons, the 3-12/Short group had consistently more favorable outcomes than the 3-12/Long. Long FU data were not available for Maintenance clients. Conclusions: The treatment benefits with 3-12 month stays arc significant, but tend to persist for relatively short FU periods only, e.g., 6 months.

A TWELVE-YEAR FOLLOW-UP OF A METHADONE MEDICAL MAINTENANCE PROGRAM

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Methadone Medical Maintenance (MDM) is an alternative for treatment of stable methadone maintained individuals. It involves a monthly physician's visit at which methadone take home doses are dispensed to last until the next appointment. The safety and efficacy of this treatment modality is currently under investigation. The purpose of this study was to evaluate the long-term safety and efficacy of MDM in a methadone program in Baltimore. A sample of 21 patients was enrolled in the study and followed for 12 years. They were evaluated once a month by a primary care physician affiliated with a methadone clinic who collected urine toxicology samples and dispensed the monthly methadone dose. The results showed that only 6 (28.6%) patients dropped out during the 12 years of the study. Twelve (0.5%) of 2,290 urine samples collected were positive for drugs. No methadone overdose or diversion was observed. Participants reported significant improvement in their quality of life. The results of this study support the safety and efficacy of medical maintenance of stable methadone maintained individuals.

RELATIONSHIPS BETWEEN A GENERAL HEALTH STATUS MEASURE (SF36) AND THE ADDICTION SEVERITY INDEX

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The objective of this study was to identify relationships between a genera1 measure of health related quality of life (HRQOL) and the Addiction Severity Index (ASI) in a substance abuse treatment program. The Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36) measures HRQOL in eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental. The Addiction Severity Index (ASI) is a commonly used psychosocial measure in substance abuse and could be considered a disease-specific instrument for addiction. Significant negative correlations between the different domains of the two instruments were considered to suggest that similar aspects of HRQOL were being measured. Data for 58 patients were collected during a double-dummy, double-blind, randomized clinical trial involving patients receiving treatment for opiate dependence. The SF-36 was self-reported by patients on a computer. The ASI was completed by a trained interviewer. Pearson correlations were calculated between different domains. The drug use scale of the ASI was found to be significantly correlated with the vitality scale of the SF-36 (r = -0.257). The family social relationships and psychiatric status scales of the ASI, were significantly correlated with the role physical scale, respectively (r = -0.277, -.450), vitality (r = -0.274, -0.597), social functioning (=-0.286, -0.564) role emotional (= 0.302, -0.481), and mental health (-0.335, -0.603) scales of the SF-36. The psychiatric status scale of the ASI was significantly correlated with the bodily pain (r = -0.316) and general health (r = -0.271), scales of the SF-36. ASI medical status scale was not significantly correlated with any SF-36 domain. The significant correlations identified suggest that the ASI psychiatric status and family/social domains measure aspects of HRQOL that are also measured within certain domains of the SF-36. The SF-36 appears to measures unique aspects of medical status not addressed by the ASI.

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YEARS OF POTENTIAL LIFE LOST AMONG NARCOTIC ADDICTS

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The objective of this paper is to examine the leading causes of premature mortality in a cohort of narcotic addicts and compare results with those observed among the general US population, so as to assess the extent of potential life lost due to narcotic addiction. This is a longitudinal prospective study comprising of a group of 581 male narcotic addicts in California followed over 33 years. In the latest follow-up conducted in 1997/1998, 282 were found dead (confirmed by death certificates). We calculated years of potential life lost (YPLL) before 65 years. YPLL/1000 was calculated for each of the leading causes of premature mortality in the cohort and compared with national values. Analysis of variance was carried out to assess ethnic differences in the cohort. On average, potential life lost before 65 in our cohort was 18.73 years (SD=10.80 years), which was significantly higher than the national average. The total YPLL for the cohort was 5345, 20.36% of which was as a result of heroin overdose, 14.57% chronic liver disease and 10.18% homicide. T-test was carried out to compare national figures with our cohort in terms of cause-specific YPLL/1000 rates. The difference was significant for all categories with p values ranging .0059 to .0001. The causes of death with the highest discrepancy in YPLL/1000 between our cohort and the national population were unintentional injuries, homicide, liver disease, and heart disease. There was significant ethnic variation in YPLL between whites (n=142; $\underline{m}$ = 20.97, SD=10.84) and Hispanics (n=113; $\underline{m}$ = 17.92, SD=9.94). Analysis of variance yielded an F-statistic of 5.40 with a p-value of 0.02. In conclusion, the YPLL among this narcotic sample was much higher than in the national population; premature mortality was even higher among white addicts. Intervention to curtail narcotic addiction is needed to prevent premature deaths.

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CEREBRAL PERFUSION ABNORMALITIES IN ABSTINENT COCAINE USERS WITH HIV

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Previous neuroimaging studies using nuclear medicine techniques have shown perfusion changes, with reduced regional cerebral blood flow (rCBF) in the cortex and the basal ganglia, in cocaine users and patients with HIV. The goal of this study is to evaluate whether there are differences in rCBF abnormalities between HIV patients with and without a history of cocaine-dependence using perfusion magnetic resonance imaging (pMRI). Methods: We evaluated 28 HIV positive patients (12 with and 16 without cocaine dependence), and 14 healthy control subjects using pMRI. After injection of a paramagnetic contrast agent (Gd-DTPA), the rCBF was calculated from the signal time course based on the tracer kinetic theory. The rCBF maps were transformed into Talairach space for group comparison using SPM96. Results: The rCBF values were statistically significantly lower in the lateral prefrontal cortices bilaterally and in the anterior cingulum in both HIV patient groups. Both temporal parietal brain regions, however, showed increased rCBF. The changes in rCBF in the corresponding brain regions correlated with the severity of the disease (measured by plasma viral load and HIV dementia scale). No differences between the two HIV patient groups were detected. Discussion: Our results arc consistent with findings from PET and SPECT studies showing perfusion deficits in patients with HIV. A larger sample size will be needed to delineate whether the cocaine-dependent subjects have more severe deficits. Perfusion MRI is cost-effective, fast, safe, and offers additional functional information even in patients with normal appearing structural MRIs; therefore it may be useful for monitoring the disease severity or the effects of therapy.

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CONDOM USE IN A SAMPLE OF DETOXIFIED HEROIN AND COCAINE ADDICTS IN THE BRONX, NEW YORK IN 1998-99

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The objectives of this presentation are to analyze the impact on condom use of a wide range of social statuses and past behaviors that are not subject to change; and to explore the additional impact of constructs drawn from four social psychological theories: The theories of reasoned action; planned behavior; interpersonal behavior; and the modified health belief model. Data presented here were collected as part of a larger study of persons seeking detoxification from heroin and cocaine/crack in two hospitals in The Bronx, New York. The dependent variable is condom use in the 30 days following discharge from the hospital. Independent variables are all measured at baseline. Four logistic regressions are conducted, one for each theory tested. Fully, 51% of the respondents had never used condoms in the past 30 days. Thirty-nine percent thought that they had no chance of becoming infected with HIV. Consistent with other studies, individuals who were HIV+ were more likely than others to use condoms. As predicted by the theory of reasoned action, and the theory of planned behavior, intention to use condoms, normative beliefs, and self-efficacy are significant predictors of condom use. Logistic regression shows that constructs drawn from both of these theories account for a significant improvement of the model. The high proportion of those who believe that they are at no risk for HIV infection, in spite of injection and/or sexual practices that are risk factors for spread of the disease, indicates the need for development of new interventions. Constructs of the theories identified would make promising targets for such interventions.

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A COMPARISON BY GENDER OF THE MAIN EFFECTS OF A BRIEF HIV INTERVENTION WITH A LONGER PERSONALIZED SKILLS BUILDING APPROACH

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A randomized field experiment was conducted with a sample of 376 out-of-treatment substance abusers to investigate differences by gender with regard to drug and sexual risk indices, and measures of distress before and after a brief and longer intervention. We conducted t-tests to measure statistical reliability, and then focused on the effect sizes to measure practical significance. Substance abusers in both interventions significantly reduced their drug use, particularly with regard to crack use among females. However, those in the longer intervention made greater strides specific to reducing alcohol, heroin, and other cocaine use. Substance abusers in both interventions reduced their overall needle use and risk. However, males, who were the majority of needle users (62% vs. 36%) reported greater changes, particularly those in the longer intervention. Substance abusers in both interventions significantly reduced their percent of unprotected sex. However, the effect was stronger among females regardless of the length of intervention. Although substance users in both interventions reduced trading sex behaviors, women, who were the majority of those trading sex for drugs, demonstrated the greatest reductions regardless of the length of intervention. Males in the longer intervention reported the largest decline in drug use at the same time as sex. Overall, both females and males in the longer intervention reported the largest reductions in the distress indices with the most dramatic decreases among females. In summary, differences in response to the interventions were detected by gender, indicating a need for interventions that address the specific concerns and issues of each gender. This was particularly true for reduction of distress, where women demonstrated higher baseline levels of distress and striking decreases in distress after participation in the longer intervention. Contact the lead author for measures and references.

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GENDER DIFFERENCES IN HIV RISK AMONG CRACK SMOKERS IN TREATMENT

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Gender differences found in an HIV-risk instrument development project were examined. The instrument being developed in a pen-and-paper assessment of HIV risk for crack cocaine smokers. HIV risk constructs for which gender differences were examined included: Self Efficacy: Sex, Crack, Sex and Crack (SE), Response Efficacy: Sex, Crack, Sex and Crack (RE), Interpersonal Efficacy: Sex, Crack, Sex and Crack (IE), Sexual Negotiation (SN), Commitment: Sex, Crack (CM), Attitudes Toward Condoms: Self, Partner, Overall (AC), and Self Control (SC), and Risk Awareness (RA). The sample of 155 participants was 48% female and 43% African American. Average time in drug abuse treatment was 40 days. Significant differences for gender were found for the following constructs with women having higher risk than men: SE-crack (t=-4.015, df=150, p=0.000); SE-sex and crack (t=-2.080, df=142, p=0.039); AC-partner (t=-4.000, df=137, p=0.000); AC-overall (t=-2.608, df=132, p=0.010); CM-crack (t=-3.900, df=152, p=0.000); IE-crack (t=-2.012, df=151, p=0.046). Men perceived themselves to be at higher risk (RA) for HIV risk associated with smoking crack after leaving treatment than did women (t=2.874, df=150, p=0.005). A high-risk profile was defined as having one or more of the following behaviors: trading sex for crack or crack for sex, crack use at least daily, injection drug use, 8 or more partners in past 6 months, less than 50% condom use. There were no gender differences in risk profiles. It was concluded that, of crack smokers in treatment, women were at higher risk for HIV than men; therefore, HIV interventions offered in substance abuse treatment programs should be gender-tailored to address this difference.

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DOES COCAINE DEPENDENCE PREDICT CHANCES IN HIV RISK BEHAVIORS? AN OBVIOUS, YET UNEXAMINED QUESTION

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Severity of drug use and drug abuse/dependence are critical factors in determining outcome among drug users yet many drug abuse studies do not include these measures. In this study, we examined the effect of dependence, as measured by the American Psychiatric Association's official criteria (DSM-IV), on change in HIV risk behaviors after 3 months. Over 1300 out-of-treatment crack/cocaine users from four NIDA Cooperative Agreement Sites (Lexington, Raleigh-Durham, San Antonio, and St. Louis) were randomly assigned to the NIDA standard or an enhanced HIV risk reduction intervention. The sample was divided into three risk categories to examine behavior change: those who 1) stopped the risk behavior, 2) maintained low risk or reduced risk, and 3) maintained high risk or increased risk. Individuals who came into the study with more cocaine use symptoms were more likely than individuals with fewer problems to increase their crack/cocaine use or trade sex for drugs or money at a 3 month follow-up. Users assigned to the enhanced intervention were more likely than those assigned to the standard intervention to improve. When all other variables like gender, ethnicity, age and intervention status were taken into consideration, the severity of the cocaine problem remained the most important predictor of behavior change. These findings indicate: 1) the serious need to add drug addiction treatment of interventions aimed at reducing HIV risk behaviors, and 2) the need for more focused HIV prevention interventions for women.

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COCAINE DEPENDENCE AND HIV RISK REDUCTION AMONG INDIGENT DRUG USERS IN RIO DE JANEIRO

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Brazil is second in terms of reported AIDS cases, with 145,327 cases identified through November 1998. Although injection drug use accounts for some 20% of those cases, drug users have not been extensively targeted by HIV prevention studies. The HIV/AIDS Community Outreach Project in Rio de Janeiro was established in 1994, to develop, implement, and evaluate a community-based HIV/AIDS intervention program for indigent cocaine users. A second purpose was to gather clinical information on the extent of drug abuse/dependence in the target population using a modified version of the DSM-IV. This interview was conducted as part of the baseline assessment of all clients between September 1996 and June 1997. Of the 336 who enrolled, 49.1% met the criteria for cocaine abuse or dependence. Compared with DSM-IV data collected on low-income cocaine users in the U.S., the proportion of the Brazilian sample reporting each of the criteria for cocaine dependence is significantly lower, and appears to be a function of differing economic circumstances. Because of extreme poverty of much of the Brazilian sample, many lack the resources to consistently purchase cocaine. When the total U.S. sample is compared only with the 55 Brazilian clients in the highest wage category, the differences in DSM-IV dependence criteria numbers 3, 5, and 7 become non-significant. Economic conditions clearly play a role in the lower levels of cocaine dependence observed in the Brazilian sample. As such, this should *not* be taken as evidence of less serious problems with cocaine among the Brazilian clients. Clearly, this indigent population is in need of HIV and drug prevention services and is seriously underserved by current health promotion efforts. Of the 245 clients who completed a 3- month follow-up interview, participation in the intervention was associated with significant decreases in cocaine use for both dependent and non-dependent clients.

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FREQUENCY OF INJECTION OF PUERTO RICAN IDUs IN PUERTO RICO AND IN NEW YORK CITY

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Frequency of injection has been found to vary markedly across geographic and ethnic/racial lines. This study compares the frequency of injection between Puerto Rican injection drug users (IDUs) in Puerto Rico and in New York City and aims to identify the factors that account for the difference in injection frequency between the two groups. A total of 269 IDUs have been recruited and assessed in both sites (115 PR, 154 NYC) using similar sampling procedures and the same interview protocol. Interview questions ascertained frequency of injection over the previous 30 day period and on the last day of injection, drugs injected, doses of injection, current enrollment in Methadone Maintenance (MM) as well as demographic and socioeconomic information. Statistical analyses employed analysis of variance and linear multiple regression. IDUs in Puerto Rico reported more days of injection in the previous 30 days (27.6 vs. 18.7, $p < 0.001$) and more injection episodes per day (5.1 vs. 2.6, $p < 0.001$) than their counterparts in New York City. In the multivariate analysis, the factors found to account for the difference in injection frequency between the two sites were injection of cocaine, injection of heroin, current enrollment in MM, and dose of injection. Both maximum and minimum dose of injection were positively associated to frequency of injection. These findings suggest the need to further investigate the nature of the association between dose injected and frequency of injection.

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HIV RISK BEHAVIORS AMONG RECENT AND MORE REMOTE INITIATORS OF DRUG INJECTION IN BAYAMON, PR AND NEW YORK CITY

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In Puerto Rico, as in the US mainland, IDUs have changed some of their HIV risk behaviors. These changes have been most pronounced for injection behaviors, although changes in sexual risk behaviors have also been reported. However, several studies have shown that new recruits continue to enter the IDU population and that those who have recent-onset of injecting are more likely to engage in HIV risk behavior than more remote-onset injectors. Their study is in search of understanding the prevalence of HIV risk behaviors among recent-onset injectors (5 years of injecting) in Bayamón, Puerto Rico and in New York City. IDUs were grouped according to number of years since onset of injection, 5 years or less (126) and 6 years or more (510). The sample comprises, 19.8% recent-onset injectors and 80.2% remote-onset injectors. Recent-onset injectors were more likely to be female and younger than remote-onset injectors. Recent-onset injectors were more likely to begin using drugs on a regular basis (21.7 vs. 18.7, injecting at a later age (27.7 vs. 18.8) and injecting more frequently than remote-onset injectors (137.3 vs. 105.9), but less likely to be in Methadone medication (25.4 vs. 45.3). None of the differences in injection risk behaviors were statistically significant. We regressed each one of the HIV risk behaviors against years since onset of injection; only frequency of injection showed a linear trend of reduced injection frequency with years of onset of injection. In Puerto Rico, as in New York, the quality of street heroin since the middle 1980s is sufficiently strong in that drug effects can be obtained through intranasal use. The fact that recent-onset injectors inject so frequently suggests that by the time they become injectors, they already were heavy drug users. Information of the circumstances under which the extended period of non-injection is sustained is critically needed to be able to formulate and develop effective interventions to arrest the path of young drug users into drug injection.

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DRUG USE PATTERNS AMONG NEWLY INITIATED INJECTION DRUG USERS BEFORE AND AFTER INTRODUCTION OF A NEEDLE EXCHANGE PROGRAM

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Objective: Baltimore introduced a needle exchange program in 1994. We examined drug use behaviors associated with initiation of an injecting career among young injection drug users (IDU) before and after introduction of NEP. Methods: Adolescent and young adult IDU (15-30 years) who initiated injection drug use <=5 years prior were prospectively studied. Year-by-year drug use histories were reconstructed over the 5-year period preceding and following initiation of injection drug at baseline. We compared drug use patterns among IDUs who initiated before (1992-94) vs. after NEP opened (1995-97), using chi-square tests and logistic regression. Results: To date, among 143 IDU, 63 % were female, and 68% were African American. Median age and age at initiation were 24 and 22 (range 10-30), respectively. In comparing IDU who initiated injection drug use before (n=51) vs. after NEP opened (n=92), a higher proportion had an increased frequency of injection in the period before vs. after the opening of NEP (75% vs. 59%, respectively, p=0.05). Similarly, among those who snorted heroin prior to initiation of injection (n=134), a higher proportion reported continued use of heroin in the period prior to NEP opening vs. after (83%) vs 60%, p=0.005). Proportions engaging in needle sharing and shooting gallery use did 'not differ significantly between the two periods (p>0.05). Adjusting for age at initiation, IDUs were 2.4 times more likely to have a short period of transition to injection in the period prior to NEP vs after NEP opened. Conclusion: We found no evidence to suggest that introduction of NEP in Baltimore was associated with an increase in injection frequency, or a shorter transition period from non-injection drug use to injection among young drug users.

EVALUATION OF A PROCEDURE THAT INCREASES RETENTION IN FOLLOW-UP STUDIES OF I.V. DRUG USERS AT RISK OF HIV INFECTION

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Background: Follow-up studies of intravenous drug users (IDUs) are needed to evaluate public health interventions and vaccine or drug trials. Retention is a critical issue in such studies.**Objective & methods:** To evaluate a stepwise procedure directed at improving the 6-month retention, we analyzed the number of participants retained at each step and their characteristics, in a follow-up study of 263 seronegative IDUs at high risk of HIV-infection. Subjects were recruited from September 1997 to June 1998 in community settings in Philadelphia. Retention procedure: At -2 weeks, a reminder letter was sent; participant was phoned at -1 week and at -1 day or day 0. If participant failed to complete or reschedule visit, the following steps were taken until 6-month visit was completed: during week +1: letters to participant at all contact addresses and daily calls; during week 12: outreach visit, letters, and at least 2 calls to participant and his/her contacts; starting at week +3: weekly calls and outreach visits, monthly letters, complemented by attempts to locate subject at shelters, food lines and prisons. **Results:** As of December 1998, 93% of the subjects completed a 6-month visit: 49% returned on time, 32% returned within 1 month of scheduled visit, and 12% beyond 1 month. Subjects lost to follow-up were more likely than those retained to have a high-school degree and to have moved frequently during past year. By contrast, subjects who returned with delay were more likely to have a low income and to live a distance from the study center. Overall, subjects did not differ regarding their drug habits. **Conclusion:** Although return diminishes at each step of increasing effort, sustained retention effort is required to conduct valid follow-up studies among IDUs at high risk of HIV infection. Socio-demographic characteristics are correlated with retention, and differ between participants late for scheduled visits and those lost to follow-up. Absence of correlation between retention and drug-related behavior might be due to our selection of subjects who were all at high risk of HIV infection.

LONGITUDINAL PATTERNS OF HIV RISK BEHAVIORS AMONG INJECTION DRUG USERS

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The main purpose of this paper is to describe the longitudinal behavioral patterns of drug injection and risky sexual practice among drug users (IDUs). A total of 415 IDUs were assessed every six months over 4 years. Drug injection and sexual behavior were used as the markers. Drug injection was coded as Yes or No. Risky sexual practice was defined as having multiple partners without consistent use of condoms. Four behavioral patterns were defined using data from pairs of contiguous assessments: 1) Initiation of safer practice, 2) Consistently risky practice, 3) Relapse into risky practice, and 4) Maintenance of safer practice. The results showed that proportions of IDUs reporting drug injection and risky sexual practice substantially decreased over the study period. Data indicated that proportions of IDUs who maintained safer practice increased over time both for drug injection and risky sexual practice. However, a substantial number of IDUs continued to engage in risky behaviors. A certain number of IDUs relapsed into risky behaviors after initiating safer practices during the study period. The findings of this study should be confirmed because the study sample may not be well representative.

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GENDER DIFFERENCES IN DRUG USE PATTERNS AND SUCCESSFUL REFERRALS TO DRUG TREATMENT AMONG BALTIMORE NEEDLE EXCHANGE PARTICIPANTS

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OBJECTIVE: To study gender differences in drug use, drug treatment referrals, and entry into drug treatment among Needle Exchange Program (NEP) participants in Baltimore, MD. **METHODS:** Between 08/94 and 02/97, NEP participants underwent a registration interview on demographics and drug use history. In addition to needle exchange and HIV testing, off-site drug treatment was also available during this time period. We compared drug use history, injection frequency at baseline, subsequent drug treatment referrals, and entry into treatment by gender. Data were analyzed using Wilcoxon rank-sum, paired t-tests, and chi-square statistics. **RESULTS:** Of 5,286 participants, 25% were female, 89% African-American, 32% HIV age was 39 years. Compared to male NEP attenders, females were younger ($p<0.001$), initiated injection drug use later in life ($p<0.001$), and subsequently had a shorter duration of drug use ($p<0.001$); but current injection frequency did not differ by gender. A higher proportion of female NEP attenders requested and were given referrals for off-site drug treatment relative to men (11% vs. 8%, $p<0.001$). However, among those referred, a significantly lower proportion of females actually entered drug treatment relative to men (23% vs. 76%; $p=0.023$). **CONCLUSION:** Although female NEP attenders had been injecting for a shorter duration and were more likely to request drug treatment referrals, females were significantly less likely to enter drug treatment relative to males. These findings suggest that 1) drug use histories differ by gender, and thus NEP-related services may need to be gender-specific; and 2) despite availability of drug treatment, significant barriers impede entry into drug treatment for female NEP attenders. Further study of these gender-specific issues is required to facilitate successful drug treatment.

DOES INTRODUCTION OF A NEEDLE EXCHANGE PROGRAM RESULT IN INCREASED CRIME IN NEEDLE EXCHANGE PROGRAM AREAS?

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The objective of this study was to compare crime patterns in Needle Exchange Program (NEP) areas with crime patterns in non-NEP areas, before and after introduction of NEP. It has been hypothesized that introduction of NEP may be associated with increased crime in NEP areas. Arrest reports were collected from the Baltimore City Police Department by location of arrest and were grouped into four categories. Arrests categories included drug possession (heroin, cocaine, and paraphernalia), economically-motivated (break-ins, theft, prostitution), resistance (resisting arrest, assaulting a police ofticer, parole violation), and violent (murder, assault, rape, robbery) arrests. Poisson regression was used to model the number of each category of arrests over time and log likelihood ratio tests were used to determine if the time trends in arrests within a 0.5-mile radius of NEP areas were significantly different than in non-NEP areas. The Poisson regression analysis did not show any significant differences in time trends in arrest frequency between NEP and non-NEP areas ($p>.05$). The data suggest that the current pattern of crime in Baltimore has not been significantly intluenced by the opening of NEP sites.

NEEDLE EXCHANGE AND HEALTH CARE UTILIZATION PROMOTE ENTRY INTO DETOXIFICATION

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Objective: To identify predictors of entry into detoxification programs among a prospective cohort of injection drug users (IDU) in Baltimore, MD. Methods: 1483 IDU undergoing semi-annual HIV tests and interviewer-administered questionnaires were studied between 1994-1998, which corresponded to the period when a needle exchange program (NEP) opened in Baltimore. Behavioral data were lagged one visit to assess potential impact on entry into detox at each subsequent visit. Logistic regression was used to identify predictors of entry into detox, adjusting for correlation between serial measures, and stratifying by HIV serostatus. Results: Similar proportions of HIV-negative (SN, n=1053), and HIV-seroprevalent (SP, n=430) subjects reported ever entering detox (26% and 23% respectively). After accounting for recent drug use, hospital admission was associated with four-fold increased odds of entering detoxification for HIV-seronegative subjects. Among HIV-infected subjects, hospital admission, outpatient medical care and having health insurance independently increased the odds of entering detoxification. After accounting for these and other variables, needle exchange attendance was also independently associated with entering detoxification for both HIV-infected [Adjusted Odds Ratio (AOR)=3.2] and uninfected IDUs (AOR=1.4). However, among HIV-infected subjects, the increased odds of detoxification associated with needle exchange diminished significantly over time, concomitant with statewide reductions in detoxification admissions. Conclusions: Health care providers and needle exchange programs represent an important bridge to drug abuse treatment for HIV-infected and uninfected IDUs. Creating and sustaining these linkages may facilitate entry into drug abuse treatment and serve the important public health goal of increasing the number of drug users in treatment.

CHARACTERIZATION OF OPIOID SUBSTITUTION PATIENTS REFERRED FROM NEEDLE EXCHANGE

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The primary goal of community needle exchange programs (NEP) is to reduce the risk of transmission of HIV and other blood-borne diseases among injecting drug users. NEPs can also serve as a vector for referral into more intensive treatment modalities. Relatively little is known about the clinical characteristics and psychiatric profiles of drug abusers enrolling in community needle exchange programs. A report by Brooner, *et al.* (1998) analyzed both baseline characteristics and short-term treatment outcomes of 82 NEP referrals to an outpatient methadone agonist treatment program. The present report includes analysis of an expanded sample of NEP referrals (N=146), and presents a more detailed baseline characterization of these patients. Problem severity was measured using the ASI, while diagnosis of substance use and non-substance use psychiatric disorders was performed using the SCID-I and SCID-II. Compared to new admissions referred from other sources, NEP-referred patients were predominantly older, minority, unemployed males with higher problem severity at baseline. Baseline criminal behavior and psychosocial problem scores were higher in NEP-referred patients, as was baseline drug use severity. Other than a lower lifetime prevalence of mood disorder in the NEP-referred patients, the prevalence of comorbid non-substance use psychiatric disorders was similar in both groups. This report indicates that patients referred to treatment by Baltimore NEP comprise a highly impaired subset of injection drug users.

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MEDICATION MANAGEMENT FOR HIV-POSITIVE DRUG ABUSERS

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We report preliminary outcomes from behavioral therapies development study that is generating a new psychosocial treatment to improve adherence to AIDS medications in drug users. Subjects are from the first of 4 planned cohorts in a study of 40 HIV+ substance abusers receiving antiretroviral therapies in methadone maintenance. They were prescribed a mean of 7 medications, taking 16 pills or capsules daily. The project refines the medication management through an iterative process of trial application and revision of the intervention. Procedures involved research intake followed by 4 weeks of baseline measurement, 8 weeks of medication management, and 4 weeks of follow-up. Medication adherence was measured using several methods. Results with the first cohort indicate a need to improve medication adherence and that the medication management intervention was associated with improved adherence in some areas:

	Baseline	During	Post	Follow-up
Doses taken yesterday	80%	76%	93%	89%
Followed special instructions	60%	65%	89%	82%
Taken as scheduled	63%	50%	100%	50%

Importance of work: Drug abuse treatment programs increasingly provide care to patients with HIV/AIDS. Patients are receiving more complicated HIV-related prescriptions; yet noncompliance to the medications is significant, resulting in drug resistance, exacerbated illness and medical costs. This Stage I behavioral therapies development project develops, refines, and pilot-tests a medication management intervention and develops measures to assess its efficacy and cost-effectiveness.

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LAAM AND METHADONE MAINTENANCE TREATMENT: RETENTION, DRUG USE AND HIV RISK BEHAVIORS

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This is a report on preliminary, second year findings of a four year shady comparing the differential effects of methadone and levo-alpha-acetyl methadol (LAAM) on retention in treatment, drug use and HIV risk behaviors among heroin addicts. This study recruited 315 addicts in the Los Angeles area and randomly assigned by a 2:1 ratio to either methadone or LAAM maintenance. The study sample is 18%) white, 40% African American and 37% Latino. Women comprise 29% of the sample. One hundred thirty-six clients have reached their one year anniversary date. Fifty-two percent of the methadone maintenance subjects completed treatment, compared to 62% of the LAAM maintenance subjects (p=NS). Incarceration continues to be the primary reason for discharge. There was less heroin use at six month follow-up by the LAAM clients (71% vs. 86%, p=.019) though equivalent crack cocaine use (40% vs. 33%, p= NS). With regard to HIV risk behaviors, there was less drug injection for the LAAM clients (69% vs. 85%, p=.020), though equivalent use of bleach to clean needles. Condom use and number of sex partners were similar across groups.

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EFFICACY OF BUPRENORPHINE TREATMENT IN REDUCING DRUG- AND SEX-RELATED HIV RISK BEHAVIOR AMONG OPIOID-DEPENDENT INDIVIDUALS

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We examined the relative efficacy of three dosing schedules of buprenorphine maintenance treatment in reducing HIV risk behavior among opioid-dependent individuals. Participants were randomly assigned to either receive their maintenance dose (either 4, 8, 10 or 12 mg, SL) daily, 3x per week (Double dose on Mon. and Wed.; Triple dose on Fri.), or 2x/week (Quadruple Dose on Mon.; Triple Dose on Fri.). Participants were administered the HIV Risk-Taking Behaviour Scale (HRBS) at study intake and at 7 timepoints during their 24-week maintenance treatment. The HRBS is a self-report measure that provides composite scores of both drug-related and sex-related HIV risk behavior. Preliminary results from 69 participants (n=24, 20, and 25 for daily, 3x/wk and 2x/wk dosing conditions, respectively) indicate that participants in all conditions demonstrated significant reductions in their drug-risk composite score during treatment ($p = .0001$), as well as in their frequency of needle use ($p = .0001$) and needle sharing ($p = .0001$). Individuals on a 3x/week dosing schedule showed significantly greater 1) reductions in needle use ($p = .00053$) and 2) movement directly from a high- to a low-risk state of HIV-risk behavior relative to those in the daily and 2x/week dosing conditions. Females reported significantly greater needle cleaning ($p = .0550$); however males were significantly less likely to re-use needles ($p = .05$). A significant time effect was found for condom use ($p = .0254$); however, this effect was not due to increased condom use; rather, it resulted from a large number of transitions during treatment from "not always using condoms" to "having no regular partner". Thus, preliminary results suggest that buprenorphine treatment and less-than-daily dosing schedules decrease drug-related HIV risk behavior among those in treatment.

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HIV SEROPREVALENCE, RISK BEHAVIOR, AND THEIR ANTECEDENTS IN METHAMPHETAMINE USERS - PRELIMINARY RESULTS

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The objectives of this study were, in methamphetamine users newly admitted to outpatient treatment, to estimate HIV seroprevalence and the association between sexual risk behaviors and possible, antecedents, including addiction severity and psychopathology. Ninety methamphetamine dependent subjects were recruited upon admission to the Drug Detoxification, Rehabilitation and Aftercare Program of the Haight Ashbury Free Clinics, Inc. HIV serostatus was assessed by ELISA with Western blot confirmation. Sexual risk behaviors were assessed with the Risk for AIDS Behaviors and the Behavior Correlates Survey. The Addiction Severity Index was used to quantify the degree of addiction; the Millon Multiaxial Clinical Inventory-Ill, the Brief Symptom Inventory, Beck Depression Inventory, and Utah Criteria for Attention Deficit Disorder were used to assess psychopathology. Subjects were 77% male and 23% female. Sixty percent were Caucasian, 10% Latino, 8% Asian/Pacific Islander, 7% African-American, and 2% Native American. Mean age was 33 years +/- 7 years and the sample was 55% heterosexual, 32% homosexual, and 12% bisexual. Usual route of administration was smoking in 35%, injection in 33%, insufflation in 27%, oral in 4%, and other in 2%. Twenty-nine percent were HIV+. Subjects reported a mean of 1.8 +/- 3.2 sexual partners in the last month and 49% reported inconsistent condom use. Psychopathology appeared to be prevalent in this sample, although measurement may have been confounded by methamphetamine intoxication or withdrawal. In correlation/regression analyses no predictor variables were significantly associated with a summary measure of sexual risk.

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THE ROLE OF GENDER AND POSTTRAUMATIC STRESS DISORDER STATUS ON HIV RISK BEHAVIORS AMONG INJECTION DRUG USERS

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To gain a more complete understanding of the relationship between injection drug use and risk for HIV infection, gender-specific differences in HIV risk behaviors among patients with psychiatric and drug use comorbidity need further study. This study examined the role of gender and Posttraumatic Stress Disorder (PTSD) status on HIV risk behaviors among 179 injection drug users enrolled in a randomized clinical trial of two methadone treatments. Patients were interviewed using the Diagnostic Interview Schedule, Addiction Severity Index, Beck Depression Inventory, and Risk of AIDS Behavior measures. Generalized linear models were used to assess the relationship between gender, PTSD, and HIV risk behaviors. Results indicated that women were more likely than men to receive a lifetime diagnosis of PTSD ($p < .001$) and to engage in risky injection drug use practices ($p < .001$). Although drug use severity was associated with riskier injection drug use among men ($p < .01$), women had higher mean risky injection drug use scores. A positive relationship was found between drug use severity and risky injection drug use practices for those without PTSD ($p < .05$), however; the PTSD group had higher mean risky injection drug use scores. Higher levels of depression were also associated with more risky injection drug use ($p < .001$). Risky sex behavior increased as a function of depression for those without PTSD ($p < .001$) but decreased for those with PTSD. These findings clearly indicate the need to assess HIV risk behavior patterns and psychiatric status of patients entering drug abuse treatment programs. Knowledge about how gender and PTSD contribute to specific patterns of risky behaviors may inform the development of HIV risk education programs for those who inject drugs.

