Neuroscience of Psychoactive Substance Use and Dependence

SUMMARY

World Health Organization
Geneva

WHO Library Cataloguing-in-Publication Data

Neuroscience of psychoactive substance use and dependence : summary.

1. Psychotropic drugs - pharmacology 2. Substance-related disorders - physiopathology 3. Psychopharmacology 4. Brain - drug effects I. World Health Organization.

ISBN 92 4 159124 2 (NLM classification: WM 270)

© World Health Organization 2004

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 2476; fax: +41 22 791 4857; email: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

Printed in Switzerland

Contents

Foreword 5

Acknowledgements 6

Introduction 7

Global use of psychoactive substances and burden to health 8
- Tobacco use 8
- Alcohol use 8
- Illicit substance use 9
- Burden of disease 10

Adverse consequences of psychoactive substances and their mechanisms of action 12

Substance use and dependence in relation to neuroscience 12

Neuroanatomy, neurobiology, and pharmacology 13
- Brain mechanisms 15

Psychopharmacology of dependence for different substance classes 17

Neurobiological and biobehavioural basis of the development of substance dependence 20
- Dependence as a learning process involving key brain regions 20
- Biobehavioural processes underlying dependence 20
- Mesolimbic dopamine pathway 20
- Motivation and incentive 21

Genetic basis of individual differences in susceptibility to substance dependence 22

Comorbidity of substance dependence and mental illness 25

Treatment and prevention: links with neuroscience, and ethical issues 26
- Types of treatment 26
- Ethical issues in neuroscience research on substance dependence 30
- Ethics and types of neuroscience research on substance dependence 30

Conclusion and implications for public health policy 32

References 34

Foreword

Substance use and dependence cause a significant burden to individuals and societies throughout the world. The World Health Report 2002 indicated that 8.9% of the total burden of disease comes from the use of psychoactive substances. The report showed that tobacco accounted for 4.1%, alcohol 4%, and illicit drugs 0.8% of the burden of disease in 2000. Much of the burden attributable to substance use and dependence is the result of a wide variety of health and social problems, including HIV/AIDS, which is driven in many countries by injecting drug use.

This neuroscience report is the first attempt by WHO to provide a comprehensive overview of the biological factors related to substance use and dependence by summarizing the vast amount of knowledge gained in the last 20-30 years. The report highlights the current state of knowledge of the mechanisms of action of different types of psychoactive substances, and explains how the use of these substances can lead to the development of dependence syndrome.

Though the focus is on brain mechanisms, the report nevertheless addresses the social and environmental factors which influence substance use and dependence. It also deals with neuroscience aspects of interventions and, in particular, the ethical implications of new biological intervention strategies.

The various health and social problems associated with use of and dependence on tobacco, alcohol and illicit substances require greater attention by the public health community and appropriate policy responses are needed to address these problems in different societies. Many gaps remain to be filled in our understanding of the issues related to substance use and dependence but this report shows that we already know a great deal about the nature of these problems that can be used to shape policy responses.

This is an important report and I recommend it to a wide audience of health care professionals, policy makers, scientists and students.

LEE Jong-wook
Director General
World Health Organization

Acknowledgements

This summary was prepared by Franco Vaccarino and Susan Rotzinger of the Centre for Addiction and Mental Health, Toronto, Canada, with contributions from Isidore Obot and Maristela Monteiro. Vladimir Poznyak and Nina Rehn helped with their advice and comments. Mylene Schreiber and Tess Narciso provided logistical support throughout the preparation and publication of the summary.

The World Health Organization also acknowledges the contributions of the following individuals to the book on which this summary is based:
Helena M. T. Barros, Lucy Carter, David Collier, Gaetano Di Chiara, Patricia Erickson, Sofia Gruskin, Wayne Hall, Jack Henningfield, Kathleen M. Kantak, Brigitte Kieffer, Harald Klingemann, Mary Jeanne Kreek, Sture Liljequist, Rafael Maldonado, Athina Markou, Gina Morato, Katherine Morley, Karen Plafker, Robin Room, Andrey Ryabinin, Allison Smith, Rachel Tyndale, Claude Uehlinger, Frank Vocci, and David Walsh.

This report has been produced within the framework of the mental health Global Action Programme (mhGAP) of the Department of Mental Health and Substance Abuse, World Health Organization, under the direction of Benedetto Saraceno.

Introduction

This report describes the current understanding of the neuroscience of psychoactive substance use and dependence.[1] Neuroscience is concerned with all of the functions of the nervous system, particularly the brain. Psychoactive substances have the ability to change consciousness, mood, and thoughts. This report draws on the explosive growth in knowledge in neuroscience in recent decades, which has transformed our understanding of the actions of psychoactive substances, and contributed new insights into why many people use psychoactive substances, and why some use them to the extent of causing themselves harm or of becoming dependent.

The need for this report comes from these advances in neuroscience research, which have shown that substance dependence is a chronic, relapsing disorder with a biological and genetic basis, and is not simply due to lack of will or desire to quit. Effective treatments and interventions for substance dependence do exist, and involve both pharmacological and behavioural interventions. The stigma associated with substance use and dependence can prevent individuals from seeking treatment, and can prevent adequate policies regarding prevention and treatment to be implemented. A WHO study of attitudes to 18 disabilities in 14 countries found that "substance addiction" ranked at or near the top in terms of social disapproval or stigma, and that "alcoholism" ranked not far behind in most of the societies studied (1). Neuroscience-based knowledge of substance dependence affords an opportunity to clarify misunderstandings, and to eliminate incorrect and damaging stereotypes.

This report covers information on the global burden of substance use and dependence, including global statistics, individual and societal consequences of the acute and chronic use of psychoactive substances, and illustrates the pervasive effects of substance dependence throughout the world. The effects of psychoactive substances on the brain, and how they promote the development of dependence is discussed, along with the genetic and environmental factors that may predispose or protect individuals from developing substance dependence. Many treatments, both biological and psychological, are available and are discussed, along with the ethical implications of such treatments. This report concludes with key recommendations and implications of neuroscientific knowledge of substance dependence for public health policy.

[1] The term "substance use" is employed in this document to refer to any form of self-administration of a psychoactive substance. It is used instead of the term "substance abuse" as a broader term encompassing all levels of substance involvement, including occasional and prolonged consumption of a substance.

Global use of psychoactive substances and burden to health

Tobacco use

Global use of alcohol, tobacco, and other controlled substances is growing rapidly, and contributing significantly to the global burden of disease. Table 1 shows the prevalence of smoking among adults and youths in selected countries. Smoking is spreading rapidly in developing countries and among women. Currently, 50% of men and 9% of women in developing countries smoke, as compared with 35% of men and 22% of women in developed countries. China, in particular, contributes significantly to the epidemic in developing countries. Indeed, the per capita consumption of cigarettes in Asia and the Far East is higher than in other parts of the world, with the Americas and Eastern Europe following closely behind (2).

Table 1. Prevalence of smoking among adults and youths in selected countries

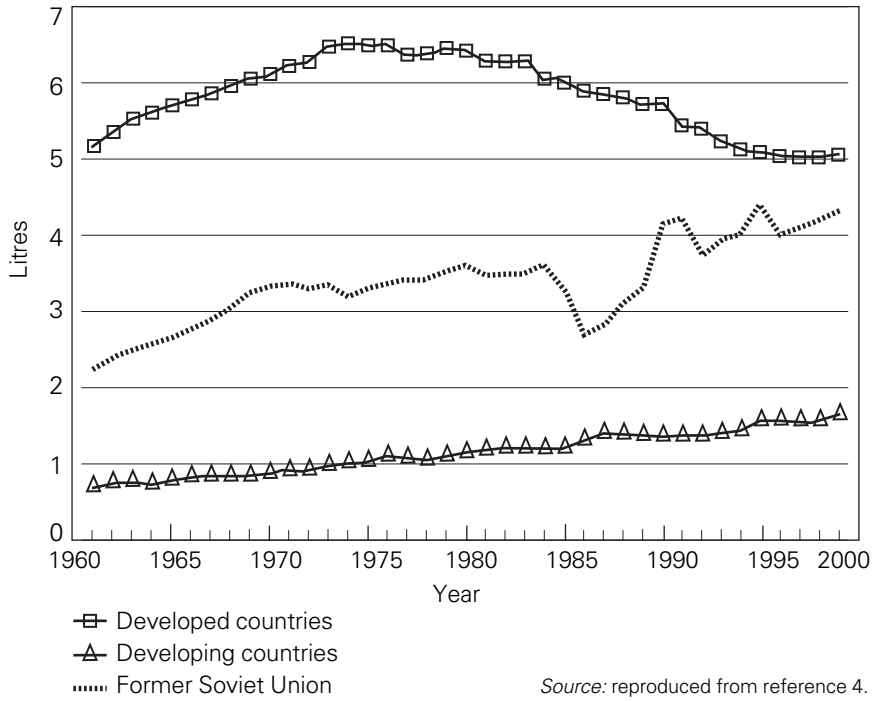
Country	Annual per capita consumption of cigarettes	Prevalence of smoking (%)			
		Adults		Youths	
		Males	Females	Males	Females
Argentina	1495	46.8	34.4	25.7	30.0
Bolivia	274	42.7	18.1	31.0	22.0
Chile	1202	26.0	18.3	34.0	43.4
China	1791	66.9	4.2	14.0	7.0
Ghana	161	28.4	3.5	16.2	17.3
Indonesia	1742	59.0	3.7	38.0	5.3
Jordan	1832	48.0	10.0	27.0	13.4
Kenya	200	66.8	31.9	16.0	10.0
Malawi	123	20.0	9.0	18.0	15.0
Mexico	754	51.2	18.4	27.9	16.0
Nepal	619	48.0	29.0	12.0	6.0
Peru	1849	41.5	15.7	22.0	15.0
Poland	2061	44.0	25.0	29.0	20.0
Singapore	1230	26.9	3.1	10.5	7.5
Sri Lanka	374	25.7	1.7	13.7	5.8
USA	2255	25.7	21.5	27.5	24.2

Source: reproduced from reference 2.

Alcohol use

Alcohol and tobacco are similar in several ways: both are legal substances, both are widely available in most parts of the world, and both are marketed aggressively by transnational corporations that target young people in advertising and promotion campaigns. According to the *Global status report on alcohol* (3) and as shown in Fig. 1 below, the level of consumption of alcohol has declined in the past twenty

Figure 1. Adult (15+) Per Capita Alcohol Consumption by Development Status



Source: reproduced from reference 4.

years in developed countries, but is increasing in developing countries, especially in the Western Pacific Region, where the annual per capita consumption among adults ranges from 5 to 9 litres of pure alcohol, and also in countries of the former Soviet Union (3). To a great extent the rise in the rate of alcohol consumption in developing countries is driven by rates in Asian countries. The level of consumption of alcohol is much lower in the African, Eastern Mediterranean, and South-East Asian regions.

Illicit substance use

Data from the United Nations Office on Drugs and Crime (UNODC) show large-scale seizures of cocaine, heroin, cannabis and amphetamine-type stimulants in different parts of the world. Availability of cocaine, heroin and cannabis depends on the level of cultivation in source countries and on the success or failure of trafficking organizations. However, even with increased levels of law enforcement activities, there always seems to be enough available to users.

According to UNODC estimates (5), about 200 million people make illicit use of one type of illicit substance or another. Table 2 shows that cannabis is the most common illicit substance used, followed by amphetamines, cocaine and the opioids. Illicit substance use is a predominantly male activity, much more so than cigarette

smoking and alcohol consumption. Substance use is also more prevalent among young people than in older age groups. The data in Table 2 show that 2.7% of the total global population and 3.9% of people 15 years and above had used cannabis at least once between 2000 and 2001. In many developed countries, for example Canada, the USA and European countries, more than 2% of youths reported heroin use and almost 5% reported smoking cocaine in their lifetime. Indeed, 8% of youths in western Europe and more than 20% of those in the USA have reported using at least one type of illicit substance other than cannabis. There is evidence of rapid

Table 2. Annual prevalence estimates of global illicit substance use, 2000-2001.

	All illicit substances	Cannabis	Amphetamine-type stimulants		Cocaine	All opioids	Heroin
			Amphetamines	Ecstasy			
Number of users (in millions)	200	162.8	34.3	7.7	14.1	14.9	9.5
Proportