Editorial

Dear Colleagues,

The Editorial Board of *Dialogues in Clinical Neuroscience* has for quite some time wished to publish an issue on addictive behaviors. The motivation for this issue was obviously not to provide an exhaustive catalog of the various substance addictions, but rather to explore the kinds of problems created by these addictions in current times, and, in particular, the incidence of these problems.

The confluence of addictive tendencies and the means to satisfy them easily, both by way of technological and scientific advances (man-made drugs) and an economy which tends towards the excessive, has led directly to an increase in the quantity and variety of addictive substances consumed.

As society in general becomes less strict and more flexible, an increasing number of oral, societal, and metaphysical references are disappearing. This does not help fragile personalities, particularly young people whose identities are maturing, to reinforce their defense mechanisms against addictive behaviors.

The variable nature of these defense mechanisms, along with feelings of frustration and poor adaptation to social conditions or to reality, can at times lead to a reinforcement of the psychological element of dependence.

Access to man-made drugs renders the cost of the product less relevant, and facilitates consumption.

It is clear that within the context of this journal we cannot remain indifferent to this problem in society. We have endeavored in this issue to present a variety of views from a series of specialists on the problems mentioned above. I would like to thank these authors for the excellent articles they have provided.

Sincerely yours,

Jean-Paul Macher, MD

Dialogues in Clinical Neuroscience is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material. All contributions are reviewed by members of the Editorial Board and submitted to expert consultants for peer review.

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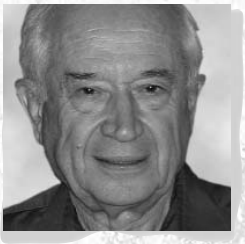

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In this issue...

As already described in the Editorial, we felt that it was of great importance to address the various problems related to recent developments in addictive behaviors.

However before turning to modern-day issues in addiction, we wished firstly to place it in a historical context. This was the task performed by Marc-Antoine Crocq, in the first ***State of the art*** article (p 355). The theme of his article is: "The historical and cultural aspects of man's relationship with addictive drugs."

Recent scientific discoveries in the area of drug dependence, and the targets and mechanisms of action of addictive substances, have required a biological approach. To this end we invited a contribution from Mary Jeanne Kreek; this is the second ***State of the art*** of this issue (p 363), and it focuses on perspectives from the Laboratory of the Biology of Addictive Diseases and related National Institutes of Health/National Institute on Drug Abuse Research Center.

The variety and extent of available substances of abuse has changed the clinical picture of substance addiction. Addictions to a single substance have to a large extent given way to multiple addictions. The need for individuals to satisfy their addictive personalities, and the ensuing generalized psychological dependence, thus predominate over the addiction to a given substance. This new scenario of substance addiction is clearly changing addictive behaviors in general.

The predominant trend appearing in modern times is based on the weakening of barriers and of moral, social, and religious taboos, and thus on the resulting increase in opportunities and permissiveness. Psychological dependence now takes center stage in the clinical picture of addiction, and in this context, addictive behavior is increasing in keeping with the discovery of new substances, or the abuse of substances designed for medicinal use.

We have attempted to target the areas about which we are asking the most questions. So, two ***Translational research*** papers follow the ***State of the art***. The first one, by Martin P. Paulus (p 379) looks at the neural basis of reward and craving, and the second, from Peter W. Kalivas (p 389), provides a review of the neurocircuitry and glutamate neuroplasticity of cocaine and amphetamine-like stimulants.

There are two ***Clinical research*** papers. The first one, by Henning Krampe, Sabina Stawicjki, Margret R. Hoehe, and Hannelore Ehrenreich (p 399) presents OLITA—Outpatient Long-Term Intensive Therapy for Alcoholics. The second, by Natalya M. Kogan and Raphael Mechoulam (p 413) presents a review of the use and effects of cannabinoids, both as a drug of addiction in healthy subjects and as a possible therapeutic option in certain diseases.

The first ***Pharmacological aspects*** article, by Tracie J. Gardner and Thomas R. Kosten (p 431), provides a very comprehensive look at the treatment options for substance abuse, and the challenges that still remain in this field. Nadia S. Hejazi (p 447), in the second ***Pharmacological aspects*** article, examines the pharmacogenetics of addictive behaviors. And in the third ***Pharmacological aspects*** paper, Herbert D. Kleber (p 455) discusses the range of pharmacologic options available for treatment of opioid dependence, and the associated detoxification and maintenance options.

Finally, the ***Poster*** by Margret Hoehe (p 471) presents individual differences in response to addictive substances, and the search for predisposing genetic aspects.

As previously stated, this issue does not claim to discuss exhaustively the theme of addictive behaviors, but rather to examine specific problems posed in this field in current times. We would like to warmly thank the various authors who have provided brilliant contributions to this issue.

Jean-Paul Macher, MD; Margret Hoehe, MD, PhD

Historical and cultural aspects of man's relationship with addictive drugs

Marc-Antoine Crocq, MD

Our taste for addictive psychoactive substances is attested to in the earliest human records. Historically, psychoactive substances have been used by (i) priests in religious ceremonies (eg, amanita muscaria); (ii) healers for medicinal purposes (eg, opium); or (iii) the general population in a socially approved way (eg, alcohol, nicotine, and caffeine). Our forebears refined more potent compounds and devised faster routes of administration, which contributed to abuse. Pathological use was described as early as classical Antiquity. The issue of loss of control of the substance, heralding today's concept of addiction, was already being discussed in the 17th century. The complex etiology of addiction is reflected in the frequent pendulum swings between opposing attitudes on issues that are still currently being debated, such as: is addiction a sin or a disease; should treatment be moral or medical; is addiction caused by the substance; the individual's vulnerability and psychology, or social factors; should substances be regulated or freely available.

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This paper endeavors to discuss (i) the cultural history of man's relationship with addictive drugs; and (ii) the historical roots of the science of addiction. The first part deals with addictive substances and their "*normal*" patterns of use across different epochs. The second part is about the recognition of *pathological use* and the appearance of the science of addiction, the definition of drug use as a disease and its inclusion in the medical constituency, and the evolution of views on etiology and intervention.

Our early ancestors lived as hunter-gatherers and—as shown by the culture of human groups who retained this lifestyle (eg, Australian aborigines, Amazon Indians, or Kalahari desert Bushmen)—they undoubtedly collected considerable information on pharmacological plants. Ötzi, the man whose frozen body was recovered in the Alps in 1991, lived about 3300 years BC, and carried in his pouch a travel pharmacy including a polypore fungus with antibacterial and hemostatic properties. After adopting a pastoral lifestyle, humans may have observed the effects of psychoactive plants on their flocks. Tradition has it that Ethiopian priests started roasting and boiling coffee beans to stay awake through nights of prayer after a shepherd noticed how his goats were frolicking after feeding on coffee shrubs.

Addictive substances and cultural patterns of use

Schematically, psychoactive substances have been used (i) in religious ceremonies by priests; (ii) for medicinal purposes; or (iii) massively, as staple commodities, by large segments of the population in a socially approved

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way. Dominant patterns of use varied according to epochs and places. An important parameter was the degree of a drug's acculturation. For instance, New World plants such as tobacco (nicotine) and coca (cocaine) are relative newcomers to the Old World. Conversely, poppy (opium) and hemp (cannabis) originated in Eurasia.[1] In contrast, alcohol can easily be produced by the action of yeast on a variety of plants containing starch or sugar, and has been used by virtually all cultures.[2] Surprisingly, however, alcohol was largely unknown throughout much of North America before the arrival of Europeans. The sudden destructive impact of alcohol on North American native cultures might be explained by the fact that traditional patterns of use had not been established; another possible factor may be the lack of previous genetic selection operating on vulnerable subjects over millennia.

Religious use

Priests or shamans have ingested plants for millennia to induce states of dissociative trance. Such substances are sometimes termed "entheogenic" (from the Greek roots "en" [inside], "theo" [god], and "gen" [create]). The mushroom *Amanita muscaria*, commonly known as fly agaric, has been at the center of religious rituals in Central Asia for at least 4000 years. Children know this beautiful white-spotted red mushroom from the illustrations of fairy tales and Christmas cards. *Amanita muscaria* had a religious significance in ancient India, and travelers recorded its use as late as the 18th century in Northeastern Siberia. It was an ingredient of *Soma*, a sacred beverage in the Rigveda in ancient India, and also of *Haoma*, a sacred beverage mentioned in the Avesta, the ancient scriptures of Zoroastrianism.[3,4] Etymologically, *soma* and *haoma* are the same words. It has long been thought that muscarine, a cholinergic substance discovered in 1869 in *Amanita muscaria* (hence the name), was the hallucinogenic compound. In fact, the hallucinogenic compounds are ibotenic acid and muscimol. In Central America, psilocybe mushrooms were used for the same purposes. Mushrooms of this genus contain the psychoactive compounds psilocin and psilocybin. Indigenous people in pre-Columbian Mexico, and also the Navajo in the southwestern United States, used peyote (*Lophophora williamsi*) to trigger states of spiritual introspection. This cactus contains psychoactive alkaloids, notably mescaline.

Medicinal use

Some drugs have been used as medications for most of human history. For instance, the medicinal use of opium is described from the earliest written records. *Nepenthes pharmakon* is mentioned in the 9th century BC in Homer's Odyssey (4, 221). It is written that the beautiful Helen of Troy had received this potion from an Egyptian queen and that she used it to treat the Greek warriors ("presently she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow"). Since the 18th century, most exegetes have thought that this potion was prepared from opium. Interestingly, this preparation is qualified as a *pharmakon*, ie, a medication, in the Greek original. According to etymology (*ne*: no, and *penthes*: grief, sorrow), nepenthes would be an anxiolytic or an antidepressant in today's parlance. There is general agreement that the Sumerians cultivated poppies and isolated opium from their seed capsules at the end of the third millennium BC; they called opium "gil" (joy), and the poppy "hul gil" (the joy plant).[5] The Ebers papyrus (c. 1500 BC), one of mankind's oldest medical documents, describes a remedy to prevent excessive crying in children using grains of the poppy plant, strained to a pulp, passed through a sieve, and administered on 4 successive days. Homer's *nepenthes* was perhaps similar to laudanum, an opium tincture attributed to Paracelsus in the 16th century. In the 19th century, laudanum was extensively used in adults and children, for numerous indications (insomnia, cardiac and infectious diseases). The working class largely consumed laudanum because it was cheaper than gin or wine, since it escaped taxation. In the early 20th century, encyclopedias in Western countries still stated that persons in good mental and physical health could use opium without risk of dependence. Griesinger (1817–1868), a German psychiatrist, one of the founders of modern psychiatry, recommended the use of opium in the treatment of melancholia.[6]

Recreational use

Some potentially addictive drugs have been used by a significant proportion of the population on a regular basis, to the point that they have been considered staple commodities. *Alcohol*, *nicotine*, and *caffeine*, being palatable for their mild psychotropic properties, are examples of widely consumed drugs. As licit psychoactive drugs, they

are used mostly by "normal" people, in contrast to illicit "hard drugs," which are traditionally viewed as the province of the deviant.[7] Alcohol, nicotine, and caffeine have permeated our culture, serving as vehicles for social interaction, shaping our urban landscape, from the Japanese teahouse to the British pub, stimulating the opening of international trade routes. Similarly, hashish (*cannabis*) has been largely consumed—eaten and later smoked—in Islamic cultures. All these substances have a long history, intricately interwoven with myth, bearing witness to man's predilection for psychoactive substances. The oldest seeds of cultivated vines so far discovered and carbon dated were found in Georgia and belong to the period from 7000 to 5000 BC.[8] According to Jewish and Christian tradition, one of Noah's first actions after coming out of the Ark was to plant a vineyard; he drank some of its wine and became drunk (Genesis 9, 20-21). Coffee was largely used throughout the Islamic world at the end of the 15th century. Its use spread rapidly in Europe, and Europeans introduced coffee plants into their colonies. Tea's history is much older, since the plant was already being harvested in China in the 3rd century BC.

These staple commodities have long been the object of official attention, for the purpose of collecting excise tax rather than controlling abuse. In order to extract revenues, rulers in Ancient Egypt and Babylon established production or sales monopolies.[9] Ordinances limiting consumption have coexisted and alternated with free supply, in close temporal and geographic proximity. Temperance movements led to a clear decrease in liquor use in Western Europe in the early 20th century, culminating with prohibition in the United States (from 1920 to 1933) and in a few Nordic countries. In preceding centuries, tobacco and cannabis had also known prohibition. Smokers ran the risk of having their lips cut under the first Romanov tsar, Michael Fiodorovich, or of being beheaded under the Ottoman sultan Murad IV. In 1378, the Ottoman emir in Egypt, Soudoun Sheikhouni, was determined to stamp out hashish use: farmers growing hashish were imprisoned or executed, and those found guilty of consuming were said to have their teeth pulled out.[10]

Devising more potent compounds

In the course of history, many psychotropic plants have been refined and administered through new routes, allowing faster access to the brain in higher concentrations. The fermentation of cereals containing starch produces beer with an alcoholic content of around 5%, whereas the same process with grape sugar yields wine containing up to 14% alcohol. Distillation made it possible to obtain beverages with a much higher alcohol content. People could drink alcohol with strength of 50% and more, making it easier to become drunk. The construction of stills, associating an alembic to distill a liquid with arrangements to condense the vapor produced, seems to have started only in the 11th or 12th century around the medical school of Salerno in Italy.[11] Distillation, though it did not create the problems with alcohol, could intensify them.[12] The "water of life," as it was called in many languages (Latin *aqua vitae*) conquered Europe with great speed. That name still survives, as in the Danish *akvavit* and through the Gaelic *uisge beatha* to the English *whisky*. In England, drunkenness was to become connected with distilled spirits, especially gin, as dramatically pictured in Hogarth's *Gin Lane*. Alcohol without liquid (AWOL) is a more recent process that allows people to take in liquor (distilled spirits) without actually consuming liquid. The AWOL machine vaporizes alcohol and mixes it with oxygen, allowing the consumer to breathe in the mixture. Vaporized alcohol enters the bloodstream faster, and its effects are more immediate than its liquid counterparts, producing a euphoric high. Traditionally, coca leaf is chewed in the regions of production in Southern America, for instance by Andean miners to diminish fatigue. At the other pharmacokinetic extreme, the smoking of crack cocaine produces short-lived and intense effects that are felt almost immediately after smoking. Opium is another example of a substance whose pattern of use changed in the last centuries, from a medication used for pain relief and anesthesia to a substance associated with abuse and dependence. Opium's capacity to induce dependence was probably bolstered by the recent purification of morphine, and the synthesis of heroin, more potent compounds that are available for injection. Similarly, cigarettes, which allow nicotine to be rapidly absorbed into the bloodstream and to reach the brain in a few seconds, were associated with more dependence than previous modes of tobacco use (snuff, cigars, chewing) which did not promote deep inhalation into the lungs.

The historical roots of addiction medicine

Chronological milestones

Abnormal patterns of substance use have been described since antiquity, at least since Alexander the Great's death

in 323 BC was precipitated by years of heavy drinking. Aristotle recorded the effects of alcohol withdrawal and warned that drinking during pregnancy could be injurious.[13] The Roman physician Celsus held that dependence on intoxicating drink was a disease.[14] The birth of addiction medicine in modern times is sometimes credited to Calvinist theologians who offered explanations for the phenomenon of compulsive drinking, which were later accepted by physicians.[15] Dr Nicolaes Tulp, a Dutch physician depicted in Rembrandt's painting "The Anatomy Lesson," adapted theological models to explain the loss of control over various types of behavior (1641). In this process, what was considered sinful behavior was given medical explanations. A few decades later, one of Tulp's colleagues, Cornelius Bontekoe, applied his teaching to the progressive loss of willful control over alcohol intake. With the colonial era, industrial revolution, and international trade, addiction became a global public health problem. In the 18th century, opium's addictive potential was recognized when a large number of Chinese people became addicted, and the Chinese government tried to suppress its sale and use. In Europe, the working classes were threatened by alcoholism.[16] At that time, psychiatry had matured into a scientific discipline, established nosological classifications, and taken stands on societal issues. The American physician Benjamin Rush, writing in the 18th century, maintained that compulsive drinking was characterized by a loss of self-control, and that the disease was primarily attributable to the drink itself and not the drinker. His remarks concerned only strong liquors; wine and beer, in his view, were salutary thirst-quenchers.[17] In German-speaking countries, the most influential physician was Constantin von Brühl-Cramer, who is credited with coining the term "dipsomania" ("*Über die Trunksucht und eine rationelle Heilmethode derselben*" [1819]). Dedicated medical journals were created in the 19th century. The *Journal of Inebriety* appeared in the United States in 1876, while the *British Journal of Addiction* was first published in 1884. Emil Kraepelin, the physician who exerted the greatest influence on the shaping of modern psychiatry, fought alcohol with extreme dedication.[18] He published the first psychometric data on the influence of tea and alcohol in the early 1890s. As a result of his research, he came to the conclusion that chronic alcoholism provoked cortical brain lesions that led to a permanent cognitive decline. Drawing from personal consequences, Kraepelin became a teetotaler in 1895. Before that, he had been a moderate drinker, recognizing alcohol's relaxing and mood-elevating effects, as in this letter to the psychiatrist August Forel in December 1891: "…I have often found that, after great exertion, and also after severe mood depression, alcohol has had a clearly beneficial effect on me…."[19] Kraepelin was particularly concerned about the social and genetic consequences of alcohol. Sigmund Freud, a contemporary of Kraepelin, laid the ground for the psychological approach to addiction. Freud wrote in a letter to Fliess in 1897: "…it has dawned on me that masturbation is the one major habit, the "primal" addiction and that it is only as a substitute and replacement for it that the other addictions—for alcohol, morphine, tobacco, etc—come into existence."[20] A consequence of the psychological approach is that the addiction to different substances (alcohol, opiates, etc) and even to certain types of behavior, such as gambling, have been gathered together under a common denominator, and regarded as different expressions of a single underlying syndrome. Interestingly, the Qur'an warns against both wine (*khamr*) and gambling (*maisir*) in the same sura (2, 219). In the 20th century, addiction medicine has been enriched by (i) diagnostic classifications and (ii) neurobiological and genetic research. Louis Lewin published his influential classification in 1924, distinguishing between stimulants (nicotine; caffeine-containing compounds such as coffee, tea, mate); inebriants (alcohol, ether); hallucinogens (lysergic acid diethylamide [LSD], peyote); euphoriants (cocaine; opium derivatives such as morphine, codeine, heroin); and hypnotics. Also, animal research and functional brain imaging studies in humans have led to the current influential hypothesis that all drugs of abuse share a common property in exerting their addictive and reinforcing effects by (i) acting on the brain's reward system and (ii) conditioning the brain by causing it to interpret drug signals as biologically rewarding or potentially salient stimuli comparable to food or sex. Cues associated with morphine, nicotine, or cocaine activate specific cortical and limbic brain regions. This conditioning involves the prefrontal cortex and glutamate systems. However, in rats, this pattern of activation displays similarities to that elicited by conditioning to a natural reward—highly palatable food such as chocolate.[21] Confronted by cues that serve as drug reminders, the individual experiences craving, and the degree of voluntary control that he or she is able to exert may be impaired. This hypothesis is partly derived from Pavlov's conditioning paradigm, where food is equated to cocaine, the animal's salivation to cocaine craving, and the

bell to the drug cue.[22] Family, adoption, and twin studies have demonstrated the intervention of genetic factors in addiction,[23] notably in alcohol abuse and dependence. Genetic factors interact in a complex way with the environment.[24-26]

Addiction—history of a word

The definition of addiction has evolved over time. Today, addiction is defined by the characteristic features that are shared by a variety of substances: (i) the pattern of administration can progress from use, to abuse, to dependence and (ii), as discussed in the previous paragraph, a common feature of several substances is that they induce pleasure by activating a mesolimbic dopaminergic reward system, and dependence by mechanisms involving adaptation of prefrontal glutamatergic innervation to the nucleus accumbens.

The term "addiction," in its current medical meaning, was used first in English-speaking countries, and then passed on to other languages that had used other terms previously. For instance, addiction has displaced the words *toxicomanie* or *assuétude* in French. Interestingly, the word *assuétude* (from the Latin *assuetudo* [habit]) had originally been introduced into French in 1885 to translate the English *addiction*.[27] German uses non-Latin roots, such as *Abhängigkeit* (dependence), *Sucht* (addiction), and *Rausch* (intoxication). In Roman law and in the Middle Ages, addiction was the sentence pronounced against an insolvent debtor who was given over to a master to repay his debts with his work. Thus, the *addictus* was a person enslaved because of unpaid debts. According to the *Oxford English Dictionary*, the term "addict," in the meaning of "attached by one's own inclination, self-addicted to a practice; devoted, given, inclined to" has been used since the first part of the 16th century. However, addiction, in its current medical meaning of "state of being addicted to a drug; a compulsion and need to continue taking a drug as a result of taking it in the past" has been in widespread use only since the 20th century. In medical English, addiction replaced older terms, such as "inebriety."

The difference between the terms dependence and addiction has long been debated. The meaning of these terms among public health professionals can only be understood in the light of their historical development. Addiction is defined as "strong *dependence*, both physiologic and emotional" in Campbell's psychiatric dictionary.[28] In 1964, the World Health Organization recommended that the term drug *dependence* replace *addiction* and *habituation* because these terms had failed to provide a definition that could apply to the entire range of drugs in use. Historically, the archetypal model of addiction was opiates (opium, heroin), which induce clear tolerance (the need to increase doses), severe physical withdrawal symptoms when use is discontinued, and have serious consequences for the social, professional, and familial functioning of users. The spread of the concept of addiction to other substances, notably nicotine, occurred only in recent decades.[29] The diagnosis of tobacco dependence or addiction did not exist in the *Diagnostic and Statistical Manual of Mental Disorders*, 2nd ed (*DSM-II*, American Psychiatric Association in 1968).[30] In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed (*DSM-IV*)[31] this diagnostic category was called "nicotine" dependence instead of "tobacco" dependence. A similar historical evolution was observed with the International Classification of Diseases (ICD), the World Health Organization's Classification of Diseases: the *ICD-10 Classification of Mental and Behavioral Disorders. Clinical descriptions and diagnostic guidelines* (*ICD-10*, published in 1992,)[32] contains a category for tobacco dependence, whereas the previous classification, the *International Classification of Diseases*, 9th Revision (*ICD 9*),[33] devised in the mid 1970s, had no such specific category and offered only a category for nicotine abuse. The current labeling of "dependence" in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, Text Revision (*DSM-IV-TR*)[34] is confusing. During the preparation of the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, revised. (*DSM-III-R*),[35] committee members disagreed as to whether "addiction" or "dependence" should be adopted. A vote was taken at a committee meeting and the word "dependence" won over "addiction" by a single vote! As pointed out by O'Brien, the term "addiction" can describe the compulsive drug-taking condition and distinguish it from "physical" dependence, which is normal and can occur in anyone taking medications that affect the brain.[36] For instance, pain patients requiring opiates become dependent, but are not automatically addicted.

Conclusion—a complex illness

Cultural history suggests that our relationship with drugs is more complex than the paradigm of the laboratory rat that is trained to self-administer cocaine. In most cases, we actively seek addictive drugs, and are not passive vic-

tims. History illustrates that our relationship with substances is shaped by multiple factors, including culture, society, religion and beliefs, individual psychology (addictive, anxious, antisocial personalities), cognition (addiction as a "learned" behavior), neurobiology, and genetics. Addictive behavior results from the conjunction of a substance and a personality. Addiction is not only a substance, but the way a person uses it. In other words, it is not only the drink, but also the drinker, as illustrated by the following dialogue in Shakespeare's Othello (Act 2, Scene 3): Cassio—"*O thou invisible spirit of wine, if thou hast no name to be known by, let us call thee devil*" … Iago—"*Come, come. Good wine is a good familiar creature, if it be well used.*" The etiological complexity of addiction is illustrated by a history of pendulum swings of social and medical opinion. There is no resting equilibrium on unanimous beliefs. It has been common to observe, at the same time and in the same place, the confrontation of opposing attitudes on issues such as: strict vs broad definition of addiction (eg including gambling or not); laissez-faire or prohibition; punishing or treating the addict; and individual responsibility. ❑

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Aspectos históricos y culturales de la relación entre el hombre y las drogas adictivas

En los primeros registros humanos hay testimonios de nuestro gusto por sustancias psicoactivas adictivas. Históricamente las sustancias psicoactivas han sido utilizadas por: 1) sacerdotes en ceremonias religiosas (ej. amanita muscaria), 2) curanderos con propósitos medicinales (ej. opio) ó 3) la población general de una manera socialmente aceptada (ej. alcohol, nicotina, cafeína). Nuestros antepasados refinaron compuestos más potentes e idearon vías más rápidas de administración, que contribuyeron al abuso. El uso patológico ha sido descrito desde la Antigüedad Clásica. El tema de la pérdida del control de la sustancia, precursor del concepto actual de adicción, ya fue discutido en el siglo XVII. La compleja etiología de la adicción está reflejada en las frecuentes oscilaciones del péndulo entre actitudes opuestas en temas que actualmente siguen siendo debatidos como: si la adicción es un pecado o una enfermedad; si el tratamiento debe ser moral o médico; si la adicción es causada por la sustancia, la psicología y la vulnerabilidad del individuo o por factores sociales; y si las sustancias deben ser reguladas o estar disponibles libremente.

Aspects historiques et culturels de la relation entre l'homme et les substances addictives

Le goût de l'être humain pour les substances psychotropes addictives est attesté par les sources historiques les plus anciennes. Historiquement, les substances psychotropes ont été employées 1) par des prêtres, dans des rituels religieux (p. ex., l'amanite tue-mouches), 2) par des guérisseurs, à des fins thérapeutiques (p. ex., l'opium), ou 3) par la population générale, d'une façon sanctionnée socialement (p. ex., l'alcool, la nicotine et la caféine). L'homme a modifié les substances disponibles pour intensifier leurs effets et accélérer leur absorption, ce qui a favorisé l'abus de ces produits. Des modes de consommation pathologiques sont décrits dès l'Antiquité classique. La question de la perte du contrôle sur la substance, à l'origine du concept actuel de dépendance, est déjà analysée au XVII^e^ siècle. L'étiologie complexe des addictions se traduit au cours des siècles par des oscillations entre des attitudes opposées, toujours débattues aujourd'hui : les addictions sont-elles un péché ou une maladie, et le traitement doit-il être moral ou médical ? ; l'addiction est-elle causée par la substance, ou par la vulnérabilité de l'individu et par des facteurs psychologiques et sociaux ? ; l'accès aux drogues doit-il être libre ou bien régulé ?

Opioids, dopamine, stress, and the addictions

Mary Jeanne Kreek, MD

The articulated goals of Dialogues in Clinical Neuroscience *are to serve as "an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects." My laboratory, the Laboratory of the Biology of Addictive Diseases at The Rockefeller University, has for years been focused on "bidirectional translational research," that is, learning by careful observations and study in patient populations with the disorders under study, in this case primarily specific addictive diseases, and then using that knowledge to create improved animal models or other laboratory-based research paradigms, while, at the same time, taking research findings made at the bench into the clinic as promptly as that is appropriate and feasible. In this invited review, therefore, the focus will be on perspectives of our Laboratory of the Biology of Addictive Diseases and related National Institutes of Health/National Institute on Drug Abuse research Center, including laboratory-based molecular neurobiological research, research using several animal models designed to mimic human patterns of drug abuse and addiction, as well as basic clinical research, intertwined with treatment-related research.*

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Innumerable reviews on addictive disorders have been written by many groups, including our own, over the past decade.[1-17] We have contributed over 20 reviews, commentaries, perspectives, or viewpoints in the last 5 years. In 2004, my laboratory published a review article on "Evolving perspectives in neurobiological research in the addictions."[18] Therefore, for this state-of-the-art review with conceptual insights, focus will be placed on research conducted in our Laboratory and Center over the last 5 years. For further information and for some relevant citations of other research groups, one can consult some reviews which we have prepared on basic molecular neurobiology, with a focus on cocaine and other stimulant addictions, opiate addiction, and alcoholism.[1-6] We have published other reviews and perspectives on research related to stress responsivity, and also genetics related to stress responsivity, and with emphasis on the role of stress responsivity.[5,7,8,11] Further, and relatively exhaustive, reviews on human molecular genetics related to the addictions may be found in yet other recent publications from our laboratory.[9,10] Finally, reviews of the history of treatment research in our own laboratory, as well as overviews of recent contributions of our group and others, have been published within the last 5 years.[12-17]

Keywords: *opioids; dopamine; stress; opiate addiction; cocaine addiction; polymorphisms*

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Selected abbreviations and acronyms

ACTH	*adrenocorticotropin hormone*
CRF	*corticotropin-releasing factor*
HPA	*hypothalamic-pituitary-adrenal*
nor-BNI	*nor-binaltorphimine*
POMC	*proopiomelanocortin*

This review will be presented in three sections: (i) laboratory-based molecular neurobiological and neurochemical studies related to cocaine and opiate addiction and potential new approaches to treatment thereof; (ii) role of stress responsivity in the acquisition and persistence of specific addictive diseases, and the impact of chronic exposure to drugs of abuse and withdrawal therefrom on components of the stress-responsive system, along with identification of potential new targets for therapeutic intervention; and (iii) basic clinical research related to specific addictive diseases, with emphasis on stress responsivity: all research focused on treatment improvement.

Laboratory-based molecular neurobiological and neurochemical studies related to cocaine and opiate addiction, and potential new approaches to treatment thereof

Over the past several years, we have developed several animal models for acute, subacute, and chronic exposure to specific drugs of abuse, with emphasis on cocaine, morphine and heroin, and alcohol. One of these models, which we have developed, validated, and used extensively in our studies, is "binge"-pattern cocaine administration mimicking the most common pattern of human abuse. In studies from our laboratory in which animals were allowed to self-administer cocaine with presentation of high, as well as moderate, and the usual low doses of cocaine, and with extended access (10 hours) provided, we found that animals will escalate their use of cocaine.[19] In fact, by 5 days of extended access to high doses of cocaine rats will self-administer more than twice the dose which we had usually used in our chronic "binge-pattern" cocaine administration (15 mg/kg x3, that is 45 mg/kg/day). We have extended this "binge-pattern," using both the steady-dose and escalating-dose "binge-pattern" administration of cocaine.[19] We have been able to study various behavioral factors, as well as impact on gene expression, comparing these two models.

One of the most important early findings from our laboratory (and others) on gene expression has been the finding of significant increased preprodynorphin gene expression in the striatum of rodents after acute, subacute, and chronic cocaine administration (eg, refs 20,21). This is especially important since we and others have shown that dynorphin peptides, which are the natural endogenous opioid ligands of the kappa-opioid receptors, serve to modulate dopaminergic tone and countermodulate cocaine-induced dopaminergic surges. In a recent study, we examined the effects of steady-dose versus escalating-dose binge-pattern cocaine administration upon striatal preprodynorphin messenger ribonucleic acid (mRNA) levels, and also on behavioral stereotypy.[22] We found that both steady-dose and escalating-dose binge cocaine administration resulted in increased preprodynorphin mRNA levels in the caudate-putamen, but not in the nucleus accumbens. These are similar to all our earlier studies of the impact of acute, subacute, and chronic cocaine administrations. In this study, there were no significant differences in preprodynorphin mRNA levels when escalating doses (up to 30 mg/kg x 3, or a total of 90 mg/day) were administered during the last five days of 14-day chronic dosing, compared with a total of 45 mg/day, the steady dose "binge pattern."[22] These data showed that the enhancement of gene expression of dynorphin response to cocaine has probably reached its maximum level at a dose of 45 mg/kg/day of cocaine, and may or may not be dose-dependent at lower doses. Further, in this study it was found that cocaine significantly affected body weight in both paradigms, and that both resulted in expression of behavioral stereotypy. However, of note, one component of stereotypy, that is, intense rapid head movements, was found to be both dose- and time-dependent, with more profound effects in the escalating-dose model.[22]

Extending our much earlier studies in the rat, the effects of the natural kappa-opioid receptor agonist, dynorphin A(1-17), on both basal striatal dopamine levels and on cocaine-induced increases in striatal dopamine levels, as well as on cocaine-induced conditioned place preference, was studied in C57BL/6J mice.[23] In earlier studies conducted in the rat, we had shown that dynorphin applied directly into the striatum causes a dose-dependent reduction in dopaminergic levels. In this recent study, dynorphin, at four different doses, was infused into the caudate-putamen, and dopamine levels were quantitatively measured, using high-performance liquid chromatography, in the extracellular fluid obtained during in vivo

microdialysis in that brain region.[23] Also, the effect of a relatively high dose of dynorphin A on increases in dopamine levels caused by 15 mg/kg of cocaine was measured using in vivo microdialysis. In related studies, the effect of this dose of dynorphin A on cocaine-induced conditioned place preference was studied.[23] We found that dynorphin significantly decreased basal dopamine levels in a dose-dependent manner and by more than 60% at the highest dose. Further, this effect was blocked by preinjection with a selective kappa-opioid receptor antagonist, nor-binaltorphimine (nor-BNI).[23] Further, it was found that the highest dose of dynorphin studied (4.4 nanomolar) resulted in a complete block of the cocaine-induced increases in dopamine levels, and also attenuated locomotor activity induced by 15 mg/kg of cocaine, and blocked the formation of cocaine-induced conditioned place preference.[23] These findings suggest that a dynorphin agonist might be helpful in managing cocaine and other stimulant dependency by preventing cocaine or other stimulant-induced dopamine surges. However, on the other hand, any significant lowering of basal dopaminergic tone could lead to dysphoria, and thus more craving for a drug of abuse such as cocaine. Therefore, it has made our laboratory suggest that a potentially effective kappa-opioid receptor-directed compound for management of cocaine addiction would probably be a kappa partial agonist, that is, with modest agonist activity, but also antagonist activity, which should render stable basal dopaminergic tones, yet significantly attenuate cocaine- or other stimulant-induced dopamine surges, as well as "liking of" cocaine.

In related studies, Zhang et al studied a related potent synthetic kappa-agonist, R-84760, on cocaine-induced increases in striatal dopamine levels in cocaine-induced conditioned place preference in C57BL/6J mice.[24] R-84760 is a novel nonpeptidic potent synthetic selective kappa-opioid receptor agonist that has been studied to a limited extent in humans for other indications. It was found that, similarly to dynorphin itself, this compound would effect a dose-dependent reduction in dopaminergic tone, as measured during in vivo microdialysis in the striatum.[24] Also, it was shown that, like dynorphin, a low dose (0.1 mg/kg) of R-84760 would block cocaine-induced increases in the dopamine levels. Also, it was found that similarly low doses of R-84760 would completely prevent the development of cocaine-induced conditioned place preference and would attenuate locomotor activity in the conditioning chamber.[24] Further, it was documented that these effects of R-84760 on lowering dopaminergic tone and cocaine-induced surges were completely blocked by a selective kappa-antagonist, nor-BNI.[23] Thus, these effects were documented to be mediated exclusively by the kappa-opioid receptor.

In different studies, we further explored the impact of extended-access (10 hours) versus short-access (3 hours) and also high- versus low-dose cocaine impact on self-administration, cocaine-induced reinstatement, and on brain mRNA levels.[25] It was again found that the escalation of cocaine self-administration under long-access conditions was greater than under short-access, and was dose-dependent. Further, we showed that such long-access, with animals who were allowed self-administration for 10 hours at high doses, resulted in an increased susceptibility to drug-induced relapse.[25] There were also differences in neurobiological indices, specifically levels of gene expression in those animals who were allowed to have long access and high doses, compared with short access. There were significant increases in proenkephalin gene expression in the caudate-putamen following long-access and high-dose self-administration.[25] Further, it was found that dopamine D2 receptor mRNA levels in the caudate-putamen and nucleus accumbens were significantly correlated with cocaine reinstatement.[25] However, there was no significant correlation between neuropeptide mRNA levels and cocaine-induced reinstatement.[25] Body weight progressively declined in the long-access self-administering rats.[25] In parallel to these findings, food consumption was also significantly reduced in each group during self-administration, but the reduction in food intake was much greater in the long-access rats.[25] During the 10-day extinction period, food consumption was significantly greater in the long-access, high-dose rats compared with both the short-access and the low-dose rats, and, in fact, food consumption during extinction in the high-dose group was significantly greater than pre-self-administration baseline levels.[25] These findings are similar to observations made by our group in human cocaine addicts in a controlled research setting. They have negative implications for some groups of people, where the desire for thinness, or the desire for attaining the self-image of thinness, may contribute to continued cocaine (or other stimulant) self-administration. The many findings from these long-access, high-dose cocaine self-administration rodent studies, both our more recent ones, as well as our earlier ones, along with the studies from other groups, particularly those of Koob and of Miczek,

suggest that the findings may not only be relevant potentially for the human situation, but provide new insights for further study both in laboratory-based and human research paradigms.[5,7,25]

We have conducted studies in collaboration with the Laboratory of Dr Paul Greengard in which we have studied the impact of change of a single amino acid in an important signal transduction protein on (i) both dopaminergic responses to binge-pattern cocaine; as well as (ii) acquisition; and then (iii) persistence and amounts of self-administration of cocaine.[26] These studies were conducted in four separate lines of mutant mice, each with a mutation code for alanine introduced into the gene for the protein DARPP-32 at four sites of phosphorylation.[26] The four sites of phosphorylation chosen were: (i) the protein kinase A site, threonine 34A; (ii) the cyclin-dependent kinase-3 site, threonine 75A; (iii) the kinase CK2 site, serine 97A; and finally, (iv) the kinase CK1 site, serine 130A. In each case, animals were bred so that both the mutant strain, as compared with the wild-type strain, could be studied, with the single amino acid change introduced into one of these four sites of critical phosphorylation involved in different pathways of the dopamine D1 receptor signal transduction through the DARPP-32 cascade pathway.[26] Acquisition of self-administration required significantly more time in the threonine 34A-/- mice. However, once self-administration was established, both threonine 34A and the serine 130A DARPP-32 mutant mice administered significantly more cocaine than did their wild-type controls.[26] This became especially apparent after training each of these strains on a high dose of cocaine (1 mg/kg) and then starting the self-administration studies for each strain using an even higher dose of cocaine per injection (2 mg/kg), but then progressing downward in concentration to 1.0, .05, and .01 mg/kg per injection. As the dose was reduced below 1.0 mg/kg per injection, both the threonine 34A and the serine 130A mice significantly increased lever pressing to obtain more cocaine than did their matched wild-type controls.[26] Such an increase during reduction of cocaine concentration was not seen in either the threonine 75A or the serine 97A mice.[26] This suggests that although somewhat slower to acquire self-administration, both the threonine 34 site and the serine 130 site of DARPP-32 phosphorylation are important for the persistence of, and though not studied, possibly also to relapse to, cocaine self-administration. Further, and in support of these findings, studies using microdialysis in the freely-moving mice could be carried out in three of the four strains (the fourth strain was not available in adequate numbers for study.) When this was performed, it was found that the same two strains that administered more cocaine, that is, the threonine 34A and the serine 130A, experienced a much lower rise in extracellular fluid dopamine after each of three binge cocaine injections than did the control mixed wild-type animals.[26] Further, this did not happen in the threonine 75A; these animals had a much higher level of dopamine achieved after each dose of binge cocaine, and these were animals that showed no difference between the single amino acid change mutant strain and the wild-type strain. These findings suggest that a single amino acid change of a critical phosphorylation site may alter the behaviors of self-administration; they also give further support to the concepts of many groups, that a lower dopaminergic tone either at rest, or achieved after any normal (for instance, a liked or desired food) or abnormal (for instance, cocaine) self-administration, may result in a lesser increase in dopamine tone. Thus, such animals (or possibly people) could be expected to seek more activation of this pleasure-related dopaminergic system, and thus have a greater vulnerability to developing an addiction.

We have conducted studies in which morphine was self-administered by animals and was available 18 hours/session/day.[27] In these studies, animals were allowed to select a more concentrated or less concentrated morphine solution and once stable choice was established, the concentrations were increased. The animals allowed such a choice both escalated their morphine use to a much greater extent than did steady-dose animals. After 14 days the animals were self-administering extremely large amounts of morphine in the extended-access and escalating high-dose model.[27] These studies showed that the average daily morphine self-administration increased from 22.5 mg on day 1 up to 66.4 mg by day 14.[27]

In addition to our neurobiological studies of drug addiction by more traditional methods, such as gene expression, we have been collaborating with Dr Virginia Pickel's laboratory in the use of immunogold electron microscopy (EM) to study drug-induced receptor trafficking. In these studies we have been exploring the effects of chronic intermittent self-administration of escalating doses of morphine on ionotropic glutamate receptor subunit trafficking in postsynaptic (ie, dendritic) sites in neurons, a process that is emerging as a critical cellular substrate of neural plasticity. Because immunogold

EM can be used to localize receptors near intracellular organelles, as well as presumably functional areas of the plasma membrane, this approach provides a more functional view than many of the more conventional methods of measuring receptor levels. We have been using immunogold EM to study glutamate receptor localization in neurons in portions of limbic-autonomic brain areas, namely the reciprocally connected nucleus tractus solitarius (NTS) and central (CeA) and basolateral (BLA) nuclei of the amygdala, a brain circuit that may play a critical role in homeostatic adaptations associated with repetitive drug use.[28-29] We have reported that the N-methyl-D-aspartate (NMDA)-NR1 receptor subunit is decreased on the dendritic plasma membrane of NTS neurons in animals self-administering morphine, compared with control animals not exposed to morphine.[28] Further, morphine self-administering rats showed region-dependent changes in the subcellular location of the AMPA-GluR1 receptor subunit in the amygdala. Specifically, there was an increase in AMPA-GluR1 labeling on the dendritic plasma membrane of BLA neurons and a concomitant decrease in dendritic AMPA-GluR1 in CeA neurons from animals self-administering morphine compared with control animals.[29] These findings suggest that chronic opiate self-administration is associated with a redistribution of postsynaptic plasma membrane glutamate receptor subunits that play an important role in neural plasticity in brain circuitry regulating homeostatic processes. These adaptations may be an important neural substrate for alterations in drug reward, autonomic function, and behavioral processes, each of which may be associated with the acquisition and persistence of an addiction.[28,29]

In four separate earlier studies from our laboratory we have shown that chronic (14 days) binge-pattern cocaine administration increases mu-opioid receptor mRNA levels and also increases density of mu-opioid receptors in specific brain regions where there are abundant dopaminergic terminals from neurons located in the ventral tegmental area.[30-33] In recent studies, Bailey and our group have shown that early withdrawal from chronic binge cocaine administration results in a recurrence of an increase in mu-opioid receptor mRNA levels in the rat frontal cortex, but only in this region.[34] In further studies, Bailey found that there is a persistent upregulation of mu-opioid receptors following long-term withdrawal from escalating-dose binge-pattern cocaine.[35] In these studies, animals were treated with our new modified paradigm of escalating-dose binge cocaine over 14 days, which also results in an increase of mu-opioid receptor density, but with no increase in endogenous endorphin levels.[35] Following 14 days of withdrawal, there was still a highly significant increase in mu-opioid receptor density, and primarily in specific brain regions, again where there are dopaminergic terminals from the ventral tegmental area neurons and in fields in close proximity to both mu-opioid receptor mRNA levels in the neurons producing mu-opioid receptors and presenting them on the cell surface.[35]

In a further set of studies, Bailey explored changes in the kappa-opioid receptors following 14-day withdrawal from escalating-dose binge-pattern cocaine.[36] Here, very different findings were made. Whereas in multiple studies from our laboratory we have found both increases in gene expression of dynorphin, and increases in kappa-opioid receptor densities, and a correlated increase in kappa-opioid receptor mRNA levels, with kappa, unlike mu-opioid receptors, which are found to be persistently increased in density following 14 days of withdrawal from binge-pattern escalating-dose cocaine, in this study there was lowering of kappa-opioid receptors in two specific brain regions in animals in long-term withdrawal from cocaine. These areas included the basolateral amygdala and septum. Such a decrease in density was not found in other regions, but also with no persistence of increase in density. These selective brain regions of decrease in kappa-opioid receptor might contribute, in part, to the biological substrate for the development of dysphoria, which is usually observed in drug-free former cocaine-dependent individuals.[36]

Role of stress responsivity in the acquisition and persistence of specific addictive diseases, and the impact of chronic exposure to drugs of abuse and withdrawal therefrom on components of the stress-responsive system, along with identification of potential new targets for therapeutic intervention

In our recent studies, we have also further explored the relative role of dopamine D1 and dopamine D2 receptors in various specific neurobiological changes, or neural plasticity, resulting from chronic exposure to cocaine. Since it has been well established that dopamine plays a major role

in the rewarding properties of cocaine, and since it has been established for a long time that one of cocaine's primary sites of action is the presynaptic reuptake transporter for dopamine, where cocaine, by blocking reuptake, effects a flooding of perisynaptic space with dopamine, we have tried to dissect out the relative role of dopamine D1-like versus dopamine D2-like receptors in some of the resultant changes, both in behaviors, but also in gene expression and neuropeptide levels. During the last 5 years, we have completed further studies of the effects of selective dopamine D1-like and also dopamine D2-like receptor antagonists during acute binge-pattern cocaine administration on corticotropin-releasing factor (CRF) mRNA levels and pro-opiomelanocortin (POMC) mRNA levels in the hypothalamus. In earlier studies, we have found that both dopamine D1-like and also dopamine D2-like antagonists attenuate the chronic binge-pattern cocaine-induced increase in adrenocorticotropin hormone (ACTH) and corticosterone levels.[37] Further, we have shown that an attenuation of cocaine-induced changes in stress hormone levels similarly occurs in animals with complete deletion of the DARPP-32 protein, which is involved directly in dopamine D1 receptor signal transduction.[38] In our recent studies, we again found that both dopamine D1-like and dopamine D2-like antagonists attenuated the elevation of corticosterone levels by acute, as well as in our earlier studies of chronic, binge-pattern cocaine.[39] The previously identified acute binge cocaine-induced increases in hypothalamic CRF mRNA levels were not found in rats pretreated either with a dopamine D1-like or D2-like antagonist. Further, we found that neither the dopamine D1-like or dopamine D2-like receptor antagonists alone, in the absence of cocaine, altered mRNA levels of CRF in the hypothalamus. Thus, these results further support our earlier concept, that both dopamine D1 receptors and dopamine D2 receptors mediate acute as well as chronic cocaine's stimulatory effects on the hypothalamic-pituitary-adrenal (HPA) axis.[39]

Since neurobiological evidence has suggested that there are functional interactions between the dopaminergic and opioid systems regulating preproenkephalin and preprodynorphin expression in the striatum, and since there is increasing evidence there may be direct connections between the dopaminergic system in the striatum and the stress-responsive components of the hypothalamus, we also raised the question of whether dopamine D1-like or dopamine D2-like antagonists could play a role in regulation of POMC mRNA levels in the hypothalamus.[39] In this part of these studies, it was found that dopamine D2-like receptor blockade increased the POMC mRNA levels in the hypothalamus, a site with a different function than POMC mRNA levels in the anterior pituitary.[39] These findings suggest that activation of the dopamine D2 receptor may play a tonic inhibitory tone on hypothalamic POMC gene expression. However, neither dopamine D2 blockade nor acute binge cocaine altered POMC mRNA levels in the amygdala, the anterior pituitary, or the neurointermediate level of the pituitary. Also, dopamine D1 receptor blockade had no impact on hypothalamic POMC expression. Thus, these results both suggest a possible specific role for dopamine D2 in at least acute cocaine effects on hypothalamic POMC gene expression.[39]

To further our studies on the relative role of the D1-like and D2-like (and also D3-like, which are D2-like) dopamine receptors in the setting of drug abuse, and, specifically the impact of binge-pattern cocaine administration, we have conducted studies using D1-/- or D3-/- selective dopamine receptor gene deletion mice.[40] In these studies, we examined mu-opioid receptor gene expression in response to binge-pattern cocaine. We found that, at basal state, there was a significant increase in mu-opioid receptor mRNA levels in the frontal cortex of both the D1-/- and D3-/- dopamine receptor gene deletion mice, as compared with each of their wild-type controls.[40] However, there were no differences in basal levels of mu-opioid gene expression in the nucleus accumbens or in the caudate-putamen in these gene deletion mice. Strikingly, and in an opposite direction from some of our earlier findings in wild-type rat models, acute binge cocaine 15 mg/kg x 3 doses resulted in the restoration of frontal cortex mu-opioid receptor mRNA levels in the gene deletion mice to the levels of those in wild-type mice.[40] Further, in the nucleus accumbens core, after acute binge cocaine, there was an actual decrease in mu-opioid receptor levels in the D1-/- mutant mice, whereas in that brain region there was an increase in mu-opioid receptor gene expression in D3-/- mice.[40] The opposite pertained in the caudate-putamen, with an increase in mu-opioid receptor levels after binge cocaine in the caudate-putamen of the D1-/- mice and a decrease in the dopamine D3-/- mice.[40] In addition, a decrease in basal orexin mRNA levels was found in the lateral hypothalamus of the D3-/- mice, which did not change with cocaine.[40] These findings suggested that both D1 and D3 receptors are involved in mu-opioid receptor gene regulation in the frontal cortex, and also that D1 and D3

receptors may play opposite roles in the effects of cocaine on mu-opioid receptor gene expression in two striatal areas, the caudate-putamen and the nucleus accumbens core. In the control wild-type mice for the D1 receptor gene deletion, binge-pattern cocaine, as expected, increased mu-opioid receptor gene expression. However, in the wild-type controls for the dopamine D3 receptor knockout mice, there was a very modest, but not significant, increase in mu-opioid gene expression after binge cocaine, which was unexpected.[40] These findings were made both in the caudate-putamen and in the nucleus accumbens core, suggesting that in the actual breeding of the wild-type animals, the controls for the D3 knockout groups may have been substantially different from the wild-type mice which were the controls to the D1 knockout mice. Of particular note was the finding of increased basal levels of mu-opioid gene expression in both the D1 and D3 knockout mice, though only in the frontal cortex. These curious findings need to be studied further in D1 and D3 gene deletion mice, and also in different strains of wild-type mice.[40]

Most of the other studies of the impact of drug-induced stress on many different parameters, with emphasis on documentations of specific changes or evidence of neuroplasticity, have been conducted in rat models. In one sequence of studies, we examined the effects of acute morphine administration; chronic intermittent escalating-dose morphine (from 7.5 mg/kg/day on day 1 up to 120 mg/kg/day on day 10); and spontaneous 12-hour withdrawal from chronic morphine administration, using the escalating dose 10-day paradigm.[41] There were no changes in mu-opioid receptor mRNA levels in the lateral hypothalamus, the nucleus accumbens core, the caudate-putamen, or the amygdala following acute single injection of morphine, nor after chronic 10-day intermittent escalating-dose morphine.[41] However, after 12 hours of withdrawal from 10-day chronic morphine administration, several indices documenting stress response in the HPA axis were found, including increased POMC mRNA levels in the anterior pituitary, coupled with increases in ACTH levels, and also increased mu-opioid receptor mRNA levels in the lateral hypothalamus, the nucleus accumbens core, and the caudate-putamen. The changes in mu-opioid receptor gene expression suggest both a rebound from the abrupt withdrawal from large doses of the exogenous opioid morphine, as well as changes integral to the HPA stress-responsive axis, as well as in the hypothalamus.[41]

Several studies from other laboratories have demonstrated a role of lateral hypothalamic orexin (hypocretin) activation in drug-related positive reward, as well as in withdrawal effects; therefore gene expression of this peptide was also studied. It has been established by others that around half of the lateral hypothalamic orexin neurons concomitantly express mu-opioid receptors. In parallel to the increase in mu-opioid receptor gene expression found in the lateral hypothalamus in acute morphine withdrawal, similarly the levels of orexin mRNA in the lateral hypothalamus were also found to be increased.[41] No changes were found in the lateral hypothalamic levels of preprodynorphin mRNA, a gene which is known to be usually coexpressed with orexin in that hypothalamic region. These findings suggest that many different responses to the stress of morphine withdrawal occur, or, alternatively, changes which occur in the setting of withdrawal may drive the HPA axis activation and stress of withdrawal, just as we have found to be the case in our clinical studies.[42,43] Further, they suggest that in the lateral hypothalamus activation of orexin gene expression occurs in parallel to mu-opioid receptor gene expression. These findings suggest a novel target for managing opiate withdrawal.[41]

In a subsequent series of studies, a similar but somewhat different opioid administration paradigm was used. In these studies, heroin, the most common human opiate of abuse, was used,[44] coupled with a chronic, intermittent escalating-dose administration paradigm and conducted with doses of heroin ranging on day 1 from 7.5 mg/kg up to 60 mg/kg by day 10 (it should be noted that in this intermittent morphine escalating-dose paradigm, the starting dose was the same for heroin and morphine (7.5 mg/kg), but after 10 days, the escalation was up to 120 mg/kg when morphine was used, and 60 mg/kg when heroin was used.[44] One group of animals was then studied at the end of chronic escalating heroin administration; other animals were studied during early 12-hour withdrawal from such chronic heroin exposure; and a third group was studied after late 10 days of withdrawal from chronic heroin exposure.[44] In this study, it was found that arginine vasopressin mRNA levels were significantly increased during early spontaneous withdrawal, and, of several brain regions examined, only in the amygdala.[44] Further, separate studies showed that arginine vasopressin mRNA levels were increased not only in early spontaneous withdrawal from heroin in the amygdala, but also following foot-shock in rats withdrawn from

heroin self-administration.[44] Such findings were not made in the self-administration control, heroin-naïve rats. This increase in arginine vasopressin mRNA levels was no longer observed following 10 days of withdrawal from chronic heroin. As in earlier studies, POMC mRNA levels in the anterior pituitary were found to be increased, both 30 min after chronic heroin administration, which probably is a sign of very early withdrawal, as well as at 12 hours of withdrawal from heroin. POMC mRNA levels had returned to normal after 10 days of withdrawal. Similarly, ACTH levels were increased in early withdrawal, coupled with a significant increase in plasma corticosterone, after 12 hours of withdrawal. Although the levels of both ACTH and corticosterone at the end of the chronic heroin administration, and thus 30 min, after the last dose, were somewhat greater than those in the saline-treated controls, these changes were not significant.[44]

In much earlier basic clinical research studies, performed in a stress-minimized research unit, documented that plasma levels of ACTH and cortisol became elevated before any signs and symptoms of opioid abstinence were observed or reported following very-low-dose opioid antagonist administration in opioid-dependent persons, suggesting that HPA axis activation drives, in part, the stress of opioid withdrawal, rather than reflecting a response to that stress.[42,43]

In separate, but related, studies, a model of heroin self-administration was used. The dose of heroin administration was 0.05 mg/kg per infusion, and 7 daily short-access (3-hour) sessions were used.[44] Since vasopressin mRNA elevations had been observed in animal models of heroin withdrawal, these studies were designed to look at the effects of a vasopressin receptor (V1B receptor) antagonist, SSR149415, in that setting. Administration of this compound was before the first extinction, or drug withdrawal, session. The vasopressin receptor antagonist dose-dependently attenuated foot-shock-induced reinstatement and blocked heroin-induced reinstatement.[44] This antagonist also blunted HPA axis activation by foot-shock.[44] All these data suggest that arginine vasopressin activation may occur during withdrawal from opiates, and suggest that this peptide also may contribute to relapse or reinstatement. Further, it is shown that, in the stress of withdrawal, when foot-shock is added, there is a significant increase in gene expression, and thus probably in the arginine vasopressin peptide. Most important, the data suggest that a vasopressin antagonist might attenuate either stress (in these experiments, withdrawal-induced and foot-shock-induced), and also drug-induced reinstatement and relapse to opiate self-administration or use. Further studies in rodent models are needed. The arginine vasopressin receptor may become a novel target for therapeutics.[44]

In other separate studies, possible alterations of arginine vasopressin mRNA levels in the amygdala were studied in animals undergoing acute withdrawal from cocaine.[45] In these studies, our model of steady-dose binge-pattern (15 mg/kg every hour x 3 hours with no cocaine for 22 hours) administration for 14 days was used, followed by acute withdrawal (3 hours), subacute withdrawal (24 hours), and long-term withdrawal (10 days).[45] It was found that, although there were no changes in arginine vasopressin mRNA levels in the amygdala immediately following 14 days of cocaine administration, there were increases in arginine vasopressin mRNA levels in acute withdrawal (3 hours) from cocaine. Further, it was found that the selective opioid receptor antagonist naloxone blocked this increase.[45]As found in previously reported studies from our laboratory, chronic cocaine did not result in increased mu-opioid mRNA levels in the amygdala, nor did acute withdrawal from cocaine in these studies. At 24 hours of withdrawal, significant increases in arginine vasopressin mRNA levels in the amygdala were still observed. However, these levels had returned to normal after 10 days of withdrawal.[45] As found in our previous studies, adaptation or tolerance to the cocaine effects on the HPA axis activation also was observed during chronic binge cocaine.[45] However there were still modestly elevated levels of ACTH during acute withdrawal. As expected, naloxone produced modest elevations in ACTH levels in cocaine-naïve rats; naloxone did not have such an effect in the acute or subacute cocaine-withdrawn animals. There were no changes in arginine vasopressin, or POMC, or mu-opioid receptor mRNA levels in the hypothalamus following chronic cocaine administration, and acute withdrawal from cocaine.[45] These findings suggested that opioid receptors may mediate the increase in arginine vasopressin in the amygdala during acute cocaine withdrawal, and suggest a potential role for arginine vasopressin in the amygdala in some of the adversive effects of withdrawal from cocaine as well as in withdrawal from opiates.[45]

A recent set of laboratory-based studies in rats affirm, and further suggest a mechanism, for observations which we have made in two separate clinical studies, around 7 years apart, and in two parts of the world.[46-48] We have deter-

mined that steady-state methadone may attenuate or eliminate the liking of cocaine, and may do so by a mu-opioid receptor-mediated mechanism[49,50] In several earlier studies, as discussed above, we have shown that chronic binge-pattern cocaine administration results in an increase in mu-opioid receptor density in multiple, but not all, brain regions, and specifically in regions where there are abundant dopaminergic terminals from dopamine neurons in the ventral tegmental area and substantia nigra compecta.[31-33] Further, we have shown that acute and subacute, but not chronic, cocaine administration results in an increase in mu-opioid receptor mRNA levels.[30] In these recent studies, different paradigms were used.[41] In one set of studies, rats were implanted with either saline- or methadone-filled osmotic minipumps and then conditioned with 1, 5, or 20 mg/kg cocaine intraperitoneally. Animals with the 20 mg/kg/day or 55 mg/kg/day methadone-filled osmotic pumps did not express cocaine-induced place preference.[46] However, methadone pumps at two doses (30 and 55 mg/kg/day) did not alter intravenous self-administration of cocaine using a continuous schedule of reinforcement with different doses of cocaine (0.1, 0.5, and 2.0 mg/kg/infusion) studied. Mu-opioid receptor mRNA levels were measured in animals treated with cocaine as part of conditioning for place preference. As in earlier studies, it was shown that this subacute cocaine administration resulted in increased mu-opioid receptor mRNA levels in the nucleus accumbens core and in the frontal cortex 10 days after cocaine conditioning.[46] However, this increase in mu-opioid receptor mRNA levels was attenuated or eliminated by the steady-dose infusion of methadone. Earlier studies have shown that the dose of 55 mg/kg/day subcutaneously by pump in the rat results in a plasma level similar to that in patients seen in methadone maintenance.[49] These studies showed that, although high doses of methadone delivered by pump did not alter the direct reinforcing effects of cocaine as seen in self-administration, those doses of methadone did block both spontaneous and cocaine-induced "seeking" or "liking" 10 days after cocaine conditioning. Further, we have suggested that this may be through the mechanism of methadone attenuating or preventing the relative endorphin deficiency resulting from the increased mu-opioid receptor density preceded by increased mu-opioid receptor gene expression, but with no concomitant increase in the endogenous opioids that bind to the mu receptor, that is, no increase in beta-endorphin or in the enkephalin peptides.[46]

These studies also build upon the early and also much more recent findings that, despite the fact that up to 70% of all persons in the middle Atlantic states, as well as currently in Tel Aviv, Israel, have concomitant dependence upon cocaine, when presenting for treatment for long-standing dependence on heroin, after 1 year or more of methadone treatment, as expected, the numbers using heroin dropped precipitously, to less than 20% of patients using heroin at any time (as contrasted to heroin use by all patients 3 to 6 times a day prior to entry). This was accompanied by the more surprising findings that during steady-dose methadone maintenance treatment, the percentage of persons dependent on cocaine drops down to less than 20%, and those using any cocaine to less than 30%.[47,48] Although these beneficial results of methadone maintenance on managing cocaine addiction were always attributed to the counseling and other psychosocial benefits derived from a good methadone maintenance program, we have, over the last decade, hypothesized that a pharmacological mechanism also is in place, a hypothesis based on our findings that binge cocaine increases acutely mu-opioid receptor gene expression and on a chronic basis, mu-opioid receptor density, and further, that a relative endorphin deficiency thus develops in humans, since there is no concomitant increase of beta-endorphin or enkephalins, as may be directly documented by stress-responsive metyrapone testing.[50] These findings suggest that possibly an opioid agonist such as methadone, or possibly a partial agonist, such as buprenorphine, might be able to be effectively used to treat very severe, long-term, cocaine-dependent persons who have not responded to any other available current treatment. Since there are no effective targeted pharmacotherapies for cocaine addiction, the potential target of the mu-opioid receptor, with now a neurobiological basis for such treatment, might be warranted.

In other studies, conducted by a collaboration with our colleagues at the Karolinska Institute in Stockholm, Sweden, yet another potential target for future therapeutic use, a nociceptin/orphanin FQ receptor agonist (Ro64-6198) was found to reduce alcohol self-administration, and, further, and importantly, to prevent relapse to alcohol drinking in a rat model.[51] Other orphanin-nociceptin (ORL-1) receptor agonists may be found to have effectiveness in treatment of alcoholism and possibly other specific addictive diseases, which involve interactions between the dopaminergic system and different components of the opioid and opioid-like system.[51]

Basic clinical research related to specific addictive diseases, with emphasis on stress responsivity: all research focused on treatment improvement

Corticotropin-releasing factor (CRF), synthesized and released in the hypothalamus, passes through the portal blood system to the anterior pituitary, where it effects processing and release of the single gene product of the POMC gene (reviewed in ref 7). This large peptide is then further processed to yield many biologically active and important neuropeptides, including the major stress-responsive and glucocorticoid-regulated peptide, ACTH, as well as the longest (31 amino acids) of the endogenous opioids, and a primary ligand of the endogenous mu-opioid receptor, beta-endorphin. ACTH and beta-endorphin are released in equimolar amounts from the anterior pituitary sites in humans (who, unlike rodents, do not possess an intermediate lobe in the pituitary except transiently during pregnancy.) ACTH and beta-endorphin pass into the general circulation. ACTH impacts directly upon the adrenal cortex to bring about the processing and release of the major glucocorticoid in humans, cortisol, in addition to altering and enhancing the biotransformation and release of several other steroid hormones. Beta-endorphin may act at many peripheral sites. There is some evidence that there may be retrograde passage of these two neuropeptides back into the hypothalamic region, which in human and nonhuman primates, but not in rodents, lies partially outside the brain barrier. Glucocorticoids have been documented for a very long time to negatively regulate the HPA axis in a negative-feedback mode, with cortisol being the primary glucocorticoid in humans, non-human primates and guinea pigs, and corticosterone, the primary glucocorticoid having this effect in rats and mice. Thus, cortisol acts at both the hypothalamic sites of CRF production and at the anterior pituitary sites of POMC processing and release, to transiently attenuate or inhibit the release of these hormones. A 24-hour circadian rhythm is thus achieved, with the lowest levels of CRF, ACTH, beta-endorphin and thus cortisol in the late afternoon and early evening in humans, and with levels rising again in the early morning hours, the opposite times pertain in rodents, with highest hormone levels at night, at the beginning of the activity period.

Based on early findings of Volavka, our group and a few others years ago began to study the possible role of the endogenous opioid system, in particular, the mu-opioid receptor system, in also modulating the HPA axis. In several studies we have shown that the HPA axis is inhibited by the mu-opioid receptor system (reviewed in refs 5,7,8). In one study from our group, we looked at high and very high doses of two different selective mu-opioid receptor antagonists, both of which can be administered intravenously in humans, naloxone and nalmefene.[52] Studies using nonhuman primate membranes and, more recently, studies using cloned human genes in proper molecular-cellular constructs, have shown that, in contrast to rodents, naloxone binds almost exclusively to the mu-opioid receptor and acts as an antagonist.[52] Nalmefene, on the other hand, binds to both mu- and kappa-opioid receptors. Very recently, in collaboration with the group of Bidlack, we have shown that the kappa opioid receptor effect of nalmefene is that of a partial agonist (that is, with some agonist and some antagonist properties), whereas the mu component is pure mu-opioid receptor antagonist.[53] Since we have studied both of these compounds in several earlier clinical research studies, we elected to use high and very high doses of each, to be sure that the ceiling of the effective doses in humans was exceeded. We found, as we and others had shown before, that naloxone activates the HPA axis by disinhibition and causes significant increases in both ACTH and cortisol. Of great interest in this study, however, was the finding that nalmefene causes a significantly greater activation of the HPA axis, with higher resultant peripheral levels of ACTH and cortisol.[46] Our more recent studies, in which we found that the kappa component of nalmefene is a partial agonist, suggest that whereas the mu antagonists act at mu-opioid receptors of the hypothalamic and anterior pituitary sites, and through the mechanism of disinhibition bring about the increased release of CRF and ACTH and beta-endorphin, the kappa partial agonist component of nalmefene may act directly to enhance release of CRF and/or of the POMC peptides, ACTH and beta-endorphin, thus directly activating the HPA stress-responsive axis, which has been suggested by several workers in preclinical studies.[52,53] This possibility has not, however, been well studied with any of the very few selective kappa agonists which have ever been introduced to human use, and only a few additional studies of these kappa agonists or partial agonists have been conducted in nonhuman primates.

In earlier studies, it has been shown that activation of the HPA axis, with increased levels of plasma ACTH and

cortisol, occurs after administration of alcohol or cocaine, and many groups have made similar findings in animal models. Further, we have shown that tolerance develops to this HPA activation effect of both cocaine and alcohol. In other studies, we have suggested that activation of the HPA axis is sought by the rat or mouse, and by the human. In human studies conducted, in collaboration, by O'Malley at Yale in a clinical research setting, naltrexone, a selective mu-opioid antagonist with some kappa antagonist activity, was administered for 1 week to alcoholics and compared with placebo administered for one week to a similar group.[54] Then a laboratory session was conducted in which limited alcohol self-administration was permitted for up to 2 hours. We found, just as in the numerous field trials, that alcoholics receiving naltrexone drank significantly fewer drinks.[54] Because of the naltrexone disinhibition of the hypothalamic-pituitary sites of the HPA axis, there was a significant increase in levels of ACTH and cortisol in alcoholics treated with naltrexone after consumption of fewer than two drinks, whereas the much larger amounts of alcohol consumed by the alcoholics receiving placebo resulted in no significant activation of this axis.[54] Further, on responding to specific questionnaires, the alcoholics receiving naltrexone, and who had consumed only a small amount of alcohol, but had experienced modest activation of the HPA axis, felt no further "craving," or desire to drink alcohol, and this decrease in craving was correlated to the increase of serum cortisol levels. The opposite pertained in those alcoholics receiving a placebo, who had consumed more alcohol, but had no activation of the HPA axis, and no increase in cortisol, a significant urge to drink alcohol persisted.[54]

Many of our earlier studies have shown that short-acting opiates, opposite from the effects of cocaine and alcohol in the HPA axis, profoundly attenuate or suppress the HPA axis, resulting in lowered levels of ACTH and cortisol after opiate administration. However, after tolerance and physical dependence have developed, in the setting of withdrawal from opiates, profound activation of the HPA axis occurs with increases in levels of ACTH and cortisol. The neuroendocrine changes of opiate withdrawal look very similar to the normal response to a specific mu opioid receptor antagonist, such as naltrexone, when given to a healthy volunteer. Therefore, it is not surprising, as we had predicted, that most opiate addicts will not willingly accept chronic daily naltrexone or other opioid antagonist treatment once experienced, whereas alcoholics would accept such treatment, and might be directly benefited. Giving an opioid antagonist to any opiate-dependent person is contraindicated, because profound activation of the stress-responsive axis will occur and creates a very adversive and noxious experience. In many of our earlier studies, we have shown that during chronic methadone maintenance treatment, which provides steady perfusion with a synthetic ligand of the mu-opioid receptor, complete normalization of the HPA axis occurs, including normalization of basal levels of hormones, as well as responsivity in various functional tests.

To dissect further the relative contribution of the glucocorticoid system contrasted to the mu-opioid receptor endogenous ligands, that is, beta-endorphins and enkephalins, we have conducted further studies using metyrapone. In humans, metyrapone blocks the final step of cortisol synthesis, that is, 11-β-hydroxylation. In the single oral dose test using metyrapone, the synthesis of cortisol is blocked for about 8 hours, and then returns to normal. Therefore, one can measure the levels of ACTH (which also reflect the equimolar release and levels of beta-endorphin) following metyrapone administration which are elevated because with cortisol synthesis blocked, and the normal negative feedback is transiently cut off. In healthy human beings, with normal endogenous opioid systems, the mu-opioid receptor system responds to bring a check, or brake, to the increased release and levels of ACTH (and beta-endorphin). However, we had shown in several earlier studies that in medication-free, drug-free former heroin addicts, there is no such mu-opioid receptor-mediated brake, and thus hyper-responsivity to metyrapone testing is observed (reviewed in refs 5,7). Further, we had reported that in abstinent cocaine addicts a similar hyper-responsivity to metyrapone testing exists.[50] This hyper-responsivity, therefore, suggests a relative endorphin deficiency, which our laboratory-based studies also support.[30-33,50] As discussed above, we have found that chronic binge cocaine administration causes an increase in gene expression in the mu-opioid receptor, as well as an increase in density in mu-opioid receptors, in specific brain regions with abundant dopaminergic terminals, and, further, in recent studies, we have found that this increase in mu-opioid receptor density persists for a protracted period of time after last cocaine exposure.[30-32,35] However, we have also shown that there is no increase of the endogenous opioids that bind at the mu receptor. Thus a relative endorphin deficiency develops (or possibly was present a priori on a genetic or environmentally-induced basis).

Subsequently, Frost and colleagues, using positron emission tomography (PET) showed similarly the mu-opioid receptor density being increased in recently-abstinent cocaine addicts, and further more recently have shown that this increase persists for protracted periods of time into successful cocaine abstinence.[55,56] Thus, a relative endorphin deficiency has been documented both in humans as well as in rodent models, in humans directly shown by testing of the stress-responsive system. In several studies, we have found that metyrapone responsivity is abnormal in opiate addicts, but becomes normalized in methadone maintenance patients (reviewed in refs 5,7). We also have shown that abnormal hyper-responsivity occurs in cocaine addicts.[5,7] In a more recent study, we again documented the normalization during methadone maintenance treatment.[50] We also conducted studies in a subgroup of methadone maintenance patients who continued during 6-month treatment or more to meet the criteria of cocaine dependence.[50] This group was maintained on moderate doses of methadone (60 to 90 mg/day). As discussed above, an early clinical study from our laboratory, a very recent clinical study from our laboratory, and a recent laboratory-based study have all suggested that increasing the dose of methadone may decrease cocaine addiction in maintenance patients with dual-dependency, and further, in the rodent model, that the addition of steady-state methadone may prevent alterations in mu-opioid receptor gene expression and attenuate or prevent conditioned place preference to cocaine.[46-48]

In another set of studies reported in the last decade we have re-explored the glucocorticoid negative feedback both in methadone-maintained former heroin addicts, as well as those with ongoing cocaine dependence.[57] In all our earlier studies, we found, surprisingly, that all of the methadone-maintained patients had normal suppression to dexamethasone and, in this study, we also used two lower doses than the usual suppression dose, that is, 0.5 and .125 mg and found that all subjects suppressed completely (as reviewed in refs 5,7,57). All the cocaine-dependent methadone-maintained patients also suppressed completely. Although not significant, the glucocorticoid feedback effects in the cocaine-dependent, methadone-maintained patients, and also in the otherwise well-stabilized methadone-maintained patients appeared to be greater than the normal volunteers in the late afternoon, suggesting that there may be a modestly altered, or enhanced, negative feedback by glucocorticoids, in at least some subjects.[57] This, in turn, may contribute to the observed attenuation of both basal and cocaine-induced responsivity of the HPA axis in humans and in rodents in other studies from our laboratory and others.

In another study, we examined the effect of corticotropin-releasing factor in methadone-maintained versus control subjects. In this study, we found differences between long-term well-stabilized methadone-maintained subjects as compared with normal control subjects.[58] In this study, two doses of CRF were used; one lower than the usual dose (0.5 µg/kg) and one dose higher (2.0 mg/kg) than usually used in the neuroendocrine diagnostic procedure (100 µg, irrespective of weight).[58] There was no difference in hormonal measurements between the two groups following placebo administration, nor during low-dose hCRF administration. However, following high-dose CRF administration, the methadone-maintained patients displayed a significantly greater increase in plasma ACTH levels than did the normal volunteers.[58] This suggested that in long-term methadone-maintained patients some abnormalities in HPA axis responsivity may pertain, in this case, a greater sensitivity of the anterior pituitary to CRF stimulation. In turn, these findings suggest that the basal and peak levels of CRF may be slightly reduced in stable methadone maintenance patients, possibly related to the increased sensitivity to negative feedback by glucocorticoids, as discussed above, or due to the steady but high and exogenous opioid tone in patients in treatment with the long-acting mu agonists.[57,58] Further studies to explore this altered sensitivity in other persons with specific addictive diseases, not in treatment, as well as in treatment, are in progress.

In another series of studies, we have been able to pursue in humans findings which we and others had made in rodents, that is, that dynorphin, the natural endogenous opioid ligand of the kappa-opioid receptor, may directly act to alter (lower) dopaminergic tone. We have been able to access dynorphin A(1-13), a natural-sequenced dynorphin four residues shorter than the natural dynorphin A(1-17) for research use under an investigator-initiated investigational new drug application (IND) approved by the US Food and Drug Administration. Building upon the established biological fact that, in humans, prolactin release is almost exclusively under dopaminergic tone, and thus, that a lowering of dopamine in the tuberoinfundibular dopaminergic region results in

a rise in prolactin levels, we conducted studies first in healthy volunteers using two different doses of intravenously-administered dynorphin A(1-13) (120 µg/kg and 500 µg/kg). Since in humans some of the hypothalamus lies outside the blood-brain barrier, we assumed that the peptide dynorphin would be able to act on this tuberoinfundibular dopaminergic system. When we conducted these studies in a stress-minimized environment of our Rockefeller Hospital clinical research center, we found that peripheral administration of dynorphin A(1-13) gave a prompt dose-dependent increase in serum prolactin levels, which then returned to normal within 120 minutes.[59] This duration of action was much longer than we predicted, based on our in vitro biotransformation studies in which we established the probable half-life of dynorphin A(1-13) in human blood.[60] Of interest, with respect to the possible effect of dynorphin on the HPA axis, we found no increment in ACTH or CRF following peripheral dynorphin administration.[59] To document whether the dynorphin effect was modulated by the endogenous opioid system, we conducted studies using the lower dose of dynorphin A(1-13) following pretreatment with either naloxone or nalmefene, both selective mu-opioid receptor antagonists, and one (nalmefene) with partial kappa-opioid agonist activity.[59] We found pretreatment with either of these compounds attenuated the rise in serum prolactin.[59] In these initial studies, a further very provocative (but not completely unexpected given the physiological differences) observation was made, an unusual finding in our human studies of addictive diseases, specifically that female subjects had modestly higher basal levels of prolactin than males, but when given dynorphin, gave a significantly exaggerated response, with higher levels of prolactin achieved after dynorphin administration and thus the reduction of dopamine in the tuberoinfundibular region.[59] Thus, a clear gender difference was observed. Our subsequent studies of dynorphin effects now must be done always considering males and females separately.

In a second set of studies, we have addressed the question of whether or not the dynorphin responsivity, with respect to lowering dopaminergic tone, will occur similarly in healthy long-term well-stabilized methadone-maintained subjects.[61] Two doses of dynorphin again were used for study in both a new group of healthy volunteer subjects and in a group of long-term stable methadone-maintained patients.[61] Again, in the healthy volunteer subjects, a dose-dependent rise in serum prolactin was observed after dynorphin administration.[61] Similarly, in the methadone-maintained patients (receiving 80 to 120 mg/day of methadone), a dose-dependent rise in prolactin occurs.[61] Because years ago (published in 1978 by our group), we had shown that methadone itself, acting as a mu opioid receptor agonist, acts to lower dopaminergic tone, causes increase in serum prolactin, which occurs at time of peak plasma levels of methadone (that is, around 2 to 4 hours after oral methadone dose), in the dynorphin studies, we withheld the methadone dose until 60 minutes after the dynorphin was given.[62] In these subjects, as in our much earlier studies, we showed a second and separate brisk rise in prolactin levels, beginning at 2 hours after methadone administration and remaining elevated at 5 hours after methadone administration. Again, in the methadone-maintained patients, as in both groups of healthy volunteer subjects, there was a dose-dependent dynorphin-induced rise in prolactin levels which returned to basal levels by 90 to 120 minutes. Thus, in this study, we were able to observe both the dynorphin- and methadone-induced lowering of tuberoinfundibular dopaminergic tone, resulting in both rises in serum prolactin levels.[61,62]

In yet another series of studies, we had observed that when given to healthy volunteers nalmefene caused a small but modest rise in serum prolactin levels.[53] Therefore, we entered into a collaboration with Bidlack, and in that collaboration addressed directly the issue of whether the kappa opioid receptor activity of nalmefene is antagonist, or possibly, as we hypothesized, partial agonist. It was found clearly that nalmefene possesses kappa-opioid receptor partial agonist activity in in vitro studies using appropriate molecular cellular constructs.[53] It was reconfirmed that the mu opioid receptor action of nalmefene is only that of antagonism; the kappa opioid receptor action is both agonism (partial agonist) and antagonism.[53] Further, we were able to show that nalmefene effects a modest elevation of prolactin levels, suggesting a modest lowering of dopaminergic tone. This suggests, however, that nalmefene or other mu-opioid receptor antagonists, which have kappa-partial agonism (probably also true for naltrexone) may have augmented benefit for management of alcoholism, and possibly even for treatment for stimulant, such as cocaine, dependency, since a modest lowering of dopaminergic tone could be helpful in decreasing or attenuating the "reward" effect, whereas the inhibition of the mu-opioid receptor regulation of the stress-responsive HPA axis could provide

modest activation of this axis, which we have directly documented to be sought by alcoholics, and in our animal modeling suggests is also sought by the cocaine self-administering animals.[19,54] In these basic clinical research studies, we have again found an extremely important role of the mu-opioid receptor system, as well as identifying a previously not-appreciated role of the kappa-opioid receptor system in modulation of the human stress-responsive HPA axis.

Our genetics work, including our work in physiogenetics, has not been discussed herein, but has been reviewed elsewhere, as discussed above.[5,8-11]

All these findings have taught us that physiogenetics may occur, that is, difference in our response to our own proteins, peptides, neurotransmitters, or steroids, based on a polymorphism of a receptor or some polymorphism of the ligand or the pathway producing the ligand. Further, such studies, in the future, may give us increasing insights into targets for therapeutics, as well as providing a basis for effective primary prevention of specific addictive diseases. ❑

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Opioides, dopamina, estrés y las adicciones

Los objetivos expresados por Dialogues in Clinical Neuroscience son servir como interfase entre la neuropsiquiatría clínica y las neurociencias al entregar información actualizada y conocimientos originales de aspectos clínicos, biológicos y terapéuticos relevantes. Mi laboratorio, el Laboratorio de la Biología de las Enfermedades Adictivas de la Rockefeller University, se ha orientado por años a la "investigación translacional bidireccional", es decir, el aprendizaje mediante cuidadosas observaciones y análisis de poblaciones de pacientes con la enfermedad en estudio, en este caso, enfermedades adictivas primariamente específicas, y luego utilizar ese conocimiento para crear modelos animales mejorados u otros paradigmas de investigación basados en el laboratorio; y al mismo tiempo, trasladar los resultados de estudios realizadas en el mesón del laboratorio a la clínica tan pronto como sea apropiado y posible. En esta revisión por invitación, el foco de atención serán las perspectivas de nuestro Laboratorio de la Biología de las Enfermedades Adictivas, del Instituto Nacional de Salud y del Centro de Investigación del Abuso de Drogas del Instituto Nacional, incluyendo investigación neurobiológica molecular basada en el laboratorio, investigación con algunos modelos animales diseñados para simular patrones humanos de abuso y adicción a drogas, y también investigación clínica básica entrelazada con investigación relacionada con el tratamiento.

Opioïdes, dopamine, stress et addictions

L'objectif des Dialogues in Clinical Neuroscience *est de servir « d'interface entre la neuropsychiatrie clinique et les neurosciences en délivrant une information à la pointe des connaissances et des points de vue originaux sur des aspects cliniques, biologiques et thérapeutiques pertinents ». Le laboratoire de* Biology of Addictive Diseases *que je dirige à l'université Rockefeller, se concentre depuis des années sur «la recherche translationnelle bidirectionnelle», composée de recueil d'informations par l'observation soigneuse et l'étude de populations de patients atteints de troubles donnés, dans le cas de notre laboratoire plus spécifiquement de maladies addictives, et de l'utilisation ultérieure de ces connaissances pour créer un modèle animal amélioré ou d'autres modèles de recherche en laboratoire. Parallèlement, il s'agit d'exporter les résultats de recherche obtenus* in vitro *aussi vite que cela est opportun et faisable, vers la clinique. Dans cette revue, nous avons donc mis l'accent sur les perspectives du laboratoire de* Biology of Addictive Diseases and related National Institutes of Health/National Institute on Drug Abuse research Center *; elles incluent la recherche neurobiologique moléculaire de laboratoire qui utilise différents modèles animaux afin d'imiter les modèles humains d'abus de drogues et d'addiction, aussi bien que la recherche clinique de base, étroitement liée à la recherche thérapeutique.*

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Neural basis of reward and craving —a homeostatic point of view

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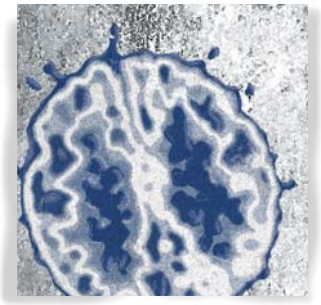

Here, it is argued that the interoceptive system, which provides information about the subject's internal state and is integrated in the insular cortex, and not the subcortical ventral striatum, is the critical neural substrate for reward-related processes. Understanding the internal state of the individual, which is processed via this system, makes it possible to develop new interventions that are aimed at treating reward-dysfunction disorders, ie, substance and alcohol dependence. Although the ventral striatum is important for signaling the degree to which rewarding stimuli are predicted to occur, this system alone cannot account for the complex affective, cognitive, and behavioral phenomena that occur when individuals come into contact with potentially rewarding stimuli. On the other hand, the interoceptive system is able to make connections between all cortical, subcortical, and limbic systems to orchestrate a complex set of responses. Craving and urges are among the most notable responses, and may have important functions to preserve homeostasis.

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Overview

Reward is a complex construct that entails a feeling and an action. Components of reward include the hedonic aspects, ie, the degree to which a stimulus is associated with pleasure, and the incentive motivational aspects, ie, the degree to which a stimulus induces an action towards obtaining it.[1] Typically, the feeling is described as "pleasurable" or "positive" and the actions comprise behavior aimed at approaching the stimulus that is associated with reward. However, importantly, both feeling and action are highly dependent on the homeostatic state of the individual.[2] That is, the degree to which a stimulus elicits a reward-consistent response depends in turn on the internal state of the subject. Therefore, to understand the neurobiology of reward, one needs to examine the neural substrates that process the feeling, and action associated with a stimulus as it relates to the internal state of the individual. As a consequence, treatments of disorders of reward systems need to be focused on modulating the interoceptive system and its underlying neural substrates, instead of altering the hedonic or incentive properties of the stimulus associated with the reward, or the underlying neural systems that process these associations. To this end, experiments will need to be conducted that examine how modulating the interoceptive state using C-fiber modulation will affect reward processing. This review provides an overview of the integration of the hedonic and incentive

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motivational view of reward with that of the homeostatic perspective of reward, and is focused on the neural substrates that underlie these processes.

The hedonic aspects of reward-pleasure

The subjective experience of pleasure is at the heart of reward-related processing. This component of reward-related processing, ie, the hedonic or pleasurable component associated with the experience, is critical for understanding why individuals approach reward-related internal representations, external stimuli, or environments. Moreover, it is this complex set of features that is associated with the use of substances. Pleasure is fundamentally an experiential state, which combines a sensation as well as an emotion or feeling associated with it.[3] Thus, it is not surprising that visceral factors profoundly affect the hedonic impact and therefore directly alter the degree of relative desirability of different stimuli.[4] Fundamentally, the pleasurable state relates to changes in perceived body state that are likely processed via ascending slow-conducting primary afferents.[2] As pointed out in ref 5, unmyelinated primary afferent fibers, designated as C-fibers when of cutaneous origin or as group IV when of muscular origin, have been traditionally linked to pain processing. More recently, however, the function of these fibers has been widely expanded to include a range of sensations such as pain,[6] temperature,[7] itch,[8] tickle,[9] sensual touch,[10,11] muscle tension,[5] air hunger,[12] stomach pH,[13] and intestinal tension,[14] which provide an integrated sense of the physiological condition of the entire body.[2] These afferents are processed in a distinct neural pathway that includes the lateral spinothalamic tract, midbrain homeostatic nuclei, the ventromedial thalamus, and the posterior insular cortex. Finally, these topographic and modality-specific organized pathways are integrated in the anterior insular cortex.[15] The anterior insular cortex in turn is integrally connected with subcortical,[16] limbic,[17] and executive control brain systems.[18] Within the anterior insular cortex, a multidimensional representation and integration of the current and possibly the predicted[19] body state provides the individual with a temporal representation of a "global moment in time" (Craig AD, personal communication). Importantly, this interoceptive network processes information in a homeostatic manner, ie, the valence of the information fundamentally depends on the nature of the individual's current state. For example, the same temperature of an air-conditioned room is pleasantly experienced in the heat of the summer but is experienced aversively on a cold winter day. It has been suggested that this network is fundamentally important for the generation of different feeling states,[2] and is closely linked to our overall awareness of ourselves.[20]

Based on this brief outline, it should be clear that the hedonic aspect of a stimulus is a property that emerges from the interplay between the stimulus characteristics and the individual state. Not surprisingly, the hedonic value of a stimulus is substantially influenced by its context. For example, in a decision-making situation, unexpected outcomes have greater hedonic impact than expected ones, and any given outcome is perceived as less pleasant if an unobtained outcome is perceived as being better.[21] That is, surprise, which strongly activates the ventral striatum,[22] and comparison with nonexperienced alternatives, contribute strongly to the experience of pleasure. Similarly, anticipation of pleasure has a profound influence on decision-making, and can explain why individuals make risky choices.[23] For example, people feel displeasure when the outcomes of selected actions fall short of the counterfactual alternative, and increased pleasure when their outcomes exceed the counterfactual alternative.[24] Moreover, predictions of future hedonic reactions result from a complex interplay between the current state of the individual and the changes that occur as the individual is getting closer in time to experiencing the stimulus. Specifically, initially the hedonic experience is based on the atemporal imagination of the stimulus, which is subsequently corrected with information about the time at which the event will actually occur.[25] The experience of the hedonic aspects of a rewarding stimulus itself has profound consequences of subsequent behaviors. In many instances individuals show deteriorating performance when they are anticipating the hedonic quality of a future experience.[26,27] Thus, to speak of the pleasurable property of a stimulus without referring to the contextual and individual state is to fundamentally misunderstand the way the brain processes hedonic aspects of reward.

Animal experiments have shown that an area within the medial caudal subregion of the nucleus accumbens shell, as well as rostral ventral pallidum, are necessary to process the hedonic reward properties of food.[28,29] Moreover, it appears that the ventral pallidum, an area adjacent to and connected with the insular cortex, [17] is a key structure in brain mesocorticolimbic reward circuits

that mediate "liking" or hedonic reactions. Specifically, firing patterns of neurons within this structure selectively track the hedonic values of tastes, even across hedonic reversals caused by changing the homeostatic state of the animal.[30] One possible way to examine the brain structures necessary to process the hedonic aspects of reward is to study individuals who are unable to experience pleasure due to an underlying psychiatric condition, ie, depressed subjects with profound anhedonia. In humans, neuroimaging investigations with depressed individuals have shown altered activation in midline cortical structures as well as putamen and thalamus that were directly related to the degree of anhedonia.[31] This was also found in another study, which showed that anhedonia was positively and negatively correlated with ventromedial prefrontal cortex and amygdala as well as ventral striatal activity.[32] Therefore, one top-down modulatory area, which is important for the assessment of hedonic valence is the midline cortical mantle, which includes medial prefrontal cortex as well as parts of the anterior cingulate, which has been referred to as limbic motor cortex.[2]

Examining other intrinsically hedonic stimuli and how these stimuli are processed in the brain provides a complementary approach to better understanding of the neural basis of hedonic processing. For example, food intake is an essential human activity regulated by homeostatic and hedonic systems. Recent neuroimaging experiments have identified that the orbitofrontal cortex is perhaps the strongest candidate for linking food and other kinds of reward to hedonic experience,[33] which has prompted some to suggest that this part of the brain may mediate the hedonic experience.[34] Similarly, cerebral blood flow changes during intensely pleasant emotional responses due to music have been observed in ventral striatum, midbrain, amygdala, orbitofrontal cortex, and ventral medial prefrontal cortex.[35] Others have suggested that cortical asymmetry contributes to the degree of hedonic experience. For example, greater left than right superior frontal activation was associated with higher levels of both forms of well-being. Appropriately engaging sources of appetitive motivation, characteristic of higher left than right baseline levels of prefrontal activation, may encourage the experience of well-being.[36]

Taken together, these observations make it clear that hedonic processing occurs on multiple levels in the brain and involves different brain structures that are important for contributing to stimulus-dependent, context-dependent, and homeostasis-related processing of the hedonic value. Common to these neural substrates that have been implicated in this process, ie, ventral pallidum, medial prefrontal and orbitofrontal cortex, is the fact that these brain areas are closely connected to the interoceptive system as outlined above.

The incentive motivational aspects of reward—urge and craving

Turning to the incentive motivational aspect of reward-related processing, it is important to also integrate these aspects within the homeostatic perspective. Surprisingly, there has been a burgeoning literature on bodily urges that has not been associated with the traditional drug addiction notion of incentive motivational processing, but can be linked easily, generating a broader perspective and enabling us to develop a neurologic formulation of drug addiction.

Urges can be conceived of as feeling states which are associated with strong incentive motivational properties to act, eg, pursue drug use. Some investigators have proposed that there may be two types of urge networks: (i) a "positive-affect" network, which is activated by appetitive stimuli, especially appetitive drug actions that activate "go" incentive motivational systems; and (ii) a "negative-affect" network, activated by aversive stimuli or consequences and by withdrawal and signals of withdrawal. The activation of this network is characterized by withdrawal symptoms and signs, negative affect, and drug-seeking.[37] Similarly, craving involves an intense feeling state associated with stimuli predictive of, or reminding the subject of, drugs. Nevertheless, the definition of craving is much less clear and is mostly described as an emotional-motivational state.[38] Thus, despite this wide use, there is little consensus on what craving means, the best way to measure it, or what mechanism accounts for the urge to use a drug. Some have proposed that there is no single model or theory of craving; this could account for the wide variation in experimental findings of craving-related phenomena.[39] Other investigators have identified several craving-related dimensions, which include specificity, strength, positive outcomes, behavioral intention, thoughts, physical symptoms, affect, and cues.[40]

Taken together, cravings and urges are important but complex components of the incentive motivational aspect of reward processing, and are often targets of clinical interventions for individuals with substance use and dependence.

Several cognitive models have been put forth to explain the concept of craving. These include cognitive labeling, outcome expectancy, dual-affect, and cognitive processing conceptualizations.[41] Another way to conceptualize these states is to view them as metacognitions, ie, statements about other cognitions. Therefore, an individual who craves is experiencing a cognitive event, eg, a thought or feeling that is aversive or unpleasant,[42] which in turn creates an increased state of awareness about this event. The degree of self-reported urge for drugs has important implications for abstinence. Relapse to drug use has been closely linked to exposure to conditioned stimuli that frequently induce craving, and a wide variety of such stimuli, many of which were unique to individuals, have been reported.[43] Specifically, those individuals who report losing urges had significant higher abstinence rates than those reporting still having the urge to use.[44] Others found a significant relationship between craving and total proportion of cocaine-positive urines.[45] Similarly, craving has emerged as a predictive factor for continued use in methamphetamine-dependent individuals.[46] However, some investigators have called into question that subjective cravings are invariably associated with drug use.[41] Moreover, there is even some evidence that cravings may actually protect some drinkers against further drinking.[47] This has led some to question the assumption that craving is the underlying basis of addiction and represents the most appropriate target for treatment.[48] Therefore, one cannot take craving in isolation, but has to consider the phenomenon of urge and craving as part of a homeostatic system, which aims to maintain an individual at some steady state-level.

Thus, urges do not occur in isolation, but are immediately incorporated into an existing homeostatic cognitive and affective system of the individual. For example, self-efficacy, ie, the confidence in being able to resist the urge, can profoundly modulate drug use behavior.[49] Moreover, temptation, ie, the contextual characteristics that are aimed to increase desire, leads to stronger urges to drink alcohol, greater difficulty controlling urges, and increased alcohol consumption, even when controlling for alcohol consumption in the past month.[50] Finally, social stress frequently occurs before, and may contribute to the degree of, cravings.[51] Substance-using individuals who perceive an opportunity to consume their drug of choice report higher urges than those who do not anticipate being able to use the drug.[52] It has been argued that the degree of urge modulates the threshold for triggering an action.[53] Therefore, craving and urges are important component processes of decision-making in the presence of ambivalence or conflict.[54] Thus, similarly to the hedonic properties of a reward processing, the incentive motivational aspects are an emerging property based on the stimulus characteristics and the individual's homeostatic state.

One way to study the neural substrates underlying urges is to examine frequently observed behaviors that are often attributed to urge-related processing. Here, four examples of urge-related behaviors are reviewed that can shed new light on the neurobiology of these metacognitive states. First, in a functional positron emission tomography (PET) study to investigate the neural substrates underlying itch and the motor intention of the urge to scratch, investigators found activation of the anterior cingulate cortex, supplementary motor area, premotor area, and inferior parietal lobule.[55] Others have observed that increases in regional cerebral blood flow in orbitofrontal cortex, neostriatum, global pallidus, and thalamus were related to urges to perform compulsive movements.[56] A functional magnetic resonance imaging (fMRI) study of intense itch and urge to scratch showed significant activity in the genual anterior cingulate, striatum, and thalamus as well as orbitofrontal, supplementary motor, posterior parietal areas, and bilateral insula.[57]

Second, air hunger, ie, the uncomfortable urge to breathe, is another urge-related phenomenon, which can be used to study the neural systems underlying urge and craving. Several neuroimaging studies have found activation of limbic and paralimbic regions during air hunger, which are often found to modulate homeostatic imbalance such as pain, thirst, and hunger for food. A recent fMRI study found that anterior cingulate, operculum, cerebellum, amygdala, thalamus, and basal ganglia were activated during air hunger. Most of all, there was a consistent activation of anterior insular cortex, which suggests that this structure acts within a network of limbic and paralimbic neural substrates to mediate urges.[58] Third, the urge to void is a frequently experienced behavioral state, and generally increases with bladder distention in a complex manner. For example, at moderate bladder filling, urge to void appears to be under cognitive control and leads to a fluctuation of the conscious urge sensation. A recent fMRI study found significant brain activity associated with an increased urge to void in the insular cortex, frontal opercula, supplementary motor area, cingulate motor area, right posterior parietal cortex, left prefrontal cortex, and cerebellum.[59] Fourth, anorectal continence is

another urge-driven behavior that is under complex cerebral control. A recent neuroimaging study showed that subjective sensation of discomfort increased during repeated rectal distension was associated with activation in the anterior cingulate gyrus, insula, thalamus, and secondary somatosensory cortex. Moreover, voluntary contraction of the anal sphincter in response to anal distention was associated with activation of motor cortex and increased activity in supplementary motor as well as insular cortex.[60] Thus, these neuroimaging studies have in common the involvement of the interoceptive system in the expression of diverse urge-related behaviors.

Imagery-based techniques are frequently used to elicit memory of drug-related craving experiences,[61] and some have even argued that stress imagery testing procedures may function as provocative tests for stress-induced drug craving.[62] Several brain systems have been implicated in modulating the degree of drug-induced cravings. For example, the degree of drug-related craving by means of administration of presentation of conditioned stimuli has been related to activity in striatum,[63] thalamus,[64] anterior cingulate,[65] inferior frontal cortex,[66,67] and orbitofrontal cortex,[68-70] but also with insula,[71,72] amygdala,[73] and cerebellum.[74] For example, when viewing videos that display cocaine-related stimuli users experience craving, which is associated with increases in amygdala and anterior cingulate cerebral blood flow relative to their responses to a nondrug video.[75] Similarly, imagery-induced drug craving has been associated with bilateral activation of amygdala, insula, and anterior cingulate gyrus as well as the nucleus accumbens area.[76] In alcohol-dependent individuals, cue-induced craving has been associated with activation in amygdala and hippocampal area as well as the cerebellum,[77] but also visual and other limbic areas.[78] Smoking-induced craving was associated with increased activation in left inferior frontal gyrus, left ventral anterior cingulate, and bilateral middle frontal gyrus.[79] Using fMRI, Garavan and colleagues[80] identified regions involved in craving that showed substance-user specificity as well as content specificity in medial and middle frontal gyri, bilateral inferior frontal gyrus, bilateral inferior parietal lobule, insula, and anterior as well as posterior cingulate gyrus. The neural substrates are not limited to drug-induced cravings. For example, food craving-related changes in fMRI studies have been identified in hippocampus, insula, and caudate.[81] However, there may be some gender differences with respect to the degree to which these areas are recruited during craving experiences.[82] For example, female subjects show more activation than males in the anterior cingulate and posterior cingulate cortices, related to craving.[83]

The four examples of physiological urges described above, and the vast literature on drug- or alcohol-induced craving, clearly point toward a core neural system, which overlaps significantly with the interoceptive system. In particular, the anterior cingulate (limbic motor cortex) and the anterior insula (limbic sensory cortex) are key neural substrates modulating the urge and craving-related aspects of reward. First, the anterior cingulate cortex forms a large region around the rostrum of the corpus callosum that is termed the anterior executive region.[84,85] This brain structure is part of what has been called the limbic motor cortex.[86] The affect division of anterior cingulate cortex modulates autonomic activity and internal emotional responses, while the cognition division is engaged in response selection associated with skeletomotor activity and responses to noxious stimuli.[87] Thus, the anterior cingulate cortex plays a crucial role in linking the hedonic experience to the incentive motivational components of reward.[88] This area has been shown to be activated in addicted subjects during intoxication, craving, and bingeing, and they are deactivated during withdrawal (for review see ref 89). Some investigators have proposed that cue-induced activation of the anterior cingulate may play a role in the attribution of incentive salience to alcohol-associated stimuli.[90]

Second, the insula (for review see refs 91,92) is one of the paralimbic structures and constitutes the invaginated portion of the cerebral cortex, forming the base of the sylvian fissure. The insular cortex has been considered to be limbic sensory cortex by some investigators.[86] A central insular sulcus divides the insula into two portions, the anterior and posterior insula. The anterior insula is composed of three principal short insular gyri (anterior, middle, and posterior) as well as the accessory and transverse insular gyri. All five gyri converge at the insular apex. The posterior insula is composed of the anterior and posterior long insular gyri and the postcentral insular sulcus, which separates them. The anterior insula is strongly connected to different parts of the frontal lobe, whereas the posterior insula is connected to both the parietal and temporal lobes.[93] The columnar organization of the insular cortex shows a highly organized anterior inferior to posterior superior gradient (for example see ref 94). Specifically, whereas posterior insula is characterized by a granular cortical architecture, the anterior inferior insula has an

agranular columnar organization, ie, lacks layer 4 granular cells. This type of transition is found in other parts of the brain whenever cortical rerepresentations are based on modulatory or selective feedback circuits.[95] Finally, the discovery of spindle cells within the anterior insular–orbitofrontal transition region[96] has provided a cellular substrate underlying the possibility of widespread cortical integration. The insular cortex has been implicated in a wide variety of processes, which includes pain,[97] interoceptive,[20] emotion-related,[98] cognitive,[99] and social processes.[100] A recent study with brain-lesioned individuals showed that those who had insular damage were more likely to experience a disruption of cigarette addiction, including abolition of the urge to smoke.[101] Relevant to reward-related processes, the insular cortex is important for subjective feeling states and interoceptive awareness,[2,20] and has been identified as taking part in inhibitory processing, together with the middle and inferior frontal gyri, frontal limbic areas, and the inferior parietal lobe.[102] Given the fact that this area receives integrated input from ascending primary afferents and is closely connected to all parts of the cortical mantle and limbic motor cortex, it is obvious that the insula is ideally suited to orchestrate craving-related processing. For a conceptual summary, see *Figure 1*. Although it is not clear at this point whether this is primarily related to the sensation of urge or the motivational component associated with it, the close connection between this structure and the anterior cingulate suggests that it may be the integrity of both that is needed to modulate urge-related behaviors.

Conclusions

Reward-related processing is an important aspect of understanding drug addiction. Nevertheless, surprisingly little insight has been gained into how pleasure and urge are integrated in the brain and how this process is modulated as part of the homeostatic dynamic state of the individual. It has been suggested that, from an evolutionary perspective, drugs that affect the hedonic systems can have profoundly adverse consequences because they bypass adaptive information processing systems and act directly on ancient brain mechanisms that control emotion and behavior.[103] For example, drugs that induce positive emotions give a false signal of a fitness benefit. In comparison, drugs that block negative emotions can impair useful defenses. Koob and LeMoal have argued that sensitization and counteradaptation processes contribute to hedonic homeostatic dysregulation in substance-dependent individuals,[104] and that prolonged exposure to drug stimuli changes the hedonic setpoint.[105] In

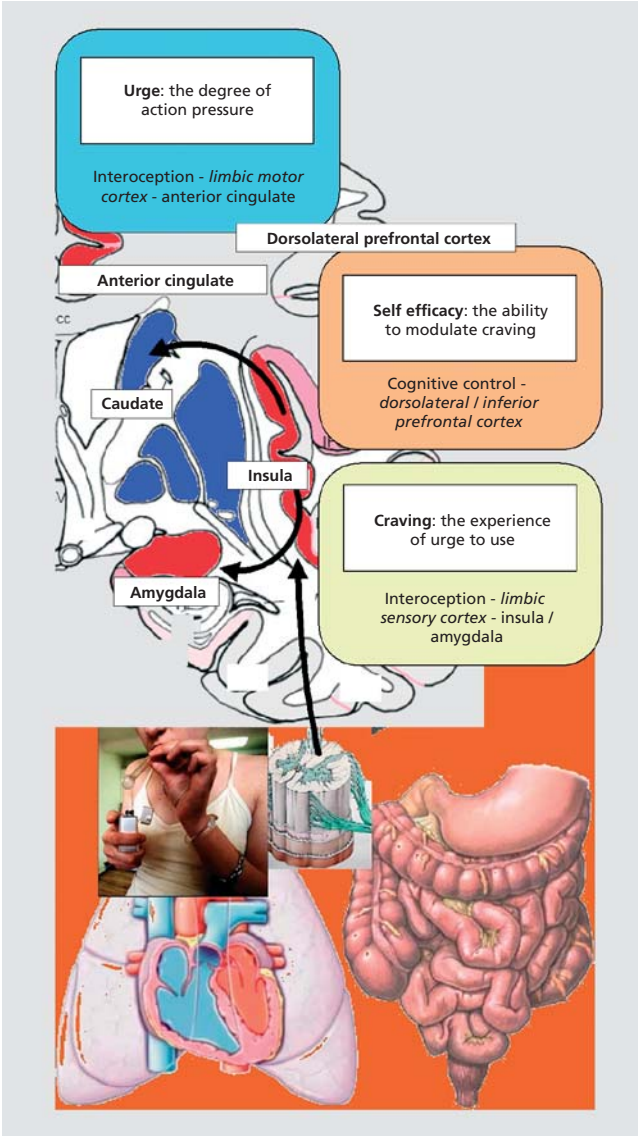

Figure 1. This figure summarizes the proposed neural circuitry that is important for the disrupted homeostasis of drug-using individuals. Briefly, ascending C-fiber afferents provide important information about the current body state (here signified by the background color) which is integrated in the insular cortex and is available for processing to the caudate/striatum and the amygdala in terms of reward and salience. Moreover, direct connections between insula and anterior cingulate provide access of the body-relevant information to the cognitive control circuitry that comprises anterior cingulate, dorsolateral, and inferior frontal cortex.

comparison, others have argued that addictive drugs produce long-lasting adaptations in those neural systems, which are involved in the process of incentive motivation and reward such that these brain systems are hypersensitive to drugs and drug-associated stimuli, primarily to the subcomponent of reward termed incentive salience (drug "wanting") but not to the pleasurable effects of drugs (drug "liking").[106] By focusing on the underlying neural substrates, ie, the insular cortex as the limbic sensory cortex and the anterior cingulate as the limbic motor cortex, and its afferent inputs from ascending primary afferents, as well as the top-down modulation via different cortical areas, one can begin to delineate how one can devise novel interventions for drug addiction. Moreover, the homeostatic viewpoint also helps to understand why there is an enormous behavioral and neural substrate activation intra- and inter-subject variability when processing rewards. Finally, a key step in moving our understanding of reward-related processing forward will be to delineate the conditions under which limbic sensory processing (the experience of pleasure) can be decoupled from the limbic motor processing (the urge or craving for a pleasurable experience). ❑

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Las bases neurales de la recompensa y del craving: un punto de vista homeostático

En este artículo se argumenta que el sistema interoceptivo -que aporta información acerca del estado interno del sujeto y está integrado en la corteza insular- es el sustrato neural crítico para los procesos relacionados con la recompensa, y no el estriado ventral subcortical. La comprensión del estado interno del individuo, que se procesa a través de este sistema, permite desarrollar nuevas intervenciones orientadas al tratamiento de trastornos en que hay alteraciones en el funcionamiento de los mecanismos de recompensa, como la dependencia de sustancias y de alcohol. Aunque el estriado ventral es importante para dar las señales acerca del grado en que se puede predecir la ocurrencia de los estímulos de recompensa, este sistema en forma aislada no puede dar cuenta de los complejos fenómenos afectivos, cognitivos y conductuales que se producen cuando los individuos toman contacto con potenciales estímulos de recompensa. Por otra parte, el sistema interoceptivo es capaz de hacer conexiones entre los sistemas cortical, subcortical y límbico para organizar un complejo conjunto de respuestas. El craving y el "urgimiento" se encuentran entre las respuestas más destacadas y pueden tener importantes funciones para preservar la homeostasis.

Bases neurales de la récompense et du désir compulsif, un point de vue homéostatique

Le substrat neural essentiel des processus liés à la récompense est présenté dans cet article comme étant le système interoceptif, intégré au cortex insulaire et qui fournit des informations sur l'état interne des sujets, et non le striatum ventral sous-cortical. La compréhension de l'état interne de l'individu, conduit par ce système, permet de développer de nouvelles méthodes pour traiter les maladies liées au dysfonctionnement du système de récompense, comme la dépendance à l'alcool et aux drogues. Bien que le striatum ventral soit important pour signaler le niveau de prédiction d'apparition des stimuli récompensants, le système interoceptif ne peut à lui seul expliquer les phénomènes complexes comportementaux, cognitifs et affectifs qui surviennent lorsque des sujets entrent en contact avec des stimuli potentiellement récompensants. D'un autre côté, le système interoceptif est capable d'établir des liaisons entre les systèmes limbiques, sous-corticaux et corticaux pour orchestrer un ensemble complexe de réponses. La compulsion et l'impulsion font partie des réponses les plus remarquables et seraient importantes dans la préservation de l'homéostasie.

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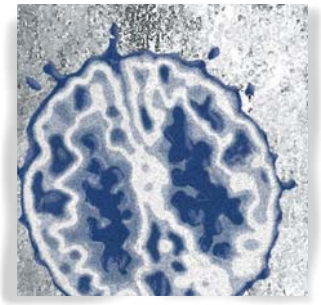
Cocaine and amphetamine-like psychostimulants: neurocircuitry and glutamate neuroplasticity

Peter W. Kalivas, PhD



Although the pharmacology of amphetamine-like psychostimulants at dopamine transporters is well understood, addiction to this class of drugs has proven difficult to deal with. The reason for this disconnection is that while the molecular mechanism of amphetamine action is critical to reinforce drug use, it is only the first step in a sequence of widespread neuroplastic events in brain circuitry. This review outlines the affect of psychostimulants on mesocorticolimbic dopamine projections that mediate their reinforcing effect, and how this action ultimately leads to enduring pathological neuroplasticity in glutamatergic projections from the prefrontal cortex to the nucleus accumbens. Molecular neuroadaptations induced by psychostimulant abuse are described in glutamate neurotransmission, and from this information potential pharmacotherapeutic targets are identified, based upon reversing or countermanding psychostimulant-induced neuroplasticity.

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Background

Cocaine and other amphetamine-like psychostimulants have been a significant part of the human pharmacopoeia for thousands of years.[1,2] However, the appearance of these substances in Western societies has been relatively recent, cocaine having debuted as both a local anesthetic and a psychostimulant in the 19th century. Over the course of the next century, it became increasingly clear that the amphetamine-like psychostimulants carried serious abuse liability, as well as producing a prominent paranoia-like syndrome among many individuals who chronically used this class of drugs.[3,4] The abuse liability of these drugs has resulted in sociological use patterns that have been described as epidemics, such as the methamphetamine epidemic in Japan in the 1950s, the cocaine epidemic in the United States in the 1980s, and the crack cocaine epidemic of the 1990s.[5,6]

The high abuse liability of this class of drugs relies on both pharmacological properties and the sociological characteristics of how the drugs are introduced into various societies around the world. This article will not significantly address the sociology of psychostimulant abuse, which involves diverse events ranging from the use of amphetamines by Japanese soldiers in World War II, to the formulation of crack as a less expensive version of cocaine in the United States, to the introduction of prescription formulations to regulate eating habits or to treat attention deficit-hyperactivity disorder.[5-8] Rather, we will review the basic pharmacology of amphetamine-like

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Selected abbreviations and acronyms

AMPA	*α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid*
DAT	*dopamine transporters*
GABA	*γ-aminobutyric acid*
MDMA	*3,4-methylenedioxymethamphetamine*
mGluR2/3	*metabotropic glutamate receptors*

drugs, integrate these molecular mechanisms into the brain circuitry of reward, and describe how these drugs are thought to create pathological changes in reward and learning circuitry. Finally, this knowledge will be amalgamated into a vision of future pharmacotherapies for treating psychostimulant addiction.

Basic pharmacology of amphetamine-like psychostimulants

The defining mechanism of action of amphetamine-like psychostimulants as a class of drugs with high abuse liability is the ability to bind to dopamine transporters (DAT).[9,10] Dopamine transporters are a member of a class of proteins that eliminate monoamines, including dopamine, from the synaptic cleft after neuronal release.[11] This protein has a high affinity for dopamine relative to other monoamines, such as norepinephrine or serotonin, and while all the readily abused psychostimulants bind to DAT, they may also bind to the other monoamine transporters with greater or lesser affinity.[9,12] To some extent, the relative profile of binding by individual drugs to the different transporter proteins explains different characteristics of the drugs. Most striking, for example, is 3,4-methylenedioxymethamphetamine (MDMA) which has a relatively higher affinity for serotonin transporters, and is thereby a mild hallucinogen and neurotoxic to serotonin axon terminals,[13,14] while methamphetamine binds more avidly to DAT, which explains its greater toxicity at dopamine terminals, as well as its propensity to induce paranoid psychosis-like symptoms.[15] While the binding to other monoamine transporters contributes to the antidepressant and hallucinogenic characteristics of some psychostimulants, it is the binding to DAT that provides the major influence on abuse liability, which is the focus of this review.

There are two major categories of interaction by amphetamine-like psychostimulants with DAT, but in all cases the end result is to inhibit the elimination of dopamine from the synapse and thereby increase the quantity and half-life of synaptic and extrasynaptic dopamine levels.[16,17] The first mechanism is typified by cocaine and methylphenidate that bind to DAT, but are not transported into the presynaptic terminal as surrogate dopamine. Therefore, when these drugs bind to DAT the increase in extracellular dopamine relies primarily on normal synaptic release, which is more amenable to physiological feedback regulation.[18] The second mechanism is typified by amphetamines, and involves not only binding to DAT, but also translocation into the cell in place of dopamine.[9] In addition, these drugs enter dopamine synaptic vesicles, where the fact that these compounds are basically charged degrades the pH gradient necessary to sequester dopamine into the vesicle.[19] This in turn results in a large buildup of dopamine in the cytosol, thereby reversing the direction of DAT to release dopamine into the extracellular space rather than facilitating its removal. Regardless of the precise interaction with DAT by individual amphetamine-like psychostimulants, this class of drugs dramatically elevates extracellular dopamine, and this action is thought to be the initiating molecular event that reinforces drug-seeking behaviors, ultimately culminating in addiction.[20,21]

How release of dopamine by psychostimulants initiates addiction

Dopamine release is physiologically employed to signal novel, motivationally relevant environmental events. Thus, when an organism encounters a novel stimulus, whether a positive stimulus such as a food reward or a negative stimulus such as a stressor, the activity of dopamine cells in the ventral tegmental area, and dopamine release in axon terminal fields in the prefrontal cortex, nucleus accumbens, and/or amygdale, are altered.[22-24] An important characteristic of this brain-environment interaction is that the ability of a given stimulus to increase dopamine cell firing and release decreases with repeated presentation of the stimulus. However, it can be shown that if a motivationally neutral stimulus (such as a light or tone) is associated with the motivational event in such a manner that the neutral stimulus predicts arrival of the motivational event, the ability of the motivational stimulus to release dopamine is transferred to the neutral stimulus.[22,25,26] Thus, the neutral stimulus now causes dopamine release in a manner predicting arrival of a motivationally relevant event. Based upon these data, the role for dopamine release in the mesocorticolimbic brain regions is twofold: (i) to cue the organism that a novel motivationally relevant event is

occurring and that adaptive behavioral responses need to be engaged (eg, approach a reward or avoid a stress); (ii) once the behavioral response is established, dopamine release is antecedent to the appearance of the motivationally relevant event and is triggered by environmental associations that the organism has made with the event as part of learning the adaptive behavioral response. In this way, dopamine serves to alert and thereby prepare the organism for an impending important event.

The primary differences between psychostimulant-induced dopamine release and release associated with normal learning about important environmental events such as rewards and stressors is: (i) since psychostimulants block the elimination of dopamine through DAT, the level of dopamine achieved far exceeds what is possible from a biological stimulus; (ii) in contrast to biological stimuli that cease to release dopamine once an approach or avoidance response to that stimulus has been learned, psychostimulants continue to release large amounts of dopamine upon every administration (with the possible exception of extended binging that can temporarily deplete dopamine stores).[27] Thus, with psychostimulants, each administration releases dopamine into mesocorticolimbic regions, causing further associations to be made between the drug experience and the environment. In this way, it is thought that the more a psychostimulant is administered, the more learned associations are made with the environment and the more effective the environment becomes at triggering craving and drug-seeking. It is this "overlearning" of drug-seeking behaviors by progressive associations formed between repeated drug-induced dopamine release and the environment that is thought to lead to increased vulnerability to relapse.

How psychostimulant-induced dopamine release creates pathological neuroplasticity in cortical regulation of behavior

As outlined above, psychostimulant-induced dopamine release is responsible for reinforcing behaviors designed to seek and administer the drugs. The dopamine projections involved in this process are outlined in *Figure 1A*, and as indicated, the most critical projection in this regard is the projection from the ventral tegmental area dopamine cells to the nucleus accumbens.[28-31] For example, if psychostimulant-induced release of dopamine in the nucleus accumbens is impaired, this affects the acquisition of drug-seeking behaviors, and can markedly influence the amount of drug taken in a well-trained subject. Thus, the learning of a task to obtain the drug and the amount of drug taken in a given session is strongly regulated by dopamine release in the accumbens. However, when an animal has been withdrawn from repeated psychostimulant use, and drug-seeking is initiated by an environmental stimulus such as a cue previously paired with drug delivery, or a novel stressor, it is dopamine release in the prefrontal cortex and amygdala, respectively, that mediates the reinstatement of drug-seeking.[32,33] Thus, relapse can be induced by dopamine release in prefrontal and allocortical brain regions, and reflects the aforementioned physiological role of dopamine release as a predictive antecendent to stimulus (drug) delivery. What this implies is that chronic release of dopamine by repeated psychostimulant administration may be modifying cortical and allocortical regulation of behavior.

Figure 1B shows that the cortical and allocortical regulation of behavior is primarily mediated by glutamater-

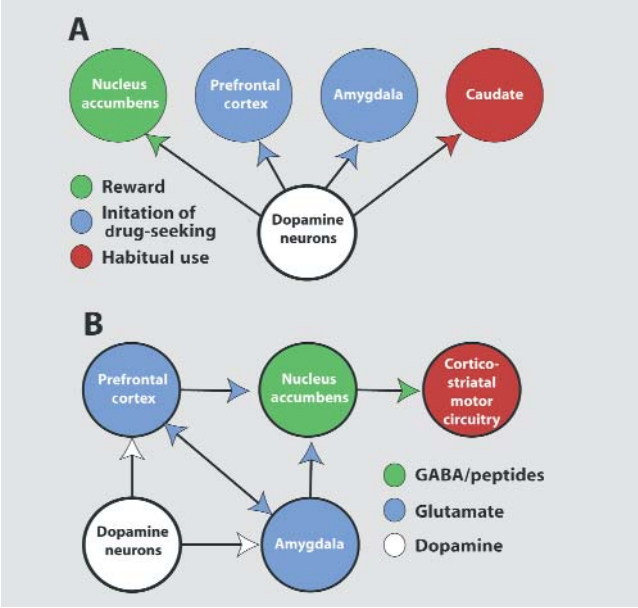

Figure 1. Models of the circuitry regulating the transition from psychostimulant reward to relapse.
A. Dopamine projections and how chronic psychostimulant use produces a transition from reliance on accumbens dopamine for drug reinforcement, to reliance on the prefrontal and amygala dopamine to trigger relapse, to dopamine in the caudate in regulating habit responding. **B.** The circuitry in which dopamine projections are embedded that initiates relapse to drug-taking. Note that dopamine input to the amygdala and prefrontal cortex is critical, as is the glutamatergic output from these regions to the nucleus accumbens. GABA, γ-aminobutyric acid

gic projections. These projections are to subcortical structures, such as the nucleus accumbens and dopamine cells in the ventral tegmental area, as well as between the cortical and allocortical regions. Thus, when dopamine is released into the prefrontal cortex or amygdala by a drug-associated cue or stressor, this is thought to stimulate glutamatergic projections between the prefrontal cortex and amygdala, as well as glutamatergic outputs to the accumbens and ventral tegmental area.[34] A variety of studies have linked this activation of corticofugal glutamate transmission with craving in psychostimulant addicts or drug-seeking in animal models of addiction.

The neuroimaging literature clearly shows metabolic activation of regions of the prefrontal cortex, including portions of the anterior cingulate and ventral orbital cortices, and the amygdala during cue-induced craving for amphetamine-like psychostimulants.[35-39] Interestingly, while a cue or low dose of psychostimlant markedly increases metabolic activity in the prefrontal cortex and amygdala, in the absence of a learned drug association the prefrontal cortex is hypoactive.[40] The reduction in basal metabolic activity is taken to indicate a potential deficit in cognitive ability to regulate relapse, and recent cognitive testing in psychostimulant addicts confirms the presence of certain cognitive dysfunctions related to impulse control and switching behaviors in an adaptive manner to changing environmental circumstances.[41-45] A strong role for activation of both the prefrontal cortex and amygdala has been confirmed in animal studies. Thus, pharmacological inhibition of either of these regions prevents the reinstatement of drug-seeking in animals withdrawn from drugs that have undergone extinction training.[46-48] Moreover, a marked release of glutamate is measured in the nucleus accumbens of animals initiating drug-seeking in response to a stressor, and this glutamate is derived from increased activity in the projection from the prefrontal cortex to the nucleus accumbens.[49,50] Accordingly, drug-seeking is abolished by inhibiting glutamate receptors in the accumbens.[51-53]

One final set of studies to be considered regarding cortical glutamate is the recent evidence that as drug-seeking becomes more compulsive there is a gradual shift to greater reliance on corticostriatal habit circuitry, and less involvement of prefrontal to accumbens circuitry.[54] This possibility is supported by animal models in two ways: (i) if animals that have been trained to self-administer cocaine are left in abstinence for an extended period, drug-seeking is augmented,[55] and in this case inhibition of the prefrontal cortex or amygdala no longer inhibits drug-seeking induced by drug-associated stimuli. However, inhibition of the dorsolateral striatum is still effective at blocking drug-seeking[56]; (ii) as training of an animal in drug-seeking paradigms progresses it is possible to show a gradual increase in dopamine released into the caudate in favor of release into the nucleus accumbens.[57] This is illustrated in *Figure 1A*, showing that dopamine release into the caudate can regulate habitual behaviors. On one hand, these data point to the possibility that in treating compulsive relapse we should be focusing on regulation of corticostriatal habit circuitry, including glutamate input to the caudate from sensorymotor cortex and dopamine input from the substantia nigra. However, these studies have been conducted in rats in whom the frontal cortex is poorly evolved, and given the marked activation produced in the prefrontal cortex and amygdala by drug-associated stimuli in psychostimulant addicts, the conclusion that compulsive relapse is entirely derived from corticostriatal habit circuitry may be an oversimplification. Indeed, it has been argued that a primary role for therapy in treating addiction is to strengthen prefrontal regulation of drug-seeking behaviors, whether through psychosocial interventions or pharmacotherapy.[27,58,59]

Enduring psychostimulant-induced neuroplasticity in the prefrontal to accumbens glutamate projection

Given the apparent critical role played by glutamatergic afferents to the nucleus accumbens in initiating drug-seeking or craving, recent studies have identified a number of enduring cellular changes in glutamate transmission that may be critical pathological neuroadaptations to psychostimulant use, and may serve as targets for pharmcotherapeutic intervention. In general the neuroplasticity can be categorized as postsynaptic, presynaptic and nonsynaptic (ie, residing predominantly in glia). However, since these processes are intimately related to each other, it is perhaps best to consider all the adaptations as changes in glutamate homeostasis, the end result of which is a psychostimulant-induced enduring change in the fidelity of communication between the prefrontal cortex and the nucleus accumbens, and the regulation by this projection of corticostriatal habit circuitry. It has been proposed that this loss of fidelity results in a weakening or loss in the capacity of psychostimulant addicts

to cognitively intervene in habitual behaviors, thereby making drug-seeking more difficult to control and increasing the vulnerability to relapse.[27]

As mentioned above, drug-seeking is associated with a large release of prefrontal glutamate into the nucleus accumbens. The large release of glutamate during drug-seeking is all the more remarkable because it was discovered using microdialysis. which is not a very sensitive measure of glutamate transmission.[60] Indeed, when animals are trained to seek a biological reward, such as food, microdialysis cannot measure glutamate release.[49] Thus, the large psychostimulant-induced release of glutamate has been hypothesized to be a pathological and perhaps critical mediator of relapse. This hypothesis is supported by the fact that treatments interrupting synaptic glutamate release also inhibit drug-seeking. This includes a variety of pharmacological treatments that have the potential to be developed into pharmacotherapeutic agents, as outlined below.

Perhaps in part a consequence of the massive synaptic glutamate release occurring during psychostimulant-seeking behavior, a number of marked changes in postsynaptic glutamate transmission have been measured in animals withdrawn from chronic cocaine or amphetamine administration. Perhaps among the most dramatic is an increase in the density of dendritic spines in the nucleus accumbens.[61] Importantly, this appears to be accompanied by an increase in the insertion of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors into the membrane of spiny neurons in the accumbens,[62] and is associated with an increase in electrophysiological sensitivity to AMPA receptor stimulation (as measured by the AMPA:N-methyl D-aspartate [NMDA] ratio).[63] Moreover, a number of other proteins regulating the fidelity of postsynaptic glutamate transmission are altered after chronic cocaine use, including proteins that regulate the structure and function of the protein scaffolding in which the glutamate receptors are embedded, including postsynaptic density (PSD)-95 and Homer proteins, among others.[64,65] Also, in addition to AMPA ionotropic glutamate receptors, signaling through metabotropic glutamate receptors is downregulated.[66,67] Finally, this psychostimulant-induced postsynaptic neuroplasticity is associated with changes in the biochemical machinery regulating spine formation, notably an increase in actin cycling and formation of F-actin (a primary structural protein regulating spine morphology and the insertion of proteins into and out of the membrane).[68] Taken together, these findings indicate that significant changes have been produced by psychostimulants in the way that synaptically released glutamate will be interpreted by postsynaptic cells. However, it is important to note that this knowledge is nascent and emerging. Thus, there remain many apparent contradictions in the literature regarding changes in specific proteins, and in the overall direction of synaptic grading (ie, is postsynaptic glutamate transmission augmented or inhibited by chronic psychostimulant administration).[69] Therefore, for now it is probably not prudent to speculate on the type of drug development that may arise from this particular direction of research into psychostimulant-induced changes in glutamate signaling.

Ideas for pharmacotherapies based upon psychostimulant-induced plasticity in glutamate transmission

As outlined above, given our current state of knowledge it is more likely that pharmacotherapeutic restoration of normal glutamate release may be a more successful approach than manipulating postsynaptic proteins responsible for and/or associated with changes in the fidelity of postsynaptic glutamate transmission. In part, this is due to the relatively contradictory status of the emerging literature on postsynaptic plasticity. Moreover, it has been hypothesized that the adaptations in presynaptic glutamate release may be at least partly causal in the postsynaptic adaptations, posing the possibility that if the pathological release of glutamate can be successfully ameliorated, postsynaptic normalization may follow.[27]

Pharmacotherapeutic targets for regulating the pathological synaptic glutamate release seen in the accumbens of psychostimulant-seeking animals can be placed into two categories: (i) targets based upon psychostimulant induced changes in proteins regulating synaptic glutamate release; (ii) proteins that produce a general decrease in excitatory transmission. Compounds in the first category are likely to be the most specific for psychostimulant addiction, and perhaps carry the least number of unwanted side effects, while the latter category may be less selective not only regarding effects on other addictive drugs, but also in terms of unwanted side effects. *Table I* lists some potential pharmacotherapeutic targets according to these two categories.

Neuroplasticity produced by chronic cocaine administration that could potentially contribute to pathological

glutamate release includes downregulation of cystine-glutamate exchange, downregulation of glial glutamate transporters, and downregulation of release-regulating presynaptic metabotropic glutamate receptors (mGluR2/3). Importantly, these three changes are interrelated due to the cystine-glutamate exchanger and glutamate transporter regulating extrasynaptic glutamate tone on release regulating mGluR2/3.[70,71] Drugs have been examined in animal models of psychostimulant addiction, and to a lesser extent in clinical trials with cocaine addicts that regulate one or more of these processes. For example, N-acetylcysteine upregulates cystine glutamate exchange, and has been shown in animal models to prevent synaptic glutamate release associated with drug-seeking, restore inhibitory tone on synaptic release through activation of mGluR2/3, and to inhibit the desire for cocaine in a double-blind cue-reactivity trial in non-treatment-seeking cocaine addicts.[71-73] Also, mGluR2/3 agonists have proven effective at inhibiting cocaine seeking in animal models; however, unlike N-acetylcysteine, food-seeking was inhibited at only a 3- to 10-fold increase in dose relative to inhibiting cocaine-seeking.[74,75] Although no studies have yet evaluated regulating glutamate transport in drug-seeking models of psychostimulant addiction, recent reports of the use of β-lactam antibiotics to increase glutamate transporter membrane insertion poses an interesting possibility for pharmacologically overcoming the cocaine-induced downregulation of glutamate transporters. Finally, while the mechanism is not clear, modafinil has been reported to increase extracellular glutamate levels, which would restore tone on release inhibiting mGluR2/3.[76] Notably, modafinil has been found to successfully decrease cocaine relapse in a number of clinical trials.[77,78]

The primary drugs in the category of nonspecific inhibitors of synaptic glutamate release include a variety of γ-aminobutyric acid (GABA)-mimetic compounds. These range from relatively specific agonists at GABAb receptors, such as baclofen, which inhibit synaptic glutamate release to a host of less selective compounds known to increase GABA transmission via interactions with synthetic or elimination mechanisms, such as topiramate or vigabatrin. For all of these compounds there is preclinical and clinical data to support some potential efficacy.[79-85] However, as predicted, especially for the nonselective GABAmimetics untoward side effects, such as sedation, are reported.

Conclusions

This review has endeavored to transport the reader from the initiating molecular actions of amphetamine-like psychostimulants on dopamine systems in the brain to enduring neuroplasticity produced in glutamate transmission responsible for communicating from prefrontal and allocortical brain regions through the nucleus accumbens to motor regulatory systems. Moreover, by examining molecular neuroplasticity produced in excitatory synapses by chronic psychostimulant administration, it is possible to make some deductions about potential pharmacotherapeutic interventions. Indeed, there already exists an emerging literature supporting this approach in developing potential pharmacotherapies for treating psychostimulant addiction. Importantly, this is a nascent and emerging science, and while much has been discovered, the cutting edge of discovery into the neuroplasticity produced by psychostimulants is understandably contradictory. As further discoveries are made that allow us to understand the nature of these contradictions, it should follow that additional targets will emerge to provide potential novel pharmacotherapies for treating psychostimulant addiction. ❑

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Directly reducing glutamate transmission		Indirectly inhibiting glutamate transmission	
Compound	**Target**	**Compound**	**Target**
N-acetylcysteine	Cystine/glutamate exchanger	Baclofen	GABA-b receptor
β-lactam	Glutamate transporter	Topiramate	GABA-a and AMPA
mGluR2/3 agonist	mGluR2/3	Vigabatrin	GABA transaminase
Modafinil	mGluR2/3		

Table I. List of compounds that affect glutamate neurotransmission with potential pharmacotherapeutic value in treating addiction to amphetamine-like psychostimulants. mGluR2/3, metabotropic glutamate receptors; GABA, γ-aminobutyric acid; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid

Cocaína y psicoestimulantes tipo anfetamina: circuitos neuronales y neuroplasticidad glutamatérgica

Aunque es bien conocida la farmacología de los psicoestimulantes tipo anfetamina a nivel de los transportadores de dopamina, ha sido difícil abordar la adicción a esta clase de drogas. La razón de esta discordancia se explica porque si bien el mecanismo molecular de la acción de la anfetamina es crítico para reforzar el uso de la droga, éste representa sólo el primer paso en una secuencia de numerosos acontecimientos neuroplásticos en los circuitos cerebrales. Esta revisión resume el efecto de los psicoestimulantes en las proyecciones mesocorticolímbicas de dopamina que median el efecto de refuerzo, y cómo esta acción en último término conduce a una neuroplasticidad patológica permanente en las proyecciones glutamatérgicas desde la corteza prefrontal hasta el núcleo accumbens. Se describen las neuroadaptaciones moleculares inducidas por el abuso de psicoestimulantes en la neurotransmisión glutamatérgica, y a partir de esta información se identifican potenciales blancos farmacoterapéuticos, en base a las modificaciones en la neuroplasticidad inducida por psicoestimulantes.

Cocaïne et psychostimulants amphétaminoïdes : circuits neuronaux et neuroplasticité du glutamate

En dépit d'une bonne compréhension de la pharmacologie des psychostimulants amphétaminoïdes au niveau des transporteurs de la dopamine, il semble difficile de faire face à l'addiction à cette classe de médicaments. Cette discordance s'explique ainsi : si le mécanisme moléculaire de l'action amphétaminique est essentiel pour renforcer l'action du médicament, il ne représente qu'une première étape dans une succession de nombreux événements neuroplastiques dans le circuit cérébral. Cette revue souligne l'effet des psychostimulants sur les projections méso-cortico-limbiques dopaminergiques qui médient l'effet de consolidation et explique comment cette action mène finalement à une neuroplasticité pathologique persistante dans les projections glutamatergiques, du cortex préfrontal au noyau accumbens. Les neuroadaptations moléculaires induites par l'abus des psychostimulants sont décrites en ce qui concerne la neurotransmission du glutamate, et des cibles pharmacothérapeutiques potentielles sont identifiées à partir de ces informations, basées sur la neuroplasticité réversible ou annulable induite par les psychostimulants.

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Outpatient Long-term Intensive Therapy for Alcoholics (OLITA): a successful biopsychosocial approach to the treatment of alcoholism

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Alcohol dependence is a frequent, chronic, relapsing, and incurable disease with enormous societal costs. Thus, alcoholism therapy and research into its outcome are of major importance for public health. The present article will: (i) give a brief overview of the epidemiology, pathogenesis, and treatment outcomes of alcohol dependence; (ii) introduce the basic principles of outpatient long-term therapy of alcohol-dependent patients; and (iii) discuss in detail process-outcome research on Outpatient Long-term Intensive Therapy for Alcoholics (OLITA). This successful biopsychosocial approach to the treatment of alcoholism shows a 9-year abstinence rate of over 50%, a re-employment rate of 60%, and a dramatic recovery from comorbid depression, anxiety disorders, and physical sequelae. The outcome data are empirically based on treatment processes that have proven high predictive validity and give concrete information about where to focus the therapeutic efforts. Thus, process-outcome research on OLITA can serve for the development of new therapeutic guidelines on adapting individual relapse prevention strategies.

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Epidemiology, pathogenesis, and long-term course of chronic alcohol dependence

Alcoholism is a chronic and relapsing disorder that imposes enormous costs on society, is one of the leading causes of death in industrialized countries, and is among the strongest cost drivers with respect to service use.[1-5] Thus, the development of successful treatment approaches and their intensive analysis is of major importance for public health. Alcohol dependence is one of the most frequent psychiatric disorders, with a 12-month prevalence of at least 3%, a lifetime prevalence of 8% to 14%, and a male:female ratio of 2-5:1.[6-11] Both, the course and the treatment of alcoholism are complicated by a high rate of comorbid psychiatric disorders, most importantly personality disorders (approximately 30% to 60%), anxiety (20% to 30%), and mood disorders (20%).[9,12-15] The alcohol-associated burden of disease is

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Selected abbreviations and acronyms

HAQ	*Helping Alliance Questionnaire*
OLITA	*Outpatient Long-term Intensive Therapy for Alcoholics*
TOPPS	*Therapy Orientation by Process Prediction Score*
VAMP	*Video-Assisted Monitoring of Psychotherapeutic Processes in Chronic Psychiatric Disease*

tremendous. Alcohol is third only to tobacco consumption and hypertension as a cause of disease and premature death in Europe. Alcohol consumption causes 6.1% of deaths, 12.3% of lost years caused by premature death, and 10.7% of all disability-adjusted life years (DALYs)—this is a measure for the estimation of the number of healthy life years lost by disease and premature death. Among young persons, alcohol constitutes the major cause of death; eg, more than 25% of deaths of European men between 15 and 29 years of age are attributable to alcohol.[16,17]

Even though the specific causes and complex etiological processes are only partly understood, five basic factors can be identified that play a major role for the development of alcohol dependence: (i) a strong genetic disposition, with the estimations of heritability ranging between 50% and 64%; (ii) irreversible damage of the so-called motivational or reward system (parts of the limbic system, above all hippocampus, amygdala, caudate nucleus, ventral tegmental area, parts of the frontal lobe and nucleus accumbens); (iii) specific changes in the interactions of centrally and peripherally acting neurotransmitters and hormones, eg, γ-aminobutyric acid (GABA), glutamate, dopamine, opioids, epinephrine, norepinephrine, serotonin, acetylcholine, cannabinoids, corticotropin-releasing factor (CRF), and neuropeptide Y. Dysregulations in these transmitter systems are responsible for acute alcohol intoxication, alcohol dependence, and the withdrawal syndrome as a consequence of long-term alcohol consumption; (iv) a strong impairment of the psychobiological stress tolerance; (v) long years of overlearning of self-destructive behavioral processes (for review see refs 5,18-62).

Data concerning the long-term course and prognosis of chronic alcohol dependence are alarming. Longitudinal studies that investigated follow-up periods between 4 and 35 years identified the following prognostic characteristics: [63-76]

- In the long term, alcohol dependence is associated with significantly increased mortality rates between 15% and 60%. Thus, the mortality risk for persons with alcoholism is 2.5 to 9 times higher than for persons without alcoholism.
- With only 5% to 30% of the samples from beginning of the studies, a small percentage maintained long-term abstinence; most patients either relapsed (25% to 60%), died (15% to 60%), or alternated with phases of abstinence, reduced consumption or relapse (10% to 16%).
- Predictors for an unfavorable course are: chronicity, severe physical sequelae, a comorbid dissocial personality disorder, frequent excessive drinking in the past, separation from the partner, and unemployment; predictors of a good prognosis are: stable partnership, reemployment, long treatment duration, long-term participation in self-help groups after a preceding addiction therapy.
- The recovery process proceeds quickly during the early years of abstinence. However, recovery takes in total 10 years or longer. The relapse risk is not significantly decreased nor stable before the third year of abstinence.

Outcome research on alcoholism therapy

A review of the current state of outcome research shows that there have not been any sensational therapeutic improvements during the last decades.

For more than 30 years, meta-analyses and literature reviews have consistently shown that alcoholism treatment is successful and cost-effective in the short term.[77-84] Good evidence exists that 12-step treatment and diverse programs of cognitive behavioral therapy (CBT) are equally effective in achieving abstinence rates of approximately 25% to 30% during the year after treatment (for examples see refs 85,86). However, most treatment studies demonstrate substantial methodological shortcomings. Treatment outcomes are normally based on subjective statements of patients concerning their state of current alcohol consumption and abstinence. On the rare occasions that studies have corroborated subjective outcome data with objective laboratory data, the results are rather inexact and fragmented. Finally, the results of the few valid investigations of long-term outcome are inconsistent: objective information on drinking status indicates that only 6% to 18% of patients are abstinent at 2-year follow-up.[87] In contrast, studies relying on self-report data suggest that approximately 30% of patients are abstinent 2 to 3 years after treatment.[88,89]

There is no evidence for a sufficient efficacy of a primarily pharmacotherapeutic treatment of alcoholism. Whereas the alcohol deterrent disulfiram has proven to be an adjunctive of psychotherapeutic alcoholism therapy for more than 50 years,[90-95] many studies have found efficacy of the anticraving substances acamprosate and naltrexone over the last 15 years.[96-100] However, the results of a recent large-scale multicenter study challenge the additional efficacy of anticraving medications over behavior therapy.[101] Anton et al studied treatment outcomes of a large sample (N=1383) of alcohol-dependent patients who were treated for 16 weeks and re-examined after 12-month follow-up. The authors investigated whether different combinations of naltrexone, acamprosate, and cognitive behavior therapy differ with regard to the outcome "number of abstinent days." Whereas acamprosate did not show any efficacy, the combinations "naltrexone plus medical management" and "naltrexone plus medical management and behavior therapy" were not more successful than a simple combination of behavior therapy, placebo medication, and medical management.[101]

A sobering conclusion can be drawn when interpreting these results critically, and taking into account a recent literature review that has compiled studies showing that the alcohol deterrent disulfiram is superior to the newer anticraving medications.[90] Even though seemingly innovative psychotherapy concepts have been presented and praised every now and then, and a number of new medications have been launched, until now no treatment concept has been found that yields superior outcome data than the well-known and clinically often practiced combination of broad-spectrum behavior therapy and medical management.

Considering the high prevalence and chronicity, the fluctuating and devastating course, the increased mortality, and the low long-term abstinence rates, a challenging understanding of alcoholism treatment emerges. Alcohol dependence is among a group of chronic diseases such as chronic polyarthritis, hypertension, bronchial asthma, and diabetes mellitus that require a flexible, intensive, and lifelong treatment.[4,94,102] Consequently, the question arises as to why therapists, therapy researchers, and social insurance agencies still recommend the so-called brief interventions as seemingly successful therapeutic options for individuals with alcohol dependence. Brief interventions may constitute treatment alternatives for individuals with risky consumption and alcohol abuse, and for these patients they can achieve outcomes with medium effect sizes. However, they are ineffective in the treatment of alcohol-dependent patients.[103-105]

Principles of an outpatient long-term treatment of alcohol-dependent patients

The basic principles of an innovative biopsychosocial treatment approach are derived from the evidence of epidemiology, pathogenesis, course, and treatment outcome of alcohol dependence[102,106,107]:

- *Strict abstinence orientation*. Alcohol dependence is an irreversible and incurable disease. Only consequent long-term abstinence can stop disease progression and enhance the recovery process. Treatment approaches that aim at so-called "controlled drinking" are contraindicated for alcohol-dependent patients.
- *Supportive, nonconfronting therapist behavior*. During the first months of abstinence, alcohol-dependent patients demonstrate a strong impairment of the psychobiological stress system which only recovers slowly. Whereas confronting and emotionally stressful therapeutic interventions like cue exposure are harmful, the supportive, client-centered, and cognitive behavioral therapeutic strategies have proven efficient.
- *Chronic disease—intensive, lifelong treatment*. Chronic alcohol dependence is associated with a strong genetic disposition, irreversible neurobiological damage, and decades of self-destructive learning processes. Only long-term and comprehensive therapies, followed by lifelong attendance of checkup sessions and self-help group participation, can guarantee long-term recovery.
- *A relapse is an emergency*. Alcohol dependence is a severe psychiatric disease demonstrating high rates of physical and psychiatric comorbid disorders, a vast number of social problems, and a significantly increased mortality risk. Similarly to relapses in other severe diseases, an alcohol relapse has to be interpreted as an emergency that requires immediate crisis intervention. Any delay clearly means a poorer prognosis.

OLITA: a successful biopsychosocial approach to the treatment of alcoholism

Outpatient Long-term Intensive Therapy for Alcoholics (OLITA) is a four-step biopsychosocial outpatient therapy program for severely affected alcohol-dependent patients, aiming at immediate social reintegration within the sheltered setting of psychotherapeutic treatment and

medical care. Therefore, basic elements of psychiatric patient care, client-centered and cognitive-behavioral psychotherapy, as well as classical addiction therapy, are integrated into a comprehensive, intensive and long-term treatment approach *(Tables I and II)*. In order to take into account both the impaired stress tolerance of the patients during early abstinence and the chronicity of the disease, the OLITA concept combines high intensity (ie,

• High-frequency short-term individual therapeutic contacts Structured, guarded attachment by supportive, nondemanding short-term contacts; initially 15 minutes daily, including weekends and holidays; slow tapering off of contact frequency aiming at regular and permanent attendance of weekly group sessions.
• Emergency service and crisis interventions In case of emergency, patients and their relatives can contact OLITA round the clock on any day of the year.
• Social reintegration and home visits Specific assistance in rearranging a social network which supports an abstinent lifestyle; explicit cooperation with family members and friends; family and marital sessions; advice and support regarding occupation, authorities, housing problems, moving, job-seeking, financial and legal problems.
• Induction of alcohol intolerance Use of calcium carbimide (Colme®) or disulfiram (Antabuse®), so-called alcohol deterrent medication (inhibition of the alcohol-metabolizing enzyme acetaldehyde dehydrogenase leads in case of alcohol consumption to accumulation of toxic acetaldehyde resulting in an "inner poisoning," the so-called "disulfiram-ethanol reaction," comprising extensive flushing, hyper- or hypotension, tachycardia, nausea, vomiting, anxiety).
• Introduction of control factors Regular urine and blood analyses for alcohol and other drugs of abuse; if necessary, additional breath tests. Supervised intake of deterrent medication and explicit exploitation of its psychological effects.
• Aggressive aftercare Aggressive therapeutic interventions to immediately interrupt beginning and to prevent threatening relapses. Patients who miss a therapeutic contact are called on to continue therapy or to restart abstinence; examples of aggressive aftercare are spontaneous house visits, telephone calls, and involvement of close friends/relatives.
• Therapist rotation An interdisciplinary cooperating team of 6 to 7 therapists is treating the patients (supervising psychiatrist, psychologist, physician, social worker, nurse and MD or PhD students). All therapists are equally responsible for all patients. The classical fixation of a single patient to a single therapist is abandoned.

Table I. The main therapeutic elements of OLITA, Outpatient Long-term Intensive Therapy for Alcoholics.

• Inpatient period: *Detoxification* 2-3 weeks; daily individual sessions, 15 minutes each; disulfiram, 100 mg daily, or calcium carbimide, 50 mg daily.
• Outpatient period I: *Intensive phase* 3 months; daily individual sessions, 15 minutes each; disulfiram, 100 mg daily, or calcium carbimide, 50 mg daily.
• Outpatient period II: *Stabilizing phase* 3-4 months, according to individual need; 3 times a week individual sessions, 15 minutes each; disulfiram, 400 mg, 3 times a week.
• Outpatient period III: *Weaning-off phase* 6 months; twice a week individual sessions, 30 minutes each; disulfiram, 400 mg, twice a week.
• Outpatient period IV: *Aftercare phase* 12 months; once-weekly group session; initially weekly individual sessions (30 minutes) which are gradually reduced; disulfiram, 400 mg, once a week; tapering off between months 13 and 20, individual extension possible.

Table II. Practical realization of the treatment program.

high frequency of therapy contacts) and long duration of therapy.[26,108] Following inpatient detoxification, the treatment extends over 2 years. The OLITA pilot study started in 1993 and was terminated successfully in 2003 after 10 years and the completion of 180 patients assigned to recruitment cohorts 1-6.[94,106] The main therapeutic elements of OLITA are: (i) frequent contacts, initially daily, with a slow reduction of contact frequency up to the end of the second year; (ii) therapist rotation; (iii) support of social reintegration and aggressive aftercare; (iv) induction of alcohol intolerance through application of alcohol deterrents (inhibitors of acetaldehyde dehydrogenase); (v) explicit control: supervised intake of alcohol deterrents and regular urine analysis for alcohol and other drugs of abuse. The therapeutic phases of OLITA consist of the inpatient period (detoxification; 2 to 3 weeks; daily individual sessions, 15 minutes), the outpatient period I (intensive phase; 3 months; daily individual sessions, 15 minutes), the outpatient period II (stabilizing phase; 3 to 4 months according to individual need; three times a week individual sessions, 15 minutes), the outpatient period III (weaning-off phase; 6 months; twice a week individual sessions, 30 minutes), and outpatient period IV (aftercare phase; 12 months; once weekly group session; initially once weekly individual session, 30 minutes, which is gradually tapered off). After completion of the 2 years of therapy, patients participate in weekly to quarterly follow-up contacts and are offered to make use of both the emergency service and the crisis interventions of the therapeutic team.

Patients in the OLITA program: sociodemographic and addiction severity characteristics

Inclusion criteria for OLITA are alcohol dependence according to DSM-IV, residence nearby, and health insurance-covered treatment costs. Exclusion criteria are presence of moderate to severe dementia and acute concurrent abuse or dependence on substances other than alcohol (with the exception of caffeine and nicotine). Thus far, 180 alcoholics (144 men, 36 women) have been treated with a 7-year follow-up success rate of over 50% abstinent patients despite a "negative selection," with regard to severity of alcohol dependence, comorbidity, and social detachment, upon entering the program. Patients were on average 44±8 years old, had a duration of alcohol dependence of 18±7 years, approximately 7±9 prior inpatient detoxification treatments, and 1±1 failed inpatient long-term therapy. Almost 60% of the patients were unemployed. Psychiatric comorbidity amounted to 80%. About 60% of the patients suffered from severe sequelae of alcoholism, such as polyneuropathy, chronic pancreatitis, or liver cirrhosis. To illustrate addiction severity in our population, representative scores of the European Addiction Severity Index[109,110] were 0.58 (±0.38) for medical status, 0.56 (±0.47) for economic status, 0.51 (±0.37) for job satisfaction, 0.83 (±0.11) for alcohol use, 0.59 (±0.30) for family relationships, and 0.46 (±0.21) for psychiatric status.

Long-term treatment outcomes

Considering this severely affected population of alcoholics, the long-term success rate of OLITA is incredibly high: More than 50% of the patients remain abstinent over up to 7 years of post-treatment follow-up *(Figure 1)*. Based on this high abstinence rate, a tremendous improvement in psychological, biological, and social parameters of this patient group could be achieved. The unemployment rate of OLITA patients declined to 22% in an area (Göttingen) with a general unemployment rate of 17% *(Figure 2)*, and the comorbid psychiatric disorders anxiety and depression decreased from approximately 60% to 13%. [76,94] Additionally, patients had a clear decrease in physical sequelae of alcoholism, ranging from liver disease to polyneuropathy. *Figure 3 a, b and c* illustrate the highly sig-

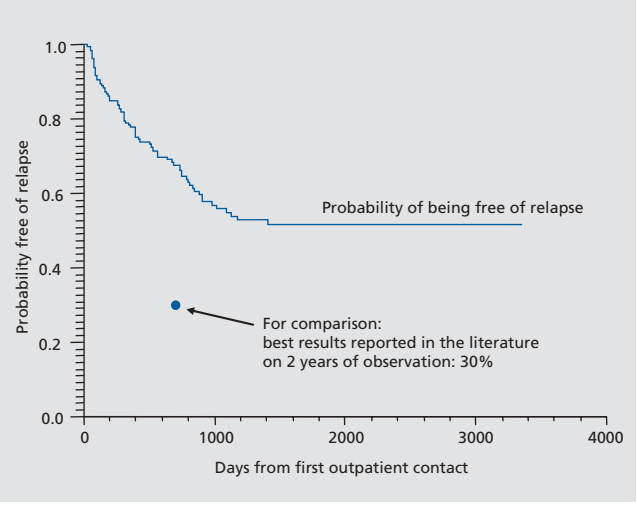

Figure 1. The cumulative abstinence probability during the 9-year study is .52 for the complete sample (N=180); Kaplan-Meier estimates; cases are censored if they have not experienced a relapse by the end of follow-up.

nificant reduction in psychiatric comorbidity. Shown are all comorbid disorders *(Figure 3a)*, anxiety disorders *(Figure 3b)*, and mood disorders *(Figure 3c)* in percentage of the study population from month 1 of therapy to 2 years, ie, the termination of the program. The global decrease of comorbid disorders during therapy is characterized by two specific features of the recovery process. Firstly, anxiety disorders show a delayed remission, ie, they do not change significantly until the first year of therapy. Secondly, the early remission of mood disorders during the first 6 months harbors the risk of reccurence of major depression during long-term abstinence. These data suggest that effective treatment of dual diagnosis patients comprises two basic elements: (i) long-term duration as prerequisite of gradual remission of anxiety and protective factor against recidivism of mood disorders; (ii) comprehensive and careful integration of dual diagnosis interventions considering temporary impairments of coping skills and the imminent danger of overtaxing current patient resources. Simple addition of some treatment elements for comorbid disorders to short-term alcoholism therapy has no effect[111] or even causes a negative outcome.[112]

A case-control study

Compared with thoroughly paralleled case controls who participated in alternative treatment programs, the outcome of OLITA patients is significantly better.[102]

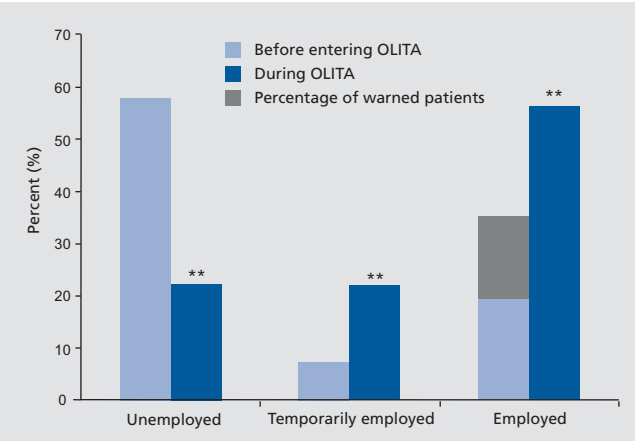

Figure 2. Employment of OLITA patients (N=180); ** *P*<0.0001 versus situation upon entering OLITA. The gray shaded area shows the proportion of patients who were working before OLITA, but who had received official warnings from their employers.OLITA, Outpatient Long-term Intensive Therapy for Alcoholics

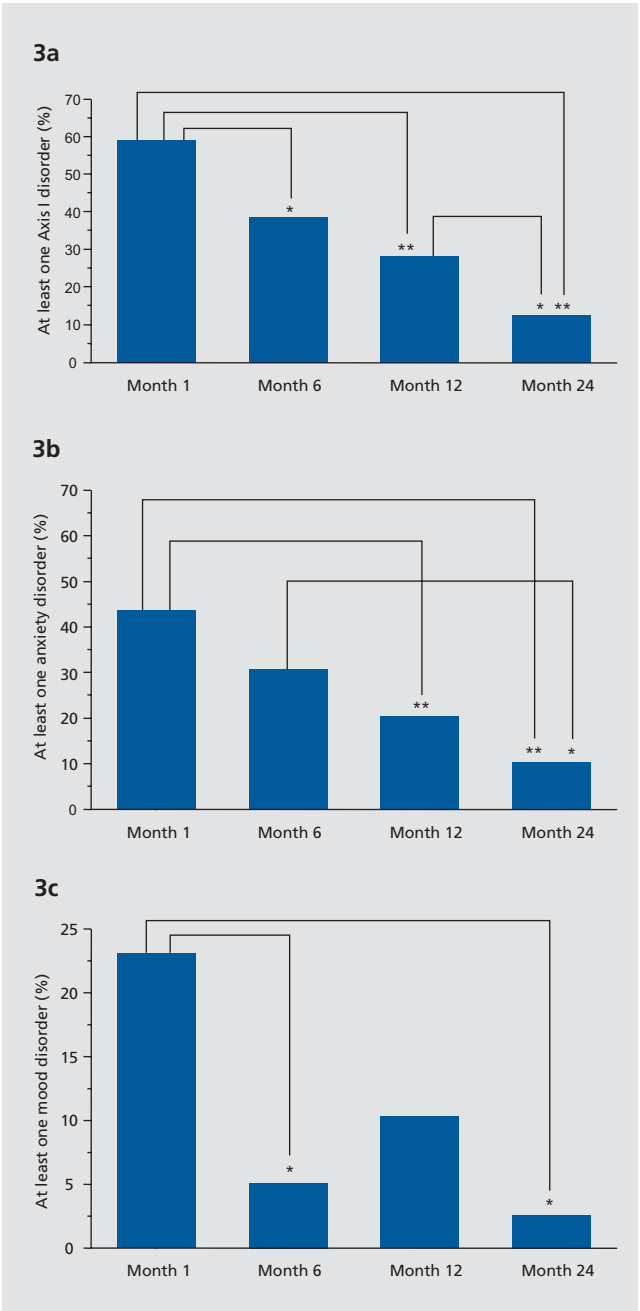

Figure 3. Two-year course of comorbid axis I disorders during OLITA, Outpatient Long-term Intensive Therapy for Alcoholics
** *P*<0.01; * *P*<.05, *P*-values were adjusted for multiple comparisons according to the stepwise rejecting Holm procedure.[121]
Figure 3a. Two-year course of all comorbid axis I disorders.
Figure 3b. Two-year course of anxiety disorders.
Figure 3c. Two-year course of mood disorders.

Separate analysis of lapses (intake of alcohol followed by immediate cessation of drinking and continuation of the OLITA program) and relapses (intake of alcohol followed by "malignant" continuation of drinking) in OLITA patients reveals that the "true relapse rate" in OLITA patients is 30% as compared with 70% in controls. Relapses plus lapses in OLITA patients amounted to 60%. Thus, the immediate stop of lapses by means of crisis interventions has prevented the progression into relapses for 30% of the patients.

Mechanisms of recovery and irreversibility

The OLITA program offers the unique possibility of following a well defined population of alcoholics over a long period of strictly controlled alcohol abstinence. In this ideal setting, we were able to study alcohol-induced pathology, as well as kinetics and mechanisms of recovery. Topics investigated include chromosomal aberrations, hematopoietic factors and circulating blood cells, stress hormones, sexual function and sex hormones, as well as neurocognitive functioning. Recently, we reported persistent alterations in many neuroendocrinological parameters, for example enduring disturbances of water/electrolyte homeostasis and thirst. These findings may prepare the ground for future pharmacological therapies. The underlying *mechanisms of irreversibility* could be directly or indirectly related to the phenomenon of dependence as well as of addictive behavior.[23,26,31-35,51,113] *Figure 4* shows the diurnal profile of epinephrine after 1 and 12 weeks of alcohol abstinence as an example of the biological basis of the patients' impaired stress tolerance during early abstinence. At both time points, data were obtained on three consecutive days from 7 AM to 3 PM from patients and controls in permanent supine position. Alcohol-dependent patients demonstrate extremely high levels of epinephrine at the beginning of abstinence that are still significantly higher than levels of healthy control subjects after 3 months of controlled abstinence (difference between alcohol-dependent patients and healthy control subjects: $P<.0001$ for the upper row, $P<.01$ for the lower row; N=11 for each group). The extent to which the stress response of the alcohol-dependent patients is impaired can be seen from

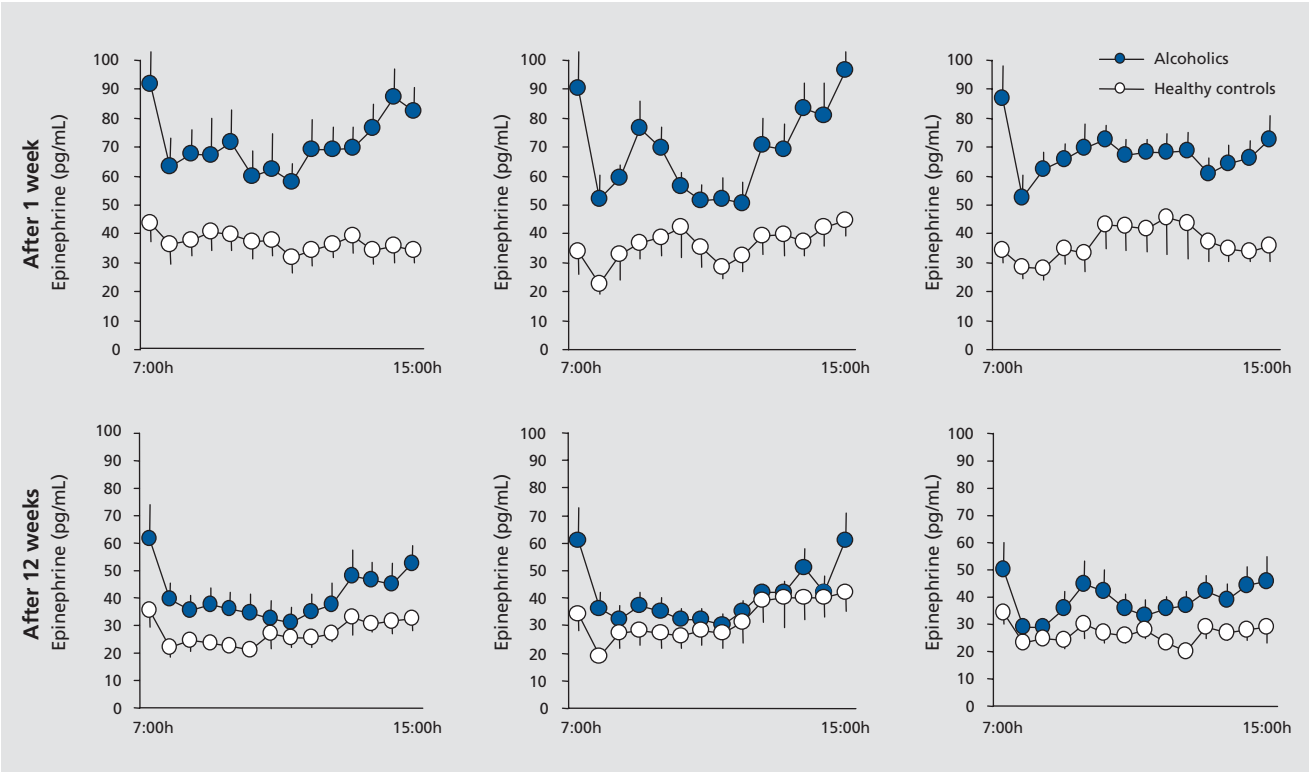

Figure 4. Diurnal profile of epinephrine during course of alcohol abstinence (see text for details).

the consistently higher stimulation of their epinephrine levels on all of the 6 days of assessment as compared with control subjects at the time point when the intravenous cannula was inserted (at 7 AM).

Personality disorder and chronicity of addiction as potent independent predictors of an unfavorable treatment outcome

A central issue of therapy research is to estimate the intensity of treatment needed on the basis of addiction severity of individuals. This approach is based on the assumption that patients whose addiction is less severe than others' might also benefit from less intensive treatment, whereas patients whose addiction is more severe need a more intensive therapy. However, it is far from clear which variables within the broad range of substance use data constitute the essential features of addiction severity.[14,69,86] The OLITA setting prepared the ground for a prospective longitudinal study that examined which components of addiction severity predict time to relapse for a subsample of 112 patients during 4-year follow-up.[108] Among the various analyzed sociodemographic, psychiatric, and alcoholism-related patient characteristics, only the presence of a personality disorder (Wald=7.83, df=1, *P*=.005) and chronicity of addiction (Wald=5.17, df=1, *P*=.023) were independently associated with a decrease of cumulative 4-year abstinence probability. Chronicity was defined as the percentage of a patient's lifetime that he or she has been addicted (ie, duration of dependence divided by age at the beginning of therapy). As illustrated in *Figure 5*, patients with a comorbid personality disorder and/or higher chronicity of addiction had a lower abstinence probability and a shorter time to relapse than patients without personality disorder and/or with lower chronicity. The four abstinence curves differ significantly (Breslow statistic=10.36, *P*=.02). Pairwise single comparisons of abstinence curves show that patients with both predictors are more at risk to relapse (.53, N=25, black line) than patients with no personality disorder and only low chronicity (.93, N=14, red line) (Breslow statistic=5.5, *P*=.02). Abstinence curves of patients who are handicapped only by personality disorder (.59, N=23, green line) or only by high chronicity (.60, N=11, gray line) approximate the abstinence curve of patients with both risk factors, indicating that these predictors independently cause a decrease of cumulative abstinence probability.

Therapist rotation: a major element of OLITA

Apart from the regained quality of life of these patients, the general health care cost reduction is enormous. How can we explain the unusual success of our very structured, intensive, and comprehensive long-term treatment? A major "mechanism of action" of OLITA seems to be the *therapist rotation.*[107] This element of OLITA represents a revolution in psychotherapy. The fact that six to seven therapists are equally responsible for each patient translates the ordinary two-way relation between therapist and patient into a most efficient multiway therapeutic network. Therapists stick to the rules of the program and the ideas of alcoholism treatment realized within the concept *(congruence)* and frequently repeat these rules and ideas *(repetition)*. Thereby, a *variety* of individual therapists with a *variety* of different thoughts create a therapeutic atmosphere characterized by vivid and multifaceted *variation*. We hypothesize that these specific factors activate common factors of psychotherapy and that, as an element of OLITA, therapist rotation has a major contribution to its success.

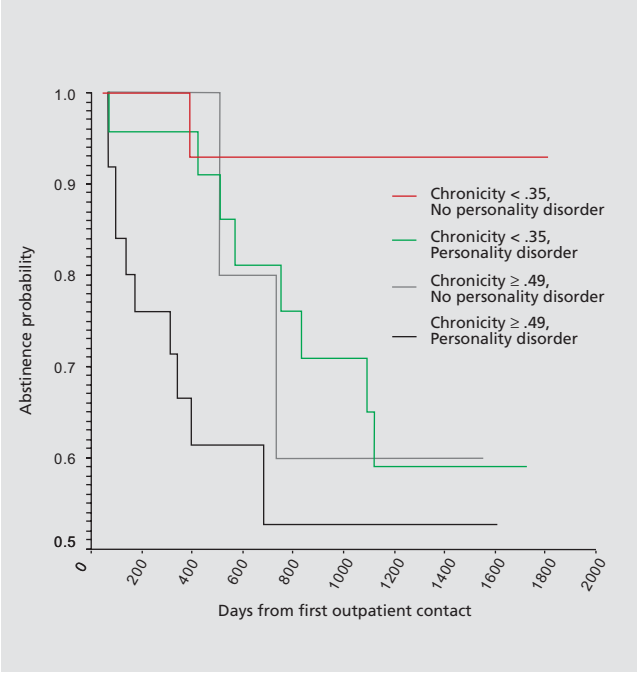

Figure 5. Prediction of cumulative abstinence probability during 4-year follow-up (Kaplan-Meier presentation). Interaction of the predictors personality disorder and chronicity (analysis of extreme groups).

How can we prove efficacy in a psychotherapeutic setting?

In contrast to pharmacological agents, psychotherapeutic effects are much more difficult to define or to measure. In addition, quality control for psychotherapy is widely missing. Therefore, and also to prove our hypotheses of how OLITA works, we have developed the Video-Assisted Monitoring of Psychotherapeutic Processes in Chronic Psychiatric Disease (VAMP). This diagnostic measure is a standardized, manualized, and video-based observational system that focuses mainly on the patients' behavior and makes it possible to assess treatment processes based on transcribed video recordings of therapy sessions.[114] The scales evaluated in the VAMP are grouped into seven modules: (i) common psychotherapeutic factors; (ii) addictive behavior; (iii) disease concept; (iv) working atmosphere; (v) psychopathological symptoms; (vi) therapeutic alliance; and (vii) problem solving. A total of 64 patients have been analyzed over the past 4 years using the VAMP. Each patient had 17 videotapes of psychotherapeutic sessions within the 2 years of OLITA recorded. These videos are the basis of both, a macroanalytical and a microanalytical evaluation of therapeutic processes and their influence on long-term outcome. An ongoing project explores the use of the VAMP in a prospective longitudinal study investigating (i) processes of change during the first year of OLITA; (ii) associations between therapeutic processes and essential outcome variables (eg, abstinence, relapse, addiction severity, course of comorbidity, and neuropsychological regeneration).[114] Therefore, treatment processes have been investigated at three time-points, t_1 (week 3), t_2 (month 6), and t_3 (month 12) during the first year of OLITA.

Reliability analyses show that the scales of the VAMP have high interjudge reliability (median intraclass coefficient of 0.80) and internal consistency (median Cronbach's α 0.81). The construct validity is indicated by pronounced intercorrelation patterns of theoretically associated specific factors. *Figures 6 and 7* demonstrate two examples. Relapse alertness *(Figure 6)* is strongly correlated with talk about relapse risk, disease concept, analytic processing and reflexion, experience of resources, as well as with func-

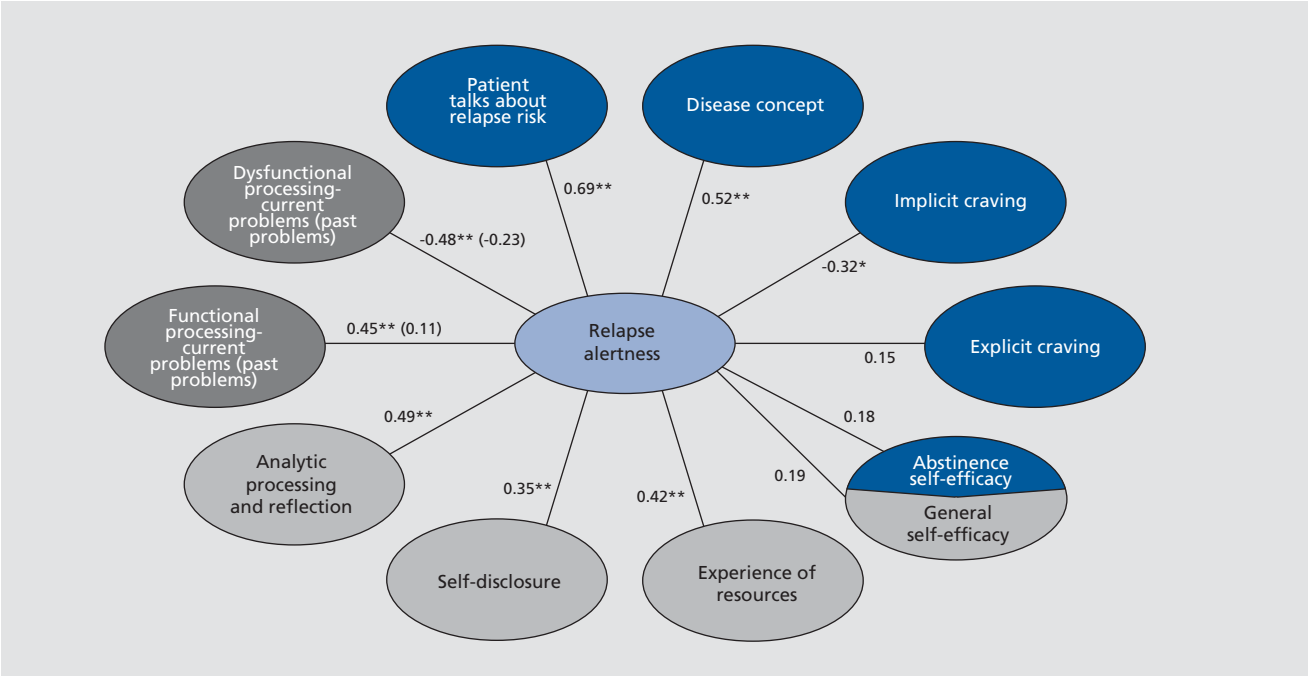

Figure 6. Intercorrelational pattern of the VAMP scales at the beginning of therapy (n=64); relapse alertness (central construct, light blue) shows correlations of different sizes with process variables belonging to the groups of common psychotherapeutic factors (light gray), problem processing (dark gray) as well as addictive behavior (dark blue).
OLITA, Outpatient Long-term Intensive Therapy for Alcoholics; VAMP: Video-Assisted Monitoring of Psychotherapeutic Processes In Chronic Psychiatric Disease

tional and dysfunctional problem solving of current problems. However, correlations are only medium-sized with self-disclosure and implicit craving. Most interestingly, relapse alertness is only weakly associated and nearly independent of explicit craving, functional and dysfunctional problem solving of past problems and both general and abstinence self-efficacy. To perform construct validation of the VAMP therapeutic alliance scales *(Figure 7)*, associations with the self-report measure Helping Alliance Questionnaire (HAQ) were analyzed.[115,116] This 11-item questionnaire has well-established psychometric properties, is available as a patient form and a therapist form and measures how patient and therapist have experienced the quality of therapeutic alliance during the session just conducted. It is based on two underlying components of the therapeutic alliance, support by the therapist and collaborative teamwork with the therapist regarding treatment goals and tasks. In the present study, the HAQ was administered directly after a therapy session, and neither patient nor therapist or VAMP raters were allowed to inspect each others' ratings. The three VAMP scales, working atmosphere, therapeutic alliance-patient and therapeutic alliance-therapist are highly correlated, suggesting an underlying common factor. Compared with the rather small associations between patient, therapist, and observer alliance ratings that are reported in the general psychotherapy literature[117] and in recent addiction therapy studies (eg, refs 118-120), both patient and therapist HAQ scores in our study show considerably higher correlations with each other and with VAMP observer ratings. This higher congruence, together with remarkably stable and high scores over 12 months in all used alliance measures,[114] lead us to the speculation that the multiple relationships developed in the setting of therapist rotation might constitute a stronger therapeutic alliance than the two-way relationships in the dyadic therapy setting. Although these data are not yet a clear proof that therapist rotation is a major factor contributing to the long-term success of OLITA, they are the first empirical evidence on therapist rotation and may stimulate future investigations of this rather unexplored research topic.

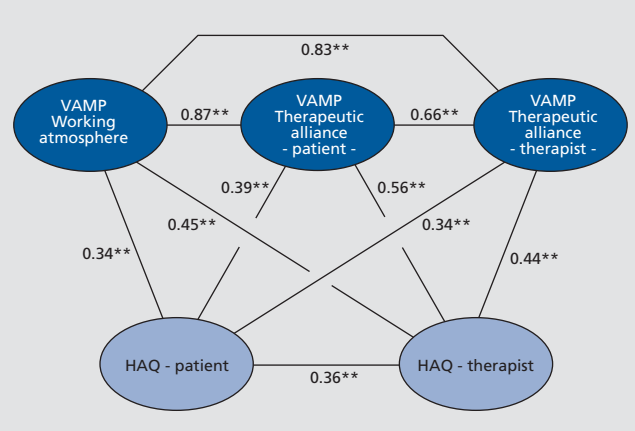

Figure 7. Aspects of therapeutic alliance in OLITA: Correlational pattern between different observer-rated (dark blue, VAMP scales) and self-reported (light blue, HAQ) measures of therapeutic alliance at the beginning of therapy (n=64).
OLITA, Outpatient Long-term Intensive Therapy for Alcoholics; VAMP: Video-Assisted Monitoring of Psychotherapeutic Processes In Chronic Psychiatric Disease; HAQ, Helping Alliance Questionnaire.[115,116]

Treatment processes in clinical practice: where to start?

Therapists in the addiction field daily face the difficulty to decide which of the many dysfunctional processes of their patients have priority and should be focused on at first. By integrating the VAMP scales with the highest predictive validity, the composite score Therapy Orientation by Process Prediction Score (TOPPS) was constructed. It includes the process variables experience of resources, abstinence self-efficacy, implicit craving, relapse alertness, relapse risk, disease concept, dysfunctional therapeutic engagement, and dysfunctional problem solving of current problems. The TOPPS strongly predicts 4-year abstinence probability at any of the 3 time-points (P<0.001). This result suggests employing the TOPPS in addiction therapy as a treatment guideline for adapting individual relapse prevention strategies. Therapists and addiction counselors can evaluate their patients according to the eight processes after individual therapy sessions as well as in team sessions. The ratings may be employed in form of a checklist that serves as a practical tool to plan, evaluate, reschedule, and regulate the course of therapy. Problems in one or more of the eight processes indicate to what extent a patient's current behavior constitutes a long-term risk factor for alcohol relapse. As a consequence, individually tailored relapse prevention strategies that target specifically the improvement of the problematic processes should be integrated into the treatment plan.
For possible interventions, a plethora of therapeutic elements are available in comprehensive addiction therapy, all of them realized within the OLITA program, eg, motivational interventions during inpatient detoxification,

smooth transition from inpatient to outpatient treatment, high-frequency short-term individual therapeutic contacts, supportive psychotherapy during the first 6 months of abstinence, therapist rotation, social support, case management, regular urine and blood tests for alcohol and other drugs of abuse, supervised intake of alcohol deterrents, house visits, crisis interventions and assistance round the clock in case of emergency, "aggressive aftercare," coping and problem-solving skills training including functional analyses, psychoeducation, and restructuring of dysfunctional thinking, eclectic cognitive-behavioral and psychopharmacological treatment of concurrent mental disorders, marital and family therapy, slow tapering of therapeutic contacts and weekly group sessions during the second year of treatment.

Conclusions and clinical implications

Alcohol dependence is a chronic, relapsing, and incurable disease that belongs to the most frequent psychiatric disorders. Personality disorder and chronicity constitute the essential features of addiction severity and result in low abstinence rates of short- and medium-term therapies after extended follow-up. A new understanding of alcoholism therapy recognizes alcohol dependence as a chronic disease such as hypertension, chronic polyarthritis, bronchial asthma, and diabetes mellitus. Similar to these diseases, alcohol dependence has to be treated with an unusually intensive biopsychosocial approach. Only comprehensive, integrated, and structured long-term therapy with a strict abstinence orientation, followed by lifelong attending of checkup sessions and self-help group participation will guarantee long-term recovery.

OLITA shows a 9-year abstinence rate of over 50%, a re-employment rate of 60%, and a dramatic recovery from comorbid depression, anxiety disorders, and physical sequelae. These outcome data are empirically based on treatment processes that have proven high predictive validity and give concrete information about where to focus the therapeutic efforts. Thus, process-outcome research on OLITA can serve for the development of new therapeutic guidelines for adapting individual relapse prevention strategies. ❑

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Terapia intensiva a largo plazo para pacientes alcohólicos ambulatorios (OLITA): una aproximación biopsicosocial exitosa para el tratamiento del alcoholismo

La dependencia al alcohol es una enfermedad frecuente, crónica, recurrente e incurable con enormes costos sociales. Por lo tanto, la terapia del alcoholismo y la investigación acerca de la evolución son de la mayor importancia para la salud pública. El presente artículo: 1) dará una breve visión acerca de cómo ha evolucionado la epidemiología, la patogénesis y la terapéutica de la dependencia al alcohol, 2) introducirá los principios básicos del tratamiento a largo plazo de pacientes ambulatorios con dependencia al alcohol y 3) discutirá en detalle la investigación del proceso y evolución de la Terapia Intensiva a Largo Plazo de Pacientes Alcohólicos Ambulatorios (OLITA). Esta exitosa aproximación biopsicosocial al tratamiento del alcoholismo muestra un porcentaje de abstinencia a nueve años sobre el 50%, una frecuencia de reincorporación laboral del 60% y una importante recuperación de la depresión, los trastornos de ansiedad y las secuelas físicas comórbidas. Los datos de la evolución se basan empíricamente en procesos terapéuticos que han probado una alta validez predictiva y dan información concreta acerca de dónde dirigir los esfuerzos terapéuticos. De esta forma, la investigación del proceso-evolución de OLITA puede servir para el desarrollo de nuevas guías terapéuticas para la adaptación individual a las estrategias para la prevención de recaídas.

*OLITA (*Outpatient Long-term Intensive Therapy for Alcoholics*) : une approche biopsychologique réussie du traitement de l'alcoolisme*

*La dépendance alcoolique est une maladie fréquente, chronique, récidivante et incurable entraînant d'énormes coûts sociétaux. Le traitement de l'alcoolisme et la recherche sur les effets de ce traitement revêtent donc une importance majeure en termes de santé publique. L'article qui suit: (i) propose un bref aperçu de l'épidémiologie, de la pathogenèse et des résultats thérapeutiques de la dépendance alcoolique ; (ii) introduit les principes de base du traitement à long terme en ambulatoire des patients alcooliques ; (iii) discute en détail des résultats du programme thérapeutique intensif OLITA (*Outpatient Long-term Intensive Therapy for Alcoholics*). Cette approche biopsychologique du traitement de l'alcoolisme s'est avérée efficace, montrant un taux d'abstinence de plus de 50 % sur 9 ans, un taux de réemploi de 60 % et une récupération très importante à la suite d'une dépression comorbide, de troubles anxieux ou de séquelles physiques. Les résultats, basés empiriquement sur des procédures thérapeutiques dont la valeur prédictive élevée a été démontrée, indiquent concrètement où porter les efforts thérapeutiques. Ainsi, la recherche concernant les effets des processus de la prise en charge OLITA peut servir à l'élaboration de nouvelles recommandations thérapeutiques pour adapter en les individualisant les stratégies de prévention de la rechute.*

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Cannabinoids in health and disease

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Cannabis sativa L. preparations, such as marijuana, hashish, and dagga, have been used in medicine for millenia.[1] Investigations into the chemistry of *Cannabis* began in the mid-19th century, following a major trend in chemical research at the time, which centered on the quest for active natural products. Numerous alkaloids were isolated in pure form from various plants, and many of them were fully or partially characterized. Morphine, cocaine, strychnine, and many others were purified and used in medicine. However, most of the terpenoids—a major class of secondary plant metabolites, to which the plant cannabinoids also belong—were not isolated until the end of the century or even much later, and in many cases their purity was doubtful.

Cannabis sativa L. *preparations have been used in medicine for millenia. However, concern over the dangers of abuse led to the banning of the medicinal use of marijuana in most countries in the 1930s. Only recently, marijuana and individual natural and synthetic cannabinoid receptor agonists and antagonists, as well as chemically related compounds, whose mechanism of action is still obscure, have come back to being considered of therapeutic value. However, their use is highly restricted. Despite the mild addiction to cannabis and the possible enhancement of addiction to other substances of abuse, when combined with cannabis, the therapeutic value of cannabinoids is too high to be put aside. Numerous diseases, such as anorexia, emesis, pain, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, glaucoma, osteoporosis, schizophrenia, cardiovascular disorders, cancer, obesity, and metabolic syndrome-related disorders, to name just a few, are being treated or have the potential to be treated by cannabinoid agonists/antagonists/cannabinoid-related compounds. In view of the very low toxicity and the generally benign side effects of this group of compounds, neglecting or denying their clinical potential is unacceptable—instead, we need to work on the development of more selective cannabinoid receptor agonists/antagonists and related compounds, as well as on novel drugs of this family with better selectivity, distribution patterns, and pharmacokinetics, and—in cases where it is impossible to separate the desired clinical action and the psychoactivity—just to monitor these side effects carefully.*

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Selected abbreviations and acronyms

ALS	*amyotrophic lateral sclerosis*
CBD	*cannabidiol*
DA	*dopamine*
HD	*Huntington's disease*
IOP	*intraocular pressure*
MS	*multiple sclerosis*
PD	*Parkinson's disease*
PTSD	*post-traumatic stress disorder*
THC	*tetrahydrocannabinol*

In 1840, Schlesinger was apparently the first investigator to obtain an active extract from the leaves and flowers of hemp.[2] A few years later, Decourtive described the preparation of an ethanol extract that on evaporation of the solvent gave a dark resin, which he named "cannabin." [3] For a detailed history of early *Cannabis* research see ref 4. The chemical research on the plant cannabinoids and their derivatives over nearly two centuries is described in ref 5. It was, however, not until 1964 that Δ^9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of *Cannabis*, was isolated in pure form and its structure was elucidated.[6] Shortly thereafter it was synthesized and became widely available. These chemical advances led to an avalanche of publications on Δ^9-THC, as well as on cannabidiol (CBD), a nonpsychoactive plant cannabinoid.[7] However, concern about the dangers of abuse led to the banning of marijuana and its constituents for medicinal use in United States and many other countries in the 1930s and 1940s. It took decades until cannabinoids came to be considered again as compounds of therapeutic value, and even now their uses are highly restricted. Here we present an overview of the addictive and side effects of cannabinoids vs their therapeutic potential.

Addiction to cannabis, and the influence of cannabis on addiction to other substances

Marijuana may produce mild dependence in humans.[8-12] This was shown to depend on the personality type of the addicts,[13] and can be successfully reversed by abstinence or treated by cognitive-behavioral therapy,[14] without the occurrence of major withdrawal symptoms. Cannabinoids act on brain reward processes and reward-related behaviors by a mechanism similar to that found with other addictive drugs. In animal models they enhance electrical brain-stimulation reward in the core meso-accumbens reward circuitry of the brain and neural firing of a core dopamine (DA) component and thus elevate DA tone in the reward-relevant meso-accumbens DA circuit. In some animal models they produce conditioned place preference (CPP) and self-administration.[15,16] Other studies, however, find THC to be a poor reinforcer, with no or little self-administration.[17]

The abuse of other substances is influenced by the cannabinoids. The cannabinoid system is involved in alcohol-consumption behavior. Cannabinoid CB1 receptor agonists have been found to specifically stimulate alcohol intake and its motivational properties in rats.[18] The high ethanol preference of young mice is reduced by the cannabinoid receptor 1 (CB1) antagonist SR141716A (rimonabant) to levels observed in their CB1 knockout littermates.[19] Dopamine release induced by ethanol in brain was reduced by SR141716A,[20] which can explain in part the antiaddictive effect of the drug. Cocaine is another substance of abuse in whose acquisition and consolidation cannabinoids may be involved. High prevalence of alcohol dependence and cannabis dependence can be found in patients with cocaine dependence.[21] Marijuana smoking increases plasma cocaine levels and subjective reports of euphoria in male volunteers.[22,23] Furthermore, a recent genetic study found an association between an n triplet repeat polymorphism in the CB1 encoding *CNR1* gene with cocaine addiction in the African-Caribbean population.[24] In another study it was found that withdrawal from repeated access or exposure to cocaine and then a reinstatement of cocaine-seeking behavior or a sensitized locomotor response to a single cocaine challenge, respectively, was potently reduced by pretreatment with rimonabant.[25] Similarly, acute administration of rimonabant blocked expression of nicotine-induced conditioned place preference.[26] Rimonabant also reduces nicotine self-administration, and may be effective not only as an aid for smoking cessation, but also in the maintenance of abstinence.[27] As the endocannabinoid system plays a role in nicotine addiction,[28] the potential of cannabinoid antagonists to treat it is self-evident.[29-31] Opiate and CB1 receptors are coexpressed in the nucleus accumbens and dorsal striatum, and the interaction between the two systems is well known.[32] The reinforcing properties of morphine and the severity of the withdrawal syndrome are strongly reduced in CB1-knockout mice[33]; this observation opens an opportunity to treat opiate addiction with rimonabant, as noted with alcohol, cocaine, and nicotine addiction.[34,35]

Negative effects of cannabis other than addiction

There are some negative effects of cannabis use other than addiction, most of them related to alterations of attentional and cognitive functions or other neuropsychological and behavioral effects. Most of them are noted as a result of early-onset cannabis use (during adolescence).[36] Electrophysiological measures have revealed long-term deficits in attention among cannabis users.[37] In another study, impairment both in cognitive function and mood following cannabis use was noted.[38] However, in another study, cannabis users and controls performed equally well in a working memory task and a selective attention task. Furthermore, cannabis users did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions.[39] Prenatal exposure to cannabis is associated with only minor impaired cognitive and attentional effects.[40-42] Cannabis use in adolescence increases the risk of schizophrenia-like psychoses.[43] Cognitive dysfunction associated with long-term or heavy cannabis use is similar in many respects to the cognitive endophenotypes that have been proposed as vulnerability markers of schizophrenia.[44] Also, evidence exists that cannabis use may trigger acute schizophrenic psychosis.[45,46] Cannabis was found to produce a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses.[46] Amotivational syndrome is a chronic psychiatric disorder characterized by a variety of changes in personality, emotions, and cognitive functions such as lack of activity, inward-turning, apathy, incoherence, blunted affect, inability to concentrate, and memory disturbance. The syndrome was first described in the 1960s among patients with a history of longtime cannabis use.[47] A useful animal model for this disorder was found in rat, where the cannabis-caused catalepsy-like immobilization is related to a decrease in catecholaminergic and serotonergic neurons in the nucleus accumbens and amygdaloid nucleus, and thus can serve as a model for amotivational syndrome.[48] In another study, heavy cannabis use was found to cause an amotivational syndrome in adolescents.[49] The treatment of cannabis use disorders has recently been reviewed.[12] However, the occurrence of amotivational syndrome as a result of cannabis exposure remains controversial.[50] The data from other studies do not support the hypothesis that marijuana impairs motivation.[51,52] Although most of the cannabis-related negative effects relate to its neuropsychologic and behavioral effects, other negative reactions to cannabis are sometimes found. For example, cannabis can cause acute pancreatitis, although the exact mechanism remains unknown.[53]

Therapeutic uses of cannabinoids

Obesity, anorexia, emesis

Cannabis has been known for centuries to increase appetite and food consumption.[54] More recently this propensity of the drug was substantiated when the CB1 receptor was shown to have a role in central appetite control, peripheral metabolism, and body weight regulation.[55] Genetic variants at CB1 coding gene *CNR1* are associated with obesity-related phenotypes in men.[56] In animals, CB1 receptor antagonism decreases motivation for palatable foods. Rimonabant administration caused suppression of the intake of a chocolate-flavored beverage over a 21-day treatment period, without any apparent development of tolerance.[57] CB1 receptors were found to be preferentially involved in the reinforcing effects of sweet, as compared to a pure fat, reinforcer.[58] Rimonabant selectively reduces sweet rather than regular food intake in primates,[59] which suggests that rimonabant is more active on the hedonic rather than nutritive properties of diets.

Rimonabant leads to significant weight loss in obese human subjects. Treatment with rimonabant was also associated with beneficial effects on different metabolic parameters and cardiovascular risk factors linked with overweight.[60,61] In clinical trials rimonabant was found to cause a significant mean weight loss, reduction in waist circumference, increase in HDL cholesterol, reduction in triglycerides, and increase in plasma adiponectin levels.[62] Patients who were switched from the rimonabant treatment to placebo after a 1-year treatment regained weight, while those who continued to receive rimonabant maintained their weight loss and favorable changes in cardiometabolic risk factors.[63,64] Rimonabant was shown to be safe and effective in treating the combined cardiovascular risk factors of smoking and obesity.[65] It also diminishes insulin resistance, and reduces the prevalence of metabolic syndrome. Many of the metabolic effects, including adiponectin increase, occur beyond weight loss, suggesting a direct peripheral effect of rimonabant.[66] Therapy with rimonabant is also associated with favorable changes in serum lipids and an improvement in

glycemic control in type 2 diabetes.[67] The activity of rimonabant in the management of obesity has been described in recent reviews.[31,68] It has been approved for the treatment of obesity in the European Union, and is sold under the trade name Acomplia. Surprisingly, the US Food and Drug Administration has declined to approve rimonabant, primarily due to its slight potential to enhance anxiety and suicidal thoughts. The atmosphere of consternation of possible legal action due to side effects may have led to this decision.

The other side of the same coin is anorexia. While in obese populations weight loss is the main goal, in other populations, such as patients with cancer or AIDS, it is an immense problem. Dronabinol (synthetic THC, known as Marinol and approved for the treatment of nausea and vomiting in cancer and AIDS patients) is associated with consistent improvement in appetite.[69] It was found to be safe and effective for anorexia associated with weight loss in patients with AIDS, and is associated with increased appetite, improvement in mood, and decreased nausea. In clinical trials, weight was stable in dronabinol patients, while placebo recipients lost weight.[70,71] Dronabinol was found to be safe and effective for treatment of HIV wasting syndrome,[72] as well as in patients with Alzheimer's disease[73] and with advanced cancer,[73,74] The possible mechanisms of these actions have been reviewed.[75] Cannabinoids have a positive effect in controlling chemotherapy-related sickness.[76] They are more effective antiemetics than the dopamine receptor antagonists such as chlorpromazine-type drugs.[77] Direct comparisons with serotonin (5-HT)3 antagonists, which are widely used as antiemetics, have not been reported. However, while these antagonists are not effective in delayed vomiting, THC is known to reduce this side effect of chemotherapy.

Pain

Cannabis has been used for millennia as a pain-relieving substance. Evidence suggests that cannabinoids may prove useful in pain modulation by inhibiting neuronal transmission in pain pathways. Considering the pronounced antinociceptive effects produced by cannabinoids, they were proposed to be a promising therapeutic approach for the clinical management of trigeminal neuralgia.[78] THC, CBD, and CBD-dimethyl heptyl (DMH) were found to block the release of serotonin from platelets induced by plasma obtained from the patients during migraine attack.[79] However, in other reports cannabinoids are much less successful in pain-relieving. In a clinical trial THC did not have any significant effect on ongoing and paroxysmal pain, allodynia, quality of life, anxiety/depression scores and functional impact of pain. These results do not support an overall benefit of THC in pain and quality of life in patients with refractory neuropathic pain.[80] Similarly, in an additional clinical trial, no evidence was found[81]of analgesic effect of orally administered THC in postoperative pain in humans. Other studies show much better results of pain relief. When THC was given to a patient with familial Mediterranean fever, with chronic relapsing pain and gastrointestinal inflammation, a highly significant reduction in pain was noted.[82] Mild improvement was noted with cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion.[83] In neuropathic pain patients, median spontaneous pain intensity was significantly lower on THC treatment than on placebo treatment, and median pain relief score (numerical rating scale) was higher.[84] It was also effective in treating central pain.[85] The administration of single oral doses of THC to patients with cancer pain demonstrated a mild analgesic effect.[86,87] Patients who suffer from pain also tend to self-medicate with marijuana. In an anonymous cross-sectional survey, 72 (35%) of chronic non-cancer pain patients reported having used cannabis for relieving pain.[88] Cannabis-treated AIDS patients reported improved appetite, muscle pain, nausea, anxiety, nerve pain, depression, and paresthesia.[89] Not only THC, but also other cannabinoids can potentially affect different types of pain. Nabilone is a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy.[90] In Canada, the United States, and the United Kingdom, nabilone is marketed as Cesamet. A significant decrease in disabling spasticity-related pain of patients with chronic upper motor neuron syndrome (UMNS) was found with nabilone.[91] Another cannabinoid, ajulemic acid (AJA), was effective in reducing chronic neuropathic pain,[92] although cannabinoid side effects (tiredness, dry mouth, limited power of concentration, dizziness, sweating) were noted. Cannabimimetic effects with ajulemic acid in rodents have also been recorded.[93]

The combination of THC with the nonpsychotropic cannabis constituent CBD has a higher activity than THC alone.[94] The CBD/THC buccal spray (Sativex) was found to be effective in treating neuropathic pain in multiple sclerosis (MS).[95] Chronic neuropatic pain can also

be treated with cannabis extracts containing THC, or CBD, or with Sativex.[96,97] The latter also was effective in reducing sleep disturbances in these patients and was mostly well tolerated.[97] Sativex is the first cannabis-based medicine to undergo conventional clinical development and be approved as a prescription drug. It is efficacious and well tolerated in the treatment of symptoms of multiple sclerosis, notably spasticity and neuropathic pain.[98] Sativex has been approved for use in neuropathic pain due to multiple sclerosis in Canada [for reviews on Sativex and on pain see refs 94, 99, and 100].

Multiple sclerosis, neuroprotection, inflammation

Inflammation, autoimmune response, demyelination, and axonal damage are thought to participate in the pathogenesis of MS. Increasing evidence supports the idea of a beneficial effect of cannabinoid compounds for the treatment of this disease. In clinical trials, it has been shown that cannabis derivatives are active on the pain related to MS,[84,85,95,97,98] However, this is not the only positive effect of cannabinoids in this disease. In rat experimental autoimmune encephalomyelitis (EAE), a laboratory model of MS, THC, given once after disease onset, significantly reduced maximal EAE score. Reduction in the inflammatory response in the brain and spinal cord was also noted in animals treated with dexanabinol (HU-211 a nonpsychoactive synthetic cannabinoid).[101] In another trial in rats, all animals treated with placebo developed severe clinical EAE and more than 98% died, while THC-treated animals had either no clinical signs or mild signs, with delayed onset with survival greater than 95%.[102] WIN-55,212-2, another synthetic cannabinoid, also was found to ameliorate the clinical signs of EAE and to diminish cell infiltration of the spinal cord, partially through CB2.[103] Using a chronic model of MS in mice, it was shown that clinical signs and axonal damage in the spinal cord were reduced by the synthetic cannabinoid HU210.[104] To more fully inderstand the involvement of the endocannabinoid system in MS, the status of cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase (FAAH) enzyme in brain tissue samples obtained from MS patients was investigated. Selective glial expression of cannabinoid CB1 and CB2 receptors and FAAH enzyme was found to be induced in MS.[105] In mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), a chronic model of MS that reproduces many of the pathological hallmarks of the human disease, a moderate decrease in the density of CB1 receptors in the caudate-putamen, globus pallidus, and cerebellum was found. These observations may explain the efficacy of cannabinoid agonists in improving motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.[106] Spasticity is a common neurologic condition in patients with MS, stroke, cerebral palsy, or an injured spinal cord. Marijuana was suggested as treatment of muscle spasticity as early as the 1980s.[107] In an experiment in mice, control of spasticity in a MS model was found to be mediated by CB1, but not by CB2, cannabinoid receptors.[108] In clinical trials, patients treated with THC had significant improvement in ratings of spasticity compared to placebo.[109] In one case report nabilone improved muscle spasms, nocturia, and general well-being.[110] In another case report, the chronic motor handicaps of an MS patient acutely improved while he smoked a marijuana cigarette.[111] THC significantly reduced spasticity by clinical measurement. Responses varied, but benefit was seen in patients with tonic spasms.[112] At a progressive stage of illness, oral and rectal THC reduced the spasticity, rigidity, and pain, resulting in improved active and passive mobility.[113] However, in other clinical trials, cannabinoids appeared to reduce tremor but were ineffective in spasticity.[114,115] Moreover, in one trial marijuana smoking further impaired posture and balance in patients with spastic MS.[116] The inconsistent effects noted might be due to dose-dependency. Improved motor coordination was seen when patients with MS, seriously disabled with tremor and ataxia, were given oral THC.[117] In another study, cannabis extract did not produce a functionally significant improvement in MS-associated tremor.[118] Suppression of acquired pendular nystagmus (involuntary movement of the eyes) was seen in a patient with MS after smoking cannabis resin, but not after taking nabilone tablets or orally administered capsules containing cannabis oil.[119] There are also findings suggestive of a clinical effect of cannabis on urge incontinence episodes in patients with MS.[120] In the treatment of MS, as well as in pain reduction described earlier, there is a preferential effect of a THC+CBD combination (Sativex).[121] A mixture of 2.5 mg THC and 0.9 mg cannabidiol (CBD) lowered spasm frequency and increased mobility, with tolerable side effects, in MS patients with persistent spasticity not responding to other drugs.[122] Oromucosal sprays of Sativex significantly reduced spasticity scores in comparison with placebo.[123] Long-term use of Sativex maintains its effect in those patients who perceive initial benefit.[124] Zajicek et al origi-

nally reported that cannabinoids did not have a beneficial effect on spasticity; however, there was an objective improvement in mobility and some patients reported an improvement in pain.[125] Later the same group also found positive effects on muscle spasticity with prolonged treatment.[126] The subject has been thoroughly reviewed.[99,127-130]

MS is not the only disease state where the neuroprotective potential of cannabinoids can be seen. In animal experiments, 2 weeks after the application of 6-hydroxydopamine, a significant depletion of dopamine contents and a reduction in tyrosine hydroxylase activity in the lesioned striatum were noted, and were accompanied by a reduction in tyrosine hydroxylase-messenger ribonucleic acid (mRNA) levels in the substantia nigra. Daily administration of THC over 2 weeks produced a significant irreversible waning in the magnitude of these changes, which may be relevant in the treatment of Parkinson's disease (see below).[131] The cannabinoids have a neuroprotective activity not only in vitro but also in vivo: HU-210, a potent synthetic analog of THC, increases survival of mouse cerebellar granule cells exposed to 6-hydroxydopamine.[131] In a model of experimental stroke, rimonabant reduced infarct volume by approximately 40%. Rimonabant exerted neuroprotection independently of its cannabinoid receptor-blocking effect.[132] In clinical trials, dexanabinol-treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure. A trend toward faster and better neurologic outcome was also observed.[133] However, in further experiments, dexanabinol was not found to be efficacious in the treatment of traumatic brain injury.[134] A wide range of cannabinoids has been shown to help in pathologies affecting the central nervous system (CNS) and other diseases that are accompanied by chronic inflammation.[130,135,136] In a rodent model of chronic brain inflammation produced by the infusion of lipopolysaccharide into the fourth ventricle of young rats, the cannabinoid agonist WIN-55212-2 reduced the number of LPS-activated microglia.[137] Direct suppression of CNS autoimmune inflammation was seen by activation of CB1 receptors on neurons and CB2 receptors on autoreactive T cells.[138]

Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and stroke in Western countries. Oral treatment with a low dose of THC inhibits atherosclerosis progression in an apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC may be a valuable target for treating atherosclerosis.[139] N-palmitoyl-ethanolamine is an endogenous endocannabinoid-like compound. Its concentrations are significantly increased in three different inflammatory and neuropathic conditions. The enhanced levels may possibly be related to a protective local anti-inflammatory and analgesic action.[140]

CBD has been shown to exert potent anti-inflammatory and antioxidant effects. High-glucose-induced mitochondrial superoxide generation, NF-kappaB activation, nitrotyrosine formation, iNOS and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs) were attenuated by CBD pretreatment.[141]

In experiments with obese vs lean rats, rimonabant was found to be a potent inhibitor of sensory hypersensitivity associated with CFA-induced arthritis in obese rats, in which the inflammatory reaction is more severe than in lean rats. It may thus have therapeutic potential in obesity-associated inflammatory diseases.[142]

Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease, epilepsy

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder. The main pathological feature of PD is the degeneration of dopamine (DA)-containing neurons of the substantia nigra, which leads to severe DAergic denervation of the striatum. The irreversible loss of the DA-mediated control of striatal function leads to the typical motor symptoms observed in PD, ie, bradykinesia, tremor, and rigidity. It has been proposed that cannabinoids may have some beneficial effects in the treatment of PD.[129] In animal experiments cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro.[131]

The majority of PD patients undergoing levodopa therapy develop disabling motor complications (dyskinesias) within 10 years of treatment. Recent studies in animal models and in the clinic suggest that CB1 receptor antagonists could prove useful in the treatment of both parkinsonian symptoms and levodopa-induced dyskinesia, whereas CB1 receptor agonists could have value in reducing levodopa-induced dyskinesia.[143] In the reserpine-treated rat model of PD, the dopamine D2 receptor agonist quinpirole caused a significant alleviation of the akinesia. This effect was significantly reduced by coinjec-

tion with the cannabinoid receptor agonist WIN 55,212-2. The simultaneous administration of the CB1 antagonist rimonabant with quinpirole and WIN 55,212-2 blocked the effect of WIN 55,212-2 on quinpirole-induced alleviation of akinesia.[144] In animal experiments, chronic levodopa produced increasingly severe orolingual involuntary movements which were attenuated by WIN 55,212-2. This effect was also reversed by rimonabant.[145] In other studies, rimonabant was found to possess some beneficial effects on motor inhibition typical of PD, at least in some doses. The injection of 0.1 mg/kg of rimonabant partially attenuated the hypokinesia shown by PD animals with no effects in control rats, whereas higher doses (0.5-1.0 mg/kg) were not effective.[146] A nigrostriatal lesion by MPTP is associated with an increase in CB1 receptors in the basal ganglia in humans and nonhuman primates; this increase could be reversed by chronic levodopa therapy, which suggests that CB1 receptor blockade might be useful as an adjuvant for the treatment of parkinsonian motor symptoms.[147] High endogenous cannabinoid levels are found in the cerebrospinal fluid of untreated PD patients.[148] Administration of inhibitors of endocannabinoid degradation reduced parkinsonian motor deficits in vivo.[149] Thus, both agonists and antagonists of CB receptors seem to help in some parkinsonian symptoms. In clinical trials, the cannabinoid receptor agonist nabilone significantly reduced levodopa-induced dyskinesia in PD.[150] THC improved motor control in a patient with musician's dystonia.[151] In contrast to these findings, some studies find no effect of cannabinoids on PD: orally administered cannabis extract resulted in no objective or subjective improvement in either dyskinesias or parkinsonism,[152] no significant reduction in dystonia following treatment with nabilone,[153] and rimonabant could not improve parkinsonian motor disability.[154] However, an anonymous questionnaire sent to all patients attending the Prague Movement Disorder Centre revealed that 25% of the respondents had taken cannabis and 45.9% of these described some form of benefit.[155] Thus cannabinoids seem to be able to treat at least some symptoms of neurological diseases.[156-158]

Huntington's disease (HD) or Huntington's chorea ("chorea" meaning "dance" in Greek) is a disorder characterized by a distinctive choretic movement, progressive motor disturbances, dementia, and other cognitive deficits. Neuropathologically, HD is characterized by a degeneration of medium spiny striato-efferent γ-aminobutyric acid (GABA)ergic neurons and by an atrophy of the caudate nucleus. Advanced grades of HD showed an almost total loss of CB1 receptors and a further depletion of D1 receptors in the caudate nucleus, putamen, and globus pallidus internus, and an increase in $GABA_A$ receptor binding in the globus pallidus internus.[159,160] Loss of cannabinoid receptors is also seen in the substantia nigra in HD.[161] These findings suggest a possible therapeutic role of cannabinoid agonists in HD. Indeed, arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of HD generated by bilateral intrastriatal application of 3-nitropropionic acid (3-NP).[162] The reduction in the increased ambulation exhibited by 3NP-lesioned rats in the open-field test caused by AM404 (anandamide's transport inhibitor, which also binds to vanilloid receptor 1) was reversed when the animals had been pretreated with capsazepine (VR1 antagonist), but not with SR141716A, thus suggesting a major role of VR1 receptors in the antihyperkinetic effects of AM404. However, both capsaicin (VR1 agonist) and CP55,940 (an CB1 agonist) had antihyperkinetic activity.[163] Quinolinic acid (QA) is an excitotoxin which, when injected into the rat striatum, reproduces many features of HD by stimulating glutamate outflow. Perfusion with WIN 55,212-2 significantly and dose-dependently prevented the increase in extracellular glutamate induced by QA. Thus, the stimulation of CB1 receptors might lead to neuroprotective effects against excitotoxic striatal toxicity.[164] In a clinical trial CBD was neither symptomatically effective nor toxic in neuroleptic-free HD patients.[165]

Tourette syndrome (TS) is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Anecdotal reports have suggested that the use of cannabis might improve tics and behavioral problems in patients with TS. Indeed, THC reduced tics in TS patients,[166] without causing acute and/or long-term cognitive deficits.[167] In another clinical trial, where tic severity was assessed using a self-rating scale and examiner ratings, patients also rated the severity of associated behavioral disorders. There was a significant improvement of motor tics, vocal tics and obsessive-compulsive behavior after treatment with THC. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration, suggesting a possible role of this THC metabolite on the positive effect of THC.[168] In another, longer clinical trial, THC was also found to be effective and safe in the treatment of tics.[169] In view of the positive effect of CB1 agonists in the treatment of TS, CB1 gene mutations were investigated. However, TS was not found to be caused by mutations in the *CNR1* gene.[170]

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. Many effects of marijuana may be applicable to the management of ALS. These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction. In addition, its strong antioxidative and neuroprotective effects may prolong neuronal cell survival.[171] Indeed, treatment of postsymptomatic, 90-day-old SOD1G93A mice (a model of ALS) with WIN 55,212-2, significantly delayed disease progression. Furthermore, genetic ablation of the FAAH enzyme, which results in raised levels of the endocannabinoid anandamide, prevented the appearance of disease signs in these mice. Surprisingly, elevation of cannabinoid levels with either WIN 55,212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in these mice, but significantly extended life span. Together these results show that cannabinoids have significant neuroprotective effects in this model of ALS, and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms.[172] THC was also found to delay the progression of disease.[173,174] Treatment with AM1241, a CB2-selective agonist, was effective at slowing signs of disease progression, when administered after onset of signs in an ALS mouse model. Administration at the onset of tremors delayed motor impairment in treated mice when compared with vehicle controls[175]; moreover, AM-1241 prolonged survival in these mice.[176] In a survey among ALS patients, cannabis was reported to be moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, and drooling.[177]
Cannabinoids were also proposed to have a role in the treatment of *Alzheimer's disease (AD)*. THC competitively inhibits acetylcholinesterase (AChE) and prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of AD.[178] THC treatment also decreased severity of disturbed behavior, and this effect persisted during the placebo period in patients who had received THC.[179] Compared with baseline, THC led to a reduction in nocturnal motor activity. These findings were corroborated by improvements in the Neuropsychiatric Inventory total score, as well as in subscores for agitation, aberrant motor, and nighttime behaviors; no side effects were observed.[180]
Studies on *cannabinoid anticonvulsant activity* began in 1975, when CBD, and four CBD derivatives, (CBD-aldehyde-diacetate, 6-oxo-CBD-diacetate, 6-hydroxy-CBD-tri-acetate and 9-hydroxy-CBD-triacetate) were shown to protect against maximal electroshock convulsions in mice, to potentiate pentobarbital sleeping-time and to reduce spontaneous motor activity.[181] Later additional CBD analogs were shown to be active.[182-184] CBD was found to be an effective anticonvulsant with specificity more comparable to drugs clinically effective in major, but not in minor seizures. Furthermore, it appears that CBD enhances the anticonvulsant effects of drugs in major seizures and reduces their effects in minor seizures.[185,186] Hence, CBD was suggested as a drug for the treatment of children with pharmacoresistant epilepsy.[187]
The application of the CB1 receptor antagonists SR141716A or AM251 to "epileptic" neurons caused the development of continuous epileptiform activity, resembling electrographic status epilepticus. The induction of status epilepticus-like activity by CB1 receptor antagonists was reversible and could be overcome by maximal concentrations of CB1 agonists.[188] Arachidonyl-2'-chloroethylamide (ACEA), a highly selective cannabinoid CB1 receptor agonist, enhances the anticonvulsant action of valproate in a mouse maximal electroshock-induced seizure model.[189] There are currently insufficient data to determine whether occasional or chronic marijuana use influences seizure frequency.[190] In one case report, marijuana smoking was proposed to induce seizures.[191] In another study, patients suffering from secondary generalized epilepsy with temporal focus treated with CBD remained almost free of convulsive crises throughout the experiment; other patients demonstrated partial improvement in their clinical condition.[192]

Bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), depression, anxiety, insomnia

Cannabis use is common in patients with *bipolar disorder,* and anecdotal reports suggest that some patients use marijuana to alleviate symptoms of both mania and depression.[193] In a case report, one female patient found that cannabis curbed her manic rages; others described the use of cannabis as a supplement to lithium (allowing reduced consumption) or for relief of lithium's side effects.[194]
The effect of cannabinoids on *schizophrenia* is controversial. Neuropsychological results in THC-intoxicated normal volunteers exhibit strong similarities with data acquired from patients suffering from productive schiz-

ophrenic psychoses, as regards disturbances in internal regulation of perceptual processes.[195] In a recent study, it was found that anandamide levels are enhanced in first-episode schizophrenic patients, and that THC downregulates anandamide signaling.[196] This observation possibly means that THC lowers endogenous production of anandamide, which may actually be a defense mechanism—presumably comparable to the known observation that administration of corticosteroids blocks corticosteroid synthesis. Data from experimental-psychological tests show that personality changes generated by schizophrenia progression are comparable to psychopathological phenomenon due to cannabis intoxication.[197] In another study, psychosis, which develops or recurs in the context of cannabis use, did not have a characteristic psychopathology or mode of onset.[198] First-episode schizophrenic patients with long-term cannabis consumption were significantly younger at disease onset, mostly male, and suffered more often from paranoid schizophrenia (with a better prognosis) than those without cannabis consumption.[199] However, a trend towards more insight and of fewer abusive or accusatory hallucinations was seen amongst cannabis users. This argues against a distinct schizophrenia-like psychosis caused by cannabis.[200] Less avolition and fewer apathy symptoms were detected in patients with schizophrenia and cannabis abuse than in those with no abuse.[201] In another clinical trial, the role of CB1 receptors in schizophrenia was studied by administration of CB1 antagonist to patients. The group receiving the CB1 antagonist did not differ from the group receiving placebo on any outcome measure.[202]

CBD causes antipsychotic effects.[203] It was found to be a safe and well-tolerated alternative treatment for schizophrenia.[204] (See, however, also ref 205).

Post-traumatic stress disorder (PTSD) is a term for severe psychological consequences of exposure to, or confrontation with, stressful, highly traumatic events. Cannabinoids are believed to help in such cases. AM404-treated animals showed decreased shock-induced reinstatement of fear.[206] In conditioned fear and Morris water maze experiments, FAAH (-/-) mice and mice treated with the FAAH inhibitor OL-135 did not display any memory impairment or motor disruption, but did exhibit a significant increase in the rate of extinction. SR141716 blocked the effects of OL-135, suggesting that endogenous anandamide plays a facilitator role in extinction through a CB1 receptor mechanism of action. In contrast, THC failed to affect extinction rates, suggesting that FAAH is a more effective target facilitating extinction than a direct-acting CB1 receptor agonist.[207] Acutely, the absence of CB1 receptors reduces the neuroendocrine response and does not affect the behavioral response to moderate stress. However, upon repeated stress or acute severe stress, CB1 receptor deficiency causes persistent behavioral inhibition. Repeated bell stress seemed to cause a cumulative fear in CB1 receptor knockout mice.[208] In self-reports of substance use among help-seeking veterans, PTSD diagnosis was significantly associated with marijuana use.[209] These observations suggest that the endocannabinoid system can be modulated to enhance emotional learning, and that endocannabinoid modulators may be therapeutically useful as adjuncts for exposure-based psychotherapies, such as those used to treat PTSD and other anxiety disorders. CB1 receptor gene polymorphism is known to modify transcription of the gene. In patients with Parkinson's disease, the presence of two long alleles, with more than 16 repeated AAT trinucleotides in the CNR1 gene, was associated with a reduced prevalence of depression.[210]

CBD, and some derivatives, were found to cause a selective anxiolytic effect in the elevated plus-maze, within a limited range of doses.[211,212] A single dose of nabilone produced only mild improvement in anxiety[213]; in a repeated-dose treatment a dramatic improvement in anxiety was noted in the nabilone group.[214]

The effects of marijuana on human sleep patterns were noticed long ago.[215-217] Reduced eye movement density was seen, with some tolerance developing to this effect.[218,219] THC is sedative, while CBD has alerting properties as it increased awake activity and counteracted the residual sedative activity of THC.[220]

Asthma, cardiovascular disorders, glaucoma

Asthma is a chronic disease of the respiratory system in which the airway occasionally constricts, becomes inflamed, and is lined with excessive amounts of mucus. In animal experiments, after methacholine-induced or exercise-induced bronchospasm, marijuana caused a prompt improvement of the bronchospasm and associated hyperinflation.[221] In humans, habitual smoking of marijuana may cause mild, but significant, functional lung impairment[222]; However, a mild and inconstant bronchodilatory action was found for THC.[223] In other clinical trials, smoking marijuana or ingesting THC were found to increase airway conduction.[224,225] Other plant cannabinoids did not provide

effective bronchodilation. The daily use of THC was not associated with clinical tolerance.[226] THC administered in metered volumes by inhalation from an aerosol device to patients judged to be in a steady state, increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV1) and produced bronchodilatation.[227] In another study, salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were not detected by radioimmunoassay. The mode of action of THC differed from that of sympathomimetic drugs.[228]

In another study, THC induced sympathetic stimulation and parasympathetic inhibition of *cardiovascular control pathways*. The peak heart rate rise after THC was attenuated by atropine and by propranolol, and nearly abolished by atropine-propranolol pretreatment.[229] Acute THC significantly increased heart rate, shortened pre-ejection period (PEP) and prolonged left ventricular ejection time (LVETc) without any change in afterload; it enhanced cardiac performance. Partial inhibition of this effect was achieved with prior β-adrenergic blockade.[230] In contrast, following the smoking of one to three marijuana cigarettes, the heart rate rose, cardiac output rose, stroke volume, ejection fraction, PEP and LVET did not change; thus, in long-term heavy users of cannabis, marijuana has no significant effect on myocardial contractility independent of its effect on heart rate.[231] Cardiovascular effects of acute THC administration included increased sympathetic and reduced parasympathetic tone; supine tachycardia and increased blood pressure with upright hypotension were observed. With repetitive dosing supine bradycardia and decreased blood pressure with tolerance to orthostatic hypotension were observed.[232,233] Rimonabant attenuated the hypotensive effect of smoked marijuana in male smokers, suggesting a role for the CB1 receptor in cannabinoid hypotensive action.[234]

A number of studies suggest that there is a correlative, but not necessarily causal, relationship between *glaucoma* and systemic hypertension. Ocular hypertension (OHT) refers to any situation in which intraocular pressure is higher than normal, and is the most important risk factor for glaucoma. THC, CBN, and nabilone were active in lowering intraocular pressure (IOP) in rabbits, while CBD was inactive.[235] Certain derivatives of THC were more active in lowering IOP than the parent cannabinoid[236]; some topically used soft analogs that have no systemic effects were also active in IOP reduction.[237] The effect on IOP of 2-AG was biphasic (ie, an initial increase in IOP followed by a reduction). In contrast, noladin ether decreased IOP immediately after topical administration, and no initial IOP increase was observed. AM251 blocked the effect on IOP of noladin ether, but did not affect the action of 2-AG.[238] Topical administration of anandamide and arachidonyl propionitrileamide decreased IOP; rimonabant antagonized the IOP reduction, suggesting that cannabinoids lower IOP through CB1 receptors.[239,240] Significantly, higher levels of CB1 mRNA levels were found in the ciliary body than in the iris, retina, and choroid. CB2 mRNA was undetectable. This expression pattern supports a specific role for the CB1 receptor in controlling IOP.[241] When delivered topically to cat eyes with osmotic minipumps, whole marijuana extract, THC and other plant cannabinoids reduced IOP, while cannabichromene was inactive. Ocular toxicity was seen after THC treatment, consisting of conjunctival erythema and chemosis as well as corneal opacification. Although these changes also occurred with marijuana extract, their intensity was much reduced. In contrast, no ocular toxicity was apparent during administration of plant cannabinoids other than THC.[242-244] Marijuana smoking was shown to reduce IOP as early as 1971; the effect was later confirmed.[245-248] The peak effect of THC on the central nervous system coincided well with the reduction in intraocular pressure induced by the drug; However, hypotonia outlasted euphoria. The results indicate that THC may have value as a hypotonizing ocular drug.[249] The functional responses after THC inhalation in sitting normotensive and hypertensive patients included invariable increases in heart rate followed by substantial decreases in systolic pressure, diastolic pressure, and intraocular pressure. The intensity and duration of the arterial and ocular pressure responses to THC were greater in hypertensives than in normotensive patients; the changes in ocular pressure paralleled the changes in blood pressure in glaucoma patients.[250] A single sublingual dose of THC, but not cannabidiol, reduced the IOP temporarily and was well tolerated by most patients.[251]

Cancer

The antiproliferative action of cannabinoids on cancer cells was first noticed in the 1970s. Since then cannabinoids were found to act on various cancer cell lines, through various mechanisms.[252,253] Cannabinoids were

also found to be suppressors of angiogenesis and tumor invasion.[254] Our knowledge on the anticancer activity of cannabinoids is rapidly expanding; hence only results of recent research on this topic are presented here. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner. Moreover, cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo.[255] The nonpsychoactive cannabidiol triggered caspase activation and oxidative stress in human glioma cells.[256] Human melanomas express CB1 and CB2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis, and metastasis, and increased apoptosis, of melanomas in mice.[257] THC, through activation of CB2 cannabinoid receptors, reduced human breast cancer cell proliferation by blocking the progression of the cell cycle and by inducing apoptosis. THC arrested cells in G2→M via downregulation of Cdc2.[258] Cannabinoids induced apoptosis of pancreatic tumor cells via stress protein p8 and endoplasmic reticulum stress-related genes. These effects were prevented by blockade of the CB2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo.[259] THC-induced apoptosis in Jurkat leukemia T cells was found to be regulated by translocation of Bad to mitochondria.[260] Exposure of leukemia cells to CBD led to CB2-mediated reduction in cell viability and induction in apoptosis (although CBD is considered not to bind to either CB1 or CB2 receptors). It is noteworthy that CBD exposure led to an increase in reactive oxygen species (ROS) production as well as an increase in the expression of the NAD(P)H oxidases Nox4 and p22(phox).[261] Cannabinoid-induced apoptosis of human prostate cancer cells LNCaP proceeded through sustained activation of ERK1/2 leading to G1 cell cycle arrest.[262] Rimonabant inhibited human breast cancer cell proliferation through a lipid raft-mediated mechanism.[263] In a pilot phase I trial, nine patients with recurrent glioblastoma multiforme, that had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumour progression, were administered THC intratumorally. THC inhibited tumor-cell proliferation in vitro, decreased tumor-cell Ki67 immunostaining and prolonged the survival time of two of the patients.[264]

Conclusion

Many drugs used today can cause addiction and are misused and abused, for example opiates,[265] cocaine,[266] benzodiazepines,[267] barbiturates,[268] cholinergic agonists,[269] ketamine,[270,271] dopaminergic agonists,[272] amphetamines,[273] and others. Nevertheless they are still an important part of our pharmacopeia. Marijuana was used for centuries as a medicinal plant, but during the last century, because of its abuse and addictive potential it was taken out of clinical practice. Now, we believe that its constituents and related compounds should be brought back to clinical use. The reasons are: (i) the therapeutic potential of CB1 agonists is huge, as described in this review; (ii) for local action, topical CB1 agonists, or agonists that do not penetrate the blood-brain barrier, can be used; (iii) cannabinoids acting specifically on CB2 receptors, which cause no psychoactivity, may be used on peripheral targets (such as osteoporosis,[274,275] which is only one of many examples); (iv) there are additional, new cannabinoid targets distinct from the CB1/CB2 receptors[276-278] which do not cause psychoactivity; (v) there are cannabinoids, such as CBD, which do not cause psychoactivity, but have various therapeutic effects.

The endocannabinoid system is a very complex one and regulates numerous processes, in parallel with other well-known systems, such as the adrenergic, cholinergic, and dopaminergic systems. Neglecting the potential clinical uses of such a system is, in our view, unacceptable; instead we need to work on more selective agonists/antagonists, more selective distribution patterns, and in cases where it is impossible to separate between the desired clinical action and the psychoactivity, to monitor these side effects carefully. ❑

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Cannabinoides en la salud y en la enfermedad

Las preparaciones de Cannabis sativa L. se han empleado en medicina desde hace milenios. Sin embargo, la preocupación acerca de los peligros del abuso condujo a la prohibición de la utilización médica de la marihuana en la mayoría de los países en la década de 1930. Sólo recientemente, los agonistas y antagonistas naturales y sintéticos de los receptores de marihuana, como también compuestos químicamente relacionados, cuyo mecanismo de acción todavía es confuso, han vuelto a reconsiderar el valor terapéutico. Pero su empleo está estrictamente limitado. A pesar de la adicción leve a cannabis y el posible incremento de la adicción a otras sustancias de abuso, cuando se combinan con cannabis, el valor terapéutico de los cannabinoides es muy alto como para no tomarlo en cuenta. Numerosas enfermedades como la anorexia, la emesis, el dolor, la inflamación, la esclerosis múltiple, trastornos neurodegenerativos (Enfermedad de Parkinson, Enfermedad de Huntington, Síndrome de Tourette , Enfermedad de Alzheimer), epilepsia, glaucoma, osteoporosis, esquizofrenia, trastornos cardiovasculares, cáncer, obesidad, y trastornos relacionados con el síndrome metabólico, por nombrar sólo algunas, están siendo tratadas o tienen el potencial de tratarse por agonistas o antagonistas de los cannabinoides o compuestos relacionados con ellos. Dada la muy baja toxicidad y los efectos secundarios generalmente benignos de este grupo de compuestos, desatender o negar su potencial clínico es inaceptable; hay que trabajar en el desarrollo de agonistas y antagonistas, y compuestos relacionados que sean más selectivos para el receptor de cannabinoides, como también de nuevos fármacos de esta familia con mejor selectividad, patrones de distribución y fármaco-cinética, y -en casos donde sea imposible separar la acción clínica deseada y la psicoactividad- igual monitorear estos efectos secundarios cuidadosamente.

Cannabinoïdes: effets chez le sujet sain et utilisation en thérapeutique

Depuis des millénaires, des préparations à base de Cannabis sativa L ont été utilisées en médecine. Dans les années 1930 cependant, des inquiétudes concernant le danger lié à l'abus de cette substance ont conduit à l'interdiction de l'utilisation médicale de la marijuana dans la plupart des pays. Ce n'est que depuis peu que la marijuana et les agonistes et antagonistes des récepteurs cannabinoïdes synthétiques et naturels, ainsi que les composés chimiquement apparentés dont le mécanisme d'action est encore obscur, sont à nouveau considérés comme ayant un intérêt thérapeutique. Leur usage est cependant très limité. Malgré la dépendance modérée au cannabis et la possible stimulation de la dépendance à d'autres drogues lorsqu'elles sont associées au cannabis, la valeur thérapeutique des cannabinoïdes est trop élevée pour être négligée. De nombreuses pathologies, telles que l'anorexie, les vomissements, la douleur, l'inflammation, la sclérose en plaques, les troubles neurodégénératifs (maladie de Parkinson, chorée de Huntington, syndrome de Gilles de la Tourette, maladie d'Alzheimer), l'épilepsie, le glaucome, l'ostéoporose, la schizophrénie, les troubles cardiovasculaires, le cancer, l'obésité et les troubles liés au syndrome métabolique, pour n'en nommer que quelques-unes, sont traitées ou pourraient être traitées par des agonistes/antagonistes des cannabinoïdes, ou substances apparentées. Au regard de la très faible toxicité et des effets secondaires généralement bénins de cette classe de produits, il serait inacceptable de négliger ou de nier leur potentiel clinique. Il faut au contraire travailler au développement de récepteurs agonistes/antagonistes des cannabinoïdes et de composés apparentés sélectifs, ainsi qu'à de nouveaux médicaments de cette famille plus sélectifs, avec un mode de distribution et une pharmacocinétique meilleurs. Et lorsqu'il est impossible de séparer l'action clinique désirée et les effets psychoactifs, il est simplement nécessaire de surveiller attentivement les effets indésirables.

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Therapeutic options and challenges for substances of abuse

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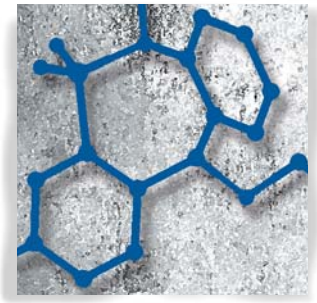

Addiction to substances continues to be a significant public health concern in the United States. The following review of current pharmacological treatments discusses a range of substances: nicotine, alcohol, cocaine, and opioids. The goal is to provide an overview of currently available and new pharmacological treatments for substance use disorders, while also addressing the pharmacotherapeutic challenges remaining. The significant advances in pharmacotherapy have had limited utilization, however. For example, naltrexone for alcoholism is infrequently prescribed, buprenorphine for opiates still has relatively few qualified prescribers, and stimulants have no Food and Drug Administration-approved pharmacotherapy. These pharmacotherapies are needed, with the rate of even the relatively uncommon abuse of opiates now rising sharply.

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The following review of current pharmacological treatments for nicotine, alcohol, cocaine, and opioid dependence addresses pharmacotherapies aimed at two stages of treatment: (i) acute withdrawal or the initial attainment of abstinence and (ii) chronic maintenance or prevention of relapse. Maintenance pharmacotherapies act as either blocking or substitution agents to attenuate protracted withdrawal symptoms. Detoxification is required prior to administration of a blocking agent, in order to prevent withdrawal from an abused agent. For example, naltrexone, a competitive opioid antagonist, completely blocks the subjective euphoria and production of physiological dependence of heroin use. Substitution agents will not precipitate withdrawal when given to drug-dependent patients, and instead act to reduce withdrawal symptoms and the desire for more drugs. Substitution agents may also produce cross-tolerance to other drugs from the same pharmacological class. Methadone is one example of an agent that is effective in reducing illicit opioid use by producing cross-tolerance to heroin. The need for these pharmacotherapies is highlighted by the sharp increase in the rate of even the relatively uncommon abuse of opiates; 12.4% of young adults abused prescription pain relievers in the past year.[1,2]

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Pharmacological aspects

Nicotine

In 2005 approximately 20.9% of US adults were cigarette smokers.[1] New medications and counseling have helped many smokers quit, but the majority of those who try to quit are still unsuccessful.[3-5] Pharmacotherapies range from nicotine replacement therapy to antidepressants for the relief of acute withdrawal symptoms and relapse prevention.

Nicotine replacement therapies

Nicotine replacement therapies (NRT) are designed to replace nicotine obtained through smoking in order to attenuate tobacco withdrawal symptoms and improve smoking cessation outcomes. There are currently five Food and Drug Administration (FDA)-approved NRT products, which include: the transdermal patch, gum, lozenge, inhaler, and nasal spray. These products are available over-the-counter or by prescription. They can be given alone or taken in conjunction with antidepressants like bupropion in order to alleviate acute withdrawal symptoms and sustain abstinence. A small dose of nicotine in these products allows the patient to reduce nicotine withdrawal symptoms after the patient has stopped smoking. Patients are often counseled to quit, provided options for treatment, and helped to establish a quit date. On the quit date the NRT is started and other forms of tobacco use are stopped.[6] Choice of specific NRT typically depends on the patient's preference, the side-effect profile, and the route of administration.[7]

The nicotine transdermal patch is available in 16- or 24-hour delivery systems. Recommended duration of use is 6 to 12 weeks, with a tapering of the patch dose over that period. Patients usually start with a high-dose patch (21 or 22 mg); however, an intermediate-dose patch (11 or 14 mg) is available for those who smoke fewer than 15 cigarettes per day.[5] Though patients usually develop tolerance to common side effects, they may experience insomnia, nausea, and vivid dreams. Skin irritation can also occur, and is usually alleviated with rotation of the patch placement site.[8-11] The nicotine patch can also be utilized in combination with other NRT, such as the gum, which increases its efficacy in treatment-resistant cases.[12]

Nicotine polacrilex gum and lozenges are available over-the-counter as aids in smoking cessation in 2 and 4 mg doses of nicotine. The 4-mg dose is recommended for heavy smokers (>25 cigarettes per day).[8,13,14] The recommended dosage of nicotine gum is to use one piece every 1 to 2 hours.[6] The nicotine lozenge should be sucked on rather than chewed. The lozenge delivers about 25% more nicotine than the gum, since some nicotine is retained in the gum and the lozenge is dissolved completely.[15] The dose can be tapered over 6 to 12 weeks by either decreasing the gum or lozenge dose from 4 mg to 2 mg or by increasing the time between doses,[6] with peak concentrations of nicotine absorbed through the buccal mucosa achieved in 15 to 30 minutes.[16,17] Nicotine absorption can be blunted with use of acidic beverages; therefore, coffee, juices, and soda should be avoided immediately before or during NRT use.[18] Side effects of the gum may include jaw soreness or difficulty chewing.[13,19] The lozenge offers an alternative to gum but also may elicit side effects such as nausea, heartburn, and mild throat or mouth irritation.[13,19]

The nicotine inhaler and nicotine nasal spray are available by prescription only and provide faster delivery of nicotine than gum or lozenge; 4 to 15 minutes for nasal spray, 15 minutes for the inhaler.[20] The spray is administered to each nostril every 1 to 2 hours with a range of 8 to 40 doses per day.[21] The usual recommended dose is 1 mg per administration over 8 weeks. Gradual taper is recommended between weeks 9 and 14.[21] Side effects of the nasal spray may include nasal and throat irritation, sneezing, coughing, and watery eyes.[22-24] The nicotine inhaler administers nicotine via cartridges placed in cigarette-like plastic rods which produce a nicotine vapor (0.013 mg/puff) when inhaled.[25,26] The nicotine is absorbed through the buccal mucosa and following inhalation. The recommended dose is 6 to 16 cartridges daily, with use for approximately 12 weeks.[6] Each cartridge contains 10 mg of nicotine and delivers a maximum of 4 mg of nicotine, and provides approximately 20 minutes of active puffing. Peak plasma nicotine concentrations are typically achieved within 15 minutes.[20] Throat irritation or coughing can occur in up to 50% of inhaler users.[26,27] Because of the rapid delivery of the spray and inhaler, there is some potential for abuse liability after quitting smoking, leading to continued use >6 months.[28-31]

Patients who utilize nicotine replacement therapy improve their likelihood of quitting by 1.5 to 2 times.[6,32] Long-term efficacy of NRT on smoking cessation may actually be modest, however (5% to 10% above placebo).[33] Most trials assess the effect of smoking reduction at 1 year or less, and the effect is attenuated by about 12% after 12 months due to relapse occurring after the first year.[33]

Antidepressants

The observed relationship between nicotine dependence and mood disorders such as depression supports the use of antidepressant medications as effective pharmacotherapies for cigarette smoking cessation.[34] Sustained-release bupropion, an atypical antidepressant agent, has been the most commonly used medication for the pharmacotherapy of smoking cessation, improving quit rates in short- and long-term follow-up. Bupropion blockade of norepinephrine and dopamine uptake may attenuate nicotine withdrawal symptoms. In addition, bupropion also blocks the nicotinic acetylcholine receptor, thus offering a potential reduction in the reinforcing effects of nicotine.[35,36] Patients start treatment at the recommended 150 mg/day 7 days prior to their target quit date, since steady-state plasma levels are achieved within 1 week of initiation. Dosing is then increased to 300 mg/day after 3 to 4 days.[6] Bupropion can also be used in combination with NRT. Two large, multicenter clinical trials demonstrated the efficacy of bupropion for the treatment of nicotine dependence, and it is recommended as a first-line treatment for smoking cessation.[21] Bupropion alone (30%), or in combination with the nicotine patch (35%), was demonstrated to be significantly more effective at 1-year follow-up than the nicotine patch alone (16%) or placebo (16%).[37] For patients with a history of depression, the bupropion dose is equivalent, allowing for the pharmacological treatment of both disorders simultaneously.[6] Side effects of bupropion primarily consist of gastrointestinal symptoms, rash, headache, insomnia, and dry mouth.[38] As with other antidepressants, bupropion lowers seizure threshold, so it should not be used in patients with a history of seizure disorders. [6]
Second-line pharmacotherapies for smoking cessation include nortriptyline, clonidine, selegiline and, most recently, varenicline. Nortriptyline, like bupropion, is an antidepressant that shows promising effects for smoking cessation.[39,40] It may also be useful in the treatment of depressed cigarette smokers; however, its efficacy does not appear to depend on comorbidity with a depressive disorder. [6] Though shown to be efficacious, nortriptyline has significant side effects which limit its safety (eg, risk of toxicity in overdose amounts).[6] Clonidine, an antihypertensive agent, is an α-22-adrenergic receptor agonist that decreases central sympathetic activity. It may be an effective treatment option for those who have failed other smoking cessation methods. Side effects from its clinical use include sedation, dizziness, dry mouth, constipation, and orthostatic hypotension.[41-43] Other agents (eg selegiline and mecamylamine) have also been studied, but their efficacy for smoking cessation has not yet been established. For example selegiline, a monoamine oxidase-B (MAO-B) inhibitor for the treatment of Parkinson's disease may also be useful in reducing nicotine craving by decreasing dopamine metabolism.[44-45]

Partial agonist

Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, is an efficacious treatment for smoking cessation. Clinical trials indicate that this partial agonist can reduce craving and withdrawal symptoms following cessation or reduction of nicotine consumption. In addition its partial antagonism can also reduce smoking satisfaction through the occupation of the receptors and blocking the full agonist nicotine from binding.[46] Varenicline, administered 1 mg twice daily, has demonstrated superiority to placebo and bupropion.[46, 47] It is generally safe and well tolerated. Nausea and insomnia are commonly reported adverse reactions to varenicline.[46,47]

Nicotine vaccine

Currently, three nicotine vaccines have completed phase I-II clinical trials; NicVAX, CYT002-NicOb, and TA-NIC. In a phase II clinical trial, 68 smokers were randomized to receive one of 3 doses of a nicotine conjugate vaccine, NicVax (50, 100, or 200 μg) or placebo. The vaccine was shown to be safe and well tolerated. In addition, vaccine immunogenicity was dose-related ($P<0.001$) with the highest rate of 30-day abstinence occurring with 200 μg ($P<0.02$).[48] The NicQb vaccine was also shown to elicit significant quantities of antinicotine antibodies,[49] and a similar observation was made that subjects in the upper third of antibody responses had almost two times the quit rate of placebo (57% vs 31%). Subjects in the TA-NIC vaccine trial were immunized with 4 doses over the first 8 weeks and then given a booster dose at 32 weeks. All subjects were encouraged to quit smoking after 12 weeks of the trial, and at 12 months, the quit rate in the highest-dose group significantly exceeded the control group (38% vs 8%).[50] Based on these studies suggesting that high antibody titers correlate with smoking cessation, evaluation of nicotine conjugate vaccines are progressing and a phase IIb/III trial was recently announced for NicQb.[51]

Pharmacological aspects

Alcohol

Alcohol dependence is a major cause of morbidity and mortality in the United States and throughout the world. Acute withdrawal from alcohol is a serious medical condition which can precipitate adrenergic activation, seizures, or delirium tremens, the last condition leading to 15% mortality when untreated.[52] Many medications have been evaluated for the treatment of alcohol dependence in recent years, including those that interact with dopaminergic, serotonergic, opioid, glutamate, and γ-aminobutyric acid (GABA) systems.

Acute withdrawal

Benzodiazepine use is the standard approach to treating withdrawal symptoms such as irritability, autonomic hyperactivity, and seizures associated with alcohol detoxification. Benzodiazepines act at GABA-A receptors to stimulate GABA release and gradually detoxify the patient from alcohol, thus avoiding associated withdrawal symptoms.[53] The current standard approach to alcohol detoxification uses tapering dosages of benzodiazepines such as chlodiazepoxide, clonazepam, diazepam, oxazepam, or lorazepam.[54,55]

Anticonvulsants, including carbamazepine and valproate, have also been studied for their efficacy in alcohol withdrawal treatment.[6] Carbamazepine has been widely used in alcohol withdrawal. Carbamazepine has demonstrated its superiority to placebo in the speed of onset to relieve alcohol withdrawal symptoms such as tremor, sweating, palpitations, sleep disturbances, depression, anxiety, and anorexia.[56] Furthermore, studies have also demonstrated that higher success rates and reduction in withdrawal symptoms in patients treated with carbamazepine than with benzodiazepines.[57-59]

Relapse prevention and maintenance

Disulfiram, acamprosate, oral naltrexone, and extended-release injectable naltrexone have FDA approval for the treatment of alcohol dependence.

Disulfiram is the first agent to be approved for treatment of alcohol dependence and has been used for over 40 years. It acts as an alcohol-sensitizing agent, creating an aversion to alcohol. Disulfiram is an irreversible inhibitor of the enzymatic conversion of acetalaldehyde to acetic acid. Accumulation of acetalaldehyde results in the disulfiram-alcohol reaction: hypotension, flushing, nausea, and vomiting.[60,61] Patients must be motivated to remain abstinent and comply with prescribed dosing; usual dosage is 250 mg/day. However, some patients may receive optimal benefit from 125 to 500 mg/day.[6] Additional unpleasant symptoms such as chest pain, seizures, hepatotoxicity, renal failure, and even death have been reported in severe cases.[6,62] Controlled trials of disulfiram versus placebo have not demonstrated significant improvement over placebo,[63,64] and meta-analyses have only shown slight improvement in drinking.[65] A large Veterans Cooperative Study with over 600 subjects found, however, that disulfiram may be effective in patients with no major comorbid psychiatric disorder and who were motivated for abstinence.[64] More recently, an evaluation of subjects with current depression on disulfiram reported lower craving over time than subjects with depression on naltrexone.[66] The utility of combining disulfiram with other therapeutic interventions has also been examined. In a trial of disulfiram and acamprosate, the number of abstinent days was greater when utilizing a combination of disulfiram and acamprosate than using either medication alone.[67]

Naltrexone acts as an antagonist at the opioid receptors, which are known to mediate the rewarding effects of alcohol and thus thought to reduce desire or craving of alcohol. Studies have found that naltrexone is more effective than placebo in promoting abstinence, reducing heavy drinking days and decreasing relapse rates,[6,68-70] particularly when it is combined with cognitive behavioral therapy.[71-73] Naltrexone has also shown greater efficacy when compared with acamprosate. In a randomized controlled trial comparing the efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, significant increases in time to first relapse was seen in those receiving naltrexone in subjects with no depression and low dependency.[74] Furthermore, combined pharmacotherapy studies have also demonstrated that naltrexone administered with behavioral therapy can significantly reduce the risk of heavy drinking.[75] Naltrexone is prescribed as 50 mg oral administration, most commonly for 12 weeks, and can also be given as a long-acting depot formulation every 4 weeks.

Acamprosate attenuates alcohol desire or craving by normalizing the dysregulation of N-methyl-D-aspartate (NMDA)-mediated glutaminergic excitation that occurs in alcohol withdrawal and early abstinence. Acamprosate, when given at 2 g administered three times daily, has increased abstinence by 50% in over 3000 patients across a dozen clinical trials.[76-78] Side effects such as diarrhea are

generally well tolerated. A placebo-controlled trial enrolled 272 patients and treated patients for 48 weeks. Compared with placebo, acamprosate-treated alcohol-dependent patients had twice the rate of sustained abstinence at 48 weeks (43% vs 21%), and this difference from placebo was sustained at 96 weeks after starting the medication (37% vs 17%).[78] Thus, this appears to be a very effective approach to treating patients in order to maintain alcohol abstinence after detoxification.

Topiramate, an anticonvulsant medication, has been shown to improve the drinking outcomes of alcohol-dependent individuals vs placebo, but only in a single study thus far, by Johnson et al.[79] In this topiramate study the patients were actively drinking when started on medication, rather than being first detoxified from alcohol and being abstinent. The outcome was remarkable, with an increase from no days abstinent at baseline to 44% of days abstinent by week 12, compared with 18% of days abstinent for the placebo group. In cases of dual dependency on opiates and alcohol, topiramate may be useful at a low dose in buprenorphine or methadone maintained, alcohol-abusing patients who do not need medical detoxification for alcohol.

Serotonergic agents, including buspirone (a serotonin [5HT]-1A agonist),[80] selective serotonin uptake inhibitors (SSRIs), and the 5-HT3 antagonist ondansetron[81] have been studied more extensively as treatments for alcohol dependence. Fluoxetine or citalopram, two SSRIs, have been effective in reducing alcohol consumption in some studies, though results have been inconsistent.[82-89] Results may be inconsistent due to heterogeneity in study populations. For example, Kranzler et al suggested that SSRIs may be more effective in heavy drinkers or those with a family history of alcoholism, as well as those with a comorbid major depressive disorder.

Cocaine

Cocaine addiction affected approximately 2.4 million people in the United States in 2005.[2] Behavioral interventions are helpful in treating cocaine addiction, but currently there are no approved medications to treat this disorder despite over 60 medications having been investigated.

Dopaminergic agents

Directly acting dopaminergic agents such as bromocriptine and pergolide have had limited efficacy, but indirect mechanisms for increasing dopamine seem to be a promising approach.[90,91] Disulfiram indirectly increases dopamine by inhibiting dopamine-β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. In outpatient clinical trials, disulfiram (250 mg/day) has been successful in reducing cocaine use with few associated adverse events,[92,93] with sustained results in reduction of cocaine and alcohol use at 1-year follow-up. Findings have been replicated.[92] Disulfiram may be an effective medication for reduction in cocaine use; however, it may not be suitable for treatment in all populations.[92,94,95] Nich et al reported that men responded to disulfiram in reduction of cocaine use, whereas women did not.[96] Further studies are needed to determine the optimum dose and duration of treatment with this agent, as well as to assess the efficacy of disulfiram related to gender and comorbid conditions such as alcohol use or opioid dependence.

Selegiline, a monoamine oxidase (MAO)-B inhibitor, blocks the catabolic enzyme that breaks down dopamine resulting in greater synaptic levels of dopamine. This medication also exhibits amphetamine–like effects and can enhance dopamine release and block dopamine reuptake.[97] A laboratory study of cocaine users showed that short-term treatment with selegiline did not alter physiological or subjective effects of cocaine.[98] In another study however, cerebral metabolic effects of cocaine and attenuated the cocaine "high" were altered by selegiline.[99]

Antidepressants

Antidepressants are another class of medications also used to treat cocaine dependence. Chronic stimulant use causes presynaptic upregulation, and antidepressants are thought to contribute the opposite effect by downregulating synaptic catecholamine receptors.[100] Although antidepressants have a relatively benign side-effect profile, good patient compliance rates, and lack of abuse liability, only desipramine, a tricyclic antidepressant, has shown some efficacy in selected populations of cocaine abusers.[6,100] Though a meta-analysis of placebo-controlled studies showed that desipiramine produced greater cocaine abstinence than placebo,[101] other studies failed to report positive findings with desipramine.[6,102] Secondary analyses of studies with imipramine, desipramine, and bupropion have suggested that depressed cocaine abusers are more likely to show significant reductions in cocaine abuse than nondepressed cocaine abusers.[103-105]

Furthermore, additional work with desipramine has suggested its efficacy in opioid-dependent patients, particularly in combination with contingency management therapies.[106,107] Early studies suggested some efficacy for fluoxetine and bupropion, but this has not been confirmed in controlled trials.[6,108]

GABA agonists

GABA agonists show promise in treatment for cocaine, following initial studies. Baclofen, for example has shown greater reduction in cocaine use compared with placebo and may be more efficacious among individuals with greater cocaine use.[109]

Tiagibine, a GABA reuptake inhibitor, has also reduced the reinforcing effects of cocaine by attenuating cocaine-induced dopamine release. In a clinical trial investigating the efficacy of tiagibine for cocaine use in opioid-dependent patients maintained on methadone, tiagabine dose-dependently attenuated cocaine use as measured with self-reports and urine drug screening.[110,111] In a 10-week double-blind, placebo controlled trial of treatment seeking, cocaine-dependent, methadone-treated subjects, clinical efficacy of gabapentin was compared with tiagabine for reduction of cocaine use. Tiagabine significantly reduced cocaine-taking behavior compared with placebo or gabapentin-treated subjects.[111]

Topiramate, another GABA-enhancing medication with a primary therapeutic indication for epilepsy, has yielded promising results for cocaine dependence as well. In a 14-week, double-blind, placebo-controlled outpatient study, subjects assigned to topiramate had more negative urine cocaine results than placebo.[112] Results suggest potential efficacy for GABAergic treatments for cocaine dependence, but outcomes must be replicated in additional, larger clinical trials.

Most recently, vigabatrin has shown efficacy in clinical studies for cocaine abusers, and placebo-controlled multisite studies are under way examining it for cocaine dependence.[113]

Other treatment agents and approaches

In addition to the dopaminergic agents and antidepressants, a number of miscellaneous agents, including amantadine, carbamazepine, and buprenorphine, have been examined for cocaine pharmacotherapy. Carbamazepine failed to show therapeutic effects in three controlled studies after an initial enthusiasm.[85,114,115] Buprenorphine also has had more negative than positive findings supporting its efficacy in treating cocaine-abusing opiate addicts.[116-119] Studies of another agent, amantadine, have reported mixed results.[120-123] In a trial of cocaine-dependent men treated for 10 days with amantadine 100 mg twice daily, urine toxicology screens were more likely to be free of cocaine among men taking amantadine at the 2-week and 1-month follow-up visits.[120] Amantadine 100 mg administered three times daily, however, was no more effective than placebo in reducing cocaine use.[122] Amantadine also effectively reduced cocaine use among subjects with severe cocaine withdrawal symptoms at the start of treatment.[123] Though results of clinical trials do not appear to support amantadine as a treatment for cocaine dependence, further controlled studies are needed to determine if amantadine is efficacious in cocaine users with high withdrawal severity.

Modafinil, a medication used to treat narcolepsy, is a generally well-tolerated with low abuse potential, therefore it is frequently used for off-label indications such as attention deficit hyperactivity disorder (ADHD), depression, and cocaine dependence and withdrawal.[124,125] The mechanism of action blunts cocaine euphoria under controlled conditions, acting as a glutamate-enhancing agent.[124,126] Reduction in impulse responding has been seen among healthy volunteers as well as in patients with ADHD.[127,128] In the first double-blind, placebo-controlled trial in 62 cocaine-dependent patients, modafinil reduced cocaine use to a greater extent than placebo. Modafinil patients provided significantly more cocaine–free urine samples compared with placebos, and were more likely to achieve a protracted period of cocaine abstinence.[126]

Cocaine vaccine

Studies evaluating the efficacy of vaccination in cocaine addicts have shown reduction in some cocaine effects. A cocaine vaccine evaluated in clinical trials has used cholera toxin B subunit as a carrier protein linked to norcocaine at the methyl ester group as an immunogen.[129] In phase I and early phase II trials of immunogenicity, safety, and efficacy, no serious adverse effects had been found and the vaccine showed a reduction in cocaine effects during human laboratory cocaine administration studies and cocaine use in outpatient studies.[129-132] In a Phase I safety and immunogenicity trial, the vaccine induced cocaine-specific IgG cocaine antibodies, both

time- and dose-dependently. The vaccine was tolerated with no serious adverse effects during 12 months of follow-up.[129] In a Phase IIa, 14-week trial of 18 cocaine-dependent subjects in early recovery, conjugated cocaine vaccine was well tolerated at two dose levels (400 µg and 2000 µg). Cocaine-specific antibodies persisted for at least 6 months.[130] Furthermore, subjects who received the higher dose of vaccine had significantly higher mean antibody titer response and were more likely to maintain cocaine-free urines than the lower-dose group.[131] Results demonstrated that a cocaine-specific vaccine can elicit a sufficient immunologic response that reduces cocaine usage and attenuates the self-reported psychological effects of cocaine during use. Since it is possible to override the effects by the vaccine by increasing the amount of cocaine usage, the vaccine is primarily for use in cocaine users who are motivated to quit.

Opiates

Chronic illicit opiate use affects over 900 000 people in the US and an estimated 13 million people abused opiate drugs worldwide in 1999-2001, according to the World Health Organization.[133] More recently, prescription opiate abuse has become widespread with an estimated 4 million additional opiate abusers.[2] Opiate dependence is a chronic and relapsing medical disorder with a well-documented neurobiological basis, and that necessitates the use of long-term pharmacologic and behavioral intervention. Following acute withdrawal, individuals can be maintained on methadone, buprenorphine, or naltrexone. Although these highly effective pharmacotherapies for opioid dependence are available, only about 20% of illicit opioid users are enrolled in treatment programs.[134] Until recently, licensed opiate treatment facilities were the only providers of opioid maintenance therapy using methadone. Recent legislation changes and availability of sublingual Suboxone (buprenorphine plus naloxone) now enable general practitioners to offer opiate agonist treatment to as many as 100 patients through their offices.[135]

Opioid agonists

Methadone is a µ-opioid agonist that directly stimulates the opiate receptor and acts as a replacement to the abused drug. Through development of cross-tolerance at doses of 100 mg or more per day, methadone blocks heroin effects as well as other opioids.[136] Morphine-like effects evident in humans and include euphoria, drowsiness, analgesia, and nausea. Since its introduction in the 1960s it has been the gold standard for opioid maintenance treatment.[137] Initial clinical trials testing methadone for efficacy in the treatment of opioid dependence have found it to be safe and effective,[138-140] particularly if combined with monitoring and behavioral interventions. Daily doses administered in methadone maintenance programs range from 30 to 100 mg, typically starting at lower levels (15 to 20 mg/day) with subsequent daily increases based on the patient tolerance.[140] Outpatient studies examining higher versus lower doses of methadone indicate greater reduction in opioid use with higher doses of methadone.[141,142] Furthermore, doses over 100 mg/day may be indicated in patients with persistent heroin abuse or with comorbid conditions such as HIV infection, since some concomitant medications for AIDS increase metabolism of methadone.[143,144] Tapering doses of methadone can be used in ambulatory detoxification, but the protracted withdrawal syndrome associated with methadone cessation contributes to a high rate of recidivism to opiate abuse.[145,146] Methadone is therefore most often used in maintenance therapy and not for acute withdrawal or detoxification.

Partial agonists act like agonists, but do not stimulate the receptor to the same degree. In combining both a blocking and substitution approach, buprenorphine, a partial agonist at the µ-opioid receptor, suppresses withdrawal symptoms and produces some subjective reinforcing properties at low doses. Initial clinical trials of buprenorphine demonstrated efficacy in the outpatient setting. At 8 mg, the sublingual buprenorphine (in liquid formulation) treatment group demonstrated better study retention and decreased opiate use than active placebo or 1mg buprenorphine.[147,148] At higher doses buprenorphine acts as an antagonist, and blocks the reinforcing properties of the agonist, resulting in lowered risk of abuse liability and potential for abuse of the drug.[149] Buprenorphine is available alone or in a 4:1 combination sublingual tablet with naloxone (Suboxone).[150] A multicenter, randomized, placebo-controlled clinical trial comparing buprenorphine tablet, Suboxone tablet, and placebo in opiate-dependent patients found that both buprenorphine alone and Suboxone reduced opiate use in the first month of the study compared with placebo.[151] Suboxone also appears to decrease the potential for abuse or diversion compared with methadone.[152] Injection of Suboxone could also precipitate opioid withdrawal.

Pharmacological aspects

Drug	Medication	Dose	Mechanism of action	Special considerations	References
Nicotine	Transdermal patch*	11-22 mg 16- or 24-h delivery 6- to 12-week duration w/ taper	Nicotine replacement therapy (NRT)	Available over-the-counter (OTC)	5,8-12
	Polacrilex gum*	2 or 4 mg 1 pc/1-2 h 6- to 12-week duration w/ taper	NRT	OTC Avoid acidic beverages	6,8,14
	Lozenge*	2 or 4 mg 6 to 12 week duration w/ taper	NRT	OTC Do not chew, avoid acidic beverages	6,8,13
	Inhaler*	1 mg/admin Each nostril Q 1-2 h 8-40 doses/day 8 weeks w/ taper wks 9-14	NRT	Rapid delivery of nicotine, therefore some potential for abuse liability	20,21
	Nasal spray*	0.013 mg nicotine/ puff 10 mg nicotine/ cartridge for 20 min of puffing 6-16 cartridges/day 12 weeks	NRT	Rapid delivery of nicotine, therefore some potential for abuse liability	25,26
	Bupropion*	150 mg/day (7 d prior to quit date) 300 mg/day after 3-4 days	Antidepressant	2nd line: recommended to start prior to quit date; can be used in conjunction with NRT	21,37
	Nortryptylene	25 mg TID-QID	Antidepressant	2nd line; toxicity in overdose amounts	39,40
	Clonidine	0.1–0.3 mg/24-h ES patch 0.1-1.3 mg tablet	Antihypertensive	2nd line	41-43
	Selegiline	5 mg BID cap 6-12 mg/24-h patch	Antihypertensive; MAO-B inhibitor	2nd line	44-45
	Varenicline*	Titrate: 0.5 mg daily to 1 mg BID	Partial agonist		46
	NicVAX	**	Nicotine vaccine	Phase II clinical trials	48
	CYT002-NicOb	**	Nicotine vaccine	Phase IIb/III trial planned	49,51
	TA-NIC	**	Nicotine vaccine	Phase II	50
Alcohol	Chlordiazepoxide*	50-100 mg IM/IV (may repeat in 2-4 h)	Benzodiazepine	Acute withdrawal	54-55
	Clonazepam*	0.25 mg bid (max 4 mg/day)	Benzodiazepine	Acute withdrawal	54-55
	Diazepam*	10 mg IM/IV, then 5-10 mg in 3-4 h prn	Benzodiazepine	Acute withdrawal	54-55
	Oxazepam*	15-30 mg TID-QID	Benzodiazepine	Acute withdrawal	54-55
	Lorazepam*	0.05 mg/kg IM 2 mg or 0.044 mg/kg IV2-3 mg BID tab	Benzodiazepine	Acute withdrawal	54-55

Table I. Pharmacotherapeutic options for substances of abuse.

Drug	Medication	Dose	Mechanism of action	Special considerations	References
	Carbamazepine	200 mg BID (Max 1200 mg/day)	Anticonvulsant; antiepileptic	Acute withdrawal, widely used	56-59
	Valproate	15 mgkg/day (Max. 60 mg/kg/day)	Anticonvulsant	Acute withdrawal	6
	Disulfiram*	250 mg/day (125 to 500 mg/day)	Alcohol-sensitizing agent - inhibits enzymatic conversion of acetylaldehyde to acetic acid	Relapse prevention and maintenance; subject should be motivated to quit	60,61
	Naltrexone*	50 mg oral admin 12 weeks Extended release Q 4 wks	Opioid receptor antagonist	Relapse prevention and maintenance; mediates rewarding effects of alcohol	68-70
	Acamprosate*	2 g/3 x day (usual dose: 666 mg TID)	Normalizes the dysregulation of NMDA-mediated glutaminergic excitation	Relapse prevention and maintenance	76,77
	Topiramate	25 mg BID (titrate weekly to 400 mg/day)	Antiepileptic; GABA agonist	Relapse prevention and maintenance	78
	Buspirone	7.5 mg BID (titrate to 20-30 mg/day)	Serotonin (5-HT)-1A agonist	Relapse prevention and maintenance	80
	Fluoxetine	6-25 mg/day 90 mg/week	Selective serotonin uptake inhibitor (SSRI)	Relapse prevention and maintenance	82,85,87
	Citalopram	20 – 40 mg/day	SSRI	Relapse prevention and maintenance	83,84,86,88
	Ondansetron	2 mg/mL, 32 mg/50 mL injection 4 mg/5 mL solution 4 – 24 mg tab	5-HT3 antagonist; prevention of nausea/vomiting	Relapse prevention and maintenance	81
Cocaine	Disulfiram (Antabuse)	250 mg/day	Nonspecific enzyme inhibitor including aldehyde dehydrogenase and dopamine beta hydroxylase	Good efficacy data in nonalcoholics, relatively contraindicated in alcohol dependence with cocaine	92,93
	Selegiline	5 mg BID cap 6-12 mg/24 h patch	Antihypertensive; MAO-B inhibitor		97-99
	Desipiramine	100-200 mg/day (max 300 mg/day)	Antidepressant		6,100,101
	Baclofen	40-80 mg/day	GABA agonist	Additive CNS effects w/ alcohol	109
	Tiagabine	4 mg/day (may increase to max 56 mg/day)	Anti-seizure; GABA agonist	Additive CNS depression w/ alcohol	110,111
	Topiramate	25 mg bid (titrate weekly to 400 mg/day)	Antiepileptic/antiseizure; GABA agonist	Potentiates CNS depression w/ alcohol; withdraw gradually	112
	Vigabatrin	**	GABA agonist		113
	Carbamazepine	200 mg BID (Max 1200 mg/day	Anticonvulsant; Antiepileptic	Inconsistent results from clinical trials	114,115
	Buprenorphine	8 mg sublingual (liquid) 1 mg tablet 4:1 combination sublingual tablet w/ naloxone (Suboxone)	Partial agonist at mu-opioid receptor	Inconsistent results from clinical trials; low abuse potential	116,119

Table I. continued

Opioid antagonists

Naltrexone is an opioid antagonist that binds to receptors, but instead of activating the receptors, it blocks them, effectively removing the opiate user's ability to get high.[153,154] Human laboratory studies of naltrexone have demonstrated the efficacy of naltrexone in blocking the effects of acute opioid use in human volunteers who have been withdrawn from opioids.[154,155] In clinical trials, high attrition rates and unblinding by study patients who guess their treatment regimen have limited the utility of naltrexone maintenance treatment trials,[156,157] though a subgroup analysis in a large controlled trial indicated potential efficacy in highly motivated patients and in those already in drug-free counseling.[157] Naltrexone has relatively few side effects, but liver function should be monitored as per labeling guidelines. Its depot formulation is particularly useful to address its main problem of poor adherence to the daily oral therapy, but the relative expense of depot compared with oral naltrexone can be a deterrent to potential widespread utilization. Patients must also be opiate free for 7 to 10 days prior to initiation in order to prevent severe withdrawal reactions. If naltrexone is intended for use as treatment of acute withdrawal symptoms, use of clonidine in combination with naltrexone reduces the severity of acute opioid withdrawal during detoxification.

Behavioral therapy

Behavioral therapies constitute an extremely important component of substance abuse treatment by helping to retain patients in treatment and improvement in abstinence.[158] These therapies form the platform for any pharmacotherapy in order to engage the patient and facilitate more long-term changes including prevention of relapse.[159,160] Contingency management (CM) deserves special mention because it has been successful to initiate abstinence and prevent relapse with many drugs of abuse, particularly for managing cocaine- and amphetamine-abusing individuals,[161-165] regardless of psychiatric severity.[166] Improvement in study retention, as well as associated abstinence outcomes in substance abusers, has been found in randomized clinical trials of cocaine users[163,166] and in cocaine and methadone-maintained cocaine abusers.[163] CM has also been successful in studies of alcohol-abusing subjects, as well as those with polysubstance dependence or abuse.[71,72,75,167] Community-based

Drug	Medication	Dose	Mechanism of action	Special considerations	References
	Amantadine	200 mg/day	Dopamine & NMDA agonist	Inconsistent results from clinical trials; potential use in severe withdrawal	120-123
	Modafinil	200 mg/day	Wakefulness-promoting agent	Low abuse potential; often used for many off-label indications	124,125
	TA-CD	**	Cocaine vaccine	Phase II trials; must be motivated to quit	129-131
Opiates	Methadone*	30 – 100 mg/daily (initial doses 15 to 20 mg/day) >100 mg/day in persistent heroin abuse or comorbid conditions	mu-opioid agonist	Gold standard for opioid maintenance treatment	136-144
	Buprenorphine*	8 mg sublingual (liquid) 1 mg tablet 4:1 combination sublingual tablet w/ naloxone (Suboxone)	Partial agonist at mu-opioid receptor & kappa antagonist	Injection of suboxone could precipitate opiate withdrawal	147-152
	Naltrexone	50 mg oral admin* Depot: extended release	Nonspecific opioid antagonist	Few side effects but monitor liver function; must be opiate free for 7 to 10 days prior to initiation	154-157

Table I. continued

efforts using CM have also been successful in improving retention and associated abstinence outcomes.[165] There is however, a significantly higher cost associated with the incentives group versus usual care group,[168] and therefore the utility of CM in real-world settings should be further evaluated based on cost-effectiveness.

Cognitive behavior therapy (CBT) is also an efficacious intervention for the treatment of substance abuse. In a pilot study CBT was examined in conjunction with pharmacotherapy to evaluate length of treatment, drug-free urinalyses, and reduction of alcohol and cocaine craving. Though CBT-treated subjects remained in treatment longer than subjects who received both disulfiram/CBT or naltrexone/CBT, the combination treatment groups achieved significantly greater reductions in cocaine positive urinalyses.[169] Where CM may be useful in engaging substance users and attaining abstinence more quickly, CBT has better long-term treatment retention and is comparable to CM in helping patients ultimately achieve abstinence.[170]

Conclusion

Substantial progress has been made in the development of pharmacotherapeutic options for substance use disorders. *Table I* summarizes the current therapeutic options for the substances of abuse mentioned in this review. Taken alone, in combination with other medications, or in conjunction with behavioral therapies, effective treatment options are available in the areas of nicotine, alcohol, cocaine, and opioid abuse. Preliminary studies on new medications and vaccines are promising for the future. ❑

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Pharmacological aspects

Alternativas terapéuticas y desafíos frente a las sustancias de abuso

La adicción a sustancias sigue siendo un importante tema de salud pública en los Estados Unidos. La siguiente revisión acerca de los tratamientos farmacológicos actuales incluye diversas sustancias: nicotina, alcohol, cocaína y opioides. El objetivo es entregar una panorámica de los actuales tratamientos disponibles y de las nuevas terapias farmacológicas para los trastornos por el uso de sustancias, consignando además el resto de los desafíos farmacoterapéuticos. A pesar de los significativos avances en la farmacoterapia, ésta ha tenido una utilización limitada. Por ejemplo, la naltrexona se prescribe infrecuentemente para el alcoholismo, la buprenorfina para los opioides todavía tiene relativamente pocos prescriptores calificados, y los estimulantes no tienen una farmacoterapia aprobada por la Food and Drug Administration*. Estas farmacoterapias son necesarias, considerando que el porcentaje de abuso de opiáceos que ha sido relativamente constante ahora está creciendo marcadamente.*

Défis et choix thérapeutiques en cas de dépendance à une substance

La dépendance à une substance reste encore un problème de santé publique préoccupant aux États-Unis. Cet article sur les traitements pharmacologiques actuels passe en revue une série de substances : la nicotine, l'alcool, la cocaïne et les opiacés. Il a pour but de donner une vue d'ensemble des nouveaux traitements pharmacologiques actuellement disponibles pour traiter les troubles liés à l'utilisation d'une substance, tout en abordant les autres options thérapeutiques pharmacologiques. Les progrès importants en pharmacothérapie ont cependant été peu utilisés. Ainsi, la naltrexone (pour l'alcoolisme) est rarement prescrite, la buprénorphine (pour les opiacés) seulement par quelques médecins qualifiés et les stimulants n'ont pas été approuvés par la Food and Drug Administration*. Ces traitements sont nécessaires, car la dépendance aux opiacés, même si elle est relativement rare, augmente maintenant nettement.*

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Pharmacogenetic aspects of addictive behaviors

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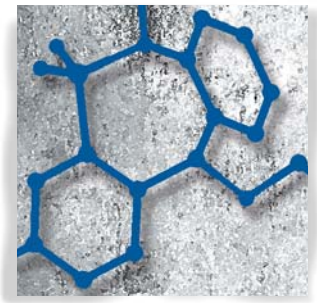

Addictions are illnesses of complex causation, including inheritance and a role for gene/environment interactions. Functional alleles influencing pharmacodynamic (tissue response) and pharmacokinetic (absorption, distribution, and metabolism) play a role, but these interact with diverse environmental factors including early life stress, underage drug exposure, availability of addictive agents, and response to clinical interventions including pharmacotherapies. Identification of genetic factors in addiction thus plays an important role in the understanding of processes of addiction and origins of differential vulnerabilities and treatment responses.

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Addictions are among the world's major health problems, both in terms of cost, and in terms of morbidity and mortality.[1] Addictions frequently are of early onset, and are associated with many other psychiatric and other medical conditions, both as cause and consequence. According to the 2005 national survey on drug and alcohol by the Substance Abuse and Mental Health Administration (SAMHSA), first-time users of alcohol, illicit drugs, and tobacco over the age of 12 years numbered 4.3 million, 2.9 million, and, 2.3 million, respectively.[2] The relapsing/remitting nature of addictive disorders, and the high frequency of suicide in addiction, are notable features of these often lifelong disorders. Pharmacogenetic factors modify both the vulnerability to addiction and response to treatment, making it vital to identify specific pharmacogenetic factors to design better treatment and prevention strategies, and to better target those interventions *(Figure 1)*.

Inheritance

Heritability accounts for 40% to 80% of the variation in vulnerability to a range of addictive disorders.[3] These heritability estimates are primarily based on a series of large studies comparing concordance of monozygotic (identical) and dizygotic (fraternal) twins *(Figure 2)*. It is important to note that heritability has been estimated from epidemiologically sampled twins and in age cohorts within national or state populations. The heritabilities computed from these studies are thus likely to reflect the average action of genes on addiction within a population, but not across populations or across time, where there are additional sources of environmental variance.[3] In the US, heritability accounts for approximately 50% of the interindividual variation in vulnerability to alcohol dependence, as

shown by meta-analysis of large methodologically sound, epidemiologically based twin studies augmented by family and adoption studies. Although alcoholism and other addictions are probably influenced by variation at many genes, alcoholism resembles other addictions in that the concordance ratios for risk in vulnerability are approximately 2:1 for monozygotic (MZ):dizygotic (DZ) twins, a finding that indicates the possibility for major gene effects and additive actions of alleles, rather than more complex epistatic interactions that are more likely to occur in diseases with high MZ:DZ concordance ratios.[3] In the addictions, sex interactions in vulnerability are frequently seen. Often, as for alcoholism and nicotine addiction, men are at higher risk than women. However the male-to-female ratios vary substantially worldwide, and have decreased in many countries as women have gained access to substances, or have actually been targeted by advertising, as in advertising campaigns for cigarettes.[4,5] For example, alcoholism is an addiction whose prevalence varies across culture, and has varied across time, and many drugs of abuse (eg, nicotine, cocaine, amphetamines) have been introduced in only the past several centuries, or even more recently.[3] The heritability of dependencies to substances with higher addictive potential tends to be higher; for example, opioids have high addictive potential and opioid addiction is highly heritable—approximately 65%, as shown by large twin studies such as the Vietnam and World War II veterans' studies.[6]

Although much is known about the heritability of addictive agents, the heritabilities of dependency to many addictive agents that are important on a worldwide basis are unknown. Heritability studies have predominantly been carried out in Western countries, and on substance dependencies that are common in these countries. In many countries, other agents play a more important role. In several instances, the active agent is similar or identical, but delivered to the body by chewing. For example, khat leaves harvested from the tree *Catha edulis* are chewed for their euphoric properties in East Africa and Yemen.[7,8] The heritability of khat addiction may be low or the genetics may be that of protective alleles, since in certain regions such as Yemen 90% to 95% of males and an increasing number of females are addicted. While the heritability of cigarette smoking is well understood—nicotine dependence heritability is approximately 60%[5]—tobacco is often chewed in the rural US and in other parts of the world. In Andean countries, the coca leaf is chewed. Finally, on a worldwide basis, young people are being exposed to video games, some Internet-based, that frequently lead to addictive use, and the heritability of this addiction is unknown.

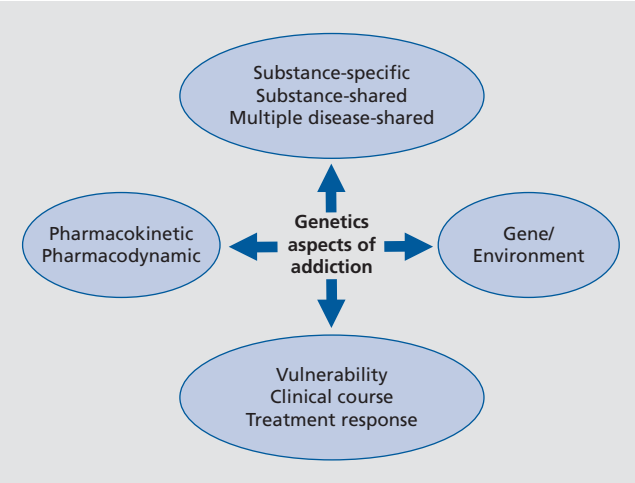

Figure 1. Genetic aspects of addiction: four nonorthogonal axes of gene action.

Cross-inheritance

Twin and family studies reveal that addictions are cross-inherited as well as influenced by substance-specific factors. Several cross-transmission studies in the Vietnam Veterans, World War II Veterans, and Virginia Adoption study all revealed a common vulnerability factor, of varying magnitude, shared by nicotine and alcohol addiction. In these studies, the risk of the second disorder was higher in the co-twin of the proband with the first disor-

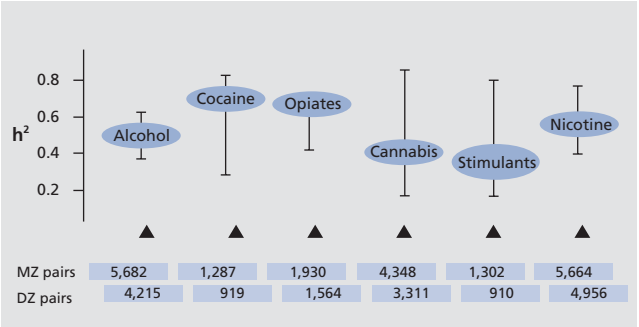

Figure 2. Heritabilities (h2) of six addictive disorders. The heritabilities are weighted means estimated by Goldman et al[3] from large twin studies.

Adapted from ref 3: Goldman D, Oroszi G, Ducci F. The genetics of addictions: uncovering the genes. *Nat Rev Genetics*. 2005;6:521-532.

der, indicating a common underlying vulnerability factor. The cross-inheritance explains, in part, the tendency for certain addictions to be comorbid (to co-occur) at higher frequencies than expected randomly. For example, it has been reported that nearly 80% of alcoholics are heavy smokers.[4] Comorbidity of cocaine dependence and opioid addiction frequently occurs, and both are frequently comorbid with nicotine dependence. The use of cocaine, opiates, and amphetamine is 10 times higher in alcoholics as compared with nonalcoholics.[9-12] Addictions also tend to be comorbid with other psychiatric diseases, and cross-inheritance again provides part of the explanation.[13] Both internalizing disorders—depression, anxiety—and externalizing disorders—antisocial personality disorder—show excess comorbidity and some evidence of cross-inheritance. The sharing of inheritance presumably reflects the effects of the same genes on mechanisms common to different addictions and diseases.[3]

A potential role for the muscarinic acetylcholine M2 receptor gene (*CHRM2*) in comorbid vulnerability to alcoholism and other drug dependencies was identified in families with alcohol addiction in the large Collaborative Study on the Genetics of Alcoholism which comprises samples collected from families with alcoholism from across six states nationwide. In a family-based study, Schuckit et al examined the role of the muscarinic acetylcholine receptor (*CHRM2*) among individuals with alcohol dependence alone and in those with alcohol dependence and comorbid drug dependence. Samples were collected from 2282 individuals in 262 COGA families. A total of 477 individuals had alcohol dependence with comorbid drug dependence, and 433 individuals had alcohol dependence without comorbid drug use. The association of *CHRM2* originated entirely in alcoholics with comorbid drug dependence. In the alcohol-dependent group without drug dependence there was no evidence of association to *CHRM2*.[12]

Studies in mice indicate that the 5HT1B receptor gene, which encodes the terminal auto receptor regulating serotonin release, is involved in cocaine and alcohol addiction. Mice lacking the 5HT1B receptor show heightened response to cocaine and alcohol and augmented cocaine and alcohol self-administration, and mice knocked out for the HTR1B receptor were more aggressive and drank more alcohol.[14,15] In humans, HTR1B was associated with antisocial alcoholism (alcoholism comorbid with antisocial personality disorder) in two populations,[16] and depression and anxiety.[17] One of the earliest observations of cross-inheritance in addictions was the tendency of fathers with antisocial personality disorder to have children with alcoholism, whether or not the child was adopted out to a family without pathology.[18]

Pharmacokinetic and pharmacodynamic variation

Pharmacokinetic variation refers to variation in drug absorption, distribution in the body, metabolism, and excretion. *Pharmacodynamic* variation refers to the response of the body and encompasses dose effects, ascending and descending limb variation, sensitization and tolerance, developmental and age effects, and genetic variation.

The classic and well-known examples of pharmacokinetic variation in addiction are the functional polymorphisms of alcohol dehydrogenase 1B (*ADH1B2*-His47Arg) which metabolizes alcohol to acetaldehyde and aldehyde dehydrogenase 2 (*ALDH* -Glu487Lys) which metabolizes acetaldehyde to acetate. Following alcohol consumption, both the Arg47 and Lys487 alleles, alone or together, can lead to the accumulation of acetaldehyde, producing aversive flushing, nausea, and headache.[19,20] People of Southeast Asian ancestry are especially likely to carry the *ADH1B* Arg47 and *ALDH2* Lys487 alleles, but individuals of Jewish ancestry also often carry the Arg47 allele.[21] Both the Arg47 and Lys487 alleles lead to a reduction in risk of alcoholism, with a protective effect of fourfold to tenfold in carriers, and an additive protective effect when both alleles are carried by the same person. The *ADH1B* alleles are codominant in action but *ALDH2* Lys487 is semidominant, such that heterozygous carriers have very low levels of *ALDH2* enzyme activity. However, *ALDH2* Lys487/Lys487 homozygotes are nearly completely protected from alcoholism. The action of these two genetic variants has an interesting pharmacologic parallel. Disulfiram, which inhibits ALDH, is one of several drugs in use for treatment of alcoholism. Metronidazole and certain other antiprotozoal drugs also inhibit ALDH, and also lead to the aversive flushing reaction following ethanol ingestion.[19-22] In addition, the Lys487 allele has been shown to be associated with higher risk of gastrointestinal cancer after alcohol consumption, and probably through the carcinogenic action of acetaldehyde.[22]

Less clear is the pharmacogenetic role of enzymes such as catalase and cytochrome P450 2E1 (*CYP2E1*) that

also play a role in the metabolism of ethanol and acetaldehyde, albeit a quantitatively more minor role.[24]
Many proteins and their genes are targets for pharmacodynamic variation in vulnerability to alcohol dependence. In a prospective study of young, relatively alcohol-naive male college students, low response to alcohol was shown to be a predictor of alcoholism, and has been used as a heritable intermediate phenotype, both for candidate gene studies and for genome linkage scans.[25]
Dopamine β hydroxylase (DβH) is the enzyme that converts dopamine to norepinephrine. *DBH* exhibits inherited functional variation that has been linked to various psychiatric disorders including depression and alcoholism. The *DBH* variant -1021 C>T predicts reduced plasma DβH enzyme activity. *DBH* linkage studies to nicotine are so far inconclusive.[26-29] However, Freier et al found that individuals with the *DBH* -1021T allele smoked less than -1021C/-1021C homozygotes. Equivocal linkage data are also reported for the DRD2 dopamine receptor, which is thought to be integral for dopamine-mediated reinforcement.[26] A "gatekeeper" for nicotine's central nervous system actions is the nicotine receptor. The α4β2 heteromer is essential for nicotine's rewarding actions, as shown by studies in knockout mice.[27] In the future more information is likely to be developed on the role of functional nicotine receptor variants, which may be rare or uncommon.
Alcohol exerts its sedative and rewarding actions in part through stimulation of GABAA receptors and inhibition of NMDA glutamate receptors, and key signaling proteins include protein kinase C enzymes, as revealed by a variety of studies including electrophysiology studies of receptors and investigations on mice knocked out for these genes. Some of these "gatekeeper" molecules have been implicated by linkage and association studies. Genetic linkage studies implicating *GABAA* subunit genes include a series of mouse ethanol-related quantitative loci (for behaviors such as alcohol preference and sensitivity to the sedating actions of ethanol) and, in the human, whole genome scans and linkage disequilibrium studies linking the Chromosome 4 GABAA receptor subunit gene complex and the *GABAA α2* gene. The Chromosome 5 *GABAA* receptor subunit complex and the *GABAAα6* gene therein at the *GABAAα6* gene is the Ser385 allele, which may correlate with LR, and a higher risk of alcoholism and variation in response to benzodiazepines.[30-34] The *GABRG1* haplotype markers showing greater allelic, genotypic, and haplotypic association with alcohol dependence compared with those of haplotype block may act in a dominant manner in relation to risk of alcohol dependence.[35]
The μ-opioid receptor gene *OPRM1* is the most extensively studied of the opioid receptor genes because of its important role in reward mediated by endogenous opioids. The functional *OPRM1* Asn40Asp variant of the μ-opioid receptor gene has been shown in some studies to be associated with opioid addiction.[36,37,38] For example, association of this *OPRM1* variant to polysubstance abuse including opioids, cocaine, and alcohol was reported by Kranzler et al.[36] Berrettini and colleagues reported that the major opioid preference quantitative trait loci in mice mapped to the location of the murine μ opioid receptor gene.[39] *OPRM1* Asn40Asp has also been variably linked to alcoholism,[29,30] and perhaps most intriguingly, appears to alter opioid-mediated release of cortisol, this effect on the hypothalamic-pituitary-adrenal axis potentially revealing its action on stress activations important in addiction.[40] A delta opioid receptor, OPRD1, variant has also been reported to be associated with substance dependence.[41] The endogenous opioid system is also critical to the reinforcing effects of nonopioid drugs including nicotine, alcohol, cocaine, and cannabinoids.[37,42]

Gene-environment interactions in addiction

Addiction is a complex disease involving the interaction of genes and environment. The vulnerability to abuse of addictive agents is in part determined by genetic variation and in part by environmental factors including exposure to addictive agents, but also such nonspecific factors as stress exposure early in life.
Several of the interacting genes found so far are stress-related, modulating resiliency and vulnerability. Early life stress exposures such as childhood sexual abuse play a powerful but apparently nonspecific role, because such stress also increases vulnerability to other psychiatric diseases. In the rat preferring/nonpreferring (P/NP) model of alcohol consumption, a major quantitative locus for ethanol preference is at the site of the gene for neuropeptide Y, an anxiolytic neuropeptide. In the human, genetic variants of neuropeptide Y have sometimes, but not always, been linked to alcoholism as well as other behaviors, including obesity.[43,44] A catechol-O-methyltransferase polymorphism that predicts anxiety and cognitive function has been associated with alcoholism and

polysubstance abuse.[45] Another stress-related gene is the serotonin transporter, which contains the functional *HTTLPR* locus. In the rhesus macaque monkey, the reduction of function allele of the orthologous *rh-HTTLPR* locus predicts enhanced alcohol consumption, but only in the context of early life stress exposure.[46] In humans with cocaine addiction, the already high rate of suicide attempts is greatly increased in carriers of the reduction of function HTTLPR allele who had a history of childhood abuse or neglect.[47] Childhood trauma is in general associated with depression and suicide in individuals with the 5-HTTLPR reduction of function allele.[48] A functional polymorphism in the promoter region of monoamine oxidase A gene (*MAOA*) resulting in a low expressing genotype has been found to interact with childhood sexual abuse to increase risk of alcoholism, and especially antisocial personality disorder (ASPD) occurring in the context of Alcohol Use Disorders in women.[49] Other environmental factors influencing vulnerability include price, availability, early life stress exposures, and underage drinking.[50] For example, alcohol prohibition from 1920 to 1933 in the US led to a large decrease in alcoholism and associated cirrhosis. Also, onset of drinking in the early adolescent or preadolescent years is a strong risk factor. However, the interactions of such factors with gene effects are even less well understood.

The pharmacogenetics of pharmacotherapy

Treatment of addiction encompasses two main phases: acute detoxification and maintenance. Maintenance treatment is aimed at maintaining abstinence, or harm reduction. Supportive therapy plays a vital role and this may include cognitive therapy and self-help groups. Categories of pharmacotherapeutics include:

- Detoxification (eg, benzodiazepines in alcoholism and clonidine in opiate withdrawal)
- Agonist (eg, methadone, levo-alpha-acetyl-methadol (LAAM])
- Partial agonist (eg, buprenorphine for opioid addiction)
- Antagonist (eg, naltrexone in alcoholism)
- Anticraving (eg, bupropion and homotaurine in alcoholism)
- Aversive (eg, disulfiram).

Because each of these drugs targets specific proteins and small molecules, there is considerable potential for specific pharmacogenetics of treatment response. Each of these drugs is also subject to metabolism, leading to a role for pharmacogenetic variation such as the cytochrome p450 2,6 which predicted response to bupropion in nicotine dependence.[51] The *OPRM1* Asn40Asp polymorphism has, in addition to its disease associations, also been associated with naltrexone treatment response in alcoholism and as recently replicated in a large clinical trial, the COMBINE study.[52] The role of *OPRM1* in smoking has been studied in relation to nicotine replacement therapy. Nicotine increases the release of β-endorphins indirectly releasing dopamine and leading to pleasurable sensations associated with smoking, as shown by several studies both in rats and humans. In a randomized study, 320 smokers of European ancestry were treated with a nicotine transdermal patch or nasal spray over a 6-month period and 41% of Asp40 carriers remained abstinent at the end of 6 months as compared with 30% of Asn40/Asn40 homozygotes.[53] However, the effect of genotype disappeared after treatment cessation. Another gene that may predict nicotine treatment response is cytochrome P450 2B6 (*CYP2B6*) which predicted treatment response with bupropion, which is metabolized by this enzyme. In a study of 426 smokers of European ancestry, participants with the low activity allele reported increased craving and higher relapse rate. This effect may also be attributable to slower nicotine metabolism.[51]

Finally, there are genetic factors that are likely to act across different drugs used in treatment and even different diseases, to predict treatment response. These may include genes that influence anxiety and stress response such as *COMT*, *NPY*, and *5-HTTLPR*, as discussed above. They may also include genes altering cognitive function, such as *COMT* which predicts executive cognition.[54,55] One such functional polymorphism is the Met66Val polymorphism of the brain-derived neurotrophic factor gene (*BDNF*), which predicts hippocampal volumes and episodic memory function.[56] At present, none of the genetic markers available has found application in clinical practice. The *OPRM1* Asn40Asp polymorphism presently has potential for immediate utility in both alcoholism and nicotine addiction treatment.[52,57,58]

Concerning methadone treatment, human genetic variation may offer an advantage to this treatment modality for opioid addictions, many identified variants of *CYP2D6*, which metabolizes codeine, have been shown to alter levels of active codeine metabolites such as oxycodone and hydrocodone, potentially altering risk of

codeine usage. On the other hand, *CYP3A4*, which metabolizes methadone, buprenorphine, and LAAM, has not been found to have functional variants to affect metabolism of these opiates.[38]

The role of CB1 cannabinoid receptors role in the reward system make them a treatment target for drugs of abuse such as cannabinoids, opiates, and nicotine, and recently rimonabant has been utilized, but the role of genetic variation is unknown. Since the modes of action of certain drugs used or proposed for use in treatment including acamprosate[59] and topiramate[60] is unknown, the pharmacogenetic gene targets are also unclear. However, in certain instances, treatment suitability may be defined by general clinical features and the genes influencing these features. For example, serotonergic abnormalities are thought to be important in early-onset alcoholics, and ondansetron, which targets 5-HT (serotonin)3 receptors, selectively reduced craving in early onset alcoholics as compared with late-onset alcoholics. Finally, variation is being uncovered in genes, such as *BDNF*, that mediate neuronal signaling and plasticity, and functional loci such as *BDNF* Met66Val may potentially be critical to long-term recovery. In the future, genetic tools are likely to become increasingly useful to increase specificity of diagnosis and to develop and better target treatments. ❑

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Aspectos farmacogenéticos de las conductas adictivas

Las adicciones son enfermedades de compleja causalidad en que se incluyen la herencia y el papel de las interacciones entre los genes y el ambiente. Los alelos funcionales que afectan la farmacodinámica (respuesta tisular) y la farmacocinética (absorción, distribución y metabolismo) también tienen un papel, pero estos interactúan con diversos factores ambientales como situaciones de estrés de vida precoces, exposición a drogas de los menores de edad, disponibilidad de sustancias adictivas y respuesta a intervenciones clínicas (incluyendo las terapias farmacológicas). La identificación de factores genéticos en la adicción juega un papel importante para la comprensión de los procesos adictivos y de los orígenes de las vulnerabilidades y respuestas al tratamiento individuales.

Aspects pharmacogénétiques des comportements addictifs

Les addictions sont des maladies aux causes complexes, dont font partie l'hérédité et les interactions gène/environnement. Les allèles fonctionnels influant sur la pharmacodynamique (réponse tissulaire) et la pharmacocinétique (absorption, distribution et métabolisme) jouent un rôle mais ils interagissent avec divers facteurs environnementaux comme les stress de vie précoces, l'exposition des mineurs aux médicaments, la disponibilité des produits addictogènes et la réponse aux interventions cliniques y compris les pharmacothérapies. L'identification des facteurs génétiques dans l'addiction joue donc un rôle important dans la compréhension du processus d'addiction et des origines des différences de vulnérabilité et de réponse thérapeutique.

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Pharmacologic treatments for opioid dependence: detoxification and maintenance options

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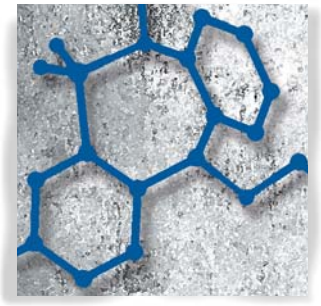

Detoxification

Although agonist maintenance therapies yield better outcomes for most opioid addicts,[1-3] they continue to seek opioid withdrawal primarily to lower the cost of their habit or as pretreatment before the residential therapeutic community or opioid antagonist maintenance. High relapse rates are probably less a function of withdrawal method and due more to reasons for seeking detoxifica-

While opioid dependence has more treatment agents available than other abused drugs, none are curative. They can, however, markedly diminish withdrawal symptoms and craving, and block opioid effects due to lapses.
The most effective withdrawal method is substituting and tapering methadone or buprenorphine. α-2 Adrenergic agents can ameliorate untreated symptoms or substitute for agonists if not available. Shortening withdrawal by precipitating it with narcotic antagonists has been studied, but the methods are plagued by safety issues or persisting symptoms. Neither the withdrawal agents nor the methods are associated with better long-term outcome, which appears mostly related to post-detoxification treatment.
Excluding those with short-term habits, the best outcome occurs with long-term maintenance on methadone or buprenorphine accompanied by appropriate psychosocial interventions. Those with strong external motivation may do well on the antagonist naltrexone. Currently, optimum duration of maintenance on either is unclear. Better agents are needed to impact the brain changes related to addiction.

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tion, postwithdrawal treatment, or brain changes developed during dependence. Those who complete detoxification tend to have longer times to relapse than dropouts.[4,5]

Clinical issues

Symptom severity is related to the specific narcotic used (short-acting yields more severe withdrawal); amount used; duration of use (at least 2 to 3 weeks, daily); and set and setting factors. Withdrawal phenomena are generally the opposite of acute agonist effects. Withdrawal from heroin begins with anxiety and craving 8 to 12 hours after the last dose, reaches its peak between 36 and 72 hours, and subsides substantially within 5 days. Methadone withdrawal begins at 24 to 36 hours, peaks at 96 to 144 hours, and may last for weeks. Individuals differ markedly, both as to which symptoms are present and their severity.[6] Acute opioid withdrawal symptoms are followed by a protracted abstinence syndrome, including dysphoria, fatigue, insomnia and irritability, for 6 to 8 months.[7]

Withdrawal agents

Methadone

Methadone is orally effective, long-acting—thus producing smoother withdrawal—and safe, if care is taken with initial dosing.

Because 40 mg of methadone has been a fatal dose in some nontolerant individuals, the initial dose should be less, eg, 10 to 20 mg. If withdrawal symptoms are not suppressed within 1 hour, more can be given, but in general the initial dose should not exceed 30 mg, and the total 24-hour dose should not exceed 40 mg the first few days. In a *nontolerant* individual, an initial tolerated dose can become risky if continued beyond 2 days because of rising methadone blood levels.[8] The clinician should be alert for signs of drowsiness or motor impairment.

Physical dependence can be ascertained by: (i) waiting until the patient develops withdrawal signs and symptoms; or (ii) precipitating withdrawal via naloxone (if pregnancy has been ruled out).

After the patient is stabilized, the dosage is gradually reduced, either by decreasing the methadone 5 mg/day until zero dosage is reached, or decreasing 10 mg/day until 10 mg is reached and then by 2 mg/day.[9]

Inpatient methadone substitution and taper is usually accomplished in 5 to 7 days, and has a retention rate of 80%; with outpatient detoxification it takes longer to minimize withdrawal symptoms and to decrease dropout and relapse, but only about 20% complete it.[10] Lingering protracted withdrawal symptoms can be helped by clonidine.

Buprenorphine

The Food and Drug administration (FDA) approved sublingual buprenorphine in 2002 for office-based treatment for detoxification or maintenance of opioid dependence. Buprenorphine is long-acting, safe, and effective by the sublingual route, but may precipitate withdrawal symptoms if given too soon after an opioid agonist. If the patient has withdrawal symptoms and has waited at least 12 hours after short-acting opioids and 36 hours after methadone, buprenorphine usually serves to relieve these symptoms and is less likely to precipitate withdrawal. It may also be useful in emergency department settings.[11]

Heroin detoxification is managed by administering buprenorphine 2 to 4 mg sublingually after the emergence of mild-to-moderate withdrawal. A second dose of buprenorphine 2 to 4 mg may be administered approximately 1 to 2 hours later, depending on the patient's comfort level. Usually a total of 8 to 12 mg of buprenorphine is sufficient the first day. For most patients, a slow taper over a week or so is a safe and well tolerated strategy. Any buprenorphine dose that worsens withdrawal symptoms suggests the buprenorphine dose is too high compared with the level of withdrawal. The symptoms should be treated with clonidine, and further buprenorphine doses withheld for at least 6 to 8 hours. Buprenorphine, even at doses of 16 mg, may not suppress all signs and symptoms of withdrawal if the patient had a very severe habit,[12] but most symptoms respond to adding clonidine 0.1 mg every 4 to 6 hours.

The duration of withdrawal from abrupt buprenorphine cessation is variable even from patient to patient. In one study, about one fifth of the patients maintained on daily buprenorphine 16 mg sublingually for 10 days experienced significant withdrawal symptoms after abrupt stopping.[13] Buprenorphine can be used to transfer patients from methadone maintenance to buprenorphine maintenance or to a drug-free state. The patient needs to be at least in mild withdrawal, and the methadone dose 40 mg or less for at least a week prior to beginning buprenorphine.[14]

Another way of using buprenorphine is for rapid withdrawal. A randomized study in heroin addicts[15] compared

anesthesia-assisted with buprenorphine-assisted detoxification, followed by antagonist induction. The buprenorphine group received a single dose of 8 mg on day 0, none on day 1, and naltrexone on day 2 at 12.5 mg, titrated up to 50 mg/day over 2 days. Symptom severity and retention at 1 month were similar in both groups. Another study also found that prior buprenorphine preparation markedly decreased post procedure morbidity.[16]

A recent systematic review compared buprenorphine to other detoxification strategies.[17] Compared with clonidine, buprenorphine was found to be more effective in ameliorating withdrawal symptoms; patients stayed in treatment longer, especially in outpatient settings, and were more likely to complete withdrawal. When compared with methadone-aided withdrawal, buprenorphine produced no significant difference in treatment completion, or severity of withdrawal, but withdrawal symptoms resolved more quickly.

Other detoxification agents and methods

Clonidine

The antihypertensive, α_2-adrenergic agonist drug clonidine has been used to facilitate opioid withdrawal in both inpatient and outpatient settings for over 25 years.[18-21] It works by binding to α_2 autoreceptors in the locus coeruleus and suppressing its hyperactivity during withdrawal. Doses of 0.4 to 1.2 mg/day or higher reduce many of the autonomic components of the opioid withdrawal syndrome, but symptoms such as insomnia, lethargy, muscle aches, and restlessness may not be adequately handled.[22]

Compared with methadone-aided withdrawal, clonidine has more side effects, especially hypotension, but is less likely to lead to post-withdrawal rebound. Dropouts are more likely to occur early with clonidine and later with methadone. In a study of heroin detoxification, buprenorphine did better on retention, heroin use, and withdrawal severity than the clonidine group.[12] Since clonidine has mild analgesic effects, added analgesia may not be needed during the withdrawal period for medical opioid addicts.

Lofexidine

Hypotensive effects may limit the optimal dosing of clonidine for opioid withdrawal. Lofexidine, an analogue of clonidine, has been approved in the UK and may be as effective as clonidine for opioid withdrawal with less hypotension and sedation.[23,24] Combining lofexidine with low-dose naloxone appears to improve retention symptoms and time to relapse.[4,25-28]

Supportive measures

Insomnia is both common and debilitating. Clonazepam, trazodone, and zolpidem have all been used for withdrawal-related insomnia, but the decision to use a benzodiazepine needs to be made carefully, especially for outpatient detoxification.

Treatments for ancillary withdrawal symptoms include nonsteroidal anti-inflammatory drugs (eg, ibuprofen or ketorolac tromethamine) for muscle cramps or pain; bismuth subsalicylate for diarrhea; prochlorperazine or ondansetron for nausea and vomiting; and α_2-adrenergic agents (eg, clonidine) for flu-like symptoms. Vitamin and mineral supplements are often given.

Rapid detoxification methods

Clonidine-naltrexone detoxification

This method[29-31] combines a rapid, precipitated withdrawal by naltrexone producing severe withdrawal symptoms, with high doses of clonidine and benzodiazepines before and after the naltrexone to ameliorate the symptoms. While shortening withdrawal to 2 to 3 days, evidence is lacking of longer abstinence or naltrexone retention.[32]

Rapid opioid withdrawal under general anesthesia

To decrease further the time needed for withdrawal, a rapid detoxification procedure using general anesthesia was developed[33] and gradually improved.[34-37] A variety of medications have been used, including naltrexone or nalmefene, propofol anesthesia or heavy midazolam sedation, the antiemetic ondansetron, the antidiarrheal octreotide, and clonidine and benzodiazepines for other withdrawal symptoms, and has been carried out on either an inpatient or outpatient basis. Post-procedure therapy varies widely. Claims of high rates of abstinence months after detoxification have been made, but no objective verification exists, and the samples are not representative.[38] Significant withdrawal symptoms may persist for days or even weeks after the procedure in humans[15,39,40] or in rats,[41] and there appears to be no longer-term improved outcome at 1 to 3 months

later.[15,42,43] Internationally, over one dozen deaths have been reported, usually within 72 hours of the procedure, with pulmonary edema a common complication.[44-47]

Pregnancy

Illicit opioid use during pregnancy can have numerous harmful effects on the woman, fetus, and neonate. Residential abstinent treatment is usually not available. Methadone maintenance is thus the standard approach.[48] While the infant will be physically dependent on methadone and about half need to be withdrawn, no birth defects are associated with such exposure, if prenatal care is adequate. Withdrawal from methadone maintenance is usually not preferable, but if carried out it should occur during the second trimester at no greater than 5 mg/week. Methadone metabolism is increased during pregnancy, and plasma half-life decreased. The clinician must balance the risk of illicit opioid use if the dose is too low, and the risks of the neonatal abstinence syndrome (NAS) if the dose is too high. This can be somewhat ameliorated by split dosing. Studies of pregnant methadone-maintained women found decreased narcotic use and improved health and prenatal care. Fetal growth and perinatal outcomes also improved. These benefits diminish with continued use/abuse of licit (alcohol and tobacco) or illicit (cocaine and marijuana) substances.[49]
Maintenance on buprenorphine is a more recent development with published reports of over 300 pregnancies, with good fetal outcomes. Buprenorphine appears comparable to methadone on outcome measures as assessed by NAS and maternal and neonatal safety.[50-54] One study[52] reported shorter hospital stays for babies born to buprenorphine-maintained mothers in comparison to methadone. Long-term effects beyond the neonatal period, however, are not sufficiently studied.

Agonist maintenance: methadone

Pioneering work by Dole and Nyswander in the 1960s[55-57] provided the initial scientific basis for using the long-acting opioid agonist methadone for maintenance. Numerous studies since then[58-62] have demonstrated that methadone maintenance of opioid addicts substantially reduces mortality and morbidity, the risk of new human immunodeficiency virus (HIV) infection, criminal activity, and illicit opioid use, especially when used with enhanced ancillary services.[63] Unfortunately, many programs do not provide these services, both because of decreased government funding and increased private ownership. In the US, there are over 240 000 individuals maintained on methadone, while in some other countries, eg, Russia, government opposition to agonist maintenance prevents its use, even when high HIV rates exist.

Federal regulations

With a few exceptions, methadone may only be dispensed for opioid detoxification or maintenance treatment by opioid treatment programs certified by the Substance Abuse and Mental Health Administration (SAMHSA) and approved by the appropriate state agency. Depending on criteria such as continued illicit drug use and employment, an increasing number of take-home doses is permitted, up to a maximum of a 1-month supply after 2 years or longer.

Pharmacology

While heroin is short-acting and relatively ineffective orally, methadone is a long-acting, and orally effective, opioid. It is excreted primarily in the urine and is an agonist at μ and δ opiate receptors.
Methadone is primarily metabolized through cytochrome P450 (CYP) enzymes, predominantly involving the CYP3A4 pathway. Drugs that increase the P450 enzymes, such as the retroviral agents for treating HIV, may increase methadone metabolism and lead to withdrawal symptoms, even in stable maintained patients. In contrast, drugs that inhibit these enzymes, such as some selective serotonin reuptake inhibitor (SSRI) antidepressants, may increase methadone levels and sedation.[64-68] Effects are more likely early in treatment before plasma levels have stabilized.[69] Physicians using methadone are advised to consult tables of drug interactions for complete listings.

Dosing

Methadone's plasma half-life, once stabilized, averages 24 to 36 hours[70] with a range of 13 to 50 hours, making it a useful once-daily maintenance medication compared with morphine or heroin. However, up to 10 days may be needed for such a steady state and before that, new patients, either in maintenance or given methadone for analgesia, are at risk of fatal overdose.[8,71] Doses should not exceed 40 mg/day the first day of dosing or be

increased over the next 2 weeks by more than 5 to 10 mg every 2 to 3 days. Individual differences in rate of metabolism may produce complaints of withdrawal symptoms, even in those on a stable dose.

Doses of 30 to 40 mg of methadone prevent most withdrawal symptoms and craving, but are not high enough to block the reinforcing effects of high doses of potent heroin. Doses of greater than 80 mg/day are associated with fewer positive urine tests than 40 mg, and programs with average doses of 80 to 120 mg have consistently better results than those with lower average doses.[72-75] As heroin potency increased, the average daily dose of methadone doubled in the 1990s.[76] Some programs today dose as high as 350 mg/day using the rationale of individual metabolic differences. Such doses have at times been associated with increased street sales.

Safety

Studies of methadone maintenance have not found long-term damage to the heart, kidneys, liver, or lungs.[77-79] Further, long-acting maintenance medications normalize the neuroendocrine alterations induced by short-acting opioids and with minimal psychoactive impairment,[80] unless accompanied by high concomitant use of benzodiazepines and alcohol found in many methadone programs. The most common side effects of methadone maintenance are constipation, sweating, urinary retention, and dose-related orgasm dysfunction in men.

Methadone overdose has been a problem with accidental ingestion by children (10 mg has been a fatal dose), use by nondependent opioid users experimenting with methadone, or during initiation of maintenance. While rapid treatment of overdose with narcotic antagonists can lead to full recovery, it is important to keep such individuals under observation for at least 24 hours and follow the initial naloxone treatment with a long-acting antagonist such as nalmefene. Death may occur even 24 hours or more after the methadone intake. Other factors associated with increased risk of overdose include medications that inhibit CYP3A4, use of alcohol or benzodiazepines, or liver disease. The possibility of cardiac conduction defects with methadone, especially at doses higher than 120 mg/day,[81] led to a black-box warning for methadone in December 2006.

Driving by patients on long-term methadone maintenance has not been found to be impaired,[82] but patients should be warned about driving after using alcohol, illicit drugs, or sedating medications. As with patients withdrawing from alcohol, patients beginning methadone maintenance may have some short-term cognitive impairment early in treatment.[83]

Nonpharmacologic components

Methadone is a medication, not a treatment. To achieve its potential, methadone maintenance should be combined with counseling aimed at lifestyle change. A classic study[63] demonstrated this by randomly assigning patients to minimal counseling, standard drug counseling, or enhanced services while maintaining them on identical standard daily methadone doses. Patients in the minimal counseling group had substantially higher illicit cocaine and opioid use than the other 2 groups. By 12 weeks, 69% of the patients in the minimal counseling group had 8 consecutive weeks of illicit opiate or cocaine use or three emergency situations compared with 41% of those receiving standard counseling and 19% of those receiving enhanced services. Recently a number of behavioral approaches, eg, contingency contracting and voucher incentives, have also shown efficacy, especially if staff is appropriately trained.[84]

While appropriate therapy is better than no therapy, some randomized studies have suggested that methadone alone is better than being on a waiting list.[85,86] Such methadone maintenance is permitted for up to 120 days in areas with long waiting lists.

Co-occurring disorders

There is high prevalence of comorbid psychiatric and substance abuse disorders among opioid addicts, as well as diseases common because of drug lifestyle, eg, acquired immune deficiency syndrome (AIDS), hepatitis B or C, and tuberculosis.[87] Since treatments for HIV and hepatitis C can stabilize these disorders, methadone programs need to screen and refer patients for medical treatment, as well as providing or referring for psychiatric disorders if patients are to adequately recover.

Pain

Over one third of methadone maintenance patients are estimated to have moderate-to-severe chronic pain. They have become tolerant to methadone's analgesic properties and may even have increased pain sensitivity.[88]

Treating methadone-maintained patients for acute pain with opioid analgesics has not been found to lead to relapse or higher methadone doses post-treatment.[89] The regular, daily methadone dose should be continued, and analgesic medications including nonopioid analgesics or short-acting opioids added as clinically indicated.[90,91] Since methadone occupies less than one third of the μ opioid receptors, unoccupied receptors are available for analgesic response.[92] However, methadone-maintained patients might require higher doses or more frequent administration of opioid analgesics than nonmaintained patients.

Office-based methadone maintenance treatment

Office-based methadone maintenance has been permitted on a limited basis for patients who have been stable for at least a few years. In general, patients on this "medical maintenance" have been successful[93,94] but a number increased their use of illicit drugs.[95-98] While the number of patients on methadone maintenance has increased to 240 000, there remain many parts of the country with inadequate availability and long waiting lists.

Discontinuation of methadone maintenance

How long patients should remain on methadone maintenance is controversial. Those on methadone do better than those who stop, with relapse common in this latter group. Methadone maintenance's contributions to improved health and functioning may increase slowly over time, but markedly decreases when methadone is discontinued. The risk of relapse following withdrawal from methadone maintenance is high, even for patients who have been on it for long periods and have made substantial changes in lifestyle. In this era of AIDS, the risk of serious adverse consequences following relapse suggest that for many patients lifetime maintenance may be necessary.[99-101]
There is substantial political opposition to methadone maintenance, which manifests itself in problems locating clinic sites, lack of economic support, and family opposition. The clinic–based nature of the programs, which mix stable patients and newly maintained patients, along with inadequate staffing, and minimal incentives for patient change, can lead to a culture of continued illicit drug use and chronic unemployment.[94] In spite of many decades of improving and saving lives, methadone maintenance is often viewed as perpetuating addiction or being immoral. The traditional method of withdrawal is decreasing the methadone dose rapidly until 30 mg is reached, and then slowly tapering from that, eg 5 mg/week or switching to clonidine.[102,103] A more recent approach involves transferring the patient to buprenorphine/naloxone and then tapering as described in the section on discontinuing buprenorphine.[103]

Partial agonist maintenance

Buprenorphine

Buprenorphine, a Schedule III controlled substance, is a high affinity partial μ-opioid agonist, κ antagonist, and ORL-1 receptor agonist.[104] Studies from 1980 on found it useful for treating opioid withdrawal and dependence.[105-109] Office-based buprenorphine maintenance has already increased treatment availability for opioid-dependent individuals and brought into treatment populations that had been unable or unwilling to attend methadone maintenance clinics, eg, prescription opioid addicts. Prescription opioid addicts seeking office-based buprenorphine are likely to present different issues than heroin addicts applying for methadone maintenance.[110] Primary-care physicians who have not treated opioid dependence will also present new challenges to the field. Anecdotal reports describe patients on buprenorphine as feeling more clear-headed, more energetic, and more aware of emotions than on methadone maintenance.[111] To diminish possible diversion to parenteral use, the recommended form of buprenorphine is a 4:1 combination with naloxone (Suboxone). The mono form (Subutex) is used for pregnant women and, at times, for induction.

Federal regulations

In 2002, the FDA approved buprenorphine for the treatment of opioid dependence in office-based practice. It was already being used for such treatment in other countries. Physicians need to receive 8 hours of specialized training in person or online, and then apply for a waiver from the Department of Health and Human Services. They are limited to 30 patients on buprenorphine for the first year, and can then apply to increase the number to 100.

Pharmacology

Buprenorphine binds to the μ receptor and activates it, but as the dose increases, there is a ceiling on some opi-

oid agonist effects, such as respiratory depression, making it safer than a full agonist as far as overdose. This has been demonstrated by the differential effects on overdose deaths in France of methadone and buprenorphine.[112] The ceiling effect is approximately 32 mg of sublingual buprenorphine, but it may be possible to increase analgesic effects above that.

Because buprenorphine is best absorbed parenterally and poorest orally,[113-115] with sublingual bioavailability in between, and naloxone is poorly absorbed orally but about 20 times more parenterally, the sublingual combination tablet yields primarily a buprenorphine effect. If crushed and injected, both drugs are bioavailable.[114,115] Naloxone will then precipitate opioid withdrawal if the individual is opioid-dependent, unless only on buprenorphine. Buprenorphine alone will also precipitate withdrawal by displacing other opiates from the receptor. Individuals who use *only* buprenorphine can get high even if they inject the combination product, but it is not as reinforcing.[116]

There have been a number of reports of buprenorphine abuse in some countries, including France,[117] Finland,[118] Great Britain,[119] and Australia.[120] Only Finland has, since 2004, the combination product. A recent study from Finland found a very high rate of buprenorphine intravenous (IV) use but 75% of such users said they were using it to self-medicate addiction or withdrawal. Over two thirds had tried the combination IV but 80% said they had a "bad experience." As a result, the street price of the combination was less than half of the mono product.[121]

Buprenorphine undergoes metabolism by the liver, primarily by the cytochrome P450 3A4 enzyme system[122,123] but studies have not found clinically significant interactions with HIV medications that interact with this system,[124] with the possible exception of atazanavir/retonavir.[125] Buprenorphine's terminal half-life of 37 hours and slow-onset and offset enables every-other-day dosing, although that tends not to be the preferred spacing by patients. Buprenorphine's high affinity at the μ receptor means it will block most opioid agonist effects,[126,127] but because of its ceiling effect, one can override the blockade by using higher agonist doses.[128,129]

Induction

For practical reasons, buprenorphine induction is usually done on an outpatient basis, with induction divided into two visits: initial evaluation for suitability, answering questions and giving instructions for the second visit; and actual induction. Induction may take 2 hours or longer, and patients should not drive that first day. When distance or other factors prevent two visits, careful telephone preparation is important.

Buprenorphine can displace a full opioid agonist from the μ receptor, but since it is only a partial agonist there could be precipitated opioid withdrawal. At induction, therefore, the addicted patient should be in withdrawal: off short-acting opioids for at least 12 to 16 hours and long-acting ones for at least 36 hours. When the patient is transferring from methadone maintenance, the program needs to verify the methadone dose as 40 mg or less and history of compliance with rules, especially drug use.

While 4 mg of buprenorphine is often used as the initial dose,[103] if there is doubt about the patient's withdrawal symptoms, the buprenorphine dose should be lowered to 2 mg. If the initial dose of 2 or 4 mg is tolerated, a similar second dose can be given an hour later and then 4 mg 6 to 8 hours later. The total dose on day 1 usually should not exceed 8 to 12 mg. If any dose *worsens* withdrawal symptoms, the buprenorphine should be temporarily halted and the symptoms treated with oral clonidine 0.1-0.2 mg. Once symptoms have improved, the buprenorphine can be restarted. *It is better to err on the side of incomplete suppression of withdrawal on day 1 than to have precipitated withdrawal, which may drive the patient away.*

By day 2 or 3, a dose of 12 to 16 mg is usually reached and resolves most withdrawal symptoms. Clonidine can be used to treat residual mild symptoms for a few days to a week as long as the patient does not become hypotensive. The most difficult and distressing symptom is usually insomnia. Depending whether there is a history of benzodiazepine abuse, agents chosen to treat this include trazodone, zolpidem, or clonazepam.

The usual maintenance dose is 16 to 24 mg/day although some patients are comfortable at 8 to 12 mg and others need 24 to 32 mg. Many patients prefer taking the buprenorphine in divided doses, two or three times a day, as opposed to only once.

Patient selection issues

The patient first needs to meet the criteria for opioid dependence. Abuse of, or dependence on, other sub-

stances such as alcohol, benzodiazepines, and cocaine, along with need for sedative detoxification, history of previous treatments, and psychiatric problems should all be explored.

Detoxification or maintenance

Many patients initially request buprenorphine detoxification and then change their minds a few weeks later and request maintenance. Given the high relapse rate post-withdrawal, this request may be reasonable. However, buprenorphine is relatively easy to detoxify *with* but harder to detoxify *from*. Thus, withdrawal should not be stretched out longer than 2 to 3 weeks if maintenance is not the ultimate goal.

Maintenance on buprenorphine vs methadone

If the patient's lifestyle is unstable, eg, homelessness, or needs the structure of regular attendance in a dispensing situation, or needs the wider range of services available in a comprehensive methadone maintenance program, or lacks the insurance or financial wherewithal to pay for buprenorphine medication and therapy, the patient may be better served by a methadone maintenance program. Since buprenorphine is a partial μ agonist with maximal efficacy approximately equal to 70 mg of methadone, it may not be adequate for some patients. Optimal methadone doses average around 100 mg/day and some patients require much higher doses.[129] A meta-analysis[130] found that both methadone and buprenorphine maintenance could be equally effective, but there was a wide variation in the studies covered. A way around this dilemma is to use a stepped approach whereby patients would be started on buprenorphine and increased as necessary up to 32 mg/day. If clinical results are inadequate, the patient would be moved to methadone maintenance and dosed as needed.[131] For patients who clearly need the structure of a methadone program, but prefer buprenorphine, it could be dispensed by a methadone program using the same rules as methadone.

Use of buprenorphine vs the buprenorphine/naloxone combination

It is preferable to maintain patients on the combination product unless they are pregnant or trying to become so. Many clinicians prefer the mono form for the initial induction, either because of concern for possible pregnancy or so that they do not need to worry about whether unrelieved withdrawal symptoms are due to increased amounts of naloxone being absorbed. The patient should be switched to the combination form once stable.

Age

While buprenorphine withdrawal or maintenance is legal above the age of 16, short-term dependence may be better handled by withdrawal and intensive counseling.

Other laboratory tests

In addition to testing for drugs of abuse, patients should be evaluated at baseline by the usual medical screening tests, as well as pregnancy, when appropriate, and tests for hepatitis B, C, HIV, and tuberculosis. Baseline tests can be carried out by the patient's own physician or ordered by the prescribing doctor.

Use of other drugs

The safety of buprenorphine on respiratory depression can be thwarted by concomitant use of benzodiazepines or other sedatives, especially when both the buprenorphine and the benzodiazepines are injected. A number of deaths have been reported from France due to this.[112,132] Low-dose oral benzodiazepines used judiciously do not appear to present the same problem.
The effect of buprenorphine maintenance on cocaine use in opiate addicts remains unclear. Some clinical studies have demonstrated efficacy in reducing cocaine use[133,134] while others have been inconclusive[135] or negative.[136]

Maintenance

Counseling

Buprenorphine and methadone are medications, not treatments, and should be combined with appropriate counseling services. The prescriber does not have to provide the counseling but convenient access will enhance compliance. Counseling can be individual, group or family therapy, or combinations. However, therapists have reported that many patients feel so well on buprenorphine compared with either methadone or their previous illicit drug use that they resist counseling.[111]

Urine testing

Drug testing, via "dipsticks" or commercial laboratories, can detect use of illicit opioids, cocaine, or benzodiazepines. The testing strips are easily used in the office but the standard opiate strips usually do not test for buprenorphine, methadone, hydrocodone, or oxycodone, so specific tests for these drugs are necessary to avoid false-negative results.[103] The test frequency and whether it is scheduled or random is a function of the physician's judgment in each case.

Maintenance

Once symptoms of opiate withdrawal and use of other opioids has been significantly decreased or eliminated, the maintenance phase begins. Dose increases may occur either because the patient is continuing illicit opioid use while apparently complying with the buprenorphine (monitored dosing may be necessary), or because the patient complains that the dose is not sufficient. Changing the frequency or scheduling of the buprenorphine doses may improve the latter. Although buprenorphine has a long half-life, some patients report better results by dosing 3 times/day, eg, 8 mg AM, PM, and late evening. The final dose is usually 8 to 24 mg/day[103] but some patients appear to need 32 mg. If illicit opioid use continues in spite of high buprenorphine doses and therapy, referral for methadone maintenance or depot naltrexone may be necessary. Before that final step, it may be worthwhile to try contingency contracting using frequency of visits or weeks prescribed as the reward.[137] Psychiatric problems can be common (over 50% in one unsolicited sample).[138] Appropriate medications or other approaches might markedly reduce the illicit drug use and make transferring unnecessary.
Office visits once a week are usually recommended initially[103] and can be reduced if the dose is stable, illicit drug use has stopped, and more intense psychological intervention is not needed. However, there may be practical obstacles to this, such as distance from the physician or problems paying for the medication and doctor's visit if not adequately covered by insurance. Frequency can be reduced gradually with stable patients to once monthly.

Side effects

Buprenorphine does not appear to cause liver abnormalities but, as with other narcotics, side effects such as constipation, nausea, and decreased sexual interest have been reported.[139] Unlike methadone, buprenorphine maintenance does not appear to be associated with electrocardiographic abnormalities.[140] Buprenorphine's desirable mood effects compared with methadone[111] may relate to methadone's producing a significant opioid effect lasting from 2 to 5 hours after dosing in maintained patients.[141,142] This may interfere with everyday activities.

Other issues

Acute pain

Acute pain is more difficult to manage with buprenorphine compared with a full agonist, but there are a number of options. These include dividing the daily buprenorphine dose into 3 or 4 doses and adding nonopioid analgesics; adding a full μ opioid analgesic on top of the buprenorphine dose; switching the patient temporarily over to a short-acting full μ agonist and increasing the dose until adequate pain relief occurs; or using nonopioid ways of dealing with pain such as regional or general anesthesia in a hospital setting.[90,91,143]

Chronic pain

Many patients with chronic pain can be treated with buprenorphine doses of 24 to 32 mg divided into 3 or 4 daily doses and supplemented if necessary by nonopioid analgesics. If pain relief is not sufficient, or the patient is resorting to illicit opioid use to control it, transfer to methadone maintenance may be needed.

Discontinuation of buprenorphine maintenance

While there is no legal limit to the length of buprenorphine maintenance, many patients ask to be withdrawn a few months after being maintained. The usual reasons are desire to be off all narcotics or the cost. Patients often have an unrealistic expectation of how easy it will be to remain abstinent[144,145] and many (perhaps most) will relapse within a short period.
Patients should be encouraged to remain on maintenance and, when possible, alternative solutions sought for issues like cost, eg, reducing frequency of visits, or exploring insurance options. There is no adequate data on the optimal length of time; each patient must be judged indi-

vidually using issues such as previous relapses, addiction history, and lifestyle stability. It is not uncommon to need a number of episodes of opioid maintenance or even long-term maintenance.

There is no consensus on the best way to withdraw from buprenorphine maintenance other than to do it gradually, eg, 2 mg/week until 4 mg is reached and then 1 mg decreased every other week or monthly. Clonidine may be useful in the final weeks to deal with the withdrawal symptoms. Relapse back to illicit opioid use should be taken seriously and the dose raised until the use stops. Continued use should probably be handled by resuming full-scale maintenance. As yet, there are no adequate controlled studies comparing the ease or severity of withdrawal from maintained buprenorphine vs methadone patients, although earlier studies suggested that buprenorphine withdrawal might be better tolerated.[146,147]

Once the patient has completed detoxification, use of naltrexone for at least 3 months may help prevent relapse. The 1-month depot naltrexone is preferable, but may be too expensive unless covered by insurance.

Naltrexone

Naltrexone was approved by the FDA as an opioid antagonist in 1984. It is effective orally and is long-acting, depending upon dose. While methadone blocks heroin effects by cross-tolerance, naltrexone blocks the effects by competitive antagonism at the μ receptor. The degree of blockade is a function of the concentrations of agonist to antagonist, and their receptor affinity.

Because of the blocking action of naltrexone, self-administration of opioids at usual doses produces no euphoria so that either individuals cease heroin use or cease taking the naltrexone.[148] Its long duration of action means that naltrexone can be given two or three times per week, but daily administration is usually preferred, both because of developing a regular habit of use and of creating a higher blockade. Less frequent administration is usually employed when an individual is taking monitored doses. Tolerance does not develop to the opioid antagonism, even after almost 2 years of regular use.[149] The FDA approved a 1-month acting depot preparation of naltrexone in 2006 for the treatment of alcoholism,[150] but it can be used off-label for treatment of opioid dependence.[151]

Dropout rates with naltrexone are high, but are significantly better where there is substantial external motivation, such as in physicians whose performance is being impaired, those involved with the criminal justice system, and those facing loss of an important job.[152-156] Retention is also better (43% at 6 months) in Russia, where addicts are often young adults living with parents who monitor intake and no agonist maintenance is permitted.[157]

Clinical aspects

If naltrexone is given to an opioid-dependent individual, it displaces the drugs from the receptor, producing rapid, unpleasant withdrawal. To avoid this, 5 to 7 days after the last use of a short-acting opioid or 7 to 10 days after the last dose of methadone is necessary before naltrexone induction. Using one of the rapid withdrawal methods described earlier can shorten the waiting period. Mild symptoms of precipitated withdrawal can usually be treated with clonidine and clonazepam. If sufficient abstinence is unclear, a test dose of a small amount of IM naloxone (eg, 0.2 mg) can be used.[157,159] Any withdrawal produced will be short-lived. Naltrexone should be initiated with a dose of 25 mg and, if that produces no withdrawal, the second 25-mg dose can be given 1 hour later. If depot naltrexone is to be used, it is useful to have 1 to 2 days of a well-tolerated 50 mg oral dose.

For oral naltrexone, virtually 100% adherence is needed because the blockade wears off around 24 to 48 hours after the last dose. Missed doses often eventuate in relapse, after which another detoxification and naltrexone induction is needed. Behavioral treatments have been found to be helpful in improving naltrexone adherence and treatment retention, doubling retention rates at 12 to 24 weeks. Approaches have included voucher incentives contingent on pill-taking adherence and involvement of family in monitoring such adherence.[160-165]

When possible, all doses should be monitored either by a family member or a health professional. Three times per week dosing (100 mg, 100 mg, 150 mg) may be useful if daily monitoring is difficult to arrange. Individuals doing monitoring should be trained to look for "cheeking" and other ways to avoid ingestion. Involvement in self-help groups such as Alcoholics Anonymous or (AA) or Narcotics anonymous (NA) should be encouraged. While such groups usually oppose agonist maintenance, naltrexone is often tolerated because of its lack of psychoactive effects. Urine tests should be carried out, if possible on a random basis, to see if the individual is using opioids, suggesting missing naltrexone doses, or has switched to drugs such as cocaine or benzodiazepines.

Side effects

Nausea, headache, and dysphoria have been reported, especially during the first 4 weeks of naltrexone administration. These symptoms resemble mild protracted opioid withdrawal and usually go away on their own or can be ameliorated by clonidine. Elevated liver enzymes, especially transaminases, were noted decades ago in patients given high doses (eg, 300 mg/day) as experimental obesity treatment. They reversed when the drug was halted, as they have when occasionally observed in patients taking normal doses.[166] If the enzymes are not reduced, brief hospitalization to stop excess alcohol intake or tests for such excessive drinking can be diagnostic.[167,168] Patients should be evaluated for viral hepatitis, which is very common among former IV users. Because of the possibility of hepatic effects, baseline liver function tests should be carried out. If abnormal (greater than 3 to 5 times normal), naltrexone should not be started. Monthly lab retests for the first 3 months can be a useful precaution.

Although naltrexone affects a variety of endocrine functions,[169-172] such effects have not been associated with particular problems. Likewise, although upregulation of opioid receptors has been reported in rodents, it was not found in a human study. Thus, the main risk of heroin overdose post naltrexone appears to be from loss of tolerance.[148]

Treatment of pain

When patients on naltrexone need analgesia, such as after surgery or in emergency situations, nonsteroidal anti-inflammatory drugs (NSAIDs, eg, Ketorolac) should be tried. If not adequate, the blockade can be surmounted by large doses of full agonists but this should only be done in an environment where emergency ventilation is available as in a hospital or emergency room because of the danger of overdose.

Duration of maintenance

There are no clear guidelines on the duration of naltrexone maintenance although, in general, 6 to 12 months are probably a minimum depending on the circumstances. Careful clinical evaluation of relapse risk should be done prior to the decision to discontinue naltrexone. The 30-day depot injection may improve compliance. Because naltrexone is an antagonist, it can be stopped abruptly without withdrawal symptoms. The high dropout rates and patient preference for agonist treatments will probably continue to keep antagonists in a secondary role and in select populations unless agonist maintenance is not available.[173,174]

Conclusion

Compared with other drugs of abuse, opioid dependence benefits from a wider range of available pharmacological tools for treatment. In spite of this, the large majority of the 1 million heroin addicts and 2 to 3 million prescription opioid abusers are not receiving treatment, and those who enter often only seek detoxification, from which early relapse is the most common outcome. The most successful treatment is long-term maintenance on agonists such as methadone and buprenorphine, but a variety of obstacles, including government regulations, cost, availability, and stigma, combine to diminish their use. The death rate among heroin addicts is approximately 2% to 3% per year, significantly higher than among their age- and socioeconomically matched cohorts. In addition to dealing with the obstacles above, what is needed to decrease this are new approaches that deal with the brain changes produced by chronic dependence and could reverse the intracellular changes related to addiction and craving. ❑

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Tratamientos farmacológicos para la dependencia de opioides: opciones para la detoxificación y el mantenimiento

Aun cuando la dependencia de opioides tiene más agentes terapéuticos disponibles que otras drogas de abuso, ninguno de ellos resulta curativo. Sin embargo, estos agentes pueden disminuir marcadamente los síntomas de abstinencia y el craving, y bloquear los efectos de los opioides debidos a las recaídas. El método más efectivo para tratar la abstinencia es la sustitución y disminución progresiva con metadona o buprenorfina. Los agentes alfa-2 adrenérgicos pueden reducir los síntomas no tratados o reemplazar a los agonistas si no se dispone de ellos. Se ha estudiado la reducción del período de abstinencia utilizando antagonistas narcóticos, pero los temas de seguridad o de la persistencia de síntomas han dificultado su desarrollo. La mejor evolución a largo plazo no se relaciona ni con los métodos ni con los agentes usados para manejar la abstinencia, sino que se asocia con el tratamiento post-detoxificación. Excluyendo a aquellos pacientes que cambian de hábito en el corto plazo, la mejor evolución ocurre cuando se mantiene metadona o buprenorfina a largo plazo, junto con adecuadas intervenciones psicosociales. En aquellos pacientes con una fuerte motivación externa puede ser útil el uso del antagonista naltrexona. Actualmente no hay claridad respecto a la duración de los tratamientos de mantenimiento. Se requiere de mejores agentes para combatir los cambios cerebrales relacionados con la adicción.

Traitements pharmacologiques de la dépendance aux opioïdes : détoxification et traitement d'entretien

Les traitements de la dépendance aux opioïdes, bien que plus nombreux que ceux des autres substances addictogènes, ne sont pas curatifs. Ils peuvent néanmoins diminuer notablement les symptômes de sevrage et la compulsion de consommation et bloquer les effets opioïdes dus aux récidives.
La méthode de sevrage la plus efficace est celle de la substitution et de la réduction progressive par la méthadone et la buprénorphine. Les agents α-2 adrénergiques peuvent améliorer les symptômes non traités ou remplacer les agonistes s'ils ne sont pas disponibles. On a cherché à raccourcir la période de sevrage en la déclenchant par des antagonistes narcotiques mais des problèmes de tolérance ou de persistance des symptômes en ont gêné le déroulement. L'amélioration à long terme n'est liée ni aux produits de sevrage ni aux méthodes mais plutôt au traitement qui suit la détoxification.
En excluant les produits avec lesquels l'accoutumance survient à court terme , les meilleurs résultats sont obtenus avec le maintien au long cours de la méthadone ou de la buprénorphine accompagné d'interventions psychosociales adaptées. Les patients dont la motivation externe est forte pourront préférer l'antagoniste naltrexone. Actuellement, la durée optimale de maintien de l'un ou de l'autre n'est pas bien définie. De meilleurs produits sont attendus pour traiter les modifications cérébrales liées à la dépendance.

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Poster

Individual variation in response to μ opiate receptor challenge—past, present, and future: a "personal" history of investigation

Margret R. Hoehe, MD, PhD

Individual differences in response to addictive substances may provide important clues to the mechanisms underlying drug action, addiction, reward, and reward-related disease states. Early psychoneuroendocrinological studies have led to the distinction of responders and nonresponders upon μ opiate receptor agonist administration. The systematic analysis of the gene encoding the μ opiate receptor reveals abundant DNA sequence diversity, suggesting numerous individually different forms of the gene. The present work illustrates the challenges of establishing complex genotype-phenotype relationships in the presence of high natural sequence variation, and provides some preliminary solutions. Progress in the future is expected to come from whole systems analysis-based approaches, integrating variation in all genes in all pathways.

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The examination of human individual differences at all levels of biological and phenotypic analysis will provide important insights into the mechanisms underlying complex traits. In particular, individual differences in response to addictive substances may help to elucidate the mechanisms underlying drug action, addiction, reward, and reward-related disease states. "The individual" has, both conceptually and concretely, been banned for far too long from approaches to scientific investigation. At the heart of endeavours to describe the functions and dysfunctions of "the" organism was the determination of mean values, as the averages of all individual values, and a standard error that indicated the extent of deviation of the individual values from the "mean," or "true" value. In other words, individual variation was conceived exclusively as the result of errors introduced in the process of measurement. At its extreme, the mean value would describe an effect that did not apply to any of the individuals studied. In this paradigm, the approach to gaining insight into the mechanisms underlying disease was based on the comparison of mean values between patients and healthy controls, usually resulting from a one-off experiment. Thus, in order to test an involvement of the opioidergic system in depressive disorders, we compared neuroendocrine and behavioral responses to the highly potent μ opiate receptor agonist fentanyl, both in patients and controls. At the time, insights into central receptor functions in humans were to be gained only indirectly: pharmacological substances known to interact with central nervous system receptors were administered intravenously, and receptor-mediated effects such as the release of hormones were measured peripherally as indicators of receptor function.

Evidence for individual variation in response to μ opiate receptor agonist administration

In order to prepare the ground for such an opiate challenge in patients, we had performed, first, a systematic dose-response study in normal volunteers. Doses of 0.1, 0.2, and 0.25 mg fentanyl per 70 kg body weight were tested in a randomized design at 3-week intervals, and specific dose-related effects on the release of prolactin, growth hormone, cortisol, catecholamines, and euphoric responses were able to be demonstrated. In particular, this work presented the first experimental evidence of a dose-dependent increase in the rewarding properties of fentanyl. A dose of 0.2 mg

per 70 kg body weight proved suitable to reliably induce an opiate-specific effect without causing adverse side effects or stress reactions.[1-4] When this dose was administered to depressive patients in a one-off experiment, both mean growth hormone and euphoric response to fentanyl was significantly reduced compared with normal controls.[5] This suggested a possible involvement of μ opioid receptor-related function in depression.

Most interestingly, when the individual responses underlying the mean euphoric effect of fentanyl in normal volunteers *(Figure 1A)* were examined, a remarkable individual variation was observed *(Figure 1B)*. One fourth of the "normal" volunteers did not exhibit any euphoric reaction, or showed a decrease in well-being. Evaluation of euphoric responses was based on: (i) application of visual analogue scales; (ii) documentation and classification of all spontaneous verbal reports of the volunteers; and (iii) detailed documentation of all observations during the experiment by two experts. These different instruments were found to be highly concordant, allowing unambiguous classification of the volunteers' behavioral patterns. Moreover, these individual response patterns proved consistently evocable over time, ie, in the course of repeated applications of fentanyl.[2,6] This suggested that individual responsiveness to this μ opiate receptor agonist might represent a trait variable, and that "normal" individuals might be classified into drug responders and nonresponders *(Figure 1C)*.[2] Similar observations were made upon administration of morphine.[2] This suggests that a subgroup of individuals may not be disposed to experience euphoria upon exposure to addictive drugs. Absence of euphoric response was not correlated with a blunted growth hormone release upon application of fentanyl or morphine, suggesting that different (opioid) mechanisms might be involved in mediation of rewarding properties of addictive substances. Thus, tracking a potential genetic basis underlying nonresponse may provide important clues the mechanisms involved in the development of addiction, or in a more general way the personal disposition to experience reward, and potentially lead to targets of intervention.

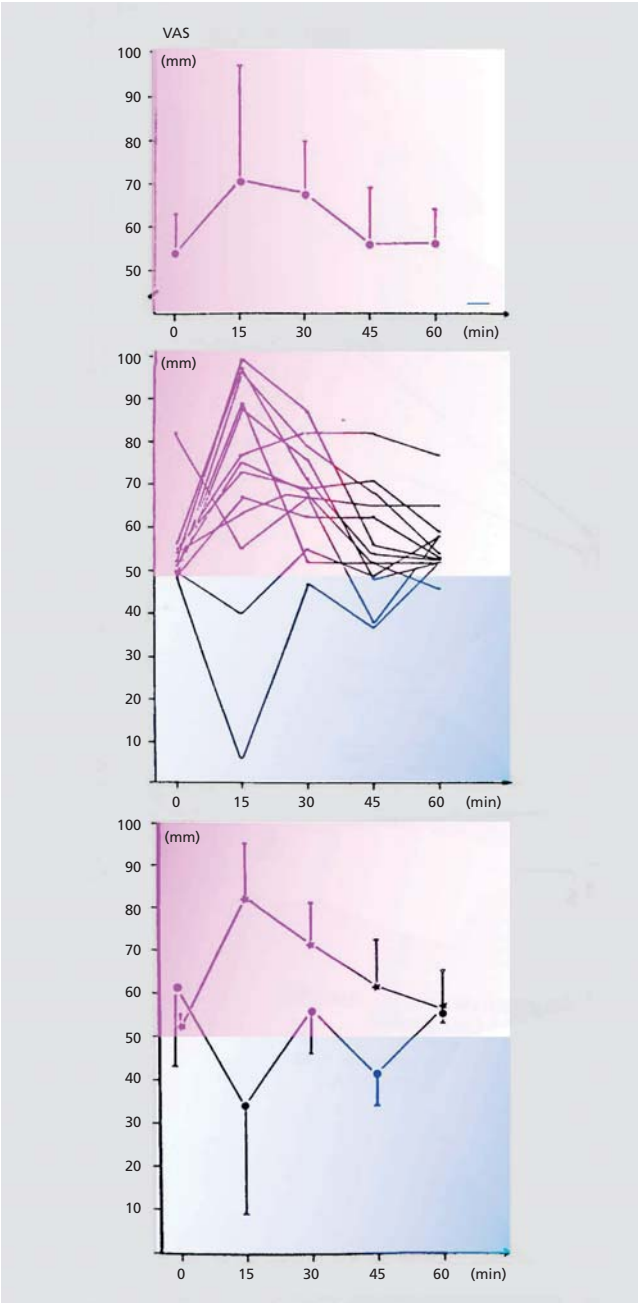

Figure 1. Euphoric responses to μ opiate receptor agonist administration.
A) Visual analogue scale (VAS) scores as mean values before and up to 60 min after administration of 0.2 mg fentanyl/kg; 0 mm = very unpleasant feelings; 100 mm = extremely positive feelings
B) Visual analogue scale scores presented as individual values before and up to 60 min after administration of 0.2 mg fentanyl/kg
C) Classification of individual VAS scores into two response types, euphoric responders / nonresponders.

Evidence for abundant DNA sequence variability in the gene encoding the human μ opiate receptor

Major advances in human molecular genetics in the late 1980s led to the cloning of numerous genes encoding

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pharmacologically characterized receptors. This allowed in principle to address the role of receptors in disease and individually different drug response for the first time at the most basic level, that is, DNA sequence information. If DNA sequence differences in the receptor gene were identified that were correlated with the individual phenotype in question, this could provide important clues on underlying receptor dysfunction and its nature. Since it is the entire gene and its encoded protein that act as the units of function which potentially affect a phenotype (and ultimately allow the first conclusions on disease mechanisms), it appeared mandatory to analyze the entire sequences of the individual genes, including their regulatory and critical intronic sequences. This required DNA sequence analyses at a previously unprecedented scale, in the Megabase range. Thus, we developed a powerful technique to perform comparative candidate gene sequencing in large numbers of patients and controls, "Multiplex Polymerase Chain Reaction (PCR) Sequencing." In principle, this technology allowed processing multiple (up to 55) sequencing reactions simultaneously in one reaction tube, increasing throughput accordingly. As a second prerequisite, we generated significant information on the genomic organization of the human μ opiate receptor gene, extending the previously cloned complimentary DNA (cDNA) sequence information[7] significantly. We determined several kb of 5' regulatory region, identified a number of potential binding sites for transcriptional regulatory factors, and cloned critical intronic sequences.[8]

These lines of research and technology development were combined to conduct the first systematic and to date most comprehensive analysis of DNA sequence variation in the human μ opiate receptor gene (OPRM1).[9] In a total of 250 individuals with a phenotype of severe substance (heroine/cocaine dependence and controls from two major populations, African-Americans and European-Americans, abundant DNA sequence diversity was revealed *(Figure 2)*. Regarding the nature and distribution of sequence variation in OPRM1, a total of 43 biallelic variants were identified. Clearly, the density of variants was higher in the 5' regulatory and untranslated regions than in the coding regions, where six variants, five of which affect the encoded protein, were found. Functional analyses of several of these mutations in the coding were performed, characterizing in particular modification of receptor density and signaling *(Figure 3)*.[10] Moreover, the influence of allelic variation in the 5' region on regulation of OPRM1 transcription was analyzed in a first study.[11]

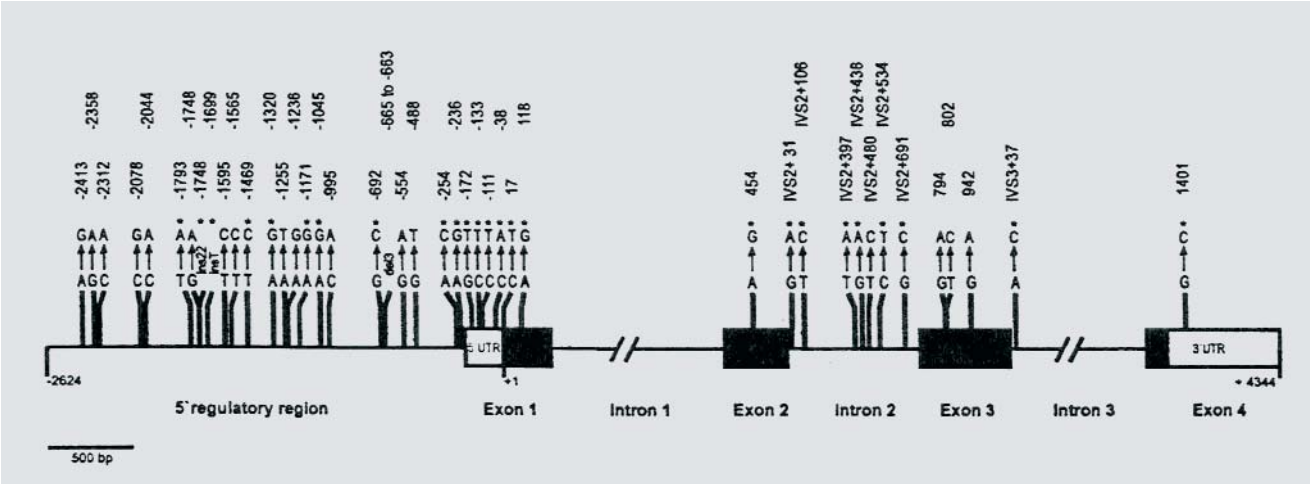

Figure 2. Polymorphic spectrum of the OPRM1 gene. The 6968 bp genomic reference sequence is presented as baseline; base pair coordinates relative to the translation start site are given. Sequences are drawn to scale, which is indicated. All gene variants are specified by position numbers and nucleotide variations (substitutions, insertions and deletions) according to mutation nomenclature. Those sites marked by an asterisk have been included in the haplotype analysis.

Multiple individually different forms of the human μ opiate receptor gene: relationship to gene function and phenotype

The given sequence variability gives rise to numerous individually different forms of the OPRM1 gene. It is essential in diploid organisms to determine the specific combinations of given gene sequence variants for each of the chromosomes defined as haplotypes. Because current experimental methods to determine the molecular haplotypes are still too labor- and cost-intensive, statistical techniques were applied at this stage to predict these. In the group of African-American substance-dependent individuals and controls, a total of 52 different haplotypes were distinguished *(Figure 4A)*.[9,12] These occurred at different frequencies in the population, as illustrated in *Figure 4B*. The five most frequent haplotypes, nos 43, 14, 4, 24, and 7 were common to both substance-dependent individuals and controls and constituted 66% to 73% of all haplotypes. An additional four of less frequent haplotypes were predicted, and a large number (43) of rare haplotypes occurring at frequencies <1% amounted to a total of 20% of all haplotypes. Thus, we will have to abandon Mendel's two-allele concept of a gene, which implicated existence of both a predominant "wild type" and various mutant forms.

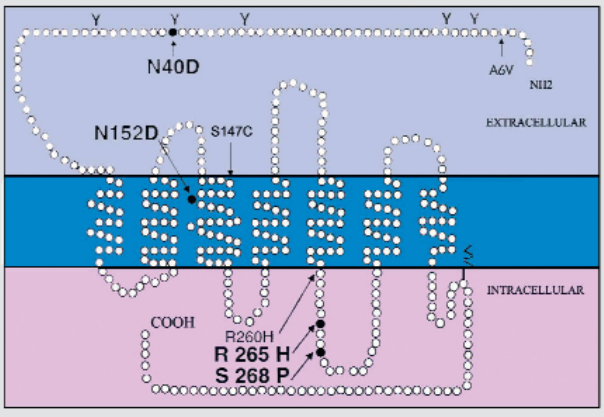

Figure 3. Site-directed mutagenesis of amino acid residues of OPRM1. A schematic representation of the putative seven transmembrane domain topology of the receptor is shown. Polymorphisms that affect protein sequence are indicated, and the mutations examined highlighted.
Reproduced from ref 10: Befort K, Filliol D, Decaillot FM, Gaveriaux-Ruff C, Hoehe MR, Kieffer BL. A single nucleotide polymorphic mutation in the human μ-opioid receptor severely impairs receptor signaling. *J Biol Chem*. 2001;276:3130-3137. Copyright © American Society for Biochemistry and Molecular Biology 2001

The picture exemplified at the model of OPRM1 apparently applies, in view of our more extended candidate gene analyses, to at least one third of all genes studied.[13] Allelic complexity in candidate genes may be large, and pose particular challenges to the analysis of genotype-phenotype relationships, particularly in the situation of complex traits. At first sight, such multiplicity of gene forms seems irreconcilable with the assumption of dichotomous traits such as health and disease, or drug response and nonresponse. Moreover, the number of different haplotypes is unfeasibly large, so that the power is not sufficient to detect an

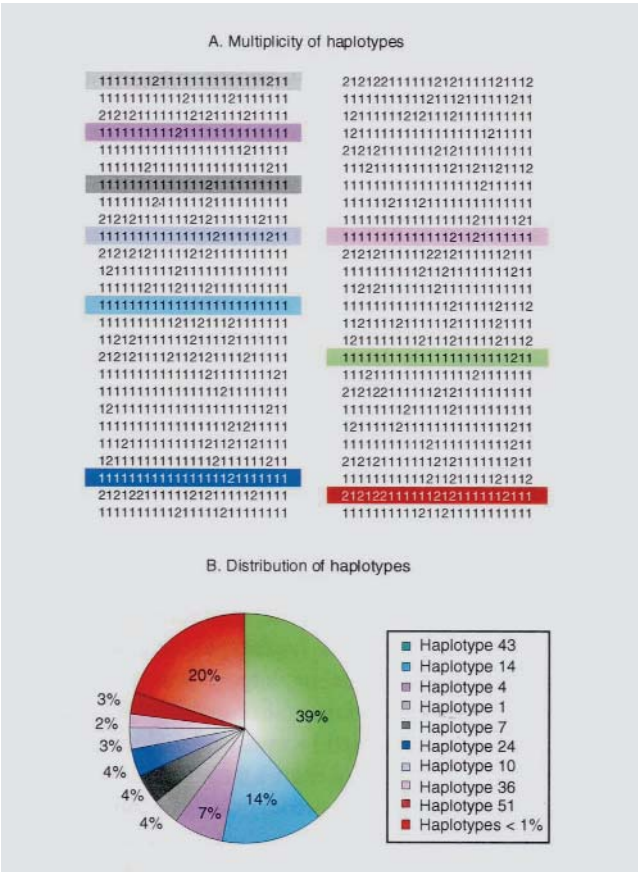

Figure 4. The human μ opiate receptor study. **A.** The multiplicity of haplotypes. The polymorphic sites are specified by positions 1–25, marked by an asterisk in *Figure 2*; 1, identical with the reference sequence; 2, different from the reference sequence. **B.** Distribution of haplotypes. Haplotype frequencies are given in percentages, different haplotypes are color-coded and correspond to the haplotypes marked in A.
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association with any single haplotype. This will require novel approaches to cope with the multiplicity of haplotypes. An appropriate approach seems the classification of haplotypes into functionally related (ideally functionally equivalent) ones based on sequence-structure-function similarity. Once a classification has been derived, the haplotype frequencies of cases and controls in the different classes can be compared. By this approach, the multiplicity of haplotypes could be condensed to two functionally related categories, one of which was more frequent in substance-dependent individuals.[9] Common to this category was a characteristic pattern of sequence variants located in the 5' regulatory region, reflecting a specific constellation of putative transcription regulatory motifs that may confer different regulatory properties.[9,12] Taken together, this analysis at the gene level demonstrates a remarkable gene sequence and haplotype diversity, the rule rather than the exception for the majority of candidate genes. This work provides, moreover, an example of approaches that can be successfully applied to establish complex genotype-phenotype relationships against a background of high natural genome sequence diversity.

Perspectives

Observed diversity presents challenges to the traditional views of the concept of "a" gene with far-reaching implications on the analysis of "gene"-"function" relationships.[13,14] Classical single mutation analysis no longer appears appropriate. The units of functional analysis must be the entire individual sequence of haplotypes, involving potentially abundant variation in *all* regulatory, coding, and intronic sequences. Analysis will include the spectrum of haplotypes existing in a population, and the pairs of haplotypes existing in each individual. We have now determined in a first comprehensive study the molecular haplotypes of a key candidate gene in hundreds of individuals, confirming the existence of multiple individually different forms of a gene at the molecular level (Hoehe et al, in preparation). This work provides at the same time knowledge of the concrete molecular templates to allow dissection of what may be an entire spectrum of functions underlying molecular gene diversity.

At this stage, individual variation and its functional implications have been addressed at the level of a single gene only. However, this is integral part of an entire network of genes as a higher-level functional unit; multiple individual molecular haplotypes interact to produce a common output signal. Thus, progress in the future is expected to come from whole systems analysis-based approaches,[13] integrating individual variation in all genes involved in all pathways of relevance. This will prepare the basis for "personalized" medicine in its true sense. ❑

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