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GAMBLING PROBLEMS IN SUBSTANCE ABUSERS ARE ASSOCIATED WITH SEXUAL RISK BEHAVIORS

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The purpose of this study was to evaluate the association between gambling problems and HIV risk behaviors in substance abusers, Subjects were 134 substance abusers recruited by advertisement from treatment programs and the community. Gambling problems were assessed using the South Oaks Gambling Screen (SOGS), and 24% scored in the range of probable pathological gamblers. Severity of drug and psychosocial problems were assessed via the Addiction Severity Index, and HIV risk behaviors were evaluated using the HIV Risk Behavior Scale. Problem gambling substance abusers were more likely to be male than non-problem gamblers, but no other differences in demographic characteristics or drug use variables were noted. Subjects with a gambling problem consistently reported more risky sexual behaviors than subjects without a gambling problem. Specifically, problem gamblers tended to report having more sex partners than non-problem gamblers. They also were less likely to use condoms with casual sex partners and more likely to exchange sex for money or drugs. Stepwise logistic regression confirmed the association between severity of gambling problems and more risky sexual behaviors; higher SOGS scores significantly predicted having more than 50 sex partners, exchanging sex for drugs/money, and engaging in anal intercourse. Subjects with gambling problems also scored lower than subjects without a gambling problem on the HIV Risk Knowledge Test. These data suggest that gambling problems among substance abusers may be a risk factor for contracting HIV. Screening and treatment for gambling problems among substance abusers arc needed.

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SUBSTANCE ABUSING AIDS PATIENTS: THE NEW MEDICAL UNDERCLASS?

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Substance abusing Aids patients present a complicated set of problems for drug treatment professionals. This poster reports treatment outcomes (N=79) for individuals entering a nursing home specializing in the treatment of substance abusing AIDS patients. The following questions are addressed: What arc some of the long-term consequences related to treating impoverished substance abusing AIDS patients'? What arc their chances of moving from welfare to work? Will poor AIDS patients, reliant on protease inhibitors, become a new medical underclass? These questions are addressed by examining changes in self-esteem, psychosocial functioning and medical status between baseline and eight months into treatment. Results indicate CD4 cell-count, self-esteem and medical status improved while viral load decreased. Despite these gains, patient demographics provide little hope for transition to gainful employment following drug treatment.

ACTIVATION OF THE VENTROMEDIAL PREFRONTAL CORTEX CORRELATES WITH GAMBLING TASK PERFORMANCE: A PET-FDG STUDY

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Lesions of the ventromedial prefrontal cortex (VmPFC) impair performance on a task that requires choices between small short-term gains and larger long-term losses (Gambling Task) (Bechara *et al.,* 1998). We previously reported impaired performance of polydrug abusers on this task (Grant *et al.,* in press). Since continued drug use despite adverse consequences is a central part of definitions of addiction, these findings suggest the hypothesis that dysfunction of the VmPFC may play a role in drug abuse. We have now begun FDG-PET studies to determine whether the VmPFC contributes to Gambling Task performance in intact individuals. In two sessions, approximately 1 week apart, subjects performed a computerized version of the Gambling Task and a computerized control task identical to the Gambling Task except that it lacked the decision-making element of the Gambling Task. In the 7 subjects studied to date, performance on the Gambling Task was positively correlated with metabolic activity in the VmPFC ($r = +0.87$, $p < 0.01$). These results complement studies in brain-lesioned patients in providing further support for the hypothesis that the VmPFC plays a critical role in decision-making processes.

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Grant, S.J.; Contoreggi, C.; and London, E.D. Drug abusers show impaired performance in a laboratory test of decision making. NeuropsYchologia, in press.

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RISK AND PROTECTIVE FACTORS FOR ILLEGAL DRUG USE AND THE DEVELOPMENT OF SUBSTANCE RELATED DIAGNOSES

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Within the project Longitudinal Analysis of Drug Abuse (LADA), data of the first survey were examined with regard to risk and protective factors for illegal drug use. Analyses were conducted for non drug users versus drug users and secondly comparing drug users without and with substance related DSM-IV diagnosis. Independent variables considered are retrospective data about family risk factors (e.g. parents problems with drugs and family relationship), the use of legal drugs (alcohol and cigarettes), deviant behavior and ADHD symptoms. To avoid mutual effects between risk factors and the use of illegal drugs only events, which occurred by age of 10, were included. Controlling for age effects we used survival analysis in combination with a logistic model separately for men and women. In a first step, univariate analyses were carried out. Secondly, significant variables were classified with regard to different domains (family, legal drugs, deviant behavior, ADHD) and analyzed by multiple logistic model. In a final step, a summarizing model was tested, including significant variables of the four domain related models. Comparing non drug users to drug users, risk factors for drug use are separation or divorce of parents, low family cohesion, deviant behavior, and symptoms of hyperactivity. The prognostic factors were slightly different for women and men. Differences were seen with regard to the range of odds ratios (men: 1.31 up to 2.52; women: 1.66 up to 5.27). Comparing drug users with and without diagnosis, for men, the use of legal drugs does no longer represent a risk factor, whereas mother's problems with legal or illegal drugs seems to be important with regard to the development of a DSM-IV diagnosis. For women separation of parents and alcohol intoxication were significant predictors for drug diagnosis. Odds ratios for women are slightly higher than for men (women: 1.51 to 2.31; men: 1.34 to 1.98). As we continue this line of research, we will examine other possible predictor variables such as traumatic experiences during childhood, which are seen to increase the

RAPID CONFIRMATION/QUANTITATION OF COCAINE AND BENZOYLECGONINE IN URINE UTILIZING HPLC AND TANDEM MASS SPECTROMETRY

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A rapid, but sensitive and selective method for confirmation and quantitation of benzoylecgonine and cocaine in urine by fast-gradient liquid chromatography/tandem mass spectrometry [LC/MS/MS] is described. The chromatographic separation was performed on a reversed phase column [Advantage Basic: 50-mm x 2.0-mm i.d.] employing fast-gradient techniques. The initial mobile phase was held constant for 0.5 min and consisted of 90% pH 4.0 HPLC Grade H_2O [pH adjusted with formic acid and ammonium hydroxide] and 10% HPLC Grade Acetonitrile. The gradient was ballistically ramped to 10% pH 4.0 HPLC Grade H_2O: 90% HPLC Grade Acetonitrile over 1.0 min, held for 1.0 min and stepped down to initial proportions at 2.1 min. Matrix prepared standards, blanks, and QC's were filtered through a MILLEX®-GV 0.22 µm filter unit, delivering 300-µL aliquots into a 96 well-plate. Injection volumes of 25-µL were made onto the analytical column, with the flow diverted from the atmospheric pressure ionization source for the first 0.5-min of the analysis. Simultaneous multiple reaction monitoring (MRM) of three discrete reactions for each compound were used to identify benzoylecgonine and cocaine. Quantitation was achieved utilizing the most prominent parent-daughter transition and internal standard calibration techniques [cocaine-d_3: IS]. Calibration curves produced for benzoylecgonine and cocaine ranged from 7.5-1000 ng/mL. The coefficients of variation for the analysis of these drugs ranged from 0.6 to 6.8% at a concentration of 150 ng/mL [n = 155]. This method suggests that fast-gradient liquid chromatography/tandem mass spectrometry may be suitable for routine confirmation of immunoassay cocaine-positive samples.

AGGRESSIVE BEHAVIOR AND OPPORTUNITY TO BUY DRUGS

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Epidemiological studies conducted by Robins, Kellam, and others link youthful aggression and deviance to illicit drug use. The underlying mechanisms remain unclear; some investigators (e.g., Jessor, Crowley) stress the possibility that drug use is just one manifestation or complication of a more general problem behavior syndrome or conduct disorder. In this work, we test the complementary hypothesis that aggressive youth are more likely to be approached with offers to buy drugs. We were able to test this hypothesis via logistic regression analyses of self-report data from a nationally representative sample of 12-17 year old youths (n=4373), a subset of participants in the 1996 National Household Survey on Drug Abuse. These youths completed the Achenbach Youth Self Report, which yields national norms and scores on an 'Aggressive Behavior' subscale. Separately, youths were asked whether they had been approached by someone trying to sell them illegal drugs in the past 30 days. The estimated probability of being offered a chance to buy drugs ranged from 7% for youths at the lowest quintile of the aggression score versus 27% for the most aggressive youths. Making statistical adjustments for age, sex, and race, we found the most aggressive youths were nearly 5 times more likely to be offered drugs for purchase (aOR=4.71; $p<0.001$). The same strength of association was observed when we matched youths on neighborhood to constrain local area differences (e.g., drug availability, police presence). Adjusting for score on the 'Delinquency' subscale decreased the strength of the association somewhat, suggesting that some of the excess risk may be due to conduct problems rather than aggression 'per se'. This study's evidence does not contradict theories that place a problem behavior syndrome or conduct disorder in a central position, but rather prompts new ideas about how aggression and drug use might be linked. One testable hypothesis is that aggressive and/or delinquent youths are more likely to enter micro-environments where drug dealing is more prevalent. Alternately, their observable behaviors (e.g., rowdiness) or physical appearance (e.g., clothing, tattoos) might function as signs of willingness to try drugs. These results add to our understanding of links between aggression, delinquency, and drug use. and introduce a new line of epidemiological inquiry focused upon drug purchase opportunities.

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXIII. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEIMS OF DRUG DEPENDENCE (1999)

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THE DRUG EVALUATION COMMITTEE (DEC) AND ITS MEMBERSIHP

Two groups are involved with the evaluation of compounds which may have analgesic activity, one at the School of Medicine. Virginia Commonwealth University (VCU). in Richmond (Drs. Mario Aceto, Ed Bowman, Louis Harris. and Everette May). and the other at the University of Michigan Medical School (UM) in Ann Arbor (Drs. James Woods. John Traynor, and Gail Winger). The Stimulant/Depressant Testing Groups are at the University of Mississippi Medical School (Dr. William Woolverton), the University of Michigan Medical School (Drs. Gail Winger and James Woods). and at the Louisiana State University Medical Center (Dr. Charles France and Lisa Gerak). Dr. T. Cicero retired as DEC Chair, and became an *ex officio* member. Dr. J. Woods now serves as the DEC Chair, and I am the Biological Coordinator. The members of the DEC are the aforementioned Drs. M. Aceto, L. Harris, J. Woods, J. Traynor, G. Winger, C. France, W. Woolverton, T. Cicero, and A. Jacobson, as well as Drs. P. Beardsley (VCU), and A. Coop (University of Maryland, School of Pharmacy, Baltimore).

The DEC, which evolved from a 1929 Committee on Drug Addiction in the Division of Medical Sciences of the National Research Council, National Academy of Sciences (Jacobson. 1997; May and Jacobson, 1989), is now sponsored by the CPDD and reports annually to the CPDD's Liaison Committee for Drug Testing and Evaluation. Its Chair. Dr. A. Young. relates DEC work to the CPDD Board at its Annual Meeting. The DEC invites representatives from NIDA, FDA, DEA, and the CPDD's Liaison Committee for Drug Testing and Evaluation, as well as its Industry Relations Committee (Dr. R. Mansbach, Chair) to attend the DEC meeting which is held during the CPDD's Annual Scientific Meeting. Two other DEC meetings are usually held during the year to discuss its work.

DEC has prepared a brochure, which describes its work and membership; it will be distributed at the CPDD meeting in Acapulco, and copies are available on request. The compounds evaluated by the DEC are listed in a database, Analgesic, Stimulant and Depressant Drug Indices, on the CPDD web site (http://views.vcu.edu/cpdd/DEC/index.html). In that database. the publication year for all of DEC's evaluated compounds is listed, and, thus. the original data can be more easily located. Also available on that site is a history of DEC, and the DEC Biological Coordinator's Annual Reports from 1990-1999 which lists the molecular structures and DEC data on the compounds released for publication during that decade.

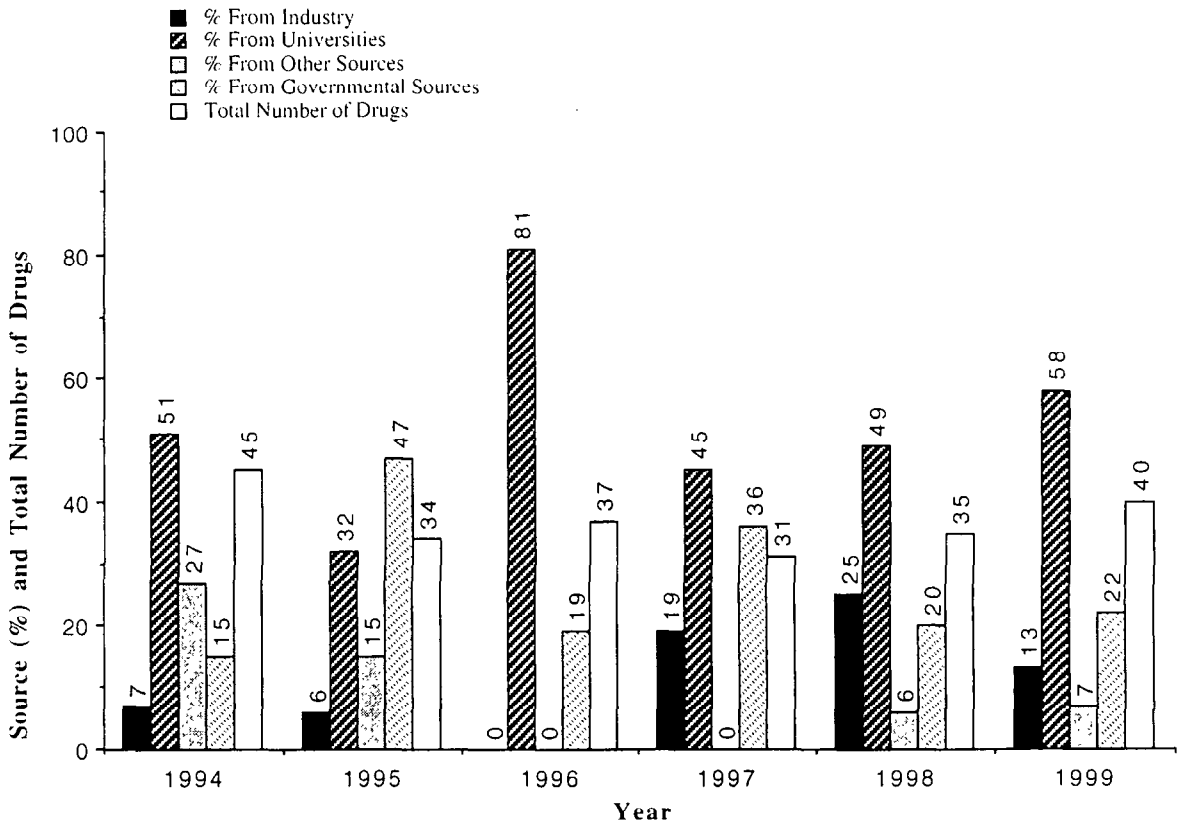
DEC has recently reinitiated work for the World Health Organization (WHO) on drugs. which may require future scheduling decisions. Only a few of the compounds which are evaluated by the various groups in DEC originate from our work with the WHO; the majority of the compounds, as noted below, have come from university researchers, and a lesser percentage from pharmaceutical industry. The data that we obtain provides the public with essential information about the physical dependence potential and abuse liability of substances before they are marketed, using well-recognized procedures from an independent, experienced, and long-established organization.

STATISTICS

Data were released for publication this year on 40 different compounds evaluated by the DEC's Analgesic Testing Program. Of these, 34 compounds were evaluated at VCU (antinociceptive assays - tail flick, hot plate, phenylquinone, and the tail-flick antagonist assay, all in mice, as well as substitution for morphine and precipitated withdrawal assays in the rhesus monkey), and 26 at UM (binding affinity to the μ, δ., and κ opioid receptors, and self-administration and thermal analgesia in the rhesus monkey). This is comparable to the number of released compounds during the past few years. Thus, of the ca. 31 released compounds in 1997,

about 27 were evaluated at VCU and 18 at UM. In 1998, data on about 35 compounds were released, ca. 28 from VCU and 2.3 from UM. As shown in Fig. 1, the compounds which underwent evaluation this year came from the following disparate sources: 58% from universitices; of these, 50% came from US universities and the remaining 8% from foreign universities: 13% of the compounds came from pharmaceutical industry, and most of them (10% out of the 13%) were from US industry. Many of the remaining compounds (22%) came from governmental sources.

FIG. 1. DEC ANALGESIC PROGRAM: PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1994-1999)



EXPERIMENTAL OBSERVATIONS

The 40 compounds tested as analgesics by the Analgesic Testing Groups. and the two tested by the Stimulant/Depressant Testing Groups, are listed in Table 1, together with the table number in which their molecular structures are shown and their pharmacological data summarized. All of the obtained data on the various released analgesics are shown in the Annual Reports of Aceto *et al.* (this volume) and Woods *et al.* (this volume), and the data on the Stimulant/Depressants are in the Annual Report of France *et al.* (this volume). Compounds are classified by molecular structure in Tables 2 - 8 to fucilitate structure-activity comparison. Thus, epoxymorphinans and a morphinan are listed in Tables 2 and 3. Three azamorphinans can be seen in Table 4, and a number of 6,7-benzomorphans are shown in Tables 5 and 6. Compounds with molecular structures that are not readily classified are included among the miscellaneous compounds in Tables 7 and 8. and the compounds examined by the Stimulant/Depressant groups are shown in Table 9. The non-classifiable miscellaneous compounds harbor some interesting drugs. Listed among them is SNC80, a δ-receptor selective agonist. There is, also, an extraordinarily selective compound for the κ-receptor, as well as a u-selective compound which, from its molecular structure, would not be predicted to have opioid antagonist activity. As expected, however, a considerable number of the miscellaneous compounds were inactive as antinociceptives.

One compound in Table 2. the endoethenomorphinan NIH 10931, was shown to have remarkable pharmacological properties. It acted in the mouse as a very potent μ-opioid receptor agonist (8-24 hour duration). Its agonist effect is antagonized by naloxone. and the agonist activity returns as the effects of naloxone wane [Husbands, 1999). In the mouse (but not in the monkey, where it acted only as a μ-agonist). after 8 or 24 hours as an agonist, NIH 10931 became an opioid antagonist, and its antagonist activity was evident for about 168 hours. It is possible that the initial agonist action lasts sufficiently long, due to its lipophilicity, to cause down-regulation of the receptor. The receptor down-regulation might, theoretically, be responsible for the observed antagonist activity, and the antagonism continues until receptor turnover occurs (Coop, 1999). The epoxymorphinan NIH 10932 showed similar activity, but was less μ-selective, less potent, and shorter acting.

Two other compounds in Table 2 were found to be very interesting. In general, the *in vivo* activity of a racemic mixture of morphine-like agonists is due to the interaction of its (-)-enantiomer with the μ-opioid receptor. The (+)-enantiomer has relatively little or no opioid effects. However, one of the few exceptions to that rule can be seen with NIH 00088 and 10316 ((-)-thebaine and (+)-thebaine, respectively). The (-)-enantiomer, NIH 00088, is toxic, inactive as an antinociceptive agent, and has low affinity for μ- (0.86 μM) and κ·-opioid receptors. Its (+)-enantiomer, NIH 10316, however, was shown to have morphine-like antinociceptive activity (Table 2), and Aceto *et al.* reported that it had somewhat higher affinity for the μ opioid receptor than the (-)-enantiomer. (Aceto, *et al.,* 1999), although the affinity was quite low. The (+)-enantiomer (NIH 10316) does not substitute for morphine in the monkey, and it is less toxic than its (-)-antipode. The low receptor affinity found for the (-)-enantiomer could be expected; almost all (-)-3-methoxy substituted 4,5-epoxymorphinans bind poorly to μ-opioid receptors; their phenolic relatives bind with much higher affinity. Thus, the (-)-oripavine NIH 09821, the phenolic relative of NIH 00088, has more than 40 times higher affinity to the μ-receptor than NIH 00088, and (-)-oripavine binds with fair affinity to the κ–opioid receptor as well (Table 2). It will be interesting to see whether (+)-oripavine. like (+)-thebaine, has μ-receptor affinity and *in vivo* activity.

The indolomorphindole structure of NIH 10889 and 10944, in Table 3, is reminiscent of naltrindole, a well-known b-selective ligand. The phenolic compound. NIH 10889. binds to b-receptors with very high affinity. and is very selective for that receptor (μ/δ = 133). Its C3-methoxy relative. NIH 10944, displays lower affinity to both μ and δ receptors. and is less selective as well. Although it cannot always be assumed that C3-phenolic morphinans will display higher receptor affinity than their blocked phenolic (ether) or non-phenolic relatives, especially with those morphinans, which preferentially interact with the δ-receptor, it is certainly true for these indolomorphindoles. The selectivity of ligands for the δ--receptor is, in fact, unpredictable. For example, SNC 80, NIH 10815 in Table 7, has been found to be more selective for the δ·-opioid receptor than its phenolic relative.

The opioid antagonist activity of NIH 10941 (Table 3) in the substitution-for-morphine assay in the monkey is anomalous, and the mechanism of its action uncertain. The compound, 3-deoxy-3-methyloxymorphindole, in which a methyl group replaces the phenolic hydroxyl moiety present in oxymorphindole, displays little affinity for opioid receptors, except for its low affinity at the δ·receptor. The *in vivo* activity of NIH 10941 might be attributable to this δ-interaction. except that an *in vitro* [^{35}S]GTPγS assay showed that it had no δ--receptor efficacy. It would not be expected to display any opioid-like *in vivo* δ·-activity it' the results of this efficacy assay were predictive of *in vivo* action.

The azamorphinans shown in Table 4 were discussed last year (Jacobson, 1998); their binding data (Woods, *et al.,* in press) are presented herein. The data on the N-alkenyl substituted N-normetazocines in Table 5 (NIH 10852 and 10855) completes our work in that series, and these data will be included in a forthcoming joint (VCU, UM, and NIH) publication (May, *et al.,* in preparation). A number of fluoroalkyl substituted N-normetazocines are shown in Table 7 and a few N-alkynyl substituted N-normetazocines are shown in Table 8. These compounds are being investigated with the hope of shedding some light on the effect of the N-substituent on the pharmacological activity of the normetazocine, Although many of the compounds which are now known to act through opioid receptors have been investigated for at least a century. we still have only a limited ability to predict the effect of new N-substituents on the *in vivo* (agonist vs. antagonist) activity of a ligand, even in those compounds which bind with high affinity to μ receptors, and we almost completely lack the ability to predict their effect on drugs which selectively act through δ receptors. Many N-substituted normetazocines interact as well, or better, with κ receptors as with μ receptors (e.g., NIH 10852, 10855, 10942, 10949, and 10952, in Table 5). The structural characteristics of opioid ligands, which are necessary to enable them to selectively interact with a particular opioid receptor, are not well known. Our qualitative knowledge about the

relationships between structure and activity have been pained from the relatively few compounds which have been experimentally found to selectively interact with one or the other opioid receptor. Thus, our exploration of the properties of a new series of N-substituted normetazocines may eventually provide necessary information for quantitative structure-activity correlation.

There are a few compounds of special interest in Tables 7 and 8. The agonist NIH 10890, for example. has exceptional affinity (0.02 nM) and remarkable selectivity (μ/κ = 3900, μ/κ = 95000) for the κ receptor. NIH 10890 is **a** very potent antinociceptive agent, and does not substitute for morphine in morphine-dependent monkeys. This compound, NIH 10890, is slightly (perhaps 3 fold) more potent than the well-known κ-receptor agonist enadoline (NIH 10672) in hot plate, tail-flick, and phenylquinone antinociceptive assays. Its clinical utility however, may be limited since previously examined compounds with high potency and selectivity for the κ_1 receptor were noted to have dysphoric and diuretic side effects.

The narcotic antagonist, NIH 10956, was found to have high affinity and good selectivity for the μ receptor. A possible explanation (Thomas, *et al.,* 1998a; Thomas, *et al.,* 1998b) for the ability of this. and similarly substituted, *m*-hydroxyphenylpiperidine compounds to act as potent opioid antagonists is the restricted rotation (relatively fixed position in 3-dimensional space) of the phenolic aromatic ring due the bulk of the vicinal alkyl substituent. In contrast, the majority of ketobemidone and phenylmorphan agonists have a freely rotating aromatic ring; these cannot be converted to opioid antagonists, no matter which N-substituent is present. It is now known, from the work of Hashimoto *et al.* (this volume), that restricted rotation of the aromatic ring in N-phenethylphenylmorphans (Thomas, *et aI.,* 1998b) appears to effect their opioid antagonist potency rather than antagonist activity.

The Stimulant/Depressant Groups evaluated the two compounds listed in Table 9, CPDD 0051 and 0054. No reinforcing effects were observed at the tested doses of CPDD 0051, and the drug did not display amphetamine-like nor midazolam or pentobarbital-like discriminative effects. CPDD 0051 was also examined by the Analgesic Testing Groups as NIH 10919 (Table 8). It displayed only a slight antinociceptive effect in the mouse phenylquinone assay and it did not produce significant thermal analgesia at 50 °C. It did not bind to opioid receptors. The drug did not substitute for morphine in the monkey substitution-for-morphine assay. CPDD 0054 had neither amphetamine-like nor midazolam or pentobarbital-like discriminative effects. Its reinforcing effects were uncertain due to the insolubility of the drug at doses necessary to produce behavioral effects. Complete details on these drugs can be found in the Stimulant/Depressant Annual Report (France, *et al.,* in press).

TABLE 1. EVALUATED COMPOUNDS

NIH#	COMPOUND NAME	TABLE #-Evaluator
00088	(-)-Thebaine hydrochloride	2-UM
09821	(-)-Oripavine hydrochloride	2-UM
10316	(+)-Thebaine	2-VCU
10589	Naltrindole (NTI) hydrochloride	3- VCU
10815	SNC80	7- VCU
10820	(-)-Eseroline (L)-ascorbate	7- VCU
10852	(-)-5,9α-Dimethyl-2'-hydroxy-2-(5-pentenyl)-6,7-benzomorphan hydrochloride	5- VCU
10855	(-)-5,9α-Dimethyl-2-(6-hexenyl)-2'-hydroxy-6,7-benzomorphan hydrochloride	5- VCU
10889	3-Hydroxy-6,7-didehydro-4,5α-epoxy-17-methy-14β-(3-methyl)butyl-6,7,2',3'-indolomorphinan hydrochloride	3- VCU
10890	(3*R*)-3-(1-Pyrrolidinylmethyl)-4-[(1*S*)-5,6-dichloro-1-indancarbonyl]-tetrahydro-1,4-thiazine hydrochloride	7- VCU & UM
10910	(+)-N-Methyl-2-azamorphinan dihydrobromide	4-UM
10911	(-)-N-Methyl-2-azamorphinan dihydrobromide	4-UM
10912	(+)-N-Methyl-3-azamorphinan dihydrobromide	4-UM
10913	(±)-1-(3-Hydroxyphenyl)-2-dimethylaminomethyl)-cylohexan-1-ol hydrochloride	7- VCU & UM
10914	3-[1-Hydroxy-2-[(methylamino)methyl]cyclohexyl]phenol hydrochloride	7- VCU & UM
10919	1,2,3,4-Tetrahydrobenzo[b]thieno[2,3-c]pyridine (CPDD 0051)	7- VCU & UM
10924	Naltriben (NTB) methanesulfonate	3- VCU
10931	N-Methyl[5β,7β,3`,5`]pyrrolidino-2`-[*S*]-phenyl, 7α-methyl, 3-hydroxy, 6-methoxy-6,14-endoethenomorphinan dihydrochloride	2- VCU
10932	14 β-(2-Methylcinnamoyl)amino-7,8-dihydromorphinone oxalate	2- VCU
10933	14β-(2-Chlorocinnamoyl)amino-7,8-dihydromorphinone oxalate	2- VCU
10936	Metanicotine oxalate	7-UM
10940	(±)-N-(2-Cyanoethyl)-N-norisonicotine dioxalate	8- VCU
10941	3-Deoxy-3-methyloxymorphindole hydrochloride	3- VCU & UM
10942	(-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluoroethyl)-2`-hydroxy-6,7-benzomorphan HCl	5- VCU & UM
10943	(+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluoroethyl)-2`-hydroxy-6,7-benzomorphan HCl	5- VCU & UM
10944	14-Isopentylhydrocodindole (+)-tartrate	3- VCU & UM
10949	(-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(3-fluoropropyl)-2`-hydroxy-6,7-benzomorphan HCl	5- VCU & UM

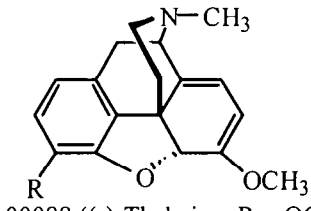
10950	(+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(3-fluoropropyl)-2'-hydroxy-6,7-benzomorphan HCl	5-UM
10951	(+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan HBr	5-UM
10952	(-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan HBr	5- VCU & UM
10953	N,N'-[Bis-(+)-(2*S*,5*S*,9*S*)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan]-1,2-ethane dihydrochloride	6- VCU & UM
10954	N,N'-[Bis-(-)-(2*R*,5*R*,9*R*)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan] -1,2-ethane dihydrochloride	6-UM
10955	(+)-4-Hydroxy-N-(1*S*-([3-hydroxyphenyl)-3*R*,4*R*-dimethyl-1-piperidinyl]methyl-2-methylpropyl-1-benzenepropanamide hydrochloride	8-UM
10956	(+)-N-(*t*-4'-Phenyl-2'-butenyl)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine fumarate	8- VCU & UM
10957	3-Chloro-N-(3-quinuclidinyl)benzamide	8- VCU & UM
10958	(+)-2*S*,5*S*,9*S*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan HCl	6- VCU
10959	(-)-2*R*,5*R*,9*R*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan HCl	6- VCU & UM
10960	(+)-2S,5S,9S)-2-(2-Butan-2-one)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan HCl	6- VCU
10961	(-)-2*R*,5*R*,9*R*)-2-(2-Butan-2-one)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan HCl	6- VCU & UM
10962	Glycine hydrochloride	8- VCU
CPDD 0051	1,2,3,4-Tetrahydrobenzo[b]thieno[2,3-c]pyridine (NIH 10919)	9-S/D Group
CPDD 0054	Carisoprodol (Soma)	9-S/D Group

NOTES FOR TABLES 2 - 9

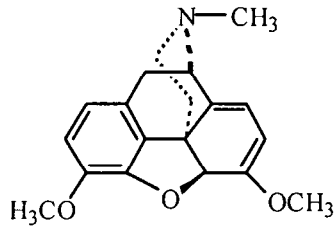
Rounded numbers are used; precise values and details of the procedures are given in the VCU and UM reports (Aceto *et al.,* in press: Woods *et al.*. in press).

1) Antinociceptive reference data:
Morphine ED_{50} (confidence limits): Hot Plate = 0.8 (0.3-1.8); Phenylquinone = 0.23 (0.20-0.25): Tail-Flick = 5.8 (5.7-5.9)
Tail-Flick Antagonism vs. morphine (naltrexone AD_{50}= 0.007 (0.002-0.02): naloxone AD_{50}= 0.035 (0.01-0.093)).
2) *In Vitro* - Subtype selective binding affinity using monkey brain cortex membranes. Selectivity for $\mu, \delta,$ and κ-opioid receptors determined with [^{3}H]-DAMGO. [^{3}H]-*p*-Cl-DPDPE and [^{3}H]-U69.593, respectively. Affinities of labeled ligands: [3H]DAMGO K_i = 0.57 nM, [^{3}H]*p*-CI-DPDPE K_i = 1.2 nM, [^{3}H] U69.593 K_i = 0.95 nM. With C6 glioma cells, morphine K_i = 1.7nM, DPDPE K_i = 8 nM.

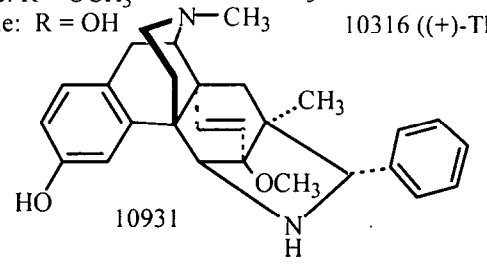
TABLE 2. 4,5-EPOXYMORPHINANS AND MORPHINAN



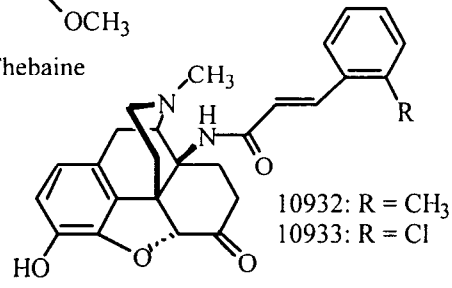
00088 ((-)-Thebaine: R = OCH_3
09821 ((-)-Oripavine: R = OH



10316 ((+)-Thebaine



10931



10932: R = CH_3
10933: R = Cl

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
00088	-	-	Inactive[a,b]	-	μ=860, δ>10000, κ=1377	-
09821	1.5[c]	1.7[c]	3.0[c,d]	Inactive[c]	μ=20, δ=89, κ=107	No substitution (0.5-2.0)[c]
10316	22.9[e]	3.9[e]	8.9[e,f]	Inactive[e]	-	No substitution (0.75-3.0)[e]
10931	0.01	0.004	0.005[g]	Inactive	-	Complete substitution (500-2000 x morphine)
10932	0.09	0.03	0.08[h]	Inactive	-	Almost complete substitution (150x morphine); side-effects
10933	0.17	0.04	0.12[i]	Inactive	-	Complete substitution (20 x morphine; many side-effects

a) Previously reported 1998.

b) Convulsions, lethal @ 20, 30 mg/kg[a]. Pretreatment with naloxone or naltrindole does not prevent lethality". Binding in C6 glioma cells. LD_{50} (NIH) = 35 (sc), 65 (oral) mg/kg.

c) Previously reported 1998, 198 1.

d) β-FNA (icv) and naltrindole pretreatment indicate μ-δ activity, and lethality not due to μ or δ interaction. Naltrindole AD_{50} = 4.6.

e) Previously reported 1984.

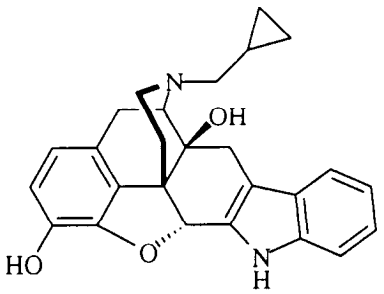
f) NaloxoneAD_{50} = 0.015, naltrindole AD_{50} = 3.8, β.FNA AD_{50} = 2.9, nor-BNI AD_{50} = no antagonism. Rat primary physical dependence: not morphine-like. Rat substitution for morphine: no substitution.

g) Naloxone AD_{50} = 0.02. Agonist activity - 8 hrs (24 hrs with high dose); antagonist after 24 hrs, peaks at 72 hrs, still present at 168 hrs.

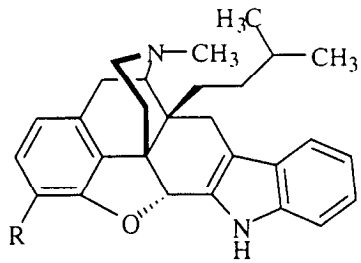
h) Naloxone AD_{50} = 0.15 (not μ-selective). Agonist activity gone by 8 hrs, low-level antag at 48, 72 hrs.

i) Naloxone AD_{50} = 0.03.

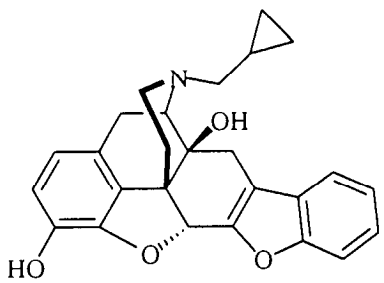
TABLE 3. 4,5-EPOXYMORPHINANS (CONTINUED)



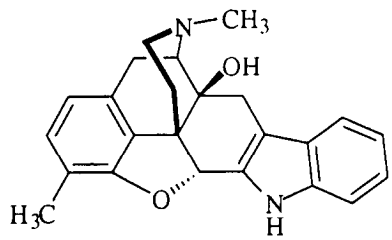
10589: Naltrindole



10889: R = OH
10944: R = OCH_3



10924: Naltriben



10941

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10589	-	Inactive[a,b]	Inactive[a]	Inactive[a]	μ=9.5, δ=0.21, κ=21[a]	No substitution; exacerbated withdrawal
10889	Inactive[c]	6.7[c,d]	Inactive[c]	Inactive[c]	μ=186, δ=1.4, κ=204[c]	-
10924	Inactive[c]	4.2[c,e]	Inactive[c,f]	0.99[c]	μ=12.4, δ=0.36, κ=17.5[c]	-
10941	Inactive	8.3	Inactive	4.6	μ=>10000, δ=315, κ=>10000[c]	No substitution
10944	Inactive	Inactive	Inactive	Inactive	μ=530, δ=46, κ=4396	No substitution

a) Previously reported 1996, 1989.

b) Naltrindole, sc (pretreat 30 min) vs DPDPE, icv: AD_{50} = 2.6. Little or no effect on morphine or κ-agonists NIH 10672 (Enadoline) and U-50,488.

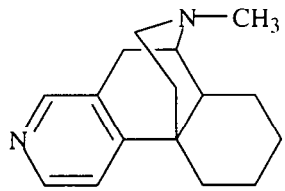
c) Previously reported 1998.

d) Naltrindole AD_{50} = 1.2;β-FNA AD_{50} = inactive.

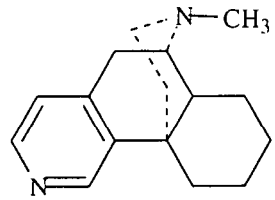
e) DPDPE (icv) AD_{50} = 3.2, naltrindole AD_{50} = inactive, μ- & δ -antagonist, agonist in PPQ.

f) Convulsions, lethal @ 30 mg/kg. Naltrindole pretreatment did not abolish lethal effects.

TABLE 4. AZAMORPHINANS



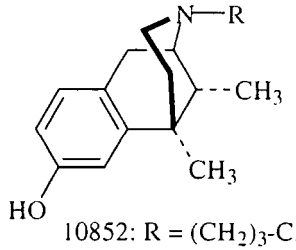
10910: (+)
10911: (-)



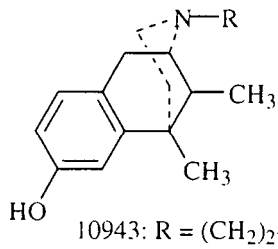
10912

NIH #	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg) Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	IN VITRO Binding Affinity, nM	MONKEY Substitution-for-Morphine (sc, mg/kg)
10910	-	-	-	-	μ=2870, δ=>10000, κ=>10000	-
10911	-	-	-	-	μ=1310, δ=>10000, κ=>10000	-
10912	-	-	-	-	μ=14.1, δ=971, κ=344	-

TABLE 5. 6,7-BENZOMORPHANS



10852: R = $(CH_2)_3$-CH=CH_2
10855: R = $(CH_2)_3$-CH=CH_2
10942: R = $(CH_2)_2$-F
10949: R = $(CH_2)_3$-F
10952: R = $(CH_2)_4$-F



10943: R = $(CH_2)_2$-F
10950: R = $(CH_2)_3$-F
10951: R = $(CH_2)_4$-F

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10852	Inactive[a]	1.4[a,b]	Inactive[a]	6.1[a]	μ=12, δ=93, κ=8[a]	No substitution or exacerbation of withdrawal[a]
10855	0.6[a]	0.3[a]	0.8[a,c]	Inactive[a]	μ=18, δ=98, κ=7[a]	Complete substitution (1 x morphine)[a]
10942	Inactive	0.1[d]	Inactive	2.7	μ=8, δ=25, κ=1.0	No substitution - exacerbates withdrawal
10943	Inactive	3.0	Inactive	Inactive	μ=395, δ=2421, κ=383	Partial substitution
10949	Inactive	0.59[e]	Inactive	0.31	μ=1.4, δ=7, κ=0.35[f]	No substitution, precipitated withdrawal (0.16 x naloxone)
10950	Inactive	Inactive	Inactive	Inactive	μ=354, δ=3767, κ=178[f]	-
10951	Inactive	Inactive	Inactive	Inactive	μ=2720, δ=10000, κ=730	-
10952	Inactive	19.1	Inactive	2.4	μ=6, δ=43, κ=3	No substitution. PptW: non dose-related exacerbation of withdrawal

a) Previously published 1996.

b) 10852 (sc) vs. ED_{80} of NIH 10672 (Enadoline - κ agonist) or DPDPE (icv): inactive

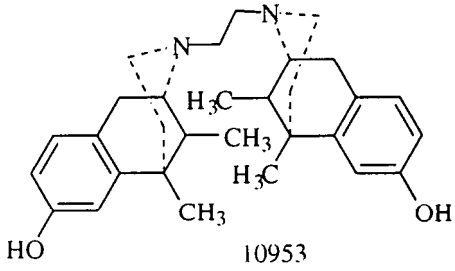
c) β-FNA AD50 = 0.46; nor-BNI and naltrindole inactive.

d) Naloxone AD_{50} = 0.35.

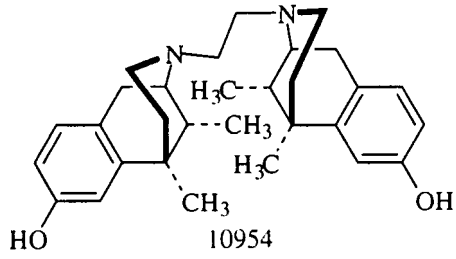
e) Naloxone AD_{50} = 1.3. Naltrindole, nor-BNI, and β-FNA (sc or icv) vs ED80 10949: inactive. NIH 10949 vs. Enadoline (κ-agonist) = 0.96, and vs. DPDPE (icv) = 0.34.

f) Binding in C6 glioma cells.

TABLE 6. 6,7-BENZOMORPHANS (CONTINUED)



10953



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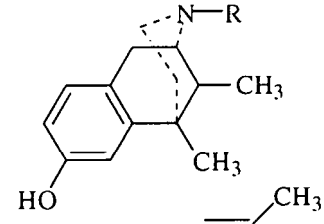
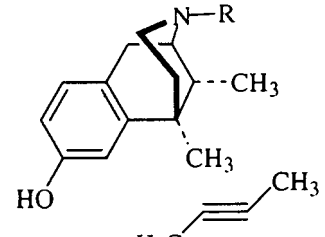


10958: R = H_2C—C≡C—CH_3

10960: R = H_2C—C(=O)—CH_3



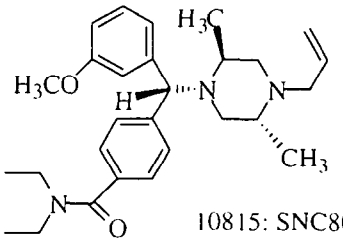
10959: R = H_2C—C≡C—CH_3

10961: R = H_2C—C(=O)—CH_3

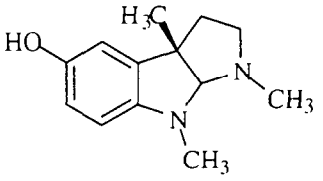
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10953	Inactive	Inactive	Inactive	Inactive	μ=2244, δ=10000, κ=3816	Partial substitution
10954	-	-	-	-	μ=857, δ=10000, κ=151	-
10958	Inactive	Inactive	Inactive	6.7	-	No substitution, no exacerbation of withdrawal
10959	Inactive	0.1[a]	Inactive	0.32	μ=0.47, δ=59, κ=3.9	No substitution. Precipitated withdrawal (0.2 x naloxone)
10960	Inactive	Inactive	Inactive	Inactive	μ=>10000, δ=>10000, κ=>10000	Partial substitution, not dose-related. Non-opioid.
10961	Inactive	Inactive	Inactive	5.08 (1.87-13.82)	μ=150, δ=1727, κ=44	No substitution or exacerbation

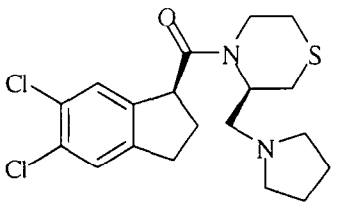
TABLE 7. MISCELLANEOUS



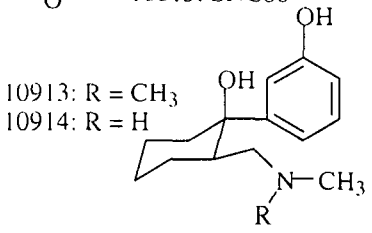
10815: SNC80



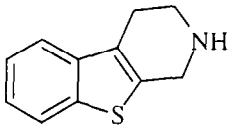
10820: (-)-Eseroline



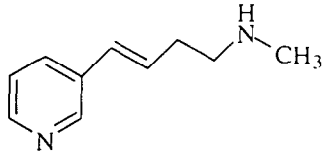
10890



10913: R = CH_3
10914: R = H



10919 (CPDD 0051)



10936: Metanicotine

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg); Self-Administration
10815	Inactive[a]	3.8[a,b]	Inactive[a,c]	Inactive[a]	μ=488, δ=0.9, κ=1170[a]	No substitution. No exacerbation of withdrawal[a]
10820	3[d]	0.3[d]	2.4[d,e]	Inactive[d]	1600[d,f]	Complete substitution (~ morphine-like)[d]
10890	0.003	0.001	0.004[g]	Inactive	μ=78, δ=1900, κ=0.02	No substitution
10913	3.9	0.8	3.5[h]	Inactive	μ=46, δ=3390, κ=2390	Complete substitution; Self-Administration: reinforcing via μ-opioid mechanisms
10914	Inactive	Inactive	Inactive	Inactive	μ=290, δ=10000, κ=10000	No substitution
10919	Inactive	9.9	Inactive	Inactive	μ, δ, κ > 10000	No substitution
10936	-	-	-	-	μ, δ, κ > 10000	-

a) Previously reported 1995, 1996.

b) Naloxone AD_{50} = 0.04 (μ-agonist)[a]: naltrindole AD_{50} = 5.48 (δ--agonist).

c) TF (sc, iv or icv) = inactive (0.1-10 mg/kg, and 5μg/brain, respectively).

d) Previously reported in 1986, 1997.

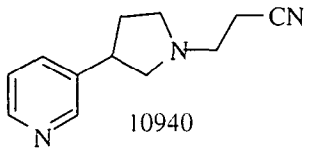
e) Naloxone AD_{50} = 0.16[d]; atropine or nor-BNI, or naltrindole or mecamylamine vs ED_{80} in TF: inactive. β-FNA (icv) AD_{50} = 0.45

f) Radioligand: [^{3}H]-etorphine, using rat brain homogenates.

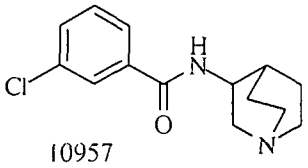
g) Naloxone AD_{50} = 0.46.

h) Naloxone AD_{50} = 0.003. Oral administration: tail flick = 7.2, phenylquinone = 0.8, hot plate = 8.5.

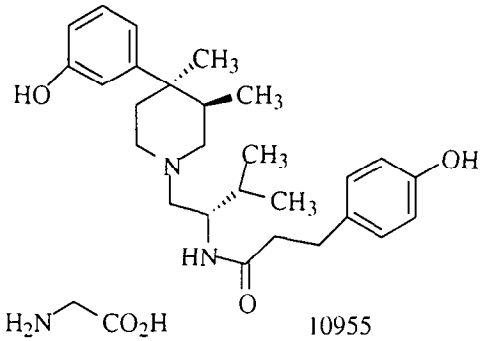
TABLE 8. MISCELLANEOUS (CONTINUED)



10940

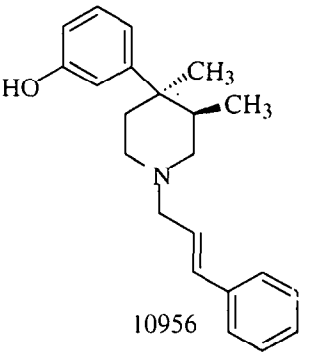


10957



10955

10962

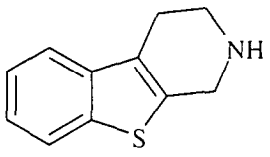


10956

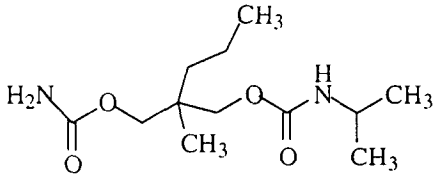
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10940	Inactive	Inactive	Inactive	Inactive	-	No substitution
10955	-	-	-	-	μ=13, δ=10000, κ=14	-
10956	Inactive	5.9	Inactive	0.02	μ=0.1, δ=127, κ=19	No substitution. Precipitated withdrawal (0.5 x naloxone)
10957	Inactive	38	Inactive	Inactive	μ, δ, κ > 10000	No substitution, exacerbated withdrawal.
10962	Inactive	Inactive	Inactive[a]	Inactive	-	-

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0051



CPDD 0054

CPDD#	Discrim. Stim. Effects In Monkeys. Comparison To Flumazenil & Midazolam (sc)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (ig)
0051	No benzodiazepine agonist or antagonist actions	No reinforcing effects.	No amphetamine or pentobarbital-like effects.
0054	No benzodiazepine agonist or antagonist actions	Some reinforcing effects. Study limited (insufficient solubility).	No amphetamine or pentobarbital-like effects.

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DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (1999)

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All compounds, except (+)-thebaine, were unknown to us when submitted by Dr. Arthur Jacobson, Laboratory of Medicinal Chemistry, NIDDK, NIH. These studies were conducted under the auspices of the Drug Evaluation Committee in association with the College on Problems of Drug Dependence. See summary of new data in Table I.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine·SO_4 every 6 hr. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 hr and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-hr observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis Anova and posthoc Mann-Whitney U-Tests.

Precipitaed-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 hr after the last dose of morphine. These animals were not in withdrawal. Naloxone·HCl (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with antagonist or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr. Occasionally, when deemed necessary, as with cocaine, infusions were given *via* the right jugular vein.

Table 1. SUMMARY OF NEW DATA

NIH No.	Chemical Name or Generic Class	MOUSE					RAT		MONKEY		
		TF	TFvsM	PPQ	HP	pA_2	SM	PPD	SDS	PPT-W	PPD
10316	(+)-Thebaine·HCl	T[a]	T	T	T		T	T	T		
10589	Naltrindole·HCl			T[b]							
10815	Piperazine			T[c]							
10820	(-)-Eseroline (L)-Ascorbate	T[d]									
10852	(-)-6,7-Benzomorphan			T[e]							
10855	(-)-6,7-Benzomorphan	T[f]									
10889	(14b)-(3-Methyl)butylmorphindole·HCl			T[g]							
10890	1,4-Thiazine	T[h]	T	T	T				T		
10913	2-(Dimethylaminomethyl)cyclohexan-1-ol	T[h]	T	T	T				T		
10914	2-(Methylaminomethyl)cyclohexan-1-ol	T	T	T	T				T		
10919	Thienotetrahydropyridine	T	T	T	T				T		
10924	Naltribene methanesulfonate	T[f]	T	T	T						
10931	6,14-Endoethenomorphinan	T[j, kfm]	T	T	T				T		
10932	Dihydromorphinone	T[jkfm]	T	T	T				T		
10933	Dihydromorphinone	T[jkfm]	T	T	T				T		
10940	(±)-Norisonicotine	T	T	T	T				T		
10941	3-Deoxy-3-methylmorphindole·HCl	T[o]	T	T	T				T		
10942	(-)-6,7-Benzomorphan	T[n]	T	T	T				T		
10943	(+)-6,7-Benzomorphan	T	T	T	T				T		
10944	14-Isopentylhydrocodindole·HCl	T[o]	T	T	T				T		

10949	(-)-6,7-Benzomorphan	T	T	T	T				T	T	
10950	(+)-6,7-Benzomorphan	T	T	T	T						
10951	(+)-6,7-Benzomorphan	T	T	T	T						
10952	(-)-6,7-Benzomorphan	T	T	T	T				T	T	
10953	(+)-Bis-6,7-benomorphan-ethane	T	T	T	T				T		
10954	(-)-Bis-6,7-benomorphan-ethane	T	T	T	T				T		
10955	4-(3-hydroxyphenyl)piperidine	T	T	T	T				T		
10956	4-(3-hydroxyphenyl)piperidine	T[o]	T	T	T				T	T	
10957	Quinuclidinylbenzamide	T	T	T	T				T		
10958	(+)-6,7-Benzomorphan	T	T	T	T				T		
10959	(-)-6,7-Benzomorphan	T[p]	T	T	T				T	T	
10960	(+)-6,7-Benzomorphan	T	T	T	T				T		
10961	(-)-6,7-Benzomorphan	T	T	T	T				T		
10962	Glycine·HCl	T	T	T	T						

T = Test Performed

[a]Special: Naltrindole, nor-BNI, β-FNA and naloxone vs ED80 of (+)-thebaine in TF. [b]Special subtype tests: Naltrindole vs ED80 of morphine, enalodine, U-50,488 and DPDPE in PPQ. [c]Special: Naltrindole vs ED80 in PPQ. [d]Special: Naltrindole, mecamylarnine and β-FNA vs ED80 in TF. [e]Special: Enalodine and DPDPE vs ED80 of in PPQ. [f]Special: β-FNA, nor-BNI and naltrindole vs ED80 of in TF. [g]Special: β-FNA vs ED80 of in PPQ. [h]Special: Naloxone vs ED80 in TF. [i]Special: Naltrindole reversal did not reverse lethal effects. [j]Special: Naloxone vs ED80 in TF. [k]Special: ED80 Agonist time-course study. [l]S.C. antagonist time-course study. [m]Special: I.c.v. antagonist time-course study. [n]Special: Naloxone vs ED80 in PPQ. [o]Special: Agonist subtype tests in PPQ and antagonist subtype tests in TF (see Text). [p]Special: Naloxone, nor-BNI and naltrindole vs ED80 in PPQ.

Substitutiton-for-Morphine (SM) Test. The rats received morphine·SO_4 (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 hr at 6, 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then. were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Mule mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.v.) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith. 1941 and Dewey *et al.,* 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed though the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 sec under control conditions. Mice were injected with drug or vehicle and tested 20 min later. In three assay for antagonism of' the antinociceptive effect, the potential antagonists were administered 10 min before the agonist, and evaluation occurred 20 min Iater.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drugs and 10 min later received 2.0 mg/kg intraperitoneally (i.p.) of a fleshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cases in groups of two each. Ten min after the PPQ injection, the total number of stretches per group were counted over a 1-min period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored it the animaI jumped or licked its paws after a delay of 5 sec or more, but no more than 30 sec beyond the control time.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12-26)	1.7 (1 .0-2.5)	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02-0.78)	0.01 (0.005-0.03)	25% at 9.0
Nalorphine·HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03-1.43)	13% at 30.0
Naloxone·HCl	None at 10.0	0.04 (0.0-0.09)	No Activity	- - - -
Naltrexone·HCl	None at 10.0	0.007 (.002-0.02)	No Activity	- - - -
Morphine·SO_4[b]	1.92 (0.89-4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39-1.86)
Codeine·PO_4	- - - -	Inactive	8.25 (5.12-13.29)	6.4 (2.4-16.8)
Meperidine·HCl	*8.37* (4.59-15.27)	Inactive	Text	4.6 (1.18-11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2. Using the tail-tlick assay, the apparent pA_2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. The mice were tested 30 min after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED50s were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-1) was plotted against the negative Iogarithm of the molar dose of the antagonist. At least 3 logs (x-l) were plotted. The pA_2 values for the antagonist were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

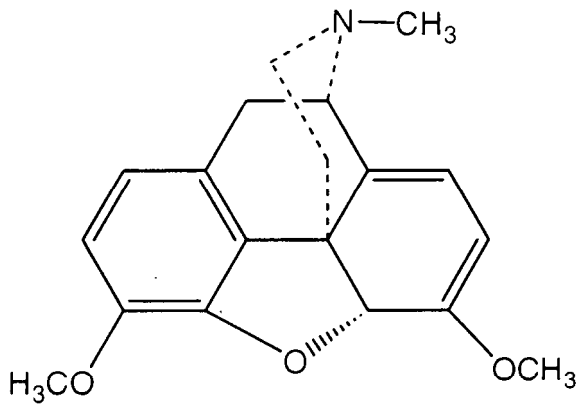
Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2 (95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1-7.6)
2) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
3) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
4) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 -0 7.6)
5) Naloxone/Sufentanil	7.0 (6.9 - 7.1)-1.0	7.0 (6.9 - 7.0)
6) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
7) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
8) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	7.0 (6.9 - 7.0)
9) Naloxone/U-50,488	6.6 (6.3 - 6.9)-1.1	7.2 (6.9 - 7.5)
kappa agonist		6.6 (6.3 - 7.0)
10) Naloxone/NIH 10672 (Enalodine)	6.1 (5.6 - 6.6)-1.2	6.2 (5.9 - 7.3)
selective kappa agonist		
11) (-)-Quadazocine/Enalodine	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
12) nor BNI/Enalodine	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
13) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	6.5 (6.4 - 6.6)

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significant from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of' the regression line is restricted to slope = - 1.

Special Intracerebroventricular Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variely of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accomodate the fact that no delta agonist is available which is active by peripheral routes of administration.

NIH 10316 (+)-Thebaine·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 8.89 (3.57, - 22.14)[a]
2) TF vs. M - Inactive at 1, 10 and 30[a]
3) PPQ - 1.9 (1.6 - 9.5)[a]
4) HP - 22.9 (10.9 - 48.1)[a]

[a]Vehicle was dilute lactic acid in water.

Special Tests:

5) Naltrindole vs ED_{80} of (+)-thebaine in TF: AD_{50} = 3.82 (1.88 - 7.77).
6) Nor-BNI vs ED_{80} of (+)-thebaine in TF: 0% antagonism at 1 and 10, 7% at 30.
7) β-FNA (i.c.v.) vs ED_{80} of (+)-thebaine in TF: AD_{50}= 2.93 (0.78 - 10.93) µg/brain.
8) Naloxone vs ED_{80} of (+)-thebaine in TF: AD_{50} = 0.015 (0.0051 - 0.043).

Comment: Antinociception is associated with mu- and delta-opioid receptors.

RAT DATA

Continuous Infusion of (+)-Thebaine in the Rat

1, Primary Physical Dependence, (PPD) Study

Mule, Sprague-Dawley rats in the weight range 260-290 g were randomly assigned to receive intraperitoneally, 8 ml every 24 hr of a solution of (+)-thebaine, or morphine or vehicle (sterile distilled water to which was added a few drops of lactic acid). Six rats per group served as subjects. The dose regimen of morphine was 50 mg/kg on day 1 , 100 mg/kg on day 2 and 200 mg/kg on days 3 and 4. The (+)-thebaine group received the same regimen except on day 4 the dose was lowered to 100 mg/kg because 2 rats were exhibiting tremors, were easily startled, and were hypertonic at the 200 mg/kg dose only. In spite of lowering the dose regimen, one rat expired 24 hr later. One rat in the morphine control group also died 72 hr after abrupt withdrawal. The results obtained before a rat died were not included in the analyses and thus n = 5 for these two groups.

The first fig. (Rat PPD: body weight) depicts the body weights during the infusion of morphine, or vehicle, or (+)-thebaine (days 1 through 4) and after abrupt withdrawal of morphine or (+)-thebaine. Vehicle was substituted for morphine or (+)-thebaine on days 5 through 8.

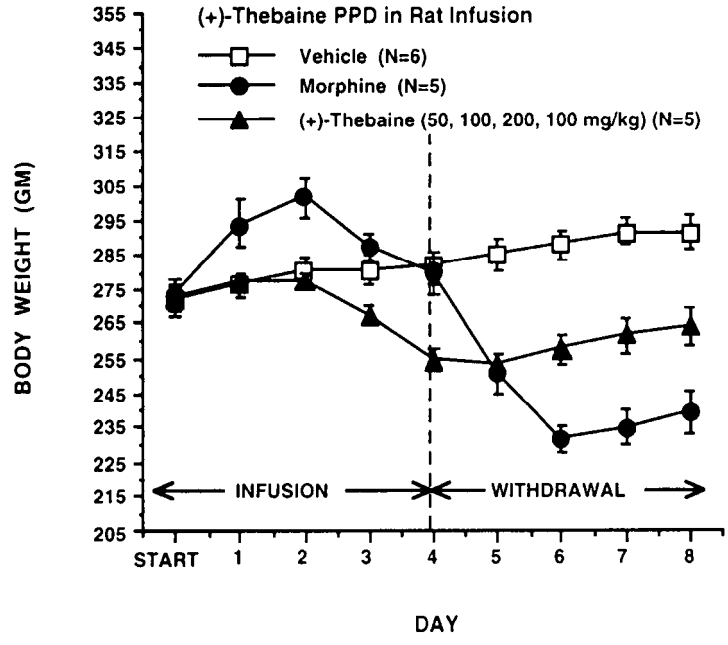


Fig. 1. Rat PPD: Body Weight

As can be seen, the vehicle controls steadily gained body weight throughout the experiment. Typically, the morphine controls initially gained weight and by day 4 the body weights had returned to normal. Then, after morphine was withdrawn, a drastic loss occurred during the first 48 hr. Some recovery was apparent on days 7 and 8. In sharp contrast, the (+)-thebaine-treated rats began losing weight during its administration and not after withdrawal. It is concluded that (+)-thebaine's effects at this dose regimen were quite unlike those of the vehicle or morphine controls.

Water consumption was also recorded (see Fig. 2, Rat PPD: Water Consumption). Each vehicle-control rat drank 20 to 25 ml of water per day throughout the study. As expected, the morphine-treated rats initially drank more during infusion. During the 24-48 hr withdrawal period, water intake was sharply curtailed. This suggests that weight loss in the rat in withdrawal from morphine is associated more with reduced fluid intake than with diarrhea as is commonly believed. Perhaps kappa-opioid related mechanisms are involved. Water intake in the (+)-thebaine-treated rats remained remarkable constant and near normal.

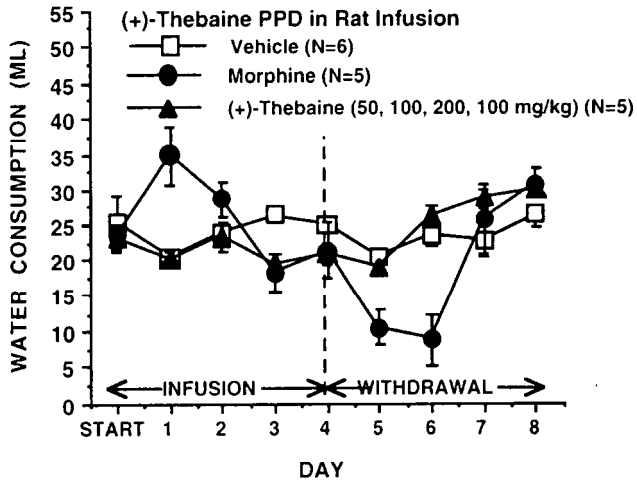


Fig. 2. Rat PPD: Water Consumption

Regarding the sign designated irritability, unlike morphine, when (+)-thebaine was abruptly withdrawn no change was scored in this regard. As shown in Fig. 3, (Rat PPD-Irritability), (+)-thebaine-treated rats behaved as did the rats receiving vehicle. Importantly, these rats did not exhibit hypertonia or startle during withdrawal.

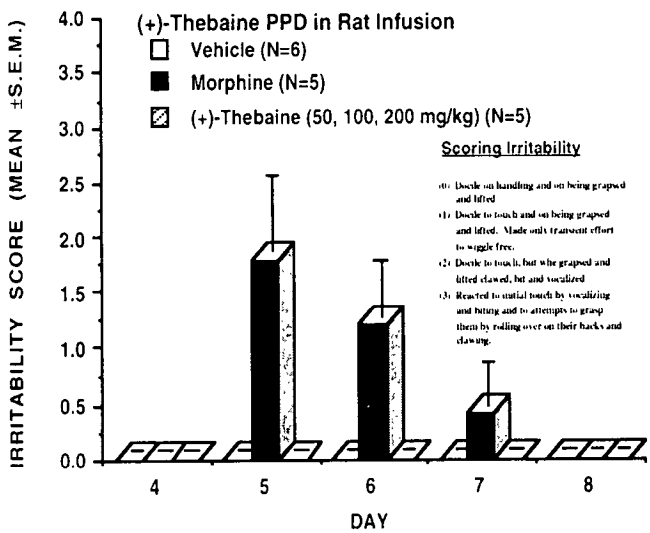


Fig. 3. Rat PPD: Irritability

In Fig. 4 (Rat PPD: Wet Dog Shakes) it is important to take into account that most of the wet-dog shakes in the (+)-thebaine -treated group were generated by one rat. This is reflected in the large SEM. All in all however, the incidence of wet-dog shakes did approximate that noted in the morphine-treated controls during the abrupt withdrawal phase of the experiment (days 5-8). Thus, abrupt withdrawal of (+)-thebaine resulted in an increased incidence of this withdrawal sign.

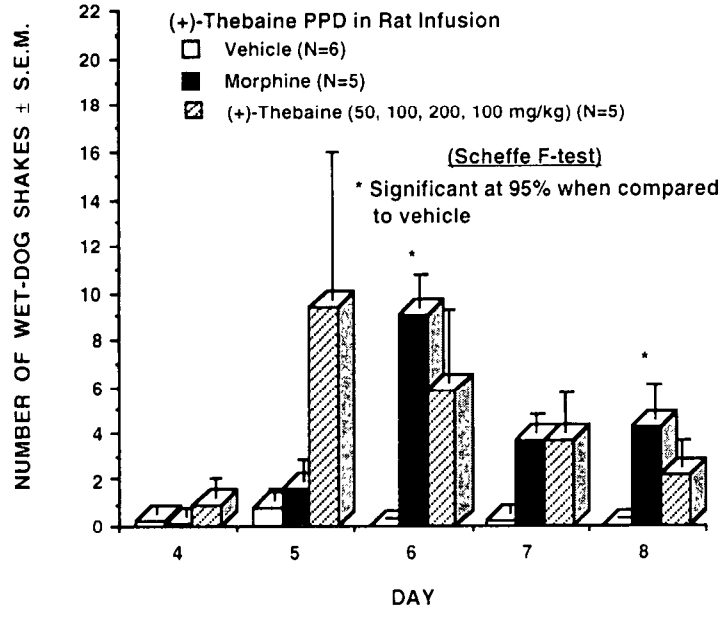


Fig. 4. Rat PPD: Wet-Dog Shakes

Even allowing for the large SEMs observed in Fig. 5, (Rat PPD: Facial Rubs), it is obvious that the morphine-treated and (+)-thebaine-treated rats exhibited an increased incidence of the sign designated facial rubs especially on day 6 (48 hr after abrupt withdrawal) when compared to the vehicle controls. However, for (+)-thebaine the increase was not statistically significant.

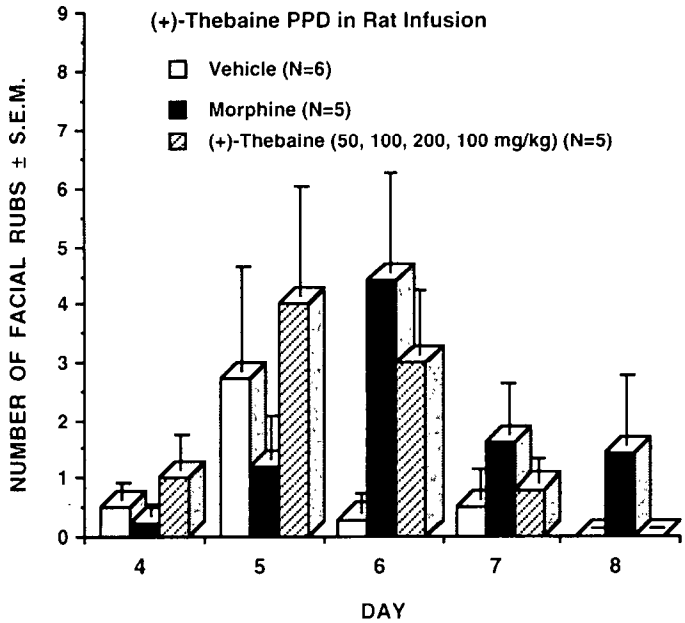


Fig. 5. Rat PPD: Facial Rubs

2.0 Substitution for Morphine Study (Rat SM Studies)

Since all the infusion studies were conducted at the same time, the same rats used as used as morphine or vehicle controls in the primary physical dependence studies above served as controls for this study. At the end of day 4, (+)-thebaine, at a dose of 100 mg/kg per day i.p., was substituted for morphine in group of rats receiving the same dose regimen of morphine as the morphine controls Thus, as illustrated in Fig. 6, (Rat SM: Body Weight), vehicle or (+)-thebaine was substituted in the appropriate groups on days 5 and 6 only. After day 6, vehicle was given to all the groups in the study. It should be noted that 2 of the 6 rats receiving (+)-thebaine died sometime during the first day it was substituted for morphine and another died the following day. It should be recalled that when morphine was abruptly withdrawn that the rats had been receiving 200 mg/kg/24 hr of morphine. This suggests an untoward interaction between morphine and (+)-thebaine. Regarding body weight and water consumption the results of the 3 surviving rats are presented below. Because of the large SEMs, irritability, wet-dog shakes and facial rubs were not analyzed.

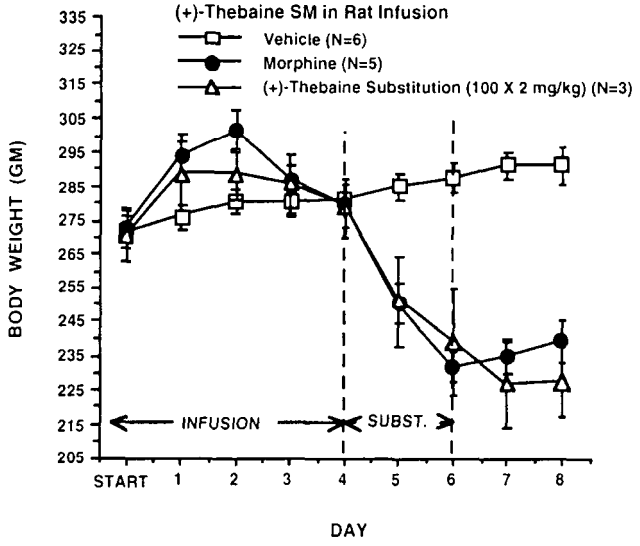


Fig. 6. Rat SM: Body Weight

As shown in Fig 6, (+)-thebaine did not substitute for morphine, i.e, the rats lost just as much body weight as the morphine controls on days 5 and 6 after morphine was abruptly withdrawn. The same effect was noted regarding water consumption (Fig. 7, Rat SM.: Water consumption). (+)-Thebaine failed to prevent the curtailment of water intake associated with opioid withdrawal.

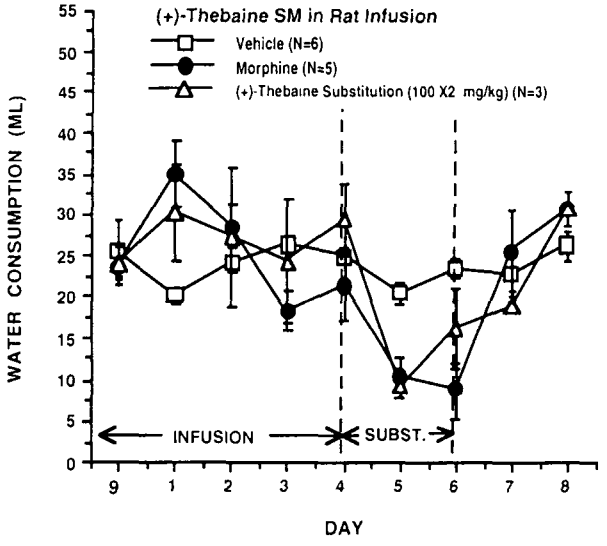


Fig. 7. Rat SM: Water consumption

NIH 10316 (Continued)

Comment: Obviously, additional studies need to be conducted. Nevertheless, the results suggest that (+)-thebaine is unlikely to substitute completely for morphine and that untoward interactions of (+)-thebaine with higher doses of morphine can be anticipated.

MONKEY DATA

(SDS)

As depicted in the figure (Fig (+)- Thebaine-SDS), the results suggest that (+)-thebaine produces a non dose-related attenuation of withdrawal. Nevertheless, at the higher dose, many signs designated as pale face, slowing, ataxia, eyelid ptosis and tremors were noted. In addition, the monkeys receiving the higher dose were reluctant to leave their pen when required to assess the response to abdominal palpation.

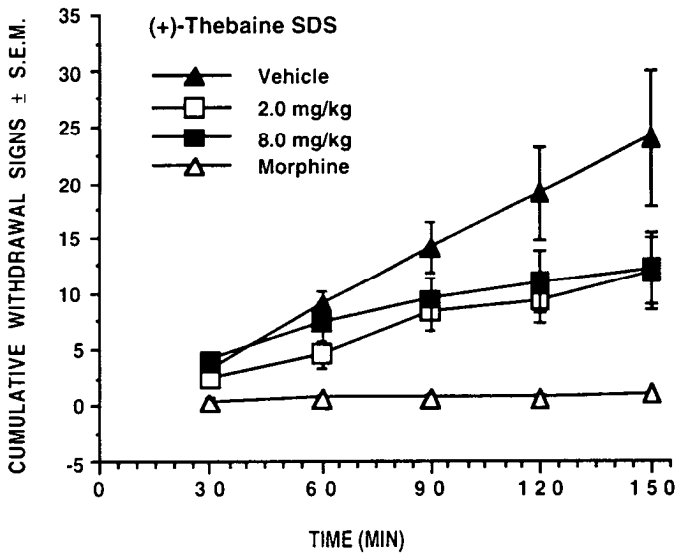
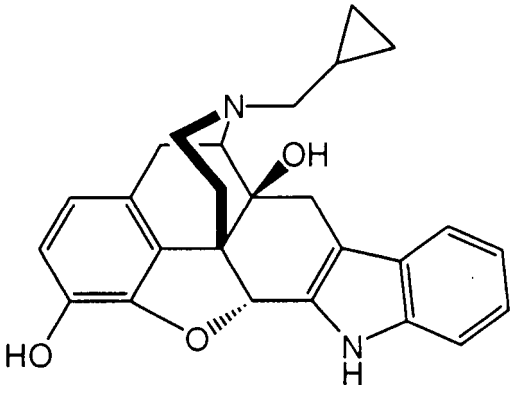


Fig (+)-Thebaine-SDS, Results of study in which single doses of (+)-thebaine were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: (+)-Thebaine does not substitute for morphine in the dose range tested. Studies using higher doses are problematic because of the high number of extra withdrawal signs observed.

Conclusions: (+)-Thebaine produces antinociception associated with mu- and delta-opioid mechanisms in mice. It did not produce physical dependence in the rat and did not substitute for morphine in the rat and monkey. However, the drug may have been lethal to one rat and produced prominent CNS effects in monkeys.

NIH 10589 Naltrindole·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a]
2) TF vs. M - Inactive at 1, 20 and 30[a]
3) PPQ - 0% at 1 and 10 and 28% at 30[a]
4) HP - Not tested

[a]Previously reported, see NIDA Res. Monog. 95, 614, 1989.

NEW DATA

Table 1. The interaction of opioid-agonists subtypes and naltrindole in the mouse PPQ test.

Antagonist	Antagonist Pretreatment Time (min)	Agonist ED_{80}	Agonist Pretreatment Time (min)	ED_{50} or AD_{50} (95% Confidence Limits)
Naltrindole (s.c.)	30	Morphine Sulfate 0.8 mg/kg (mu agonist) (s.c.)	20	30.0 mg/kg: 7% antagonism 10.0 mg/kg: 7% antagonism 1.0 mg/kg: 7% antagonism
Naltrindole (s.c.)	30	NIH 10672 (Enadoline) (kappa agonist) 0.03 mg/kg (s.c.)	20	30.0 mg/kg: 0% antagonism 10.0 mg/kg: 0% antagonism 1.0 mg/kg: 0% antagonism
Naltrindole (s.c.)	30	U-50,488 ED_{80} (kappa agonist) 1.0 mg/kg (s.c.)	20	30.0 mg/kg: 29% antagonism 10.0 mg/kg: 8% antagonism 1.0 mg/kg: 0% antagonism
Naltrindole (s.c.)	30	DPDPE delta agonist (i.c.v.)	10	AD_{50} = 2.59 mg/kg (1.27 - 5.28) Slope - 3.63

NIH 10589 (Continued)

MONKEY DATA (Previously reported, see NIDA Res. Monog. 95, 615, 1989
(SDS)

This compound did not substitute for morphine. It exacerbated withdrawal at 3 and 12 mg/kg (see Fig NIH 10589).

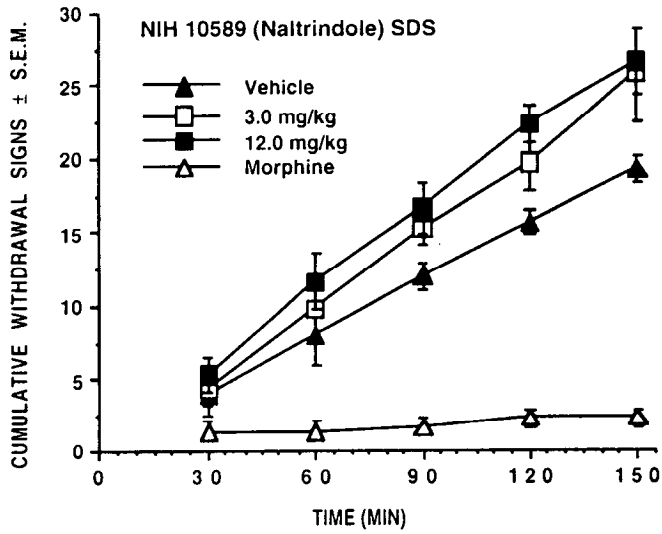
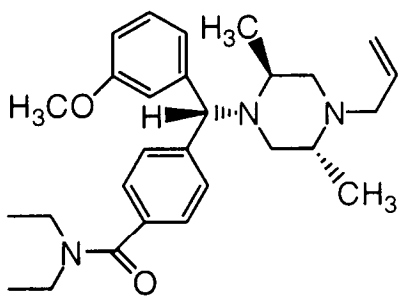


Fig NIH 10589. Results of study in which single doses of NIH 10589 (Naltrindole) were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Naltrindole is a selective delta opioid antagonist in the PPQ test. Note however, that the drug also acts as a mu antagonist in the morphine-dependent monkey or perhaps reveals a delta component of withdrawal.

NIH 10815 (+)-4-[(α*R*)-α-((2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1 and 10, 27% 30[a]
2) TF vs M - Inactive at 1 and 10, 15% at 30[a]
3) PPQ - 3.8 (1.6 - 9.3)[a]
4) HP - Inactive at 1, 10 and 30[a]

Route of administration was s.c.
[a]Data reported previously.
(NIDA Res. Monog.162, 432, 1995).

Special: Intravenous and intracerebral injections in TF test.

5) Inactive at 0.1, 0.3, 1 and 10 mg/kg (i.v.).
7) Table 1. Time-course study for NIH 10815 in TF test (s.c.).

NIH 10815 (Continued)

Dose	Time (min)	% M.P.E.
1 mg/kg	5	8
	10	11
	40	1
10 mg/kg	5	12
	10	10
	40	4

8) Special: Naloxone AD50 vs ED80 of NIH 10815 in PPQ test = 0.04 (0.02 - 0.09)
9) Special: Naltrindole (s.c.) vs ED_{80} of NIH 10815 in PPQ test = AD50 = 5.48 (2.97 - 10.11)

Note: All of the above data except (9) were reported in NIDA Res. Monog. 162, 432, 1995 and 174, 369, 1996.

MONKEY DATA (Data reported previously (NIDA Res. Monog. 162, 433, 1995).
(SDS)

Due to limited supplies of NIH 10815, only 2 subjects per treatment regimen were tested. The results are illustrated in fig NIH 10815. Based on these results, it is concluded that this compound neither suppressed nor exacerbated withdrawal. Ataxia and slowing were observed in monkeys receiving NIH 10815.

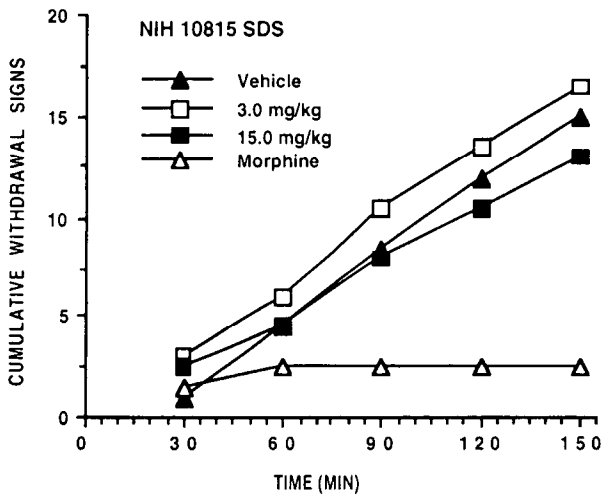
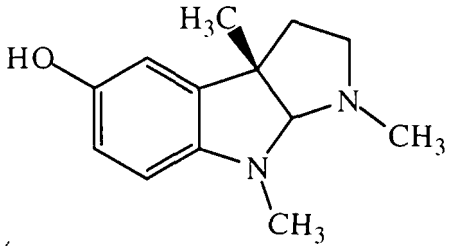


Fig NIH 10815. Results of study in which single doses of NIH 10815 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 10815 was inactive when given subcutaneously, intravenously and intracerebrally in the TF test. In addition, when tested at intervals up to 40 min, no antinociceptive activity is observed. The low AD50 seen in the naloxone antagonist studies in the PPQ test suggests that this drug possesses mu-agonist activity. The new data also provides evidence that NIH 10815 has delta opioid-receptor agonist properties.

NIH 10820 (-)-Eseroline (L)-Ascorbate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 2.4 (1.2 - 4.5)
2) TF vs M - Inactive at 1, 10 and 30.
3) PPQ - 0.3 (0.1 - 0.7)
4) HP - 3.0 (1.5 - 6.0)

(5) Special: Naloxone vs ED_{80} of NIH 10820 in TF: AD_{50} = 0.16 (0.05 - 0.55).

(6) Special: Naloxone - NIH 10820 pA_2 in TF = 6.9 (4.2 - 9.6); Slope - 0.33.

(7) Special: Nor-binaltorphimine (a kappa antagonist) vs ED_{80} of NIH 10820 in TF; (0% antagonism 1, 10, 30 and 60 mg/kg).

(8) Special: Atropine (muscarinic antagonist) vs ED_{80} of NIH 10820 in TF: (20% at 3, 41% at 10 and 48% at 30).

(9) Special: Naltrindole (a delta-opioid receptor antagonist) vs ED_{80} of NIH 10820 in TF: 0% at 1, 21% at 10 and 16% at 32.

(10) Special: Mecamylamine (a non competitive nicotinic-receptor antagonist) vs ED_{80} of NIH 10820 in TF: 0% at 1. 10 and 30.

(11) Special: β-FNA (i.c.v.) (a selective mu-opioid antagonist) vs ED_{80} of NIH 10820 in TF: AD_{50} = 0.45 (0.17 - 1.18).

Note: All of the above except (9), (10) and (11) were reported previously (see NIDA Res. Monog. 178, 370, 1998).

MONKEY DATA (Published previously, see NIDA Res. Monog. 178, 371, 1998)
(SDS)

Dose-dependently substituted completely for morphine at 2.5 and 10.0 mg/kg (fig NIH 10820).

NIH 10820 (Continued)

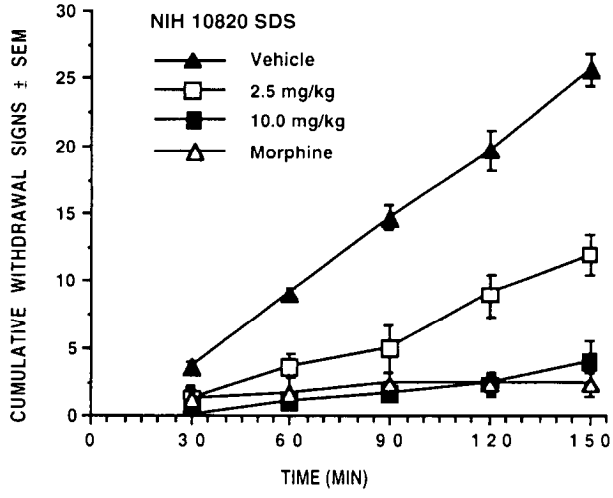
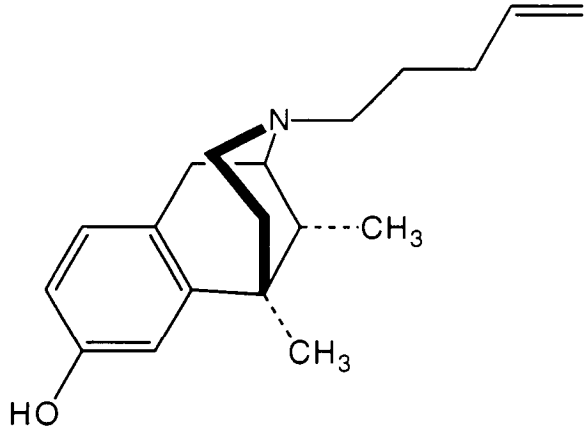


Fig NIH 10820. Results of study in which single doses of NIH 10820 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Suppression of withdrawal in the monkey and antagonism of antinociception in the mouse by β-FNA and atropine suggests that eseroline has mu-opioid and, to a lessor extent, muscarinic properties.

NIH 10852 (-)-(2*R*,5*R*,9*R*)-Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzonorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 0.3, 10.0 and 30.0. 20% at 1.0[a,b,c]
2) TF vs. M - 6.1 (2.2 - 16.9)[a,c]
3) PPQ - 1.4 (0.6 - 3.5)[a,c]
4) HP - 0% at 1.0, 13% at 10.0 and 38% at 30.0[a,c]

[a]Vehicle 5% hydroxypropyl-β-cyclodextrin.
[b]At 10.0 and 30.0 slight ataxia, increased locomotor activity and moderate Straub tail observed.
[c]Published previously, See NIDA Monog. 174, 377, 1997).

NEW DATA

Special tests: 1) NIH 10852 (s.c.) vs ED_{80} of NIH 10672 in PPQ: Inactive at 1, 10 and 30.
2) NIH 10852 (s.c.) vs ED_{80} of DPDPE (i.c.v.) in PPQ: Inactive at 1, 10 and 30.

NIH 10852 (Continued)

MONKEY DATA (Published previously, see NIDA Res. Monog. 174, 377, 1997)

(SDS)

Up to doses that produced slowing and ataxia, NIH 10852 neither substituted for morphine nor exacerbated withdrawal (see Fig NIH 10852). The results are depicted in the accompanying figure. Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.

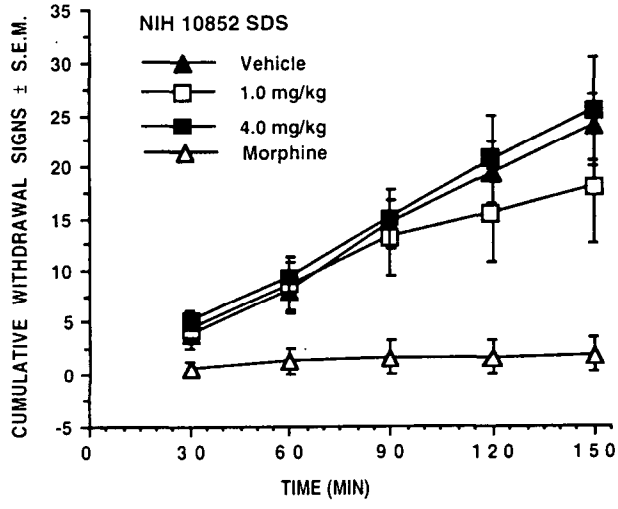
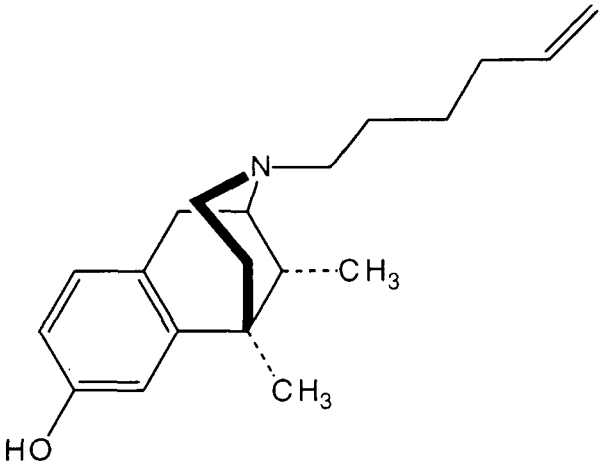


Fig NIH 10852. Results of study in which single doses of NIH 10852 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results suggest that NIH 10852 is a weak selective mu opioid-receptor antagonist. It appears to be devoid of kappa and delta opioid-receptor antagonist activity.

NIH 10855 (-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.8 (0.4 - 1.5)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0"
3) PPQ - 0.3 (0.1 - 0.6)[a]

[a]Vehicle 5% hydroxypropyl-β-cyclodextrin.
[b]Straub tail, increased locomotor activity at 30.0.

Special: 1) Naloxone AD_{50} vs ED_{80} of NIH 10855 in TF - AD50 = 0.04 (0.01 - 0.11).

(All of the above published in NIDA Monog. 174, 380, 1997)

NEW DATA

Special: 2) β-FNA vs ED_{80} of NIH 10855 in TF: AD50 = 0.46 (0.15 - 1.42).
3) nor-BNI vs ED_{80} of NIH 10855 in TF: Inactive at 1, 10 and 30.
4) Naltrindole vs ED_{80} of NIH 10855 in TF: 19% at 1, 12% at 10 and 9% at 30.

MONKEY DATA (Published in NIDA Res. Monog. 174, 380, 1997)
(SDS)

NIH 10855 substituted completely for morphine at 3.0 mg/kg (see Fig NIH 10855)) without producing overt behavioral effects. Onset and duration of action were similar to those of morphine as was the potency estimate. Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.

NIH 10855 (Continued)

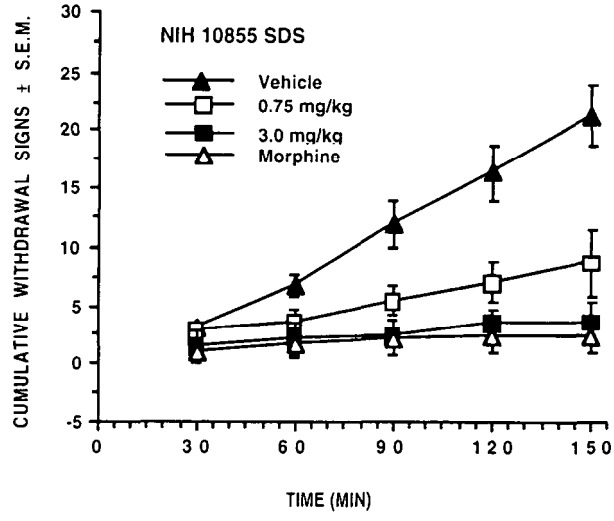
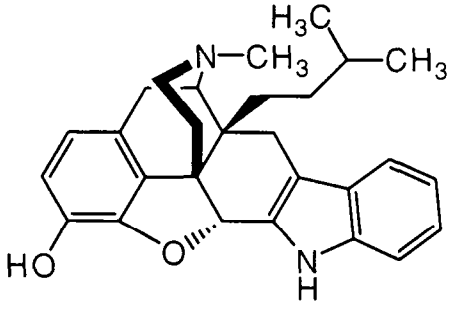


Fig NIH 10855. Results of study in which single doses of NIH 10855 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity is strongly reminiscent of that of morphine.

Additional Comment: Apparently, NIH 10855 is a selective mu-opioid receptor agonist.

NIH 10889 3-Hydroxy-6,7-dehydro-4,5α-epoxy-17-methy-14 β-(3-methyl)butyl-6,7.2',3'-indolomorphinan·HCl (14β--(3-methyl)butylmorphindole·HCl)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 8% at 1.0, 5% at 10.0 and 38% at 30.0"
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0"
3) PPQ - 6.73 (3.14 - 14.45)[a]
4) HP - Inactive at 1.0, 10.0 and 30.0[a]

[a]Vehicle - 5% DMSO in water + heat.

Published previously NIDA Monog. 179, 343, 1998.

Special: Naltrindole vs ED80 of NIH 10889 in the PPQ test: AD50 = 1.22 (0.46 - 3.18).

NIH 108139 (Continued)

New Data

Special: β-FNA (i.c.v.) vs ED80 of NIH 10889 in PPQ test: 0% at 1, 4% at 3, 0% at 10 and 10% at 30 µg/brain.

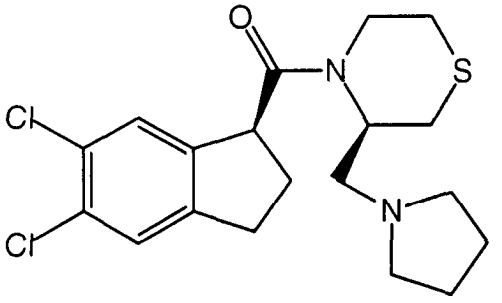
MONKEY DATA

(SDS)

Not Tested

Comment: The new data provide evidence that NIH 10889 has delta opioid-agonist properties. Interestingly. no convulsions were noted.

NIH 10890 (3*R*)-3-(1-Pyrrolidinylmethyl)-4-[(1 *S*)-5,6-dichloro-1-indancarbonyl]-tetrahydro-1,4-thiazine hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.004 (0.002 - 0.008)[a]
2) TF vs. M - Inactive at 1.0, 10.0 and 30.0
3) PPQ - 0.001 (0.0005 - 0.003)
4) HP - 0.003 (0.001 - 0.009)

[a]Mice immobile at 0.003 and 0.0 I.

Special Test: Naloxone AD50 vs ED80 of NIH 10890 in TF = 0.46 (0.24 - 0.88).

MONKEY DATA

(SDS)

Doses of 0.001 and 0.004 mg/kg had little or no effect in morphine-dependent monkeys in withdrawal (see Fig. NIH 10890). Some body sag and eyelid ptosis were observed at the high dose. In the preliminary study, the sign designated slowing was also observed.

NIH 10890 (Continued)

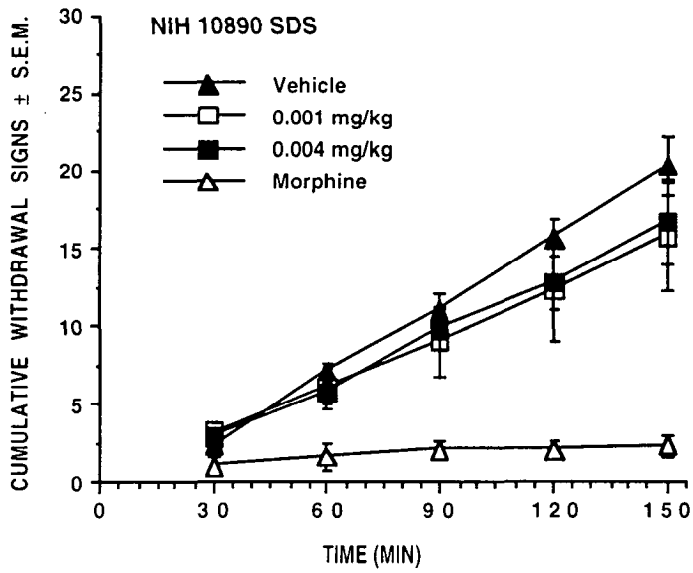
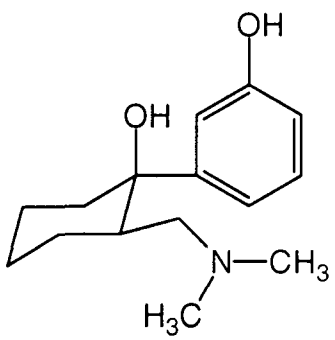


Fig NIH 10890. Results of study in which single doses of NIH 10890 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 10890 is a potent antinociceptive agent. The relatively high naloxone AD50 suggests kappa and/or delta opioid activity rather than mu. This is in accord with the results in the monkey, i.e., NIH 10890 did not substitute for morphine in the dose range producing overt behavioral effects.

NIH 10913 (+)-1-(3-Hydroxyphenyl)-2-(dimethylaminomethyl)-cylohexan-1-ol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3.5 (1.5 - 8.6) s.c.
7.2 (2.9 17.58) p.o.

2) TF vs M - Inactive at 1, 10 and 30 s.c.
Inactive at 1, 10 and 30 p.o.

3) PPQ - 0.8 (0.31 - 2.0) s.c.
0.8 (0.3 - 2.1) p.o.

4) HP - 3.9 (1.8 - 8.4) s.c.
8.5 (3.2 - 22.5) p.o.

Special Test: Naloxone AD_{50} vs ED_{80} of NIH 10913 in TF = 0.003 (0.0009 - 0.01).

NIH 10913 (Continued)

MONKEY DATA

(SDS)

There was a dose-dependent suppression of withdrawal signs at 1.25 and 5.0 mg/kg (see Figure NIH 10913). Onset appeared prompt and offset approximately equal to that of morphine. The potency is morphine-like.

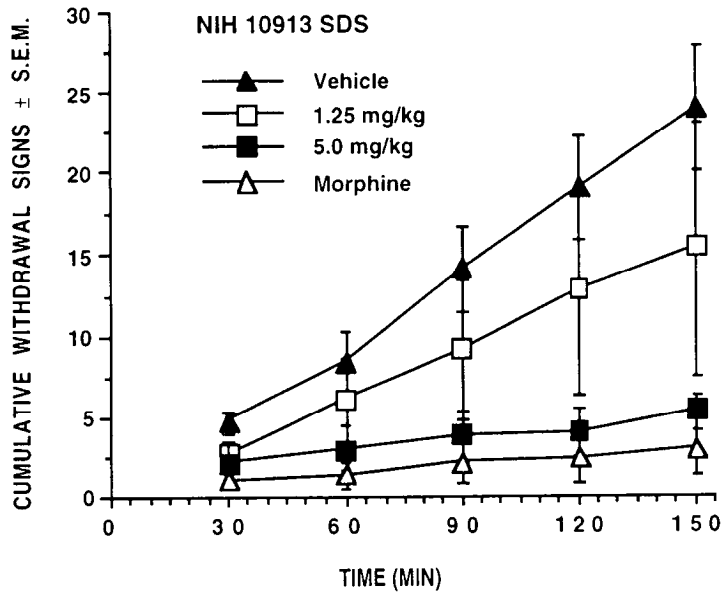
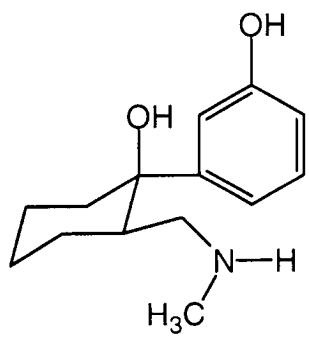


Fig NIH 10913. Results of study in which single doses of NIH 10913 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of biological activity of this compound indicates that it possesses mu-opioid properties. There is good correspondence regarding the s.c. and p.o. routes of administration.

NIH 10914 (+)-1-(3-Hydroxyphenyl)-2-(methyluminomethyl)-cyclohexan-1-ol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs M - Inactive at 1, 10 and 30
3) PPQ - 10% at 1, 38% at 10, 67% at 30 and 62% at 60
4) HP- 13% at 1 and 10 and 0% at 30

NIH 10914 (Continued)

MONKEY DATA

(SDS)

NIH 10914 neither substituted for morphine nor exacerbated withdrawal at 5 and 20 mg/kg (see Figure NIH 10914).

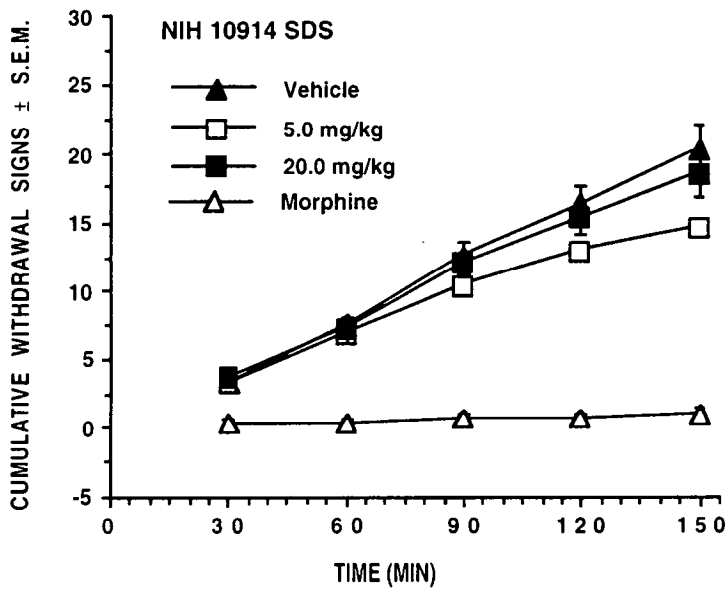
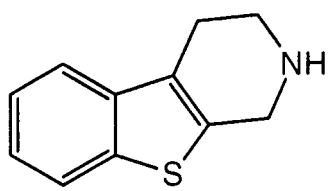


Fig NIH 10914. Results of study in which single doses of NIH 10914 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This compound seems to be devoid of opioid properties.

NIH 10919 1,2,3,4-Tetrahydrobenzo[b]thieno[2,3-c]pyridine



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1 and 10, 20% at 30[a]
2) TF vs M - 0% at 1, 18% at 10 and 2% at 30[b]
3) PPQ - 9.89 (4.30 - 22.78)
4) HP - 0% at 1, 13% at 10 and 50% at 30[c]

[a]Spasticity at 30 mg/kg: Extend all limbs when picked up by tail. No deaths.
[b]No spasticity noted.
[c]Spasticity at 30 but no deaths.

NIH 10919 (Continued)

MONKEY DATA

(SDS)

That a apparent non dose-related attenuation of withdrawal signs in withdrawn morphine-dependent monkeys (as shown in Figure NIH 10919) may reflect non-opioid CNS activity.

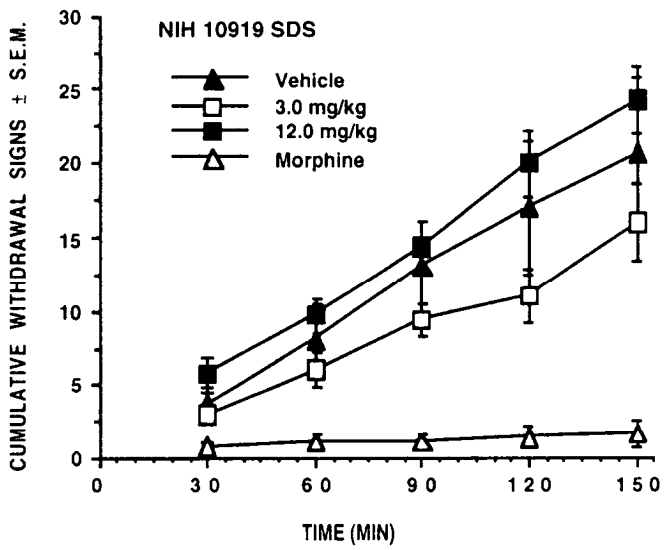
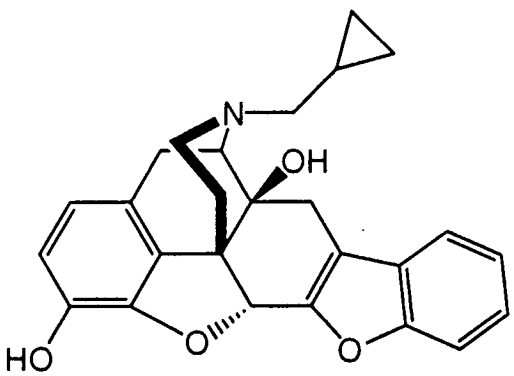


Fig NIH 10919. Results of study in which single doses of NIH 10919 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Except for some weak analgesic activity in the PPQ test, NIH 10919 appears devoid of opioid receptor activity in mice.

NIH 10924 17-Cyclopropylmethyl-6,7-dehydro-4,5α-epoxy-j,14-dihydroxy-6,7-2',3'-benzofuranomorphinan methanesulfonate (Naltriben methanosulfonate; NTB methanesulfonate)



MOUSE DATA - ED50 OR AD50
(95% C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a,b,c,d]
2) TF vs M - 0.99 (0.42 - 2.35)[a,d]
3) PPQ - 4.2 (3.1 - 5.7)[a,d]
4) HP - Inactive at l and 3, 25% at 30[a,d]

[a]10% DMSO aqueous solution.
[b]1 of 6 had convulsions and died at 10 and 6 of 6 had convulsions and died at 30.
[c]Naltrindole pretreatment did not abolish lethal effects at 30.
[d]Published Previously, see NIDA Monog. 179, 354. 1998.

NIH 10924 (Continued)

OLD DATA (Published in NIDA Monog. 179, 354, 1998)

Special: NIH 10924 (s.c.) vs ED80 DPDPE (i.c.v.) in TF: AD50 = 3.15 (1.36 - 7.27).
Special: Naltrindole (s.c.) vs NIH 10924 ED80 in PPQ: Inactive at 1, 10 and 30.

NEW DATA

Special: NIH 10924 (s.c.) vs ED80 DPDPE (i.c.v.) in PPQ: AD50 = 3.15 (1.36 - 7.27).
Special: Naltrindole (s.c.) vs NIH 10924 ED80 in PPQ: Inactive at 1, 10 and 30.

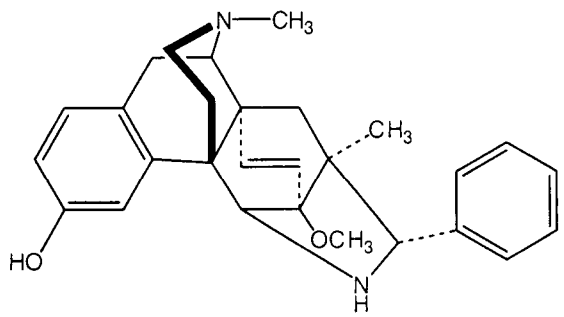
MONKEY DATA

(SDS)

Not tested.

Comment: NIH 10924 has a curious mix of agonist/antagonist effects. The opioid subtype antagonists mu. kappa and delta are inactive vs the ED80 of this compound in the PPQ test. However, it does have delta antagonist activity in the tail-flick test. The convulsions are not be delta-opioid receptor related.

NIH 10931 N-Methyl[5β,7β,3',5']pyrrolidino-2'-[*S*]-phenyl,7α-methyl, 3-hydroxy, 6-methoxy-6,14 endoethenomorphinan·2HCl



MOUSE DATA - ED50 OR AD50

(95 % C.L.) (mg/kg s.c., µg/brain (i.c.v.) or % change)

1) TF - 0.005 (0.003 - 0.008)[a].
TF - 0.07 (0.03 - 0.15) µg/brain[b]
2) TF vs. M - Inactive at 1, 10 and 30[a].
3) PPQ - 0.004 (0.002 - 0.006)[a].
4) HP - 0.01 (0.003 - 0.29)[a].
[a]Pretreatment time was 10 min before morphine.
[b]Admistered i.c.v. (New Data) Loss of righting reflex at 30.

Special Tests

1) Naloxone vs ED80 of NIH 10931 in TF: AD50 = 0.02 (0.01 - 0.04) (See [a] above)
2) ED80 Agonist Time-Course Study: The results are depicted in Fig NIH 10931 below.
3) Subcutaneous Antagonist Time-Course Study: The data are reported in the table below.
Apparently, antagonist activity is not evident until 24 hr have elapsed, peaks at 72 hr and is still present at 168 hr (7 days). Also, note that at 30 mg/kg during the time periods 4 and 24 hr, no antagonist activity was present, suggesting that at this high dose, agonist effects predominated. (See Table 1).

NIH 10931 (Continued)

4) Intracerebroventricular Antagonist Time-Course Study: Some delayed opioid agonist (Straub tail) and antagonist activity was observed at 8 and 24 hr (See Table 2).

Table 1. Antagonist activity of NIH 10931 vs the ED80 of morphine sulfute in the tail-flick test.

Pretreatment Time (hr)	AD50 (mg/kg s.c.)[a]	% Antagonism (mg/kg s.c.)
4	-	0% antagonism at 1, 10 and 30
24	-	26% at 1, 51% at 10 and 0% at 30
48	2.9 (1.0 - 8.4)	-
72	1.4 (0.5 - 4.3)	-
96	3.6 (0.8 - 10.7)	-
120	-	64% at 1, 83% at 10 and 52% at 30
144	-	51% at 1, 2% at 3, 45% at 10 and 69% at 30
168	-	0% at 1, 0% at 3, 61% at 10 and 30% at 30

[a]The variability of the data may be related to the fact that only 6 mice per dose regimen were tested and that the expression of antagonist and antagonist es was related to the dose. For example. at 30 mg/kg during the time periods 4 and 24 hr. no antagonist activity was observed. In fact, at this dose the mice exhibited Straub tails.

Table 2. Effect of (i.c.v.) NIH 10931 -pretreatment time on morphine-induced antinociception (ED80, s.c.) in the tail-flick test.

Pretreatment Time	AD50 or % Antagonist Effect ug/brain	Comment
10 min	Inactive at 1, 10 and 30.	Loss of righting reflex at 10 and 30 ug/brain.
8 hr	AD50 = 10.67 (2.9-39.1).	Straub tail at 30 ug/brain observed before morphine.
24 hr	21% at 1, 37% at 3, 71% at 10 and 18% at 30.	1/6 died at 30 ug/brain before morphine could be given.

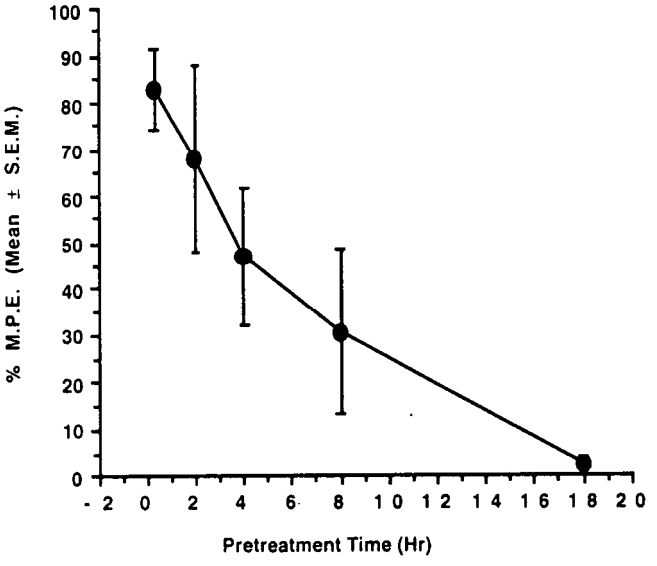


Fig. NIH 10931 (Time-course study) NIH 10931-induced antinociception in mice (ED80 dose 0.5 mg/kg s.c.).

MONKEY DATA

(SDS)

NIH 10931 substituted for morphine in a dose-related manner (see Fig NIH 10931). Onset was prompt and duration of action was at least 2 1/2 hr. Potency is conservatively estimated to be 500 to 2000 times that of morphine. Some eyelid ptosis and body sag was noted at the higher dose.

NIH 10931 (Continued)

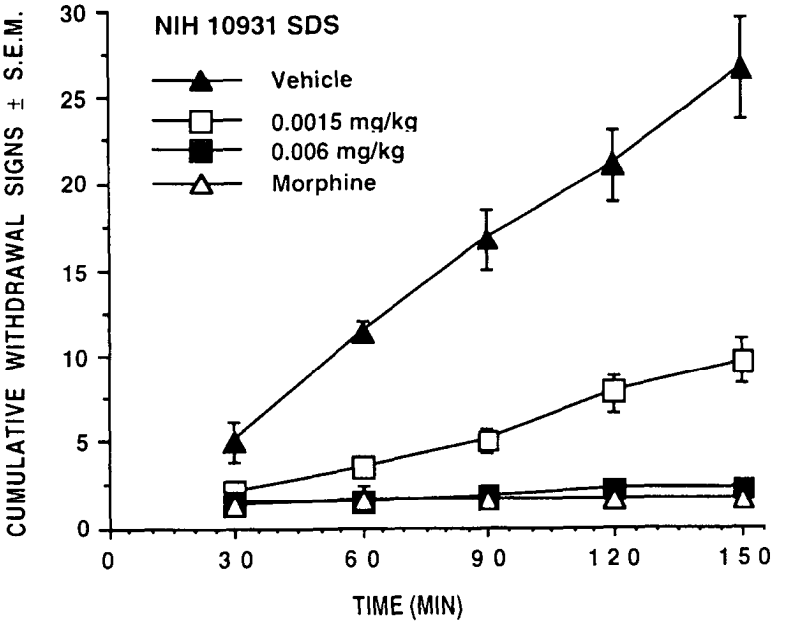
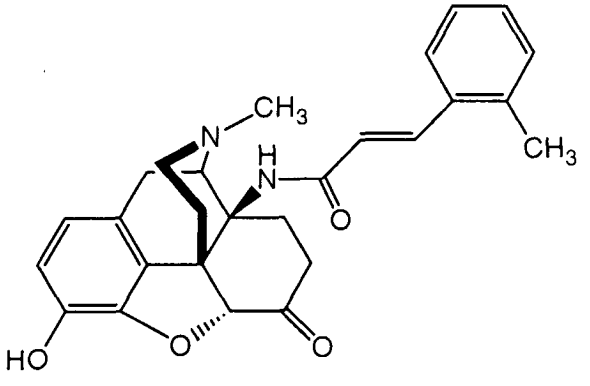


Fig NIH 10931-SDS. Results of study in which single doses of NIH 10931 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, when given by the subcutaneous route, this compound displayed potent opioid antinociceptive effects of long duration followed by antagonist activity lasting at least 168 hr. When given by the intracerebroventricular route, it followed the same pattern of activity as in the subcutaneous study except that the duration of action was abbreviated. NIH 10931 is a potent long-acting mu-opioid agonist which. possibly, is metabolized to an (irreversible ?) opioid antagonist with a very long duration of action. In the monkey, NIH 10931 behaved essentially as a potent mu agonist.

NIH 10932 14β-(2-Methylcinnamoyl)amino-7,8-dihydromorphinone oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.08 (0.03 - 0.25)[a,b]
2) TF vs. M - Inactive at 1, 10 and 30[a,b]
3) PPQ - 0.03 (0.001 - 0.07)[a,b]
4) HP - 0.09 (0.03 - 0.3)[a,b]

[a]Vehicle was 3% hydroxypropyl-β-cyclodextrin in water.

[b]30 min pretreatment time.

NIH 10932 (Continued)

Special Tests:

1) Naloxone vs ED80 of NIH 10932 in TF: AD50 = 0.15 (0.09 - 0.27) (see footnote a,b,c above).
2) ED80 Agonist Time-Course Study: These results are depicted in the figure below. At this dose (ED80), antinociceptive activity is no longer evident by 8 hr.
3) Subcutaneous (s.c.) Antagonist Time-Course Study: The results are presented in Table I below. They appeared to be very erratic. Some low level antagonist activity was present during the 48 and 72 hr studies.
4) Intracerebroventricular (i.c.v.) Antagonist Time-Course Study: (See Table 2). There is evidence for weak mu-opioid receptor agonist (Straub tail) and antagonist activity which is evident after an initial delay of 8 hr.

Table 1. Antagonist activity of (s.c.) NIH 10932 versus ED80 (s.c.) of morphine sulfate in the tail-flick test.

Pretreatment Time (hr)	**% Antagonism (mg/kg s.c.)**
24	0% at 1 and 10, 13% at 30
48	13 at 1, 38% at 10 and 29% at 30
72	2% at 1, 12% at 10 and 32% at 30[a]

[a]At 30 mg/kg 3 of 6 mice died.

Table 2. Effect of (i.c.v.) NIH 10932-pretreatment time on morphine-induced antinociception (ED80, s.c.) in the tail-flick test.

Pretreatment Time Before Morphine	AD50 or % Antagonist Effect ug/brain	Comment
10 min	Inactive at 1, 10 and 30	Straub tail at 1, 10 and 30 ug/brain before morphine.
8 hr	14% at 1; 6% at 3; 54% at 10; and 10% at 30	Straub tail at 30 ug/ brain observed before morphine.
24 hr	40% at 1; 0% at 3; 20% at 10; and 0% at 30	3/6 expired before morphine could be given.

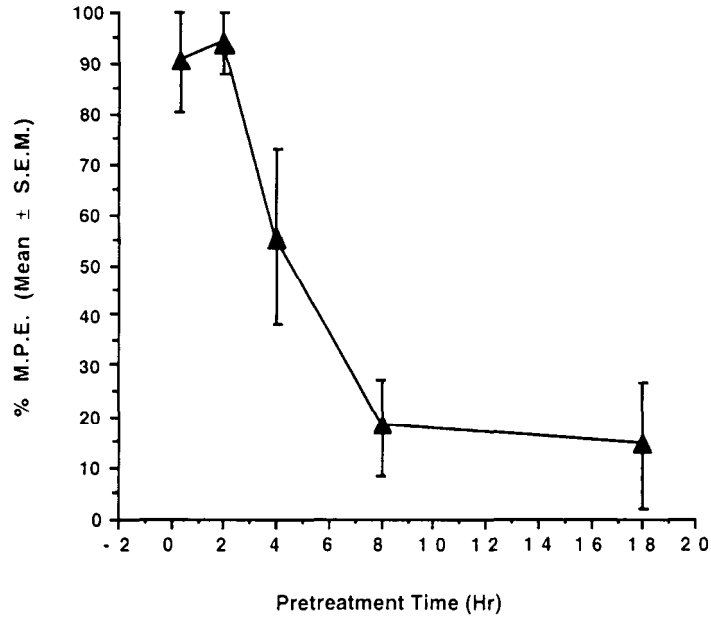


Fig NIH 10932 (Time-course study): NIH 10932-induced antinociception in mice (ED80 dose 0.5 mg/kg s.c.).

MONKEY DATA

SDS

This compound nearly replaced morphine in dependent monkeys. However, the effectiveness was associated with severe jaw sag and scratching. One monkey receiving a dose of 0.4 mg/kg became unconscious and required naloxone to resuscitate it. Onset and offset of action is morphine-like. Potency estitnate is 150 times that of morphine. Vehicle was 10% hydroxypropyl-β-cyclodextrin in sterile water.

NIH 10932 (Continued)

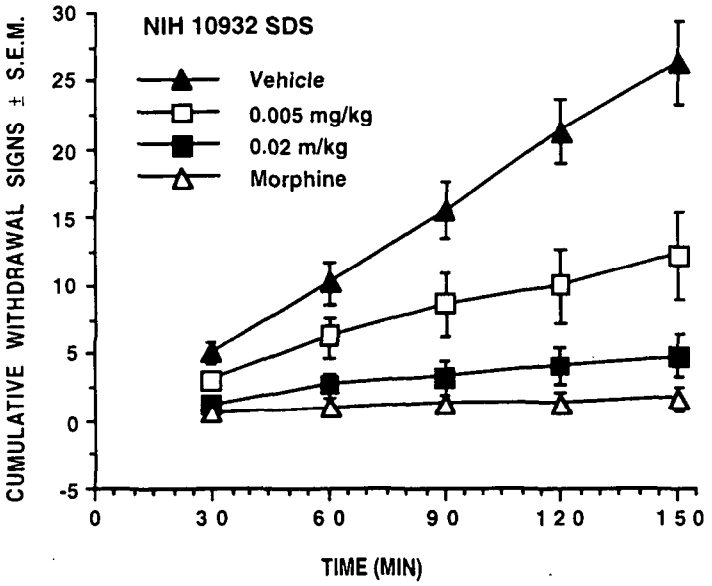
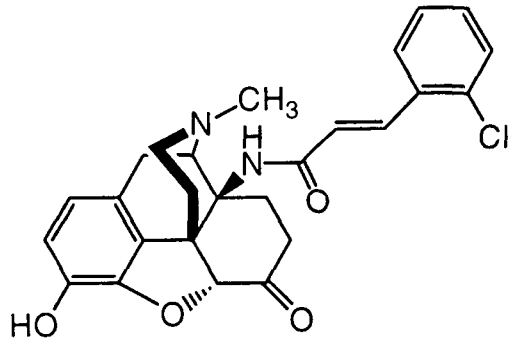


Fig NIH 10932. Results of study involving the substitution of single doses of NIH 10932 for morphine in morphine-dependent monkeys in withdrawal

Comment: The high naloxone AD50 in the mouse antinociceptive study suggested heterogeneous antinociceptive opioid-subtype activity. In the monkey, NIH 10932 displayed mu-opioid receptor agonist activity. Given by the s.c. or i.c.v. routes of administration in the mouse, some weak mu-opioid receptor agonist/antagonist activity of delayed onset was observed. Perhaps metabolism accounts for these results.

NIH 10933 14β-(2-Chlorocinnamoyl)amino-7,8-dihydromorphinone oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0.12 (0.04 - 0.31)[a,b]
2) TF vs. M - Inactive at 1, 10 and 30[a,b]
3) PPQ - 0. 04 (0. 02 - 0.09)[a,b]
4) HP - 0.17 (0.08 - 0.39)[a,b]

[a]Vehicle was 3% hydroxypropyl-β-cyclodextrin in water.

[b]Pretreatnient was 10 min.

NIH 10933 (Continued)

Special Tests:

1) Naloxone vs ED80 of NIH 10933 in TF: AD50 = 0.03 (0.01 - 0. 1).
2) ED80 Agonist Time-Course Study: These results are shown in the figure below. At the ED80 dose, agonist activity was evident for at least 8 hr.
3) Subcutaneous Antagonist Activity Time-Course Study: The data are presented in Table 1. NIH 10933 displays feeble, it at all, antagonist activity when given at 0.5, 24, 48 and 72 hr before testing.
4) Intracerebroventricular Antagonist Time-Course Study: Little, if any, antagonist activity noted. Soon after administration of NIH 10933, agonist activity expressed as Straub tail is evident and at 8 hr (see Table 2).

Table 1. Antagonist activity of NIH 10933 vs the ED80 of morphine sulfate in the tail-flick test.

Pretreatment Time (hr)	% Antagonism (mg/kg s.c.)
24	0% at 1 and 10, 13% at 30
48	0% at 1, 9% at 10 and 22% at 30
72	10% at 1, 18% at 10 and 11% at 30[a]

Table 2. Effect of (i.c.v.) NIH 10933-pretreatment time on morphine-induced antinociception (ED80, s.c.) in the tail-llick test.

Pretreatment Time	AD50 or % Antagonist Effect ug/brain	Comment
10 min	Inactive at 1, 10 and 30	Straub tail at 1, 10, and 30 ug/brain observed before morphine.
8 hr	41% at 1; 28% at 3; 0% at 10 and 30.	Straub tail at 30 ug/brain observed before morphine.
24 hr	0% at 1, 3, 10 and 17% at 30.	

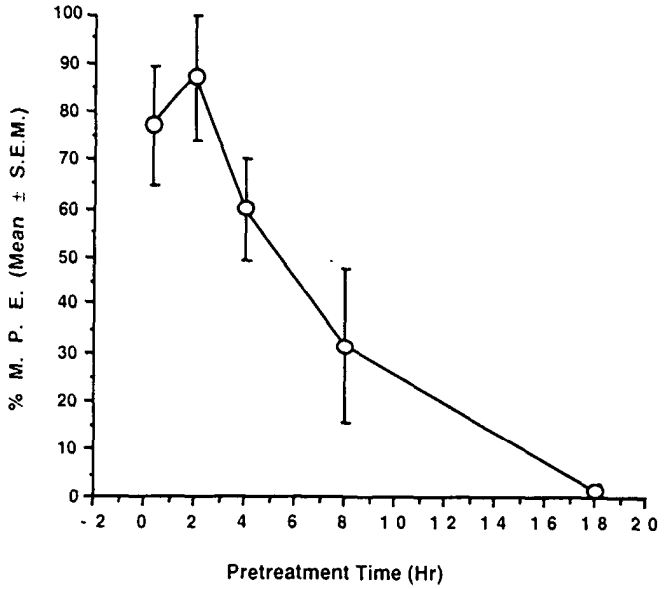


Fig NIH 10933 (Time-course study): NIH 10933-induced antinociception in mice (ED80 dose, 0.5 mg/kg s.c.).

MONKEY DATA

SDS

NIH 10933 dose-dependently substituted for morphine (see Fig NIH 10933). However, substitution at the high dose was accompanied by opioid-agonist behavioral signs such as jaw and body sag, eyelid ptosis, slowing and scratching. Onset was rapid and offset shorter that morphine. Potency is 20 times that of morphine.

NIH 10933 (Continued)

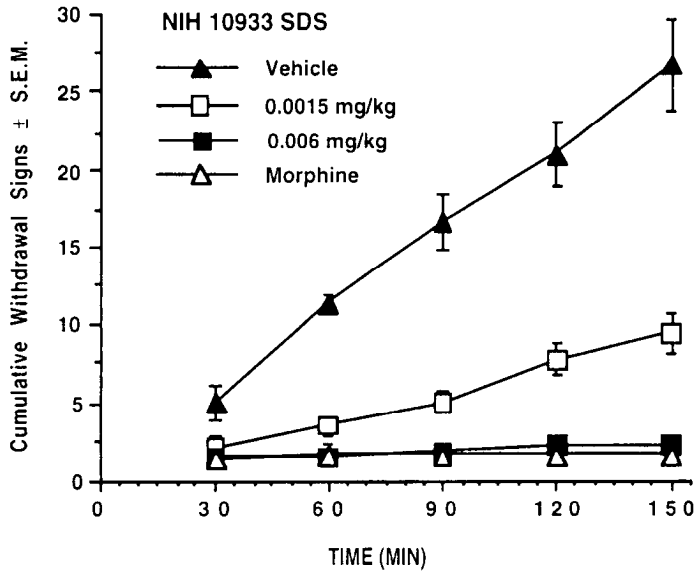
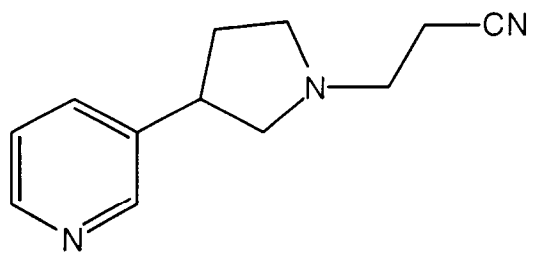


Fig NIH 10933. Results of study in which single doses of NIH 10933 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of biological activity suggests that NIH 10933 has mu-opioid agonist properties. Onset of action was rapid in mice and monkeys. Duration of action appeared to be at least as long as that of morphine in monkeys and at least of 8 hr duration in mice. Finally, the drug did not show remarkable antagonist properties.

NIH 10940 (+)-N-(2-Cyanoethyl)-N-norisonicotine dioxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive to 30
2) TF vs. M - 0% at 1, 8%at 10 and
3) PPQ - 0% at 1, 3% at 10 and 43% at 30
4) HP - Inactive to 30

MONKEY DATA

(SDS)

As shown in the accompanying figure (Fig NIH 10940-SDS), at doses of 2.25 and 9.0 mg/kg, NIH 10940 neither substituted for morphine nor exacerbated withdrawal.

NIH 10940 (Continued)

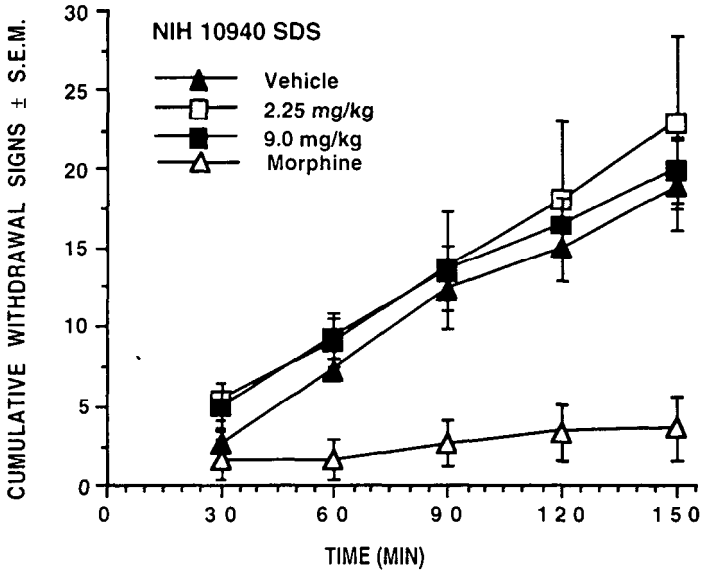
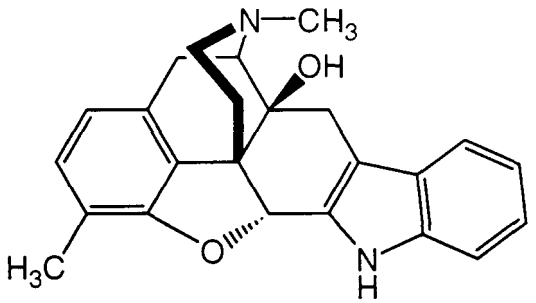


Fig NIH 10940-SDS. Results of study in which single doses of NIH 10940 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 10940 appears to be devoid of in vivo antinociceptive activity and opioid interaction.

NIH 10941 3-Deoxy-3-methyloxymorphindole·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 4.63 (1.30 - 16.52)
3) PPQ - 8.33 (1.80 - 38.47)
4) HP - 13% at 1, 0% at 10 and

Special: Naloxone vs ED_{80} of NIH 10941 in PPQ test: AD_{50} = 0.86 (0.34 - 2.16).

MONKEY DATA

(SDS)

The results were not remarkable (see Fig NIH 10941). NIH 10941 showed slight but not significant exacerbation of withdrawal at the high dose. In contrast, the lower dose tended to reduce withdrawal scores over time or the opioid effects were indirect.

NIH 10941 (Continued)

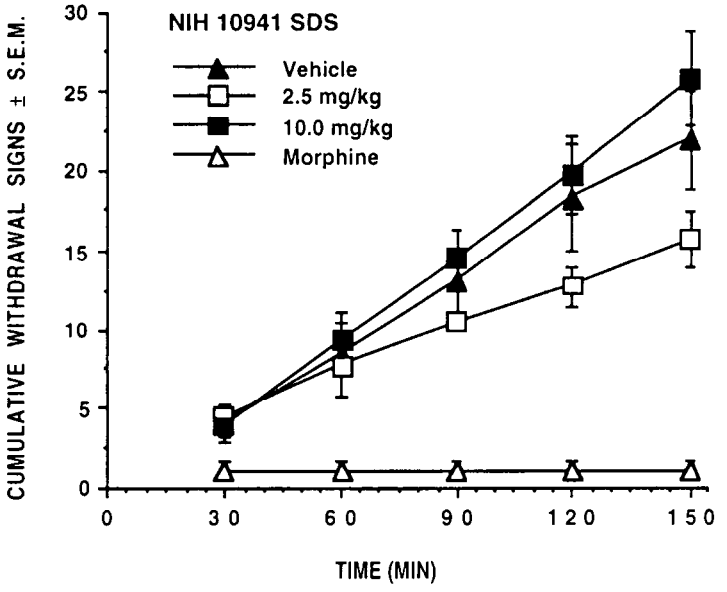
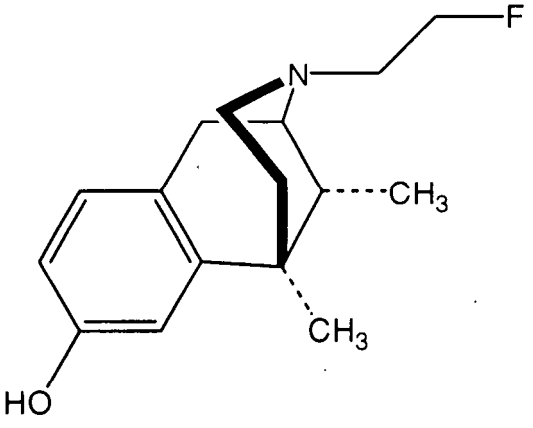


Fig NIH 10941. Results of study in which single doses of NIH 10941 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Indications are that NIH 10941 has weak agonist/antagonist opioid effects

NIH 10942 (-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluoroethyl)-2'-hydroxy-6,7-bcnzomorphan·HCl



MOUSE DATA - ED50 OR AD50

(95 % C.L.) (mg/kg or % change)

1) TF - 13% at 0.1, 25% at 0.5, 29% at 1, 37% at 5, 13% at 10 and 0% at 30[a,b]
2) TF vs. M - 2.66 (0.68 - 10.46)
3) PPQ - 0.10 (0.04 - 0.24)
4) HP - 13% at 1, 10 and

[a]Ataxia.
[b]Moderate Straub tail and increased locomotor activity.

New Mouse Data

Special: Naloxone vs ED80 of NIH 10942 in PPQ: AD50 = 0.35 (0.13 - 0.98).

NIH 10942 (Continued)

MONKEY DATA

(SDS)

As shown in Fig NIH 10942 below, NIH 10942 did not substitute for morphine, instead, it exacerbated withdrawal. A precipitated-withdrawal assay may be in order.

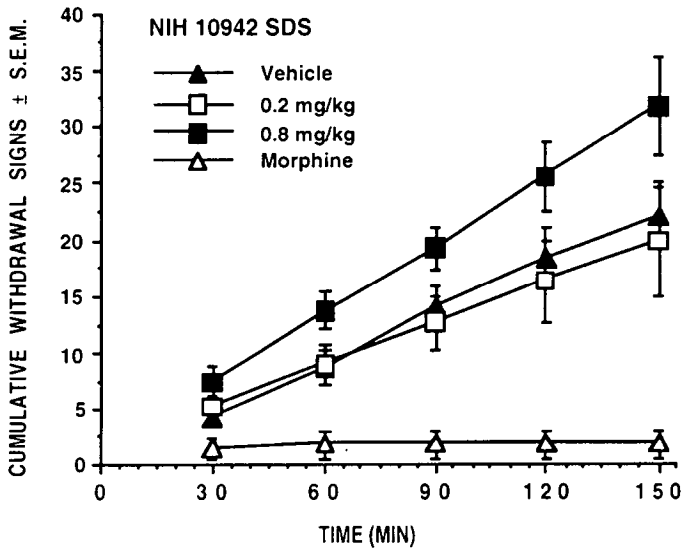
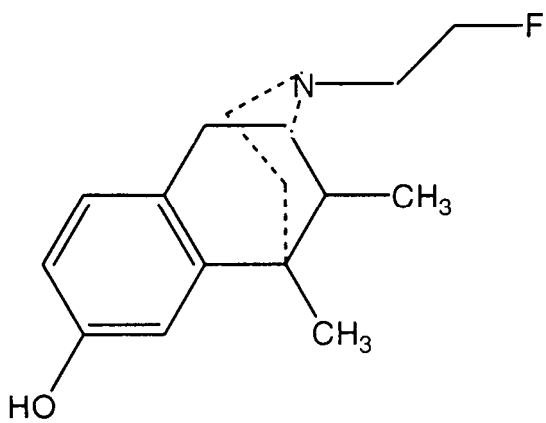


Fig NIH 10942. Results of study in which single doses of NIH 10942 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 10942 appears to have agonist/antagonist effects in the mouse and antagonist properties in the monkey. The high AD_{50} for naloxone in the PPQ test suggests heterogeneous opioid effects.

NIH 10943 (+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluoroethyl)-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1 and 10, 4% at 30[a]
2) TF vs M - Inactive at 1, 10 and 30
3) PPQ - 3.00 (1.41 - 6.37)
4) HP - Inactive at 1 and 10, 13% at 30[b]

[a]Jumping and ataxia at 10 and 3.
[b]Slight ataxia at 1, increased locomotor activity at 10, some popcorn seizures, popcorn seizures, incoordination and rapid respiration at 30.

NIH 10943 (Continued)

MONKEY DATA

(SDS)

NIH 10943 reduced the number of withdrawal signs at the high dose but did not completely substitute for morphine (see Fig NIH 10943). The reduction in scores was associated with a reduction in the number of signs designated vocalization when abdomen were palpated and central nervous system behaviors termed slowing and ataxia. Eyelid ptosis and salivation were also noted.

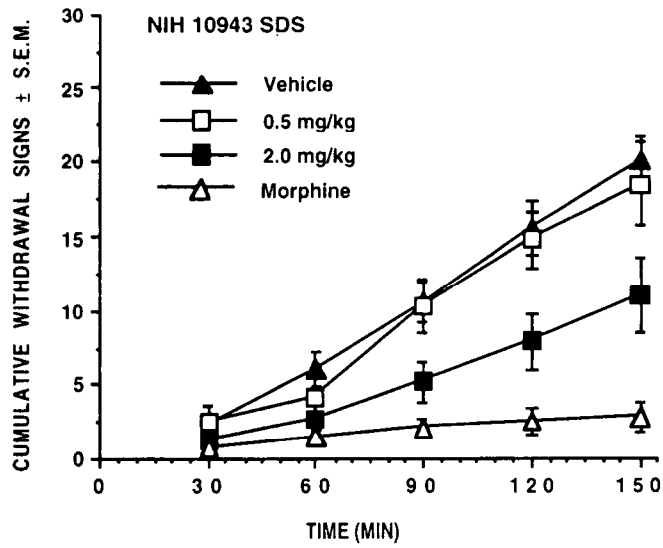
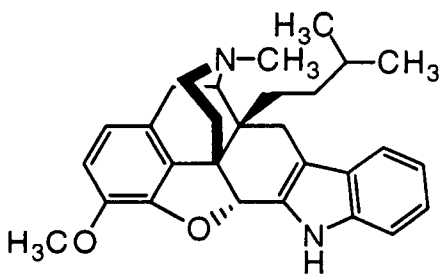


Fig NIH 10943. Results of study in which single doses of NIH 10943 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity suggests non specific central nervous and possibly autonomic effects.

NIH 10944 14-Isopentylhydrocodindole (+)-tartrate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 1% at 1, 3% at 10 and 6% at 30[a]
2) TF vs M - Inactive at 1, 10 and 30[a]
3) PPQ - 6% at 1, 9% at 10 and 37% at 30[a]
4) HP - 0% at 1, 13% at 10 and 0% at 30[a]

[a]Vehicle was 5% hydroxypropyl-β-cyclodextrin in water.

NIH 10944 (Continued)

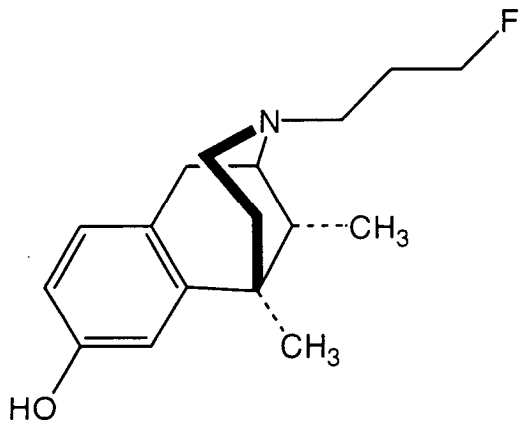
MONKEY DATA

(SDS)

A preliminary study in one monkey was conducted. With a cumulative dose of 11 mg/kg given in four 15 min doses of 1, 2, 4 and 4 respectively, NIH 10944 did not suppress or exacerbate withdrawal. Drug supply was exhausted. The compound was dissolved in 10% hydroxypropyl-β-cyclodextrin.

Comment: NIH 10944 does not seem to express opioid activity in the mouse or morphine-dependent monkey.

NIH 10949 (-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(3-fluoropropyl)-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)
1) TF - 8% at 1, 4% at 10 and 0% at 30[a]
2) TF vs. M - 0.31 (0.13 - 0.74)
3) PPQ - 0.59 (0.12 - 2.93)
4) HP - Inactive at 1, 10 and 30[b]

[a]Mice were very ataxic at 30.

[b]Increased locomotor activity at 30. Mice were very ataxic. Some mice vocalized and some had difficulty righting themselves.

Special Tests:

A - NIH 10949 as an agonist in the PPQ test

1) Naloxone (s.c.) vs ED_{80} of NIH 10949 (s.c.) in PPQ: AD_{50} = 1.32 (0.57 - 3.06).
2) Naltrindole (s.c.) vs ED_{80} of NIH 10949 (s.c.) in PPQ: AD_{50} = Inactive to 30.
3) nor-BNI (s.c.) vs ED_{80} of NIH 10949 (s.c.) in PPQ: AD_{50} = 14% at 1, 10 and 30.
4) β-FNA (i.c.v.) vs ED_{80} of NIH 10949 (s.c.) in PPQ: AD_{50} = Inactive to 30.

B - NIH 10949 as an antagonist the TF test

1) NIH 10949 (s.c.) vs ED_{80} of morphine (s.c.) in TF: AD50 = 0.32 (0.13 - 0.74).
2) NIH 10949 (s.c.) vs ED_{80} of NIH 10672 (Enadoline) (kappa agonist) in TF: AD_{50} = 0.96 (0.40 - 2.29).
3) NIH 10949 (s.c.) vs ED_{80} of DPDPE (delta agonist) (i.c.v.) in TF: AD_{50}= 0.34 (0.11 - 1.00).

NIH 10949 (Continued)

MONKEY DATA

1) SDS

As illustrated in the Fig NIH 10949-SDS, at doses of 0.05 and 0.2 mg/kg, this compound neither substituted for morphine nor exacerbated withdrawal.

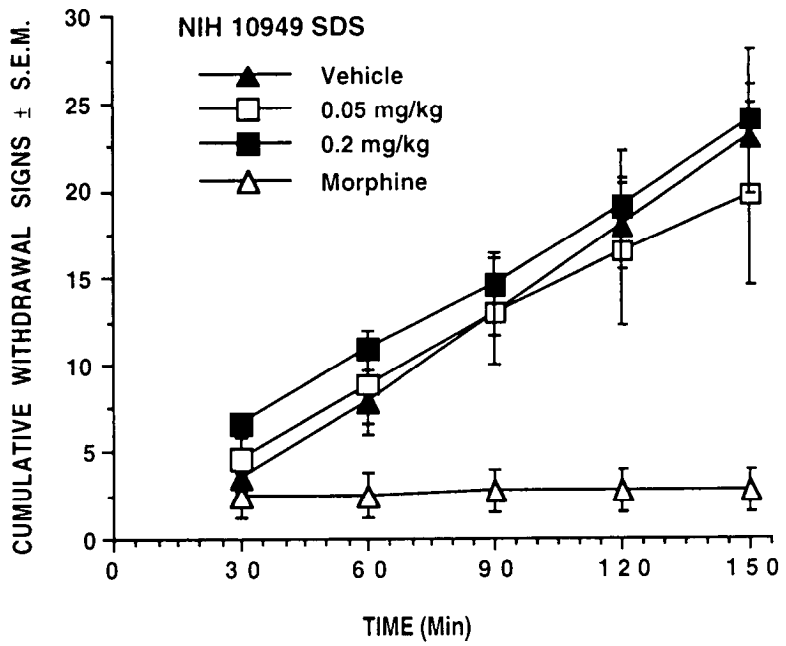


Fig NIH 10949-SDS. Results of study in which single doses of NIH 10949 were substituted for morphine in morphine-dependent monkeys in withdrawal.

MONKEY DATA

B. PPT-W

NIH 10949 precipitated withdrawal (Fig NIH 10949-PPt-W). The effect was immediate and dose-related. Potency was approximately one sixteenth that of naloxone. At the high dose, the signs designated jaw sag, slowing and salivation were noted suggesting that the drug might have other pharmacological properties.

NIH 10949 (Continued)

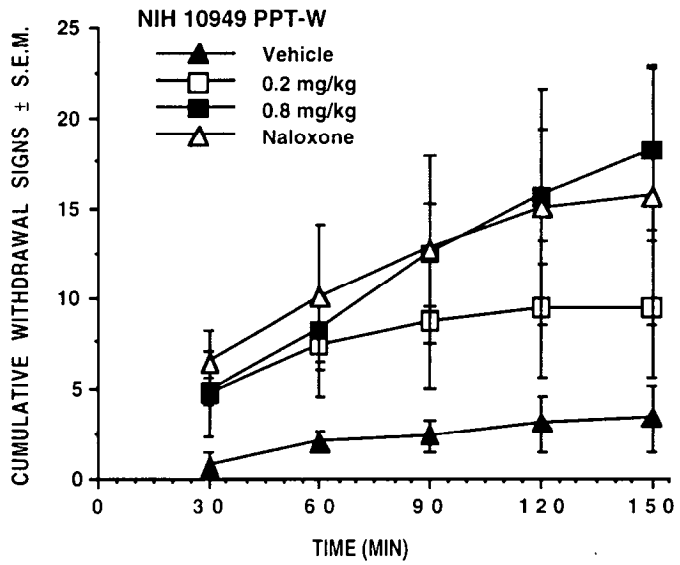
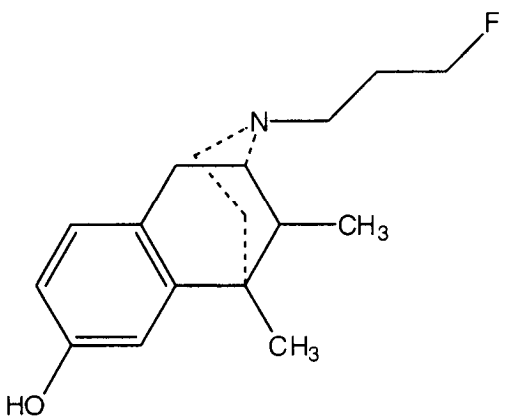


Fig NIH 10949-PPt-W. Results of precipitated withdrawal. to morphine-dependent monkeys 2 h after they had received morphine.

Comment: NIH 10949 has an unusual profile of activity. It produced antinociception unrelated to classical opioid subtype mechanisms yet, naloxone at a high dose was effective as an antagonist. It also displayed non-selective opioid antagonist properties. In the morphine-dependent monkey, it behaved as a weak mu-receptor antagonist.

NIH 10950 (+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(3-fluoropropyl)-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0% at 1, 14% at 10 and 3% at 30
2) TF vs. M - 0% at 1, 23% at 10 and 35% at 30
3) PPQ - 0% at 1, 6% at 10 and 43% at 30
4) HP - Inactive at 1 and 10, 13% at 30

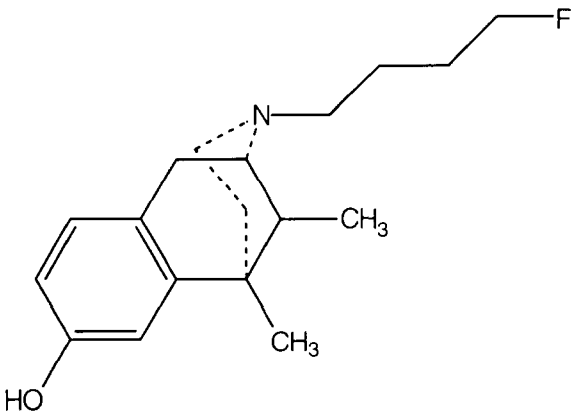
NIH 10950 (Continued)

MONKEY DATA
(SDS)

Not tested.

Comment: NIH 10950 has very weak mu-opioid antagonist activity.

NIH 10951 (+)-(2*S*,5*S*,9S)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

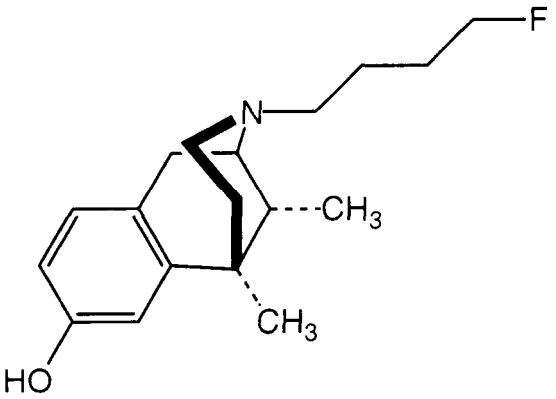
1) TF - Inactive to 30
2) TF vs. M - Inactive to 30
3) PPQ - 0% at 1, 26% at 10 and 0% at 30
4) HP - Inactive to 30

MONKEY DATA
(SDS)

Not tested.

Comment: This compound seems to be devoid of opioid activity.

NIH 10952 (-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan·HBr



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 2.41 (0.93 - 6.25)
3) PPQ - 19.12 (9.18 - 39.83)
4) HP - 0% at 1, 13% at 10 and 0% at 30

NIH 10952 (Continued)

MONKEY DATA

A. SDS

As can be seen in the Fig NIH 10952-SDS, NIH 10952 did not substitute for morphine at doses of 0.75 and 3.0 mg/kg. At the high dose, some evidence for exacerbation of withdrawal is noted. In addition to the elevated withdrawal scores, one monkey who is usually aggressive toward other pen mates, was more subdued after receiving drug. Perhaps higher doses would provide more definitive answers.

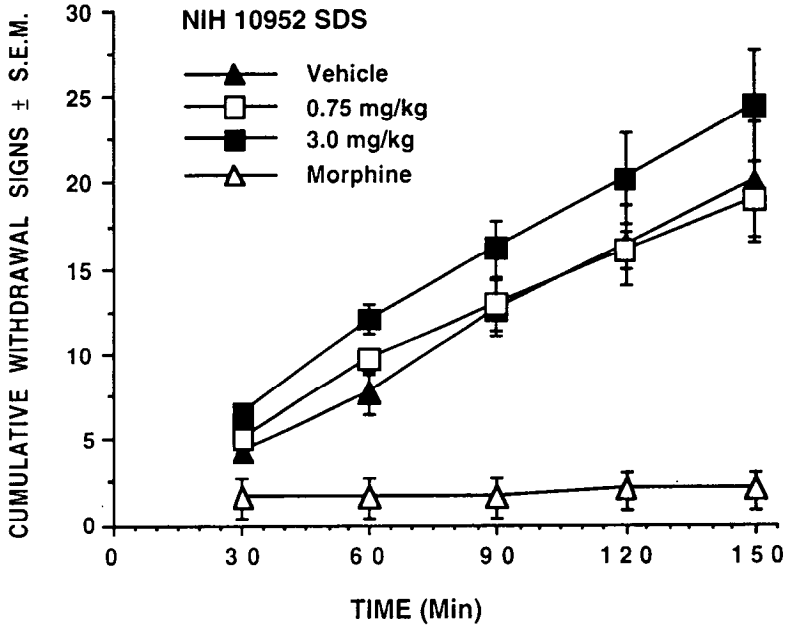


Fig NIH 10952-SDS. Results of study in which single doses of NIH 10952 were substituted for morphine in morphine-dependent monkeys in withdrawal.

MONKEY DATA

B. PPt-W

This compound exacerbated withdrawal, however, the results were not dose-related (See Fig NIH 10952-PPt-withdrawal). In addition to the unusual precipitated withdrawal signs, eyelid ptosis, slowing and salivation were noted at the high dose (6.0 mg/kg).

NIH 10952 (Continued)

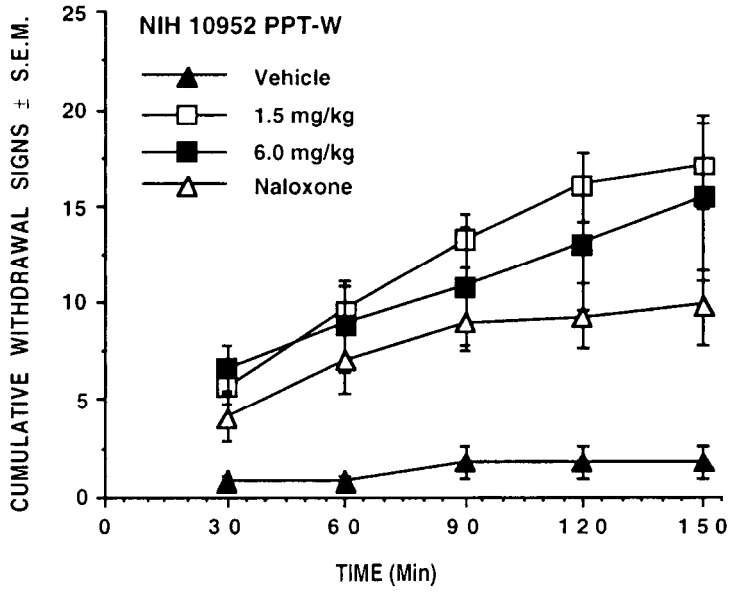
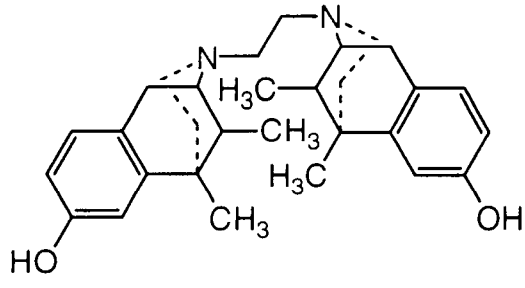


Fig NIH 10952-PPt-withdrawal. Results of precipitated withdrawal. Single doses of NIH 10952 were given to morphine-dependent monkeys 2 hr after they had received morphine.

Comment: In the mouse and monkey this compound manifests mu-opioid receptor antagonist effects. As an antagonist in the monkey, the potency estimate is 1/30 that of naloxone, the reference standard. In the mouse, some antinociceptive agonist properties are also evident. The signs slowing, eyelid ptosis and salivation in the monkey suggest other heterogeneous opioid-receptor subtype activity or extra-opioid effects.

NIH 10953 N,N'-[Bis-(+)-(2*S*,5S,9*S*)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan]-1,2-ethane•2HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 6% at 1, 34% at 10 and 19% at 30
3) PPQ - 20% at 1, 20% at 10 and 17% at 30
4) HP - Inactive at 1, 10 and 30

MONKEY DATA

(SDS)

At the low dose, NIH 10953 appeared to attenuate withdrawal signs (see Fig NIH 10953). However, the incidence of important signs designated, vocalization when palpated and rigid abdomen were not reduced. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 10953 (Continued)

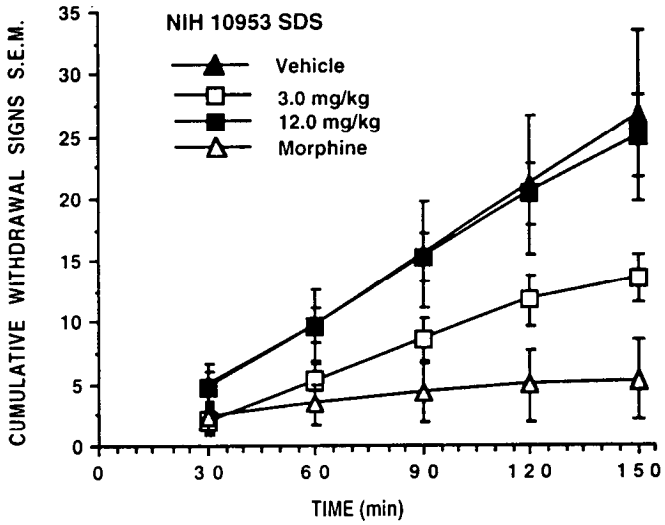
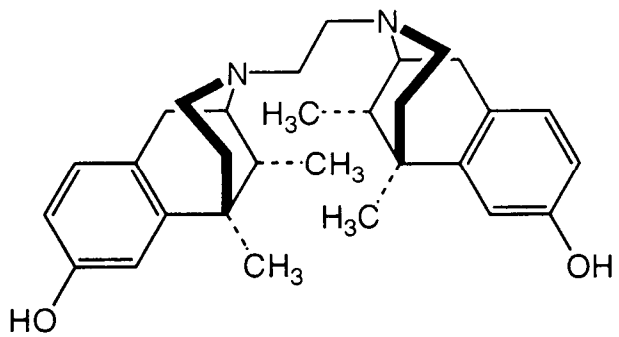


Fig NIH 10953. Results of study in which single doses of NIH 10953 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The effects noted for this compound in the mouse or monkey were not remarkable and do not implicate opioid mechanisms.

NIH 10954 N,N'-[Bis-(-)-(2 *R*,5*R*,9R)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan]-1,2-ethane•2HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3% at 1,0 % at 10 and
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 6% at 1,9% at 10 and 6% at 30
4) HP - 0% at 1 and 10, 15% at 30

MONKEY DATA

(SDS)

As doses of 4 and 16 mg/kg, NIH 10954 neither substituted for nor exacerbated withdrawal (see Fig NIH 10954).

NIH 10954 (Continued)

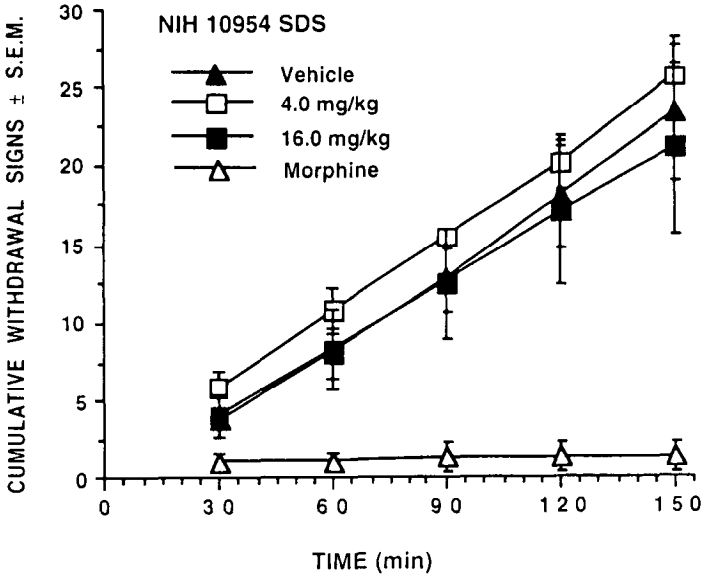
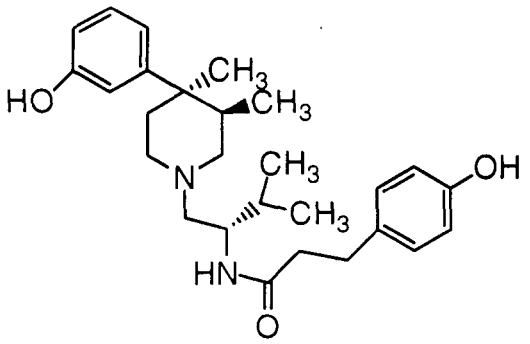


Fig NIH 10954 Results of study in which single doses of NIH 10954 were substituted for morphine in morphine-dependent monkeys in withdrawal,

Comment: NIH 10954 seems devoid of antinociceptive effects in mice and mu-opioid properties in morphine-dependent monkeys.

NIH 10955 (+)-4-Hydroxy-N-(1 *S*-((3-hydroxyphenyl)-3 *R*,4*R*-dimethyl-1-piperidinyl]l-methyl-2-methylpropyl-1-benzenepropanamide•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 3% at 1,0 % at 10 and
2) TF vs. M - Inactive at 1, 10 and 30
3) PPQ - 0% at 1, 40% at 10 and 49% at 30
4) HP - 0% at 1, 13% at 10 and 0% at 30

NIH 10955 (Continued)

MONKEY DATA

(SDS)

As shown in the figure below (Fig NIH 10955), at the high dose, NIH 10955 appeared to attenuate withdrawal after a delay of 90 m. Supply precluded additional testing. Vehicle was 10% hydroxypropyl-β-cyclodextrin aqueous solution.

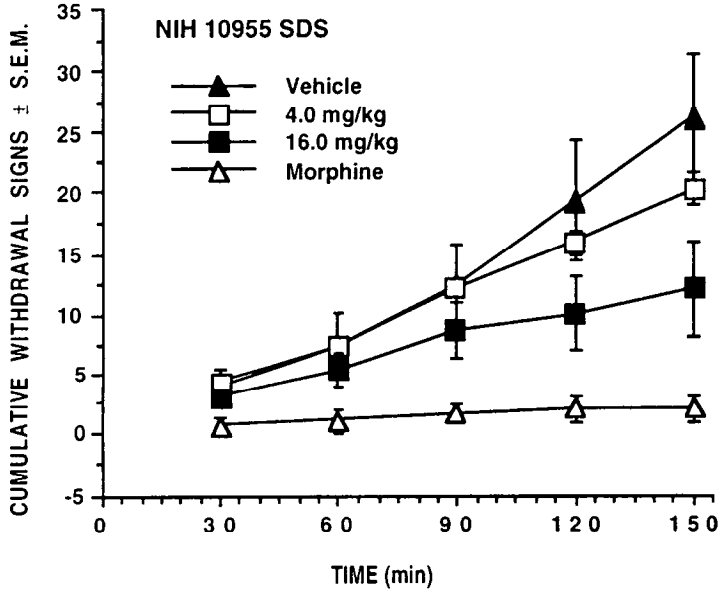
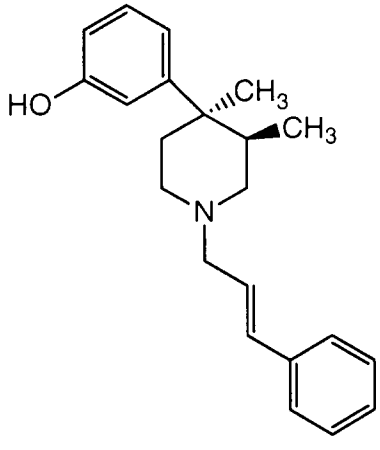


Fig NIH 10955-SDS. Results of study in which single doses of NIH 10955 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Lack of antinociceptive activity and opioid antagonist effects in mice coupled with weak effects in the morphine-dependent monkey do not portend remarkable mu-opioid properties.

NIH 10956 (+)-N-(*trans*-4'-Phenyl-2'-butenyl)-(3 *R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine fumarate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 0% at 1, 4% at 10 and 10% at 30[a]
2) TF vs. M - 0.02 (0.01 - 0.04)[a]
3) PPQ - 5.94 (3.05 - 11.54)[a]
4) HP - 0% 1, 13% at 10 and 38% at 30[a]

[a]Dilute HCl or 5% hydroxypropyl-β-cyclodextrin in water or lactic acid in water.

NIH 10956 (Continued)

Special:

A. NIH 10956 as an agonist in the PPQ test

1) Naloxone (s.c.) vs ED80 of NIH 10956 (s.c.): Inactive at 0.1, 1 and 10 mg/kg.
2) nor-BNI (s.c.) vs ED80 of NIH 10956 (s.c.): 7% at 1, 14% at 10 and 10% at 30.
3) β-FNA (i.c.v.) vs ED_{80} of NIH 10956 (s.c.): 0% antagonism at 1, 10, and 30 μg/brain
4) Naltrindole (s.c.) vs ED_{80} of NIH 10956 (s.c.): 0% at 1, 7% at 10 and 14% at 30.

B. NIH 10956 as an antagonist in TF test

1) NIH 10956 (s.c.) vs ED_{80} of DPDPE (i.c.v.): AD_{50} = 0.03 (0.01 - 0.09).
2) NIH 10956 (s.c.) vs ED_{80} of NIH 10672 (Enadoline) (i.c.v.): AD_{50} = 0.21 (0.06 - 0.71).
3) NIH 10956 (s.c.) vs ED_{80} of morphine (s.c.): (see AD_{50} above).

MONKEY DATA

A. SDS

NIH 10956 exacerbated withdrawal (see Fig NIH 10956-SDS below). The drug acted promptly and the duration of action was at least 2.5 hr. Potency was in the naloxone range. One monkey at the low dose had a severe episode of vomiting. Precipitated withdrawal testing is recommended. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

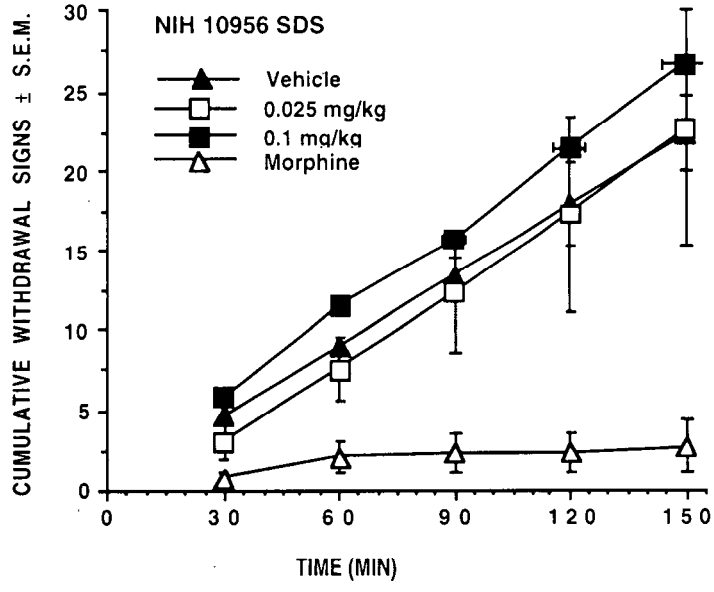


Fig NIH 10956-SDS. Results of study in which single doses of NIH 10956 were substituted for morphine in morphine-dependent monkeys.

NIH 10956 (Continued)

MONKEY DATA

B. PPt-W

This compound precipitated withdrawal (See Fig NIH 10956 PPt-withdrawal). Curiously, it appeared to be as active or slightly more active at the low dose. Perhaps, other CNS properties interfered with the expression of withdrawal signs at the higher dose producing a "ceiling" effect. The drug acted promptly and its duration of action was longer than that of the control naloxone. Potency is estimated as 1/2 that of naloxone.

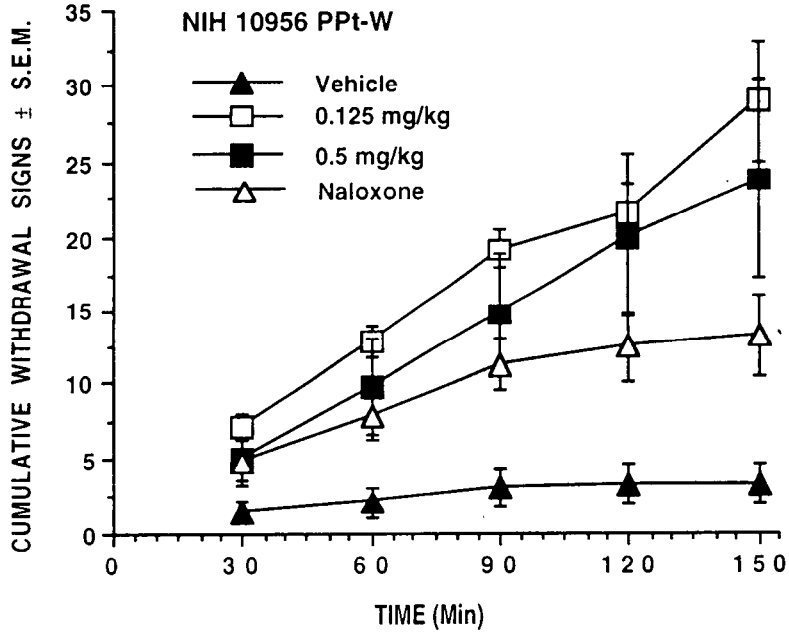
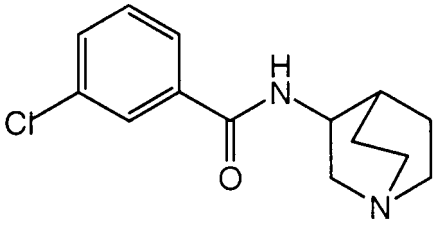


Fig NIH 10956- PPt-withdrawal. Results of precipitated withdrawal. Single doses of NIH 10956 were given to morphine-dependent monkeys 2 hr after they had received morphine.

Comment: In the mouse, NIH 10956 is a potent non-selective antagonist versus mu-, kappa- and delta-opioid agonists. Interestingly, as an agonist in the PPQ test, non-opioid activity was manifested. In the morphine-dependent monkey, it displays mu-opioid antagonist properties.

NIH 10957 3-Chloro-N-(3-quinuclidinyl)benzamide



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30[a]
2) TF vs. M - Inactive at 1, 10 and 30[a]
3) PPQ - 38.05 (17.00 - 85.23)[a]
4) HP - 13% at 1 and 0% at 10 and 30[a]

[a]Vehicle was 0.1 N HCl.

NIH 10957 (Continued)

MONKEY DATA

(SDS)

At doses of 4.5 and 18.0 mg/kg, NIH 10957 did not substitute for morphine or exacerbate withdrawal (see Fig NIH 10957).

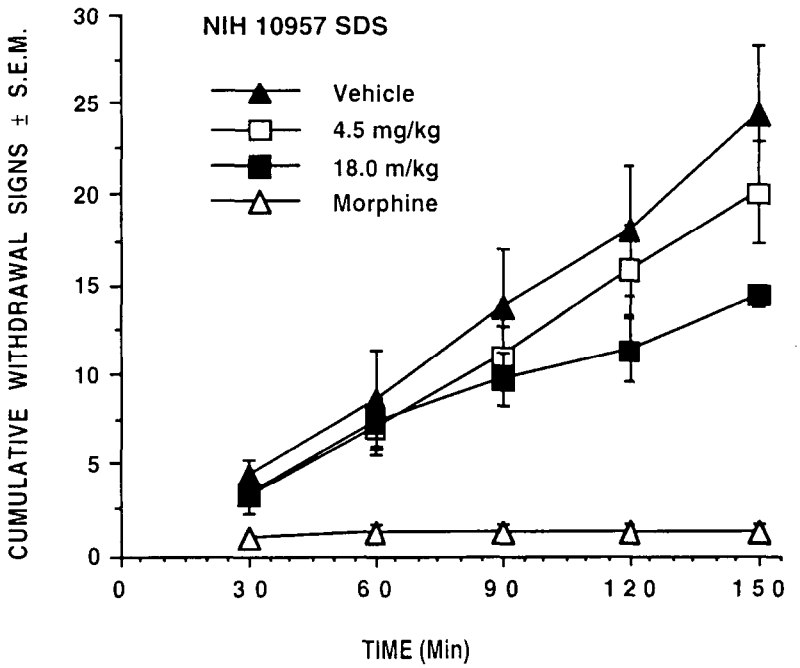
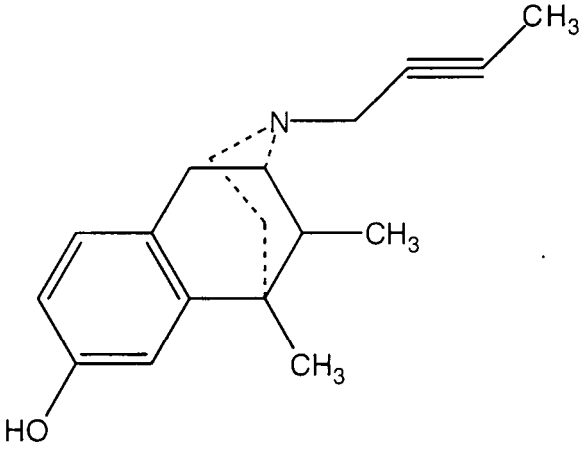


Fig NIH 10957. Results of study in which single doses of NIH 10957 were substituted for morphine in morphine-dependent monkeys.

Comment: The results in mice and morphine-dependent monkeys do not portend remarkable opioid properties.

NIH 10958 (+)-2*S*,5*S*,9*S*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 6.68 (2.40 - 18.62)
3) PPQ - 23% 1, 20% at 10 and 17% at 30
4) HP - Inactive at 1, 10 and 30

MONKEY DATA

(SDS)

This compound did not substitute for morphine at doses of 1 and 4 mg/kg. Neither did it exacerbate withdrawal. The results are shown in the figure designated Fig NIH 10958.

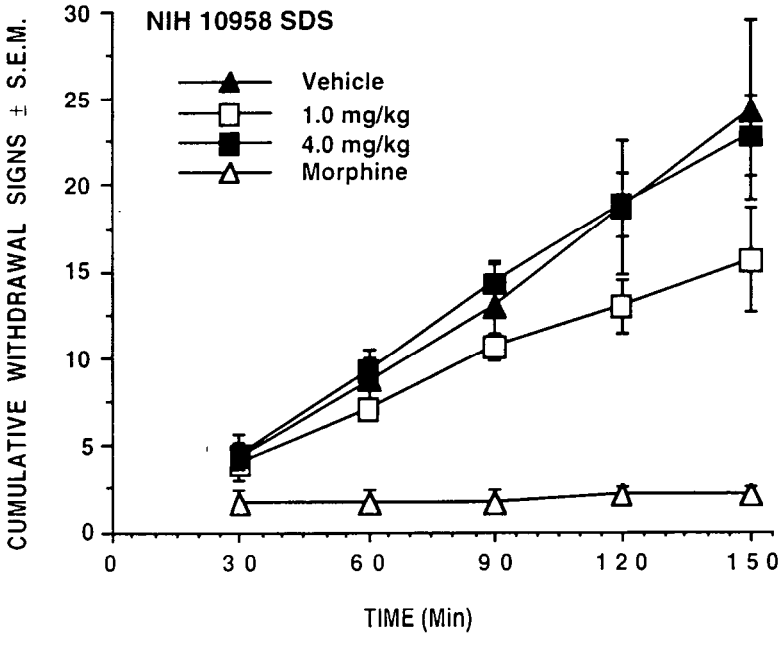
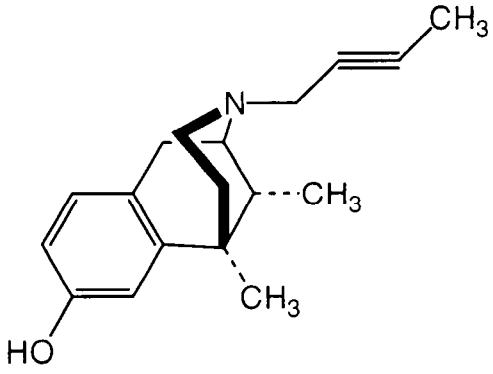


Fig NIH 10958. Results of study in which single doses of NIH 10958 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Based on the results in the mouse assay, NIH 10958 has very weak opioid antagonist properties. In morphine-dependent monkeys, at doses of 1 and 4 mg/kg the compound neither substituted for morphine nor exacerbated withdrawal.

NIH 10959 (-)-2*R*,5*R*,9*R*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 11% at 1, 0% at 10 and 3% at 30[a]
2) TF vs. M - 0.32 (0.14 - 0.72)
3) PPQ - 0. 1 (0.04 - 0.25)
4) HP - 0% at 1, 13% at 10 and 0% at 30
[a]Ataxia and decreased locomotor activity.

Special Tests:

1) Naloxone vs ED80 of NIH 10959 in PPQ test = 2.9 (1.4 - 5.9).
2) Nor BNI vs ED80 of NIH 10959 in PPQ test = Inactive at 1, 10 and 30.
3) Naltrindole vs ED80 of NIH 10959 in PPQ test = Inactive at 1, 10 and 30.

MONKEY DATA

SDS

NIH 10959 did not substitute for morphine at doses of 0.25 and 1.0 mg/kg as depicted in the accompanying figure designated NIH 10959-SDS. Some eyelid ptosis was noted at 1.0 mg/kg. In one experiment a monkey received 2.0 mg/kg (data not shown in figure). In this monkey, severe vomiting developed during the first 1/2 hr. Morphine was given, however, withdrawal signs were still evident 1 hr post morphine.

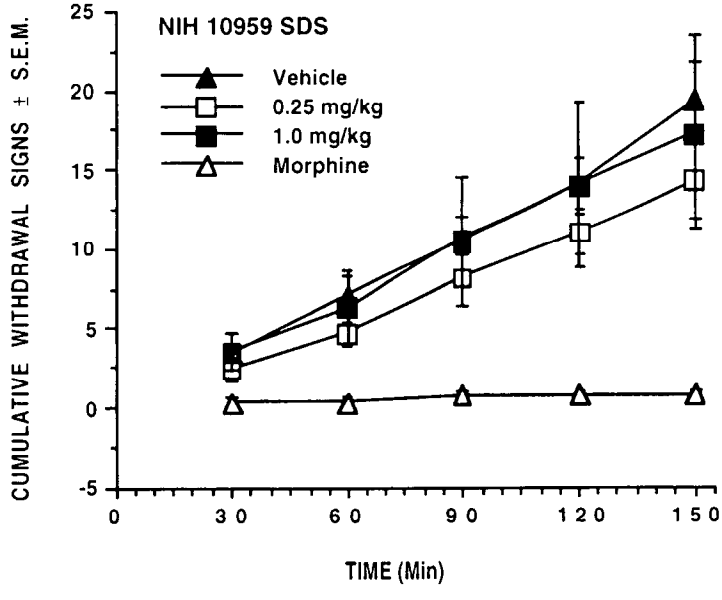


Fig NIH 10959-SDS. Results of study in which single doses of NIH 10959 were substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 10959 (Continued)

MONKEY DATA
B. PPt-W

NIH 10959 was also tested for its ability to precipitate withdrawal in morphine-dependent subjects. It promptly precipitated withdrawal in a dose-dependent manner. The drug is approximately 1/5 as potent as naloxone and has a similar duration of action (see Fig NIH 10959-PPt-W). Some eyelid ptosis, salivation and ataxia were noted.

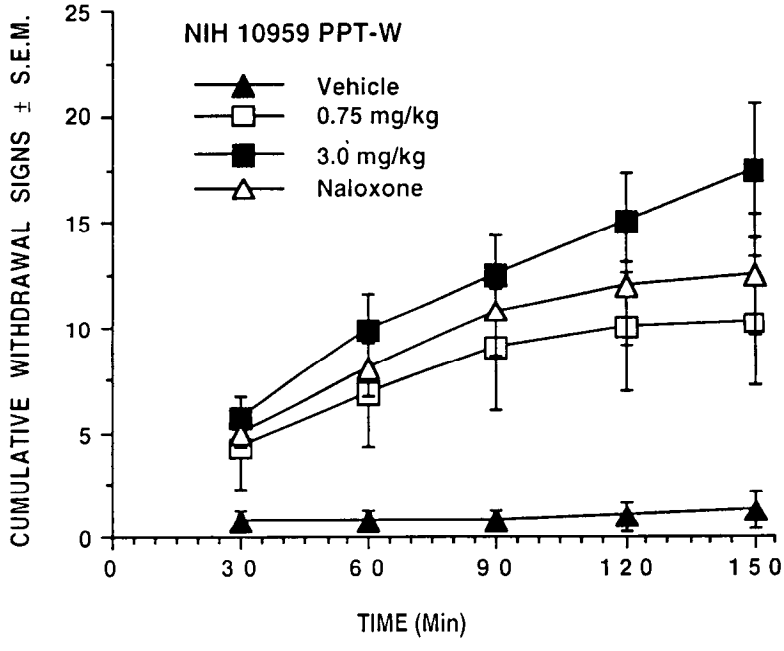
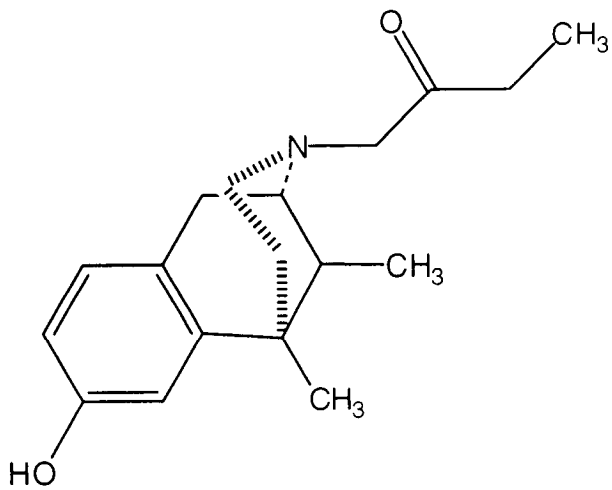


Fig NIH 10959-PPt-W. Results of precipitated withdrawal. Single doses of NIH 10959 were given to morphine-dependent monkeys 2 hr after they had received morphine.

Comment: The data in the mouse and monkey indicate that NIH 10959 is an opioid antagonist.

NIH 10960 (+)-2S,5S,9S)-2-(2-Butan-2-one)-5,9-dimethyl-2'hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 0R AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 10, 10 and 30
2) TF vs. M - 16% at 1, 0% at 10 and 30
3) PPQ - 4%: at 1, 6% at 10 and 9% at 30
4) HP - 25% at 1, 0% at 10 and 30

MONKEY DATA

(SDS)

Although NIH 10960 reduced the total number of withdrawal signs, the effect was not dose-related and variability of the data was high (see Fig NIH 10960). The results suggest non-opioid effects. At the high dose, jaw sag and eyelid ptosis were noted in 1 of 4 monkeys tested.

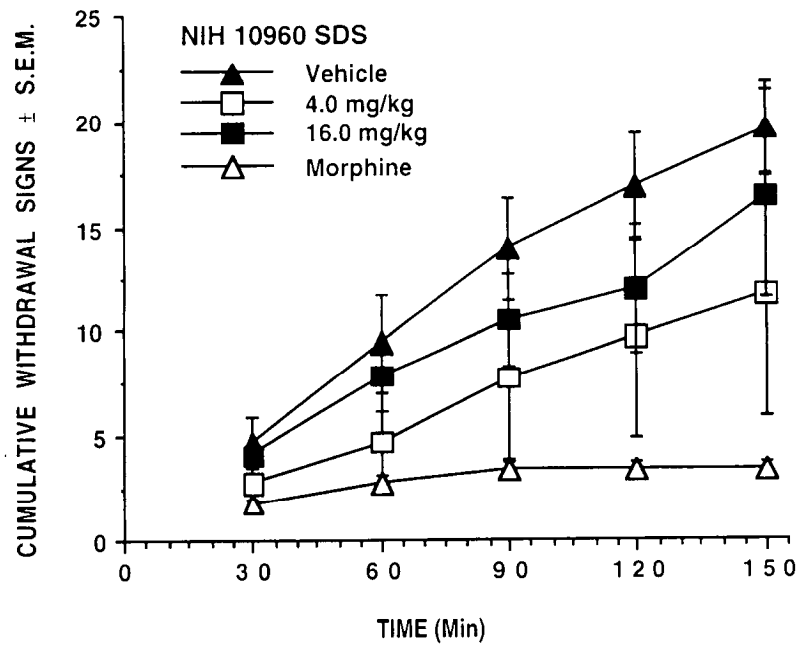
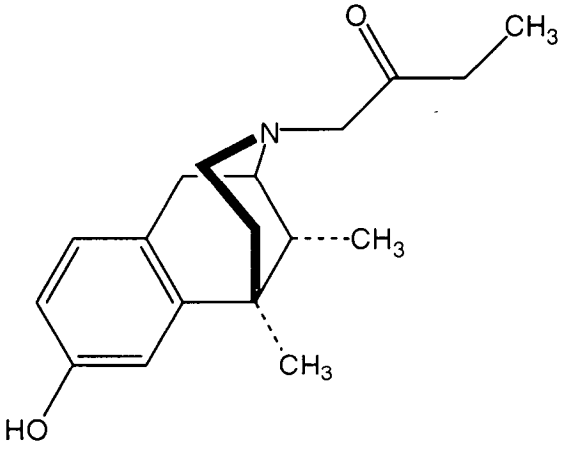


Fig NIH 10960. Results of study in which single doses of NIH 10960 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in the mouse and monkey are not indicative of remarkable opioid properties.

NIH 10961 (-)-2*R*,5*R*,9*R*)-2-(2-Butan-2-one)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan•HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30
2) TF vs. M - 5.08 (1.87 - 13.82)
3) PPQ - 3% at 1, 0% at 10 and 31% at 30
4) HP- 13% at 1, 10 and

MONKEY DATA
(SDS)

This compound neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys in spontaneous withdrawal at 15 hr (See Fig NIH 10961). Some myoclonic jerks were noted at the high dose.

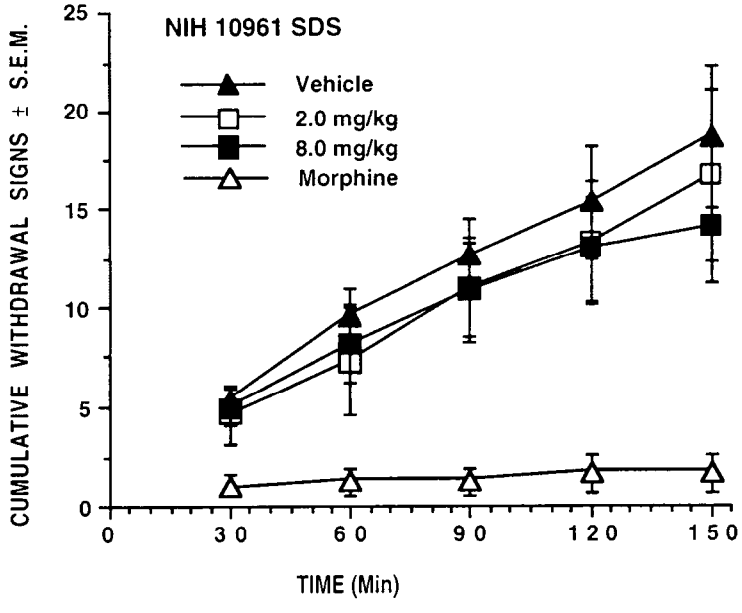
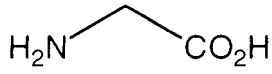


Fig NIH 10961. Results of study in which single doses of NIH 10961 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: All in all, NIH 10961 does not manifest remarkable opioid activity. It should be noted however, that in the mouse some weak mu-opioid receptor activity was noted.

NIH 10962 Clycine·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - 7% at 1, 0% at 10 and 30
2) TF vs. M - 4% at 1,9% at 10 and 11% at 39
3) PPQ - 3% at 1 and 10, 6% at 30
4) HP - 0% at 1, 25% at 10 and 30

MONKEY DATA
SDS

Not Tested.

Comment: Glycine is an important inhibitory neurotransmitter, Apparently. it is devoid of analgesic effects.

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ACKNOWLEDGMENTS

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EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (1999)

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This report contains information on opioid abuse liability evaluations on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained usually involves *in vitro* evaluation in opioid binding assays. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys. Each of these assays is described below. Usually when limited information is provided (*e.g., in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is coordinated by Dr. Arthur E. Jacobson, Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, MD. The compounds, which come originally from pharmaceutical companies, universities, government laboratories, and international organizations are submitted to Dr. Jacobson.

At the UM and MCV laboratories, drug samples arrive from Dr. Jacobson with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information and (4) a recommended starting dose. After the evaluation is complete and the report submitted to Dr. Jacobson, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported herein.

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts 15-min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced

during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete, 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively (*i.e.,* fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 mg/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.,* irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.,* alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (*i.e.,* precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (*i.e.,* withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during

the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40°C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.,* alfentanil) or κ (*e.g.,* U-50,488) opioid agonist.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 1/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g.,* alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four

components of a session. Other procedural details are given in Winger *et al.* (1989).

OPIOID RECEPTOR BINDING AND IN VITRO EFFICACY ASSESSMENT

Details of the binding assay based on the displacement of ^{3}H-ligands in monkey cortex membranes have been described previously (Emmerson et al., 1994). Briefly, aliquots of a membrane preparation from monkey cortex are incubated with ^{3}H-DAMGO (μ), ^{3}H-DPDPE (δ) or ^{3}H-U69593 (κ) in the presence of different concentrations of the drug under investigation at 25° C for 1 hr. Specific, *i.e.,* opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10μM naloxone. The potency of the drugs in displacing the specific binding of ^{3}H-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted to Ki values by the method of Cheng and Prussoff (1973). In some cases μ and δ binding was performed in membranes from C_6 rat glioma cells expressing recombinant μ (rat) or δ (rat). The binding assay in cell homogenates expressing the μ opioid receptor (Emmerson et al., 1994) or δ-opioid receptor (Clark et al., 1997) is essentially as the monkey cortex assay but using 25 μg protein and [^{3}H]diprenorphine (0.3 nM) as the radioligand. The affinity (Kd) values of [^{3}H]diprenorphine at the receptors are: μ (0.15 nM);δ (0.45 nM).

The selection of **monkey brain** as the tissue for the selective binding assays strengthens the correlation between this in vitro assessment and the behavioral evaluation of the tested compounds. The use of recombinant receptors means no cross-reaction with other receptors and allows for direct comparison with cellular functional assays. In the **ANNUAL REPORT,** the results of the selective binding assays are given as means ± SEM from three separate experiments, each performed in duplicate. Ki values for standard compounds in the monkey brain cortex assay are: μ (DAMGO, 0.79nM; morphine 1.06 nM),δ (BW373U86,0.32 nM) and κ (U69593,0.87 nM), and using recombinant receptors and [^{3}H]diprenorphine as radioligand are: μ (DAMGO, 7.6 nM; morphine, 11.2 nM),δ (SNC80, 0.8 nM).

[35S]GPγS assays are carried out using membranes from C6 cells expressing either mu (Emmerson et al., 1996) or delta (Clark et al., 1997) receptors or CHO cells expressing kappa receptors (Zhu et al., 1997). Assays are performed as described by Traynor and Nahorski (1995). Values are given as EC_{50} with % effect compared to standard agonist (DAMGO, SNC80, or U69593) or as maximal stimulation achieved at 3 μM.

EC_{50} values (nM) for standard compounds are as follows:

Mu receptor:	morphine (28.3), DAMGO (16.4)
Delta receptor:	SNC80 (67.0), DPDPE (330)
Kappa receptor:	U69593 (31.0), bremazocine (0.5)

DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standard SNC80 and U69593. Morphine and DAMGO give equivalent responses.

NIH #	SA	BINDING		DD	ANLG	RSP	Date Submitted to Biol. Coordinator
		MC	GTPγS				
10954		X					05 Nov 1998
10955		X	X				05 Nov 1998
10956		X	X				05 Nov 1998
10957		X					05 Nov 1998
10959		X	X				09 Dec 1998
10960		X					14 Apr 1999
10961		X					09 Dec 1998

MC = Monkey Cortex

* All assays were performed using monkey cortex except those labeled with an asterisk (*), in which case, μ and δ binding were performed in C6 cells expressing recombinant receptors.

SUMMARY OF TESTS PERFORMED

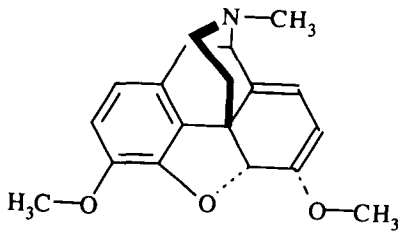
The compounds which were evaluated at the University of Michigan during the past year, and the individual tests which were performed are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator, Dr. A.E. Jacobson, in which results are reported.

SUMMARY OF TESTS PERFORMED

NIH #	SA	BINDING		DD	ANLG	RSP	Date Submitted to Biol. Coordinator
		MC	GTPγS				
00088		X*					08 Oct 1998
09821		X*					08 Oct 1998
10890		X					10 Mar 1998
10910		X					30 Mar 1997
10911		X					30 Mar 1997
10912		X					30 Mar 1997
10913		X					02 Jun 1997
10914		X					02 Jun 1997
10919		X			X		08 Oct 1997 18 Jun 1997
10936		X					02 Jan 1998
10941			X				14 May 1999
10942		X	X				19 Jan 1998
10943		X					09 Dec 1998
10944		X					20 Mar 1998
10949		X*	X				08 Oct 1998
10950		X*					08 Oct 1998
10951		X					05 Nov 1998
10952		X	X				05 Nov 1998
10953		X					05 Nov 1998

NIH 00088

(-)-Thebaine hydrochloride



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 860 ± 158
δ-receptor: >10 μM (28.3 % inhibition at 10 μM)
κ-receptor: 1377 ± 154

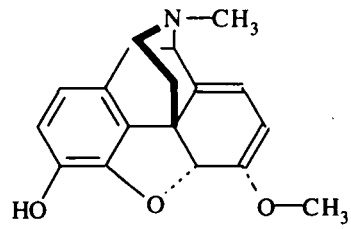
SUMMARY

NIH 00088 had low affinity for μ and κ receptors, and extremely low affinity for the δ receptor.

* * *

NIH 09821

(-)-Oripavine hydrochloride



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 20.3 ± 3.4
δ-receptor: 89.2 ± 22.1
κ-receptor: 107.1 ± 29.3

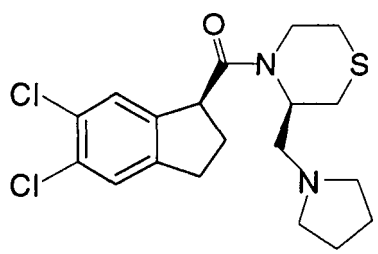
SUMMARY

NIH 9821 had good affinity for μ receptors, and was slightly selective for μ over κ (5-fold) and δ (4-fold) receptors.

* * *

NIH 10890

(3*R*)-3-(1-Pyrrolidinylmethyl)-4-[(1*S*)-5,6-dichloro-1-indancarbonyl]-tetrahydro-1,4-thiazine.HCl



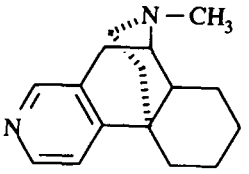
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 77.5
δ-receptor: 1900
κ-receptor: 0.0199

SUMMARY

NIH 10890 was highly selective for the kappa opioid receptor; marked by its very, very high affinity for this site. It would be appropriate to examine in vivo for kappa activity.

NIH 10910 **(+)-N-Methyl-2-azamorphinan dihydrobromide**



OPIOID RECEPTOR BINDING

μ-receptor: 2.87 ± 0.78 μM
δ-receptor: >> 10 μM (0% inhibition at 10 μM)
κ-receptor: >10 μM (29.0 ± 2.9% inhibition at 10 μM)

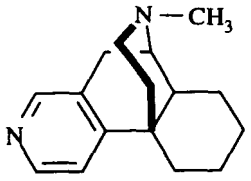
NOTE: A very small amount (0.001g) of non-crystalline compound was provided for this study which did not allow for three fully independent assays of separate samples of the material. This should be considered when interpreting the results.

SUMMARY

NIH 10910 had poor affinity for the μ opioid receptor, approximately 3500 times less than the standard μ peptide, DAMGO. However, it does appear to have some degree of selectivity for μ- over κ- and especially δ-opioid receptors at which no binding could be observed.

* * *

NIH 10911 **(-)-N-Methyl-2-azamorphinan dihydrobromide**



OPIOID RECEPTOR BINDING

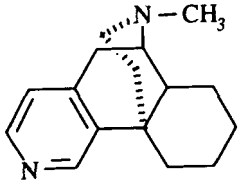
μ-receptor: 1.31 ± 0.16 μM
δ-receptor: >> 10 μM (0% inhibition at 10 μM)
κ-receptor: >10 μM (47.9 ± 3.7% inhibition at 10 μM)

SUMMARY

NIH 109 11 had poor affinity for the μ opioid receptor, approximately 1600 times less than the standard δ-opioid receptors at which no binding could be observed.

* * *

NIH 10912 **(+)-N-Methyl-3-azamorphinan dihydrobromide**



OPIOID RECEPTOR BINDING (nM)

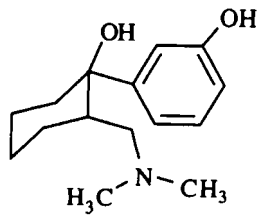
μ-receptor: 14.12 ± 1.58
δ-receptor: 971 ± 267
κ-receptor: 344 ± 62.8

NOTE: A very small amount (0.014g) of non-crystalline compound was provided for this study which did not allow for three fully independent assays of separate samples of the material. This should be considered when interpreting the results.

SUMMARY

NIH 10912 had high affinity for the μ-opioid receptor, approximately 18-times less than the standard μ peptide, DAMGO. It also recognizes δ- and κ-opioid receptors, but has a δ/μ selectivity ratio of 69 and a κ/μ selectivity ratio of 24.

NIH 10913



***trans*-(±)-2-[(Dimethylamino)methyl]-1-(2-hydroxyphenyl)cyclohexanol hydrochloride**

OPIOID RECEPTOR BINDING (nM)

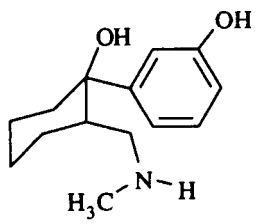
μ-receptor:	45.8 ± 10.8
δ-receptor:	3390 ± 1210
κ-receptor:	2390 ± 420

SUMMARY

NIH 10913 has affinity for the μ-opioid receptor, approximately 80-times less than the standard μ-peptide DAMGO. It has some selectivity for the μ-receptor over δ- and κ-receptors with a δ/μ selectivity ratio of 74 and a κ/μ selectivity ratio of 52.

* * *

NIH 10914



***trans*-(±)-2-[(Methylamino)methyl]-1-(2-hydroxyphenyl)cyclohexanol hydrochloride**

MONKEY CORTEX OPIOID RECEPTOR BINDING

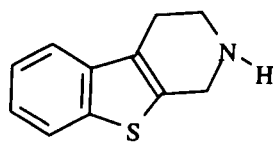
μ-receptor:	289.6 ± 23.1 nM
δ-receptor:	>10 μM (40.9 ± 7.1% inhibition at 10 μM)
κ-receptor:	>10 μM (46.3 displacement at 10 μM)

SUMMARY

NIH 109 14 has some degree of affinity for the μ-opioid receptor, approximately 500-times less than the standard μ-peptide DAMO and 6 times less than NIH 10913. It has some selectivity for the μ-receptor over δ- and κ-receptors with δ/μ and κ//μ selectivity ratios of >34.

* * *

NIH 10919



1,2,3,4-Tetrahydrobenzo[b]thieno[2,3-c]pyridine hydrochloride

OPIOID RECEPTOR BINDING

μ-receptor:	>10 μM (30.4 ± 2.0% inhibition at 10 μM)
δ-receptor:	>10 μM (16.0 ± 3.3% inhibition at 10 μM)
κ-receptor:	>10 μM (5.0 ± 8.0% inhibition at 10 μM)

THERMAL ANALGESIA IN RHESUS MONKEYS

NIH 10919 was given on two occasions to the same three monkeys. Effects on opioids in this thermal analgesic assay are given in a number of references (e.g., Woods et al., NIDA Res. Monogr., 162:376-407, 1996). Opioid agonists active at either μ or κ receptors are effective as are a number of compounds of a non-narcotic nature, especially clonidine-like and phencyclidine-like compounds.

NIH 10919 (continued)

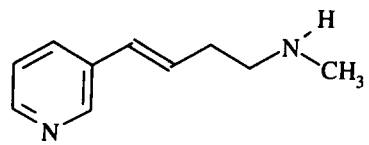
NIH 10919 was administered first in a set of doses ranging from 0.003-0.3 mg/kg s.c. with 30 minute intervals between injections. On a second occasion, separated by 7 days, the compound was injected at higher set of doses (0.32-32 mg/kg). Only on the second occasion was there any indication of very slight analgesic effect at 32 mg/kg, and following this dose, the effect was minimally detected in 50° C water. Thus, at these doses, the compound does not appear to produce significant thermal analgesia. At 32 mg/kg, there appeared to be other behavioral (motor function slowed) and potential cardiovascular effects (e.g., pale face)

SUMMARY

NIH 10919 had very low affinity for μ-, δ-, and κ-opioid receptors (>> 1000 times less than the standard agonists at these receptors) and very weak analgesic effects

* * *

NIH 10936 **Metanicotine.oxalate**



OPIOID RECEPTOR BINDING

μ-receptor:	7.0 ± 3% inhibition at 10 μM
δ-receptor:	19.0 ± 1.5% inhibition at 10 μM
κ-receptor:	6.3 ± 5.3% inhibition at 10 μM

SUMMARY

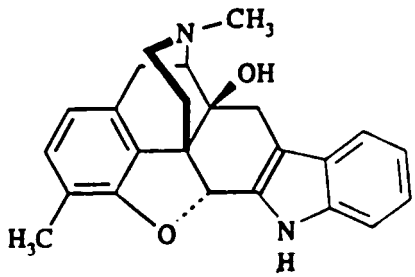
NIH 10936 had no binding affinity at μ-, δ- and κ-opioid receptors.

* * *

NIH 10941 **3-Deoxy-3-methyloxymorphindole.HCl**

[^{35}S]GTPγS BINDING
EC$_{50}$ (Maximal Stimulation)

μ-receptor:	Not tested
δ-receptor:	9.7 ± 2.0% stimulation at 3 μM
κ-receptor:	Not tested

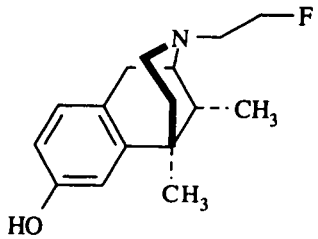


SUMMARY

The binding data were reported last year. NIH 10941 had affinity for δ opioid receptors, but this was approximately 150-fold less than the affinity of DPDPE. It was also at least 30-fold selective for the δ- over μ- and κ-receptors. In the GTPγS binding assay, it had little efficacy at δ receptors, and was not examined at μ and μ receptors due to its very low binding affinity.

NIH 10942

(-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluoroethyl)-2'-hydroxy-6,7-benzomorphan hydrochloride



OPIOID RECEPTOR BINDING (nM)		[^{35}S]GTPγS BINDING EC_{50} (Maximal Stimulation)
μ-receptor:	7.5 ± 1.6	17.3 ± 3.4% @ 3 μM
δ-receptor:	25 ± 3.4	23.7 ± 4.6% @ 3 μM
κ-receptor:	1.0 ± 0.2	26.4 ± 3.0 nM (maximal effect = 81.5 ± 1.1%)

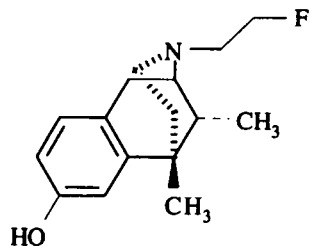
SUMMARY

NIH 10942 had good affinity for all opioid receptors, with highest affinity at the -receptor, for which it had limited selectivity. It was a good, potent κ agonist that produced only a weak agonist signal at μ and δ receptors. Thus, the compound would be predicted to be a mixed agonist (κ))-antagonist (μ and δ receptors).

* * *

NIH 10943

(+)-(2*S*, 5*S*, 9*S*)-5,9-Dimethyl-2-(2-fluoroethyl)-2'-hydroxy-6,7-benzomorphan hydrochloride



OPIOID RECEPTOR BINDING (nM)

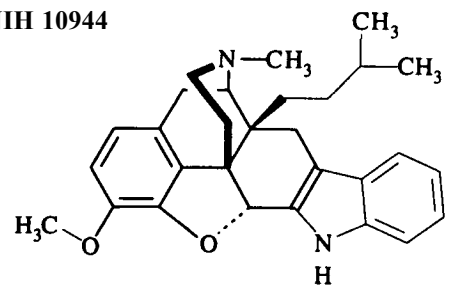
μ-receptor:	395 ± 91
δ-receptor:	2421 ± 75
κ-receptor:	383 ± 41

SUMMARY

NIH 10943 had low, but equal, affinity for μ and κ opioid receptors, and even lower affinity for δ receptors.

* * *

NIH 10944



14-Isopentylhydrocodindole (+)-tartrate

OPIOID RECEPTOR BINDING (nM)

μ-receptor:	530 ± 117
δ-receptor:	45.9 ± 2.8
κ-receptor:	4396 ± 400

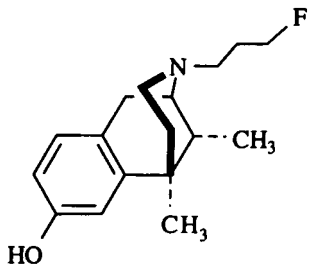
NIH 10944 (continued)

SUMMARY

NIH 10944 reasonable affinity for the δ opioid receptor (approximately 1/20th of that for DPDPE) and is 12-fold selective for δ over μ and 96-fold selective for δ over κ.. The compound will soon be assessed for δ receptor efficacy.

* * *

NIH 10949 **(-)-(2*R*,5*R*,9*R*)-5,9-Dimethyl-2-(3-fluoropropyl)-2'-hydroxy-6,7-benzomorphan hydrochloride**



OPIOID RECEPTOR BINDING (nM)		**[^{35}S]GTPγS BINDING EC_{50} (Maximal Stimulation)**
μ-receptor:	1.35 ± 0.45	8.7 ± 2.2% stimulation at 3 μM
δ-receptor:	7.0 ± 3.2	2 1.3 ± 3.0% stimulation at 3 μM
κ-receptor:	0.35 ± 0.04	4.1 ± 0.3 nM (maximal effect = 65.0 ± 0.7%)

SUMMARY

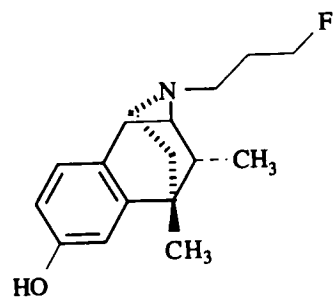
NIH 10949 had affinity for all three opioid receptors types in the order κ > μ >δ.. The selectivity for κ is 4-fold over μ and 20-fold over δ.. It was a κ agonist giving a somewhat less maximal response than U69593. It had low μ and δ receptor efficacy.

* * *

NIH 10950 **(+)-(2*S*,5*S*,9*S*)-5,9-Dimethyl-2-(3-fluoroethyl)-2'-hydroxy--6,7-benzomorphan hydrochloride**

OPIOID RECEPTOR BINDING (nM)

μ-receptor:	354 ± 33.7
δ-receptor:	3767 ± 1441
κ-receptor:	177.9 ± 37.5

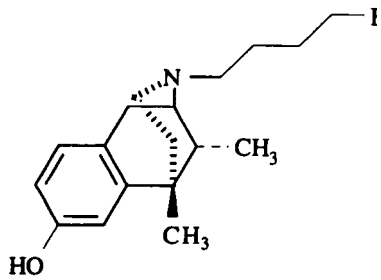


SUMMARY

NIH 10950 had similar, but low, affinity for μ and κ receptors. Its affinity for the δ receptor is at least 10-fold less.

NIH 10951

(+)-(2*S*, 5*S*, 9*S*)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan.HCI



OPIOID RECEPTOR BINDING (nM)

μ-receptor:	2720 ± 230
δ-receptor:	>10 μM (8.3 ± 8.3% inhibition at 10 μM)
κ-receptor:	730 ± 209

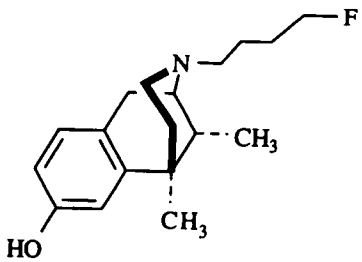
SUMMARY

NIH 10951 had very weak affinity for opioid receptors in the order κ>μ>>δ.

* * *

NIH 10952

(-)-(2*R*, 5*R*, 9*R*)-5,9-Dimethyl-2-(4-fluorobutyl)-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)		**[^{35}S] GTPγS BINDING EC_{50} (Maximal Stimulation)**
μ-receptor:	5.8 ± 0.7	11.3 ± 4.2% stimulation at 3 μM
δ-receptor:	43.4 ± 9.0	7.0 ± 0.7% stimulation at 3 μM
κ-receptor:	3.3 ± 0.5	32.2 ± 1.0% stimulation at 3 μM

SUMMARY

NIH 10952 had high affinity for the μ- and κ-opioid receptors with approximately 7 to 13-fold selectivity for these over δ-receptors. It appeared to be a high affinity, non-selective compound. It produced a low agonist response at μ,δ and κ receptors. Thus, NIH 10952 could be a non-selective, competitive antagonist -- or low efficacy agonist at all three receptors.

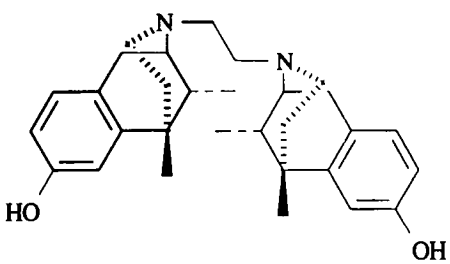
* * *

NIH 10953

N,N'-[Bis-(+)-(2*S*, 5*S*, 9*S*)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan]-1,2-ethane dihydrochloride

OPIOID RECEPTOR BINDING

μ-receptor:	2244 ± 351 nM
δ-receptor:	>10 μM (13.1 ± 8.1% inhib. at 10 μM)
κ-receptor:	3816 ± 633 nM



NIH 10953 (continued)

SUMMARY

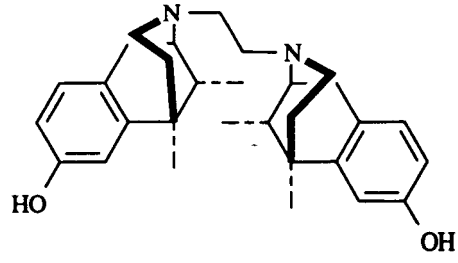
NIH 10953 had low affinity for opioid receptors.

* * *

NIH 10954 **N,N'-[Bis-(-)-(2*R*, 5*R*, 9*R*)-5,6-dimethyl-2'-hydroxy-6,7-benzomorphan]-1,2-ethane dihydrochloride**

OPIOID RECEPTOR BINDING

μ-receptor: 857 ± 150 nM
δ-receptor: >10 μM (49.0 ± 1.4% inhib. at 10 μM)
κ-receptor: 151 ± 45 nM

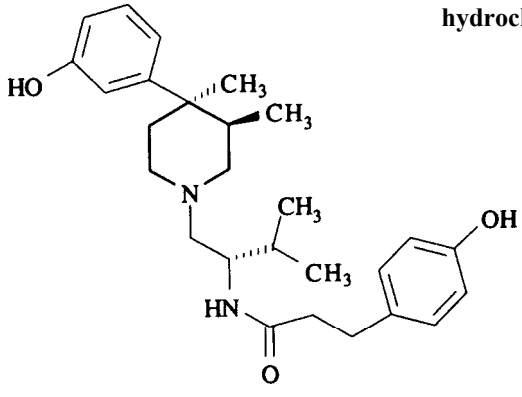


SUMMARY

NIH 10954 had low affinity for μ- and κ-opioid receptors, and yet lower affinity for δ-opioid receptors.

* * *

NIH 10955 **(+)-4-Hydroxy-N-(1*S*-([4-(3-hydroxyphenyl)-3 *R*, 4*R*-dimethyl-1-piperidinyl]methyl-2-methylpropyl-1-benzenepropanamide hydrochloride**



OPIOID RECEPTOR BINDING

μ-receptor: 13.3 ± 2.4 nM
δ-receptor: >10 μM (49.3 ± 5.0% inhib. @ 10 μM)
κ-receptor: 13.5 ± 3.4 nM

[^{35}S]GTPγS BINDING
EC_{50} (Maximal Stimulation)

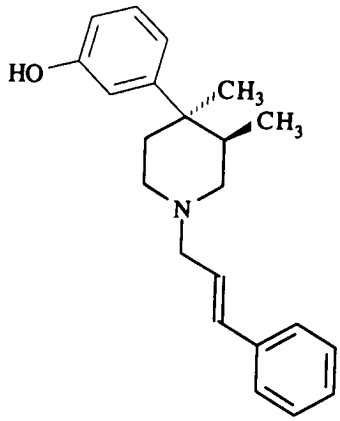
7.7 ± 6.1% stimulation at 3 μM
Not tested
7.6 ± 2.4 % stimulation at 3 μM

SUMMARY

NIH 10955 was a non-selective, high-affinity μ-/κ-compound, but had good selectivity for these receptors over the δ-opioid receptor. The compound gave a very small agonist effect at μ and κ receptors, even at 3 μM. It was not tested at δ receptors due to its very low binding affinity. It should be a μ/κ-antagonist.

!NIH 10956

(+)-N-(*trans*-4'-Phenyl-2'-propenyl)-(3*R*,4*R*)-dimethyl-4-(3-hydroxyphenyl)piperidine fumarate



OPIOID RECEPTOR BINDING (nM)		[^{35}S]GTPγS BINDING EC_{50} (Maximal Stimulation)
μ-receptor:	0.11 ± 0.04	0.8 ± 1.6% stimulation at 3 μM
δ-receptor:	127 ± 14.4	4.3 ± 1.3% stimulation at 3 μM
κ-receptor:	19.1 ± 3.7	5.4 ± 2.5 % stimulation at 3 μM

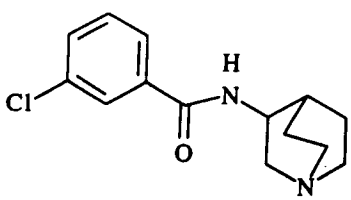
SUMMARY

NIH 10956 had very high affinity for the μ-opioid receptor, giving a good selectivity over both κ- (173-fold) and δ- (1154-fold) receptors. NOTE: NIH 10956 binding seemed to be variable at μ-receptors, giving values from 0.047 nM through 0.21 nM. It gave no significant agonist response. It may be a pure antagonist at all three opioid receptors

* * *

NIH 10957

3-Chloro-N-(3-quinuclidinyl)benzamide



OPIOID RECEPTOR BINDING

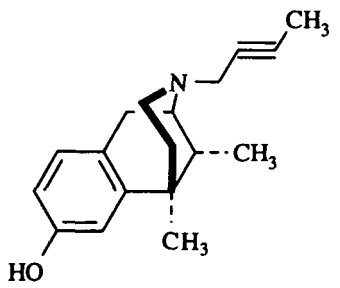
μ-receptor:	>10 μM (5.7 ± 4.9% inhibition at 10 μM)
δ-receptor:	>10 μM (11.3 ± 5.7% inhibition at 10 μM)
κ-receptor:	>10 μM (13.0 ± 9.0% inhibition at 10 μM)

SUMMARY

NIH 10957 had no opioid receptor affinity.

NIH 10959

(-)-(2*R*, 5*R*, 9*R*)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride



OPIOID RECEPTOR BINDING (nM)		**[^{35}S]GTPγS BINDING EC_{50} (Maximal Stimulation)**
μ-receptor:	0.47 ± 0.27	26.7 ± 4.9% stimulation at 3 μM
δ-receptor:	59.2 ± 10.0	4.6 ± 4.6% stimulation at 3 μM
κ-receptor:	3.9 ± 0.5	27.3 ± 2.8 % stimulation at 3 μM

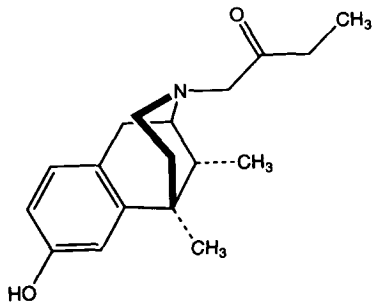
SUMMARY

NIH 10959 had high μ receptor affinity with selectivity for μ over κ of 8-fold, and μ over δ of 126-fold. It had limited efficacy at μ and κ receptors, but no agonist action is apparent at δ receptors at the concentrations examined -- possibly a **μ-κ mixed** agonist.

* * *

NIH 10960

(+)-(2*S*, 5*S*, 9*S*)-2-(2-Butan-2-one)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride.



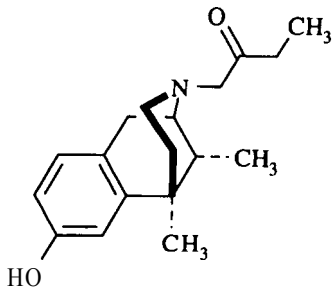
MONKEY CORTEX OPIOID RECEPTOR BINDING

μ-receptor:	>10 μM (10.5 ± 10.5% inhibition at 10 μM)
δ-receptor:	>100 μM (0% inhibition at 10 μM)
κ-receptor:	>10 μM (20.6 ± 7.5% inhibition at 10 μM)

SUMMARY

NIH 10960 had no significant binding affinity for opioid receptors.

NIH 10961



(-)-(2*R*, 5*R*, 9*R*)-2-(Butan-2-one)-5,9-dimethyl-2'-hydoxy-6,7-benzomorphan hydrochloride.

OPIOID RECEPTOR BINDING (nM)

μ-receptor:	150 ± 25
δ--receptor:	1727 ± 199
κ–receptor:	43.7 ± 6.5

SUMMARY

NIH 10961 had affinity for opioid receptors in the order κ > μ >> δ., with little selectivity for κ over μ (3-fold), but improved selectivity (40-fold) for κ over δ. Compare to NIH 10960, previous page.

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (1998)

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INTRODUCTION

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately 15 years. The group now includes laboratories at Louisiana State University Medical Center (France, Gerak), University of Mississippi Medical Center (Rowlett, Woolverton), and the University of Michigan (Briscoe, Winger, Woods) and is part of the Drug Evaluation Committee (Dr. J. Woods, Chair) of the College on Problems of Drug Dependence (CPDD) which is supported by both CPDD and the National Institute on Drug Abuse (NIDA). One of the purposes of the group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and physical dependence potential. Compounds are received, coded and distributed by Dr. A. Jacobson at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), for blind testing in the various laboratories. They are evaluated for reinforcing effects in monkeys that previously self-administered cocaine or methohexital (UM), and for discriminative stimulus effects in pentobarbital-trained monkeys (UMMC), amphetamine-trained monkeys (UMMC), midazolam-trained monkeys (LSUMC), and flumazenil-trained monkeys that receive diazepam daily (LSUMC). This report includes the results of evaluation of CPDD-0051 and CPDD-0054. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee, Louisiana State University Medical Center New Orleans, University of Mississippi Medical Center, University of Michigan, and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

METHODS

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects

Subjects were rhesus monkeys (*Macaca mulatta*) experienced with self-administration of cocaine hydrochloride or sodium methohexital. Animals were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. Catheters passed subcutaneously (s.c.) to the mid-scapular region, exited the body and continued, through a hollow restraining arm, to the outside rear of the cage.

Apparatus

The restraint and catheter protection devices are described in detail by Deneau et al. (1969). Each monkey wore a tubular stainless steel harness that protected the exit site of the catheter and allowed relatively unrestricted movement within the cage. A Teflon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection for animals who tended to locate and pull their catheters. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 1.5 cm apart, were three circles, 2.5 cm in diameter, covered with translucent plastic and capable of being illuminated from behind by 5 W colored bulbs. The two side lights could be illuminated red and the center light green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by a force of 0.010 to 0.0 15 N. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairfield, VT) software and located in an adjoining room.

Procedure

Reinforcing effects of CPDD-0051 and CPDD-0054 were evaluated in a substitution self-administration procedure in separate groups of monkeys who were experienced with i.v. self administration of either cocaine or methohexital, respectively. Test sessions and baseline sessions had the same general structure. At the start of each session, a red light was illuminated over one of two levers. When a monkey completed the fixed-ratio requirement of 10 presses on that lever (fixed-ratio [FR] 10), a 5-second, 1.0 ml injection of saline, cocaine hydrochloride (0.03 mg/kg), sodium methohexital (0.1 mg/kg), or a test compound was delivered. The red light was extinguished and a center green light was illuminated for the duration of the infusion. Each injection was followed by a lo-minute (cocaine baseline) or lo-second (methohexital baseline) timeout during which all stimulus lights were extinguished and responding had no programmed consequence.

Twice daily experimental sessions lasted 130 min each. On approximately half of the baseline sessions, the monkeys could respond for saline. All animals showed clear and consistent differential responses to saline and either cocaine or methohexital before test compounds were evaluated. In test sessions a dose of the test compound was made available for one session. Other conditions were similar to those of the baseline sessions.

Drugs

Five doses of CPDD-0051 (0.00 1, 0.003, 0.01, 0.03 and 0.1 mg/kg/injection) were studied in one monkey and three doses in another; two observations were made at most of the tested doses in each monkey. Doses of CPDD-0051 larger than 0.1 mg/kg/injection could not be studied due to limitations in solubility. Three doses of CPDD-0054 (0.03, 0.1 and 0.3 mg/kg/injection) were studied in three monkeys; each dose was evaluated at least twice in each monkey. CPDD-0054 was dissolved in a solution of 5% ethanol (v/v), 10% emulphor (EL-620) and sterile water; this solution was further diluted with sterile water as needed and immediately prior to experimental sessions. Cocaine hydrochloride and methohexital sodium were dissolved in sterile saline and sterile water, respectively.

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital and d-amphetamine discriminations, UMMC)

Subjects

The subjects were seven adult rhesus monkeys weighing between 6.4 and 12.2 kg. Monkeys were housed individually in stainless steel cages in which water was available continuously. They were fed 150 to 200 g of Teklad monkey chow after each session and were given a chewable vitamin tablet 3 times per week.

The monkeys had been trained previously to discriminate d-amphetamine (Ou3, 8405, and 8515) or pentobarbital (AQ63, Ef3, 8814 and 8902) from saline in a two-lever, discrete-trial shock avoidance procedure. All monkeys had received other test drugs prior to CPDD-0051 or CPDD-0054.

Apparatus

During experimental sessions animals were seated in primate restraint chairs and placed inside sound-attenuating cubicles. All chairs were fitted with shoes containing brass plates in the soles that permitted delivery of electric shock produced by a shock generator (SG 903 BRS/LVE, Laurel, MD). Chambers were equipped with two response levers (PRL-001, BRS/LVE, Laurel, MD) mounted on one wall. There were four white lights above each lever. Chambers were illuminated with ceiling-mounted 40w incandescent house lights. Experimental events were programmed and recorded with an Apple Macintosh 11 computer that was located in a room adjacent to the one in which animals were tested.

Procedure

The training and test procedures have been reported in detail elsewhere (Woolverton et al., 1994). A monkey was placed in the restraint chair and either saline (1-2 ml) or the training drug was administered intragastrically (i.g.) via a nasogastric tube, followed by a 1.5 ml saline flush. Fifty-five minutes after infusion, the monkey was placed into the experimental chamber.

The session began with a 5-minute timeout that was followed by 30 trials. On each trial the house light and lever lights were illuminated and responding on the correct lever postponed scheduled shock and extinguished the lights. Incorrect responses reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR 5) was not satisfied on the correct lever within 10 seconds of the onset of the lights, shock (250-msec duration, 5-mA intensity) was delivered. If the response requirement was not satisfied within 4 additional seconds, a second shock was delivered and the trial automatically ended. The session was terminated when 2 shocks were delivered during 2 consecutive trials or after 30 trials. Trials were separated by 30-sec timeouts.

Training sessions were conducted five days a week according to the following schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline and D denotes sessions preceded by drug. Discrimination training continued until at least 90% of the responses in the first trial were on the correct lever and subjects avoided shock on at least 90% of the trials (27/30) for seven out of eight consecutive sessions. When subjects failed to satisfy criteria, the training sequence was conducted until the criteria were once again satisfied. Test sessions were identical to training sessions except that test drugs were administered and completing the response requirement on either lever avoided shock.

Drugs

A stock solution of d-amphetamine sulfate (National Institute on Drug Abuse, Rockville, MD) was prepared by dissolving drug in saline in a concentration of 5.0 mg/ml. The training dose of amphetamine was 1.0 mg/kg i.g. Pentobarbital was mixed daily by diluting Nembutal (Abbott Laboratories, N. Chicago, IL). The training dose of pentobarbital was 10 mg/kg i.g. Three doses of CPDD-0051 (1.0, 3.0 and 10.0 mg/kg) were studied in monkeys discriminating amphetamine and in monkeys discriminating pentobarbital. Three doses of CPDD-0054 (3.0, 10.0 and 30.0 mg/kg) were studied only in monkeys discriminating pentobarbital. CPDD-0051 was dissolved in saline in a concentration of 5.0 mg/ml and the infusion volume was 0.25 ml/kg for 1.0 mg/kg. For doses larger than 1.0 mg/kg, infusion volume was increased as appropriate using the 5.0 mg/kg solution. CPDD-0054 was dissolved in an equal volume of propylene glycol and sterile 0.9% saline immediately before infusion (0.25 ml/kg).

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, LSUMC)

Subjects

The subjects were six rhesus monkeys weighing between 3.5 and 10.5 kg. Monkeys were housed individually in stainless steel cages in which water was continuously available and they received primate chow (Harlan Teklad, Madison, WI) daily as well as fresh fruit and peanuts several days per week.

Apparatus

Monkeys were seated in chairs that provided restraint at the neck. Chairs were equipped with shoes containing brass electrodes, to which brief (250 msec) electric shock could be delivered from an a.c. shock generator located adjacent to the chambers. During experimental sessions, chairs were located in sound-attenuating, ventilated chambers that were equipped with several response levers, a food cup and an array of stimulus lights.

Procedure

Flumazenil Discrimination. Monkeys consumed 5.6 mg/kg of diazepam in 45-50 ml of fruit punch 3 hrs prior to daily sessions in which they discriminated between s.c. injections of 0.32 mg/kg of flumazenil and vehicle (Gerak and France, in press) while responding under a FR 5 schedule of either stimulus-shock termination (monkeys DU and IG, CPDD-0051 study) or food presentation (monkeys RO and CR, CPDD-0054 study). Daily training sessions consisted of several discrete, 15-minute cycles. Each cycle comprised a lo-minute timeout, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated either green (food schedule) or red (stimulus-shock termination schedule) and monkeys could either receive food or postpone scheduled shock (for 30 seconds) by responding five times on the appropriate lever as determined by the s.c. injection administered during the first minute of the 10-minute timeout (e.g., left lever after vehicle, right lever after flumazenil). Under the schedule of stimulus-shock termination, failure to satisfy the response requirement within 10 seconds resulted in the delivery of a brief shock. The response period ended after 5 minutes, the delivery of 4 shocks (stimulus-shock termination) or the delivery of 10 food pellets, whichever occurred first. Under both schedules responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were identical to training sessions except that various doses of flumazenil or a test compound were administered during the first minute of each timeout and 5 consecutive responses on either lever postponed scheduled shock or resulted in food delivery.

Midazolam Discrimination, Monkeys discriminated between s.c. injections of 0.56 mg/kg of midazolam and vehicle while responding under a FR 5 schedule of stimulus-shock termination (Lelas et al., 1999). Daily sessions comprised multiple, 15-minute cycles as described above for the flumazenil discrimination study. Each cycle comprised a lo-minute timeout, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and monkeys could postpone scheduled shocks by fulfilling the response requirement.

Test sessions were identical to training sessions except that various doses midazolam or a test compound were administered during the first minute of the timeout and 5 consecutive responses on either lever postponed the shock schedule.

Drugs

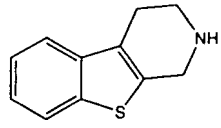
Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 45-50 ml (depending on body weight) of fruit punch containing suspending Agent K to yield a dose of 5.6 mg/kg/daily drinking episode. Flumazenil (F. Hoffman LaRoche, LTD, Basel, Switzerland) was dissolved in a vehicle of 10% ethanol, 40% propylene glycol and 50% saline; midazolam hydrochloride (Roche Pharma, Inc., Manati PR) was purchased as a

commercially-prepared solution. CPDD-0051 was dissolved in sterile water and lactic acid; once in solution, the pH was increased to ≥ 5 with NaOH. Four doses of CPDD-0051 (0.32, 1.0, 3.2 and 10.0 mg/kg) were studied s.c. in two monkeys discriminating each compound. CPDD-0054 was dissolved in a vehicle comprising 25% ethanol, 20% emulphor and 55% saline. Four doses of CPDD-0054 (3.2, 10.0, 17.8 and 32.0 mg/kg) were studied s.c. in two monkeys discriminating each compound.

RESULTS

CPDD-0051

1,2,3,4-Tetrahydrobenzo[b]thieno[2,3-c]pyridine



Reinforcing Effects in Rhesus Monkeys

The average rates of responding for injections of 0.03 mg/kg of cocaine were 2.02 (monkey TA) and 1.46 (monkey SH) responses per second (Table 1). Both monkeys received the maximum possible number of injections (i.e., 13) in sessions in which cocaine was available. Response rates and number of injections received per session decreased markedly when saline was substituted for cocaine. When CPDD-0051 was substituted for cocaine, neither of the monkeys responded at rates above those maintained by saline. Monkey TA received a maximum average of 11 injections of CPDD-0051 at a dose of 0.003 mg/kg/injection and monkey SH received a maximum average of 8.5 injections at a dose of 0.03 mg/kg/injection.

Table 1. Self- administration of cocaine, saline and CPDD-0051.

	Subject			
	TA		SH	
Drug (dose [mg/kg])	R/sec	Inj	R/sec	Inj
Cocaine (0.03)	2.02	1 3	1.46	13
Saline	0.19	7.4	0.05	6.2
CPDD-0051				
(0.001)	0.09	8	n.s.	n.s.
(0.003)	0.24	11	n.s.	n.s.
(0.01)	0.06	6.5	0.05	6.5
(0.03)	0.13	9.5	0.09	8.5
(0.1)	0.05	6	0.01	2

n.s. = not studied
R/sec = responses (lever presses) per second
Inj = number of i.v. injections received during the session

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital and d-amphetamine discriminations)

Monkeys that discriminated between saline and either amphetamine or pentobarbital responded greater than 95% on the injection-appropriate lever during test sessions with the training drug or vehicle (Tables 2 and 3). Up to a dose of 10.0 mg/kg, CPDD-0051 failed to substitute for either the amphetamine (Table 2) or pentobarbital (Table 3) discriminative stimulus while having little or no effect on rate of responding. A maximum of 40% responding on the pentobarbital lever was obtained in one monkey (Ef3) at a dose of 3.0 mg/kg of CPDD-0051. Up to a dose of 10.0 mg/kg, CPDD-0054 failed to occasion any pentobarbital-appropriate responding in two monkeys and produced a maximum of 40% pentobarbital-appropriate responding in a third monkey (Table 4).

Table 2. Discriminative stimulus effects of CPDD-0051 in monkeys discriminating d-amphetamine.

	Subject					
	Ou3		8405		8515	
Drug (dose [mg/kg)	%DR	R/sec	%DR	R/sec	%DR	R/sec
Amphetamine (1.0)	100	2.82	100	1.43	100	3.21
Saline	0	1.96	0	2.77	0	2.69
CPDD-0051						
(1.0)	0	1.90	0	2.43	0	2.21
(3.0)	0	1.46	0	2.31	0	3.20
(10.0)	0	1.13	0	2.23	0	2.32

%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

Table 3. Discriminative stimulus effects of CPDD-0051 in monkeys discriminating pentobarbital.

	Subject							
	AQ63		Ef3		8814		8902	
Drug (dose [mg/kg])	%DR	R/sec	%DR	R/sec	%DR	R/sec	%DR	R/sec
Pentobarbital (10.0)	100	1.63	100	0.96	96.5	1.10	100	2.02
Saline	0	2.10	1.5	2.43	0	1.65	0	2.17
CPDD-0051								
(1.0)	0	2.11	0	2.21	0	1.57	0	1.66
(3.0)	0	1.87	40.0	2.02	0	1.52	0	2.45
(10.0)	0	1.75	21.5	2.48	0	1.53	0	1.68

%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

TABLE 4. Discriminative stimulus effects of flumazenil and CPDD-0051 in diazepam-treated monkeys discriminating flumazenil.

	Subject			
	DU		IG	
Dws (dose [mg/kg])	%DR	R/sec	%DR	R/Sec
Flumazenil				
(0.01)	0	1.53	0	1.84
(0.032)	30.0	1.69	0	2.13
(0.1)	93.8	1.14	30.0	1.79
(0.32)	n.s.	n.s.	100	1.81
Vehicle	0	1.76	0	0.77
CPDD-0051				
(0.32)	4.1	1.58	0	1.69
(1.0)	0	1.25	0	0.62
(3.2)	10.4	1.41	0	0.87
(10.0)	0	1.54	0	1.07

n.s. = not studied
%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

TABLE 5. Discriminative stimulus effects of midazolam and CPDD-0051 in monkeys discriminating midazolam.

	Subject			
	MA		RO	
Drug dose [mg/kg])	%DR	R/sec	%DR	R/Sec
Midazolam				
(0.032)	0	1.93	0	2.35
(0.1)	100	2.06	90.0	2.36
Vehicle	0	1.67	0	2.45
CPDD-0051				
(0.32)	0	1.39	0	1.98
(1.0)	0	1.42	0	1.69
(3.2)	0	1.36	0	1.75
(10.0)	0	1.67	0	1.96

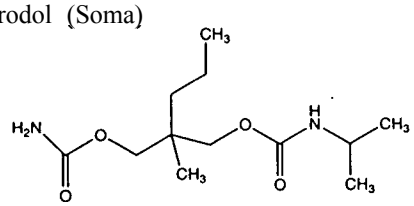
%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

In monkeys receiving diazepam daily and discriminating between flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.1 (DU) or 0.32 (IG) mg/kg occasioning >80% drug-lever responding (Table 4). Up to a dose of 10.0 mg/kg, CPDD-0051 failed to substitute (i.e. produce >80% DR) for the flumazenil discriminative stimulus in either monkey and did not systematically alter rates of responding.

In monkeys discriminating between midazolam and vehicle, midazolam produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.1 mg/kg occasioning >80% drug-lever responding (Table 5). Up to a dose of 10.0 mg/kg, CPDD-0051 failed to substitute for midazolam in either monkey and did not systematically alter rates of responding.

CPDD-0054
Carisoprodol (Soma)



Reinforcing Effects in Rhesus Monkeys

The average rates of responding for i.v. injections of 0.1 mg/kg of methohexital were 0.25 (monkey NI), 0.74 (monkey RO), and 0.13 (monkey MA) responses per second (Table 6). On average, these three monkeys received 140.2, 80.2 and 8 1.7 injections of methohexital per session. Response rates and number of injections received per session decreased markedly when saline or vehicle was substituted for methohexital, although more injections were received during vehicle sessions than during saline sessions. All three monkeys responded for CPDD-0054 and received a maximum of 88.7 (0.3 mg/kg in monkey NI), 75.5 (0.3 mg/kg in monkey RO), or 35.3 (0.01 mg/kg in monkey MA) injections per session

Table 6. Self- administration of methohexital, saline and CPDD-0054.

	Subject					
	NI		RO		MA	
Drug (dose [mg/kg])	R/sec	Inj	R/sec	Inj	R/sec	Inj
Methohexital						
(0.1)	0.25	140.2	0.74	80.2	0.13	81.7
Saline	0.03	18.2	0.02	15.0	0.03	19.5
Vehicle	0.04	30.0	0.04	28.0	0.01	10.0
CPDD-0054						
(0.03)	0.04	27.0	0.01	7.5	0.02	9.5
(0.1)	0.09	65.0	0.07	49.5	0.05	35.3
(0.3)	0.43	88.7	0.12	75.5	0.02	17.5

R/sec = responses (lever presses) per second
Inj = number of i.v. injections received during the session

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital discrimination)

Monkeys responded >95% on the pentobarbital-associated lever after receiving the training dose (10.0 mg/kg) of pentobarbital and responding exclusively on vehicle-associated lever after receiving saline (Table 7). Up to a dose of 30.0 mg/kg, CPDD-0054 occasioned predominantly vehicle-lever responding and failed to systematically alter rates of responding (Table 7).

Table 7. Discriminative stimulus effects of CPDD-0054 in monkeys discriminating pentobarbital.

	Subject					
	Ef3		8814		8902	
Drug (dose [mg/kg])	%DR	R/sec	%DR	R/sec	%DR	R/sec
Pentobarbital (10.0)	100	1.72	100	1.33	96.5	1.94
Saline	0	2.33	0	1.65	0	2.03
CPDD-0054						
(3.0)	0	2.34	0	1.17	0	0.60
(10.0)	0	2.41	0	1.89	0	1.70
(30.0)	0	2.16	0	1.87	3.0	1.98

%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

TABLE 8. Discriminative stimulus effects of flumazenil and CPDD-0054 in diazepam-treated monkeys discriminating flumazenil.

	Subject			
	RO		CR	
Drug (dose [mg/kg])	%DR	R/sec	%DR	R/Sec
Flumazenil				
(0.01)	1.9	1.00	5.4	1.37
(0.032)	9.3	1.11	0	1.20
(0.1)	98.2	0.62	89.1	0.86
Vehicle	1.9	0.70	0	1.26
CPDD-0054				
(3.2)	0	1.20	0	1.27
(10.0)	0	1.32	0	1.24
(17.8)	0	1.09	0	1.27
(32.0)	1.9	1.00	0	1.15

%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

Flumazenil produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.1 mg/kg occasioning >80% drug-lever responding in both monkeys (Table 8). Up to a dose of 32.0 mg/kg, CPDD-0054 failed to substitute for the flumazenil discriminative stimulus and did not systematically alter rates of responding.

Midazolam produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.32 mg/kg occasioning >80% drug-lever responding in both monkeys (Table 9). Up to a dose of 32.0 mg/kg, CPDD-0054 failed to substitute for midazolam and did not systematically alter rates of responding.

TABLE 9. Discriminative stimulus effects of midazolam and CPDD-0054 in monkeys discriminating midazolam.

	Subject			
	MA		RO	
Drug (dose [mg/kg])	%DR	R/sec	%DR	R/Sec
Midazolam				
(0.032)	0	1.81	0	1.81
(0.1)	60.8	1.89	0	2.12
(0.32)	100	1.26	88.9	1.53
Vehicle	0	1.49	0	1.75
CPDD-0054				
(3.2)	0	1.49	0	1.69
(10.0)	0	1.47	0	1.45
(17.8)	0	1.53	0	1.56
(32.0)	0	2.14	0	1.52

%DR = percentage of responses on the drug-appropriate lever
R/sec = responses (lever presses) per second

CONCLUSIONS

CPDD-0051

In self-administration studies, CPDD-005`1 failed to maintain responding at rates above those maintained by saline. Solubility limits precluded self-administration studies on doses of CPDD-0051 larger than 0.1 mg/kg/injection. CPDD-0051 also failed to substitute for a flumazenil discriminative stimulus in diazepam-treated monkeys or for the d-amphetamine, pentobarbital or midazolam discriminative stimulus in untreated monkeys. While it is possible that other doses of CPDD-0051 might have reinforcing effects or discriminative stimulus effects under other conditions, in the current studies CPDD-0051 was not a positive reinforcer and did not exert d-amphetamine-like, pentobarbital-like, midazolam-like or benzodiazepine antagonist actions in rhesus monkeys.

CPDD-0054

CPDD-0054 (carisoprodol) maintained self-administration responding that was greater than rates maintained by saline, although less than rates maintained by i.v. injections of methohexital. Solubility limits precluded studies on doses of CPDD-0054 larger than 0.3 mg/kg/injection. CPDD-0054 also failed to substitute for the flumazenil discriminative stimulus in diazepam-treated monkeys or for the pentobarbital or midazolam discriminative stimulus in untreated monkeys. While it is possible that other doses of CPDD-0054 might have discriminative stimulus effects under other conditions, in the current studies CPDD-0054 did not exert pentobarbital-like, midazolam-like or benzodiazepine-antagonist actions in rhesus monkeys.

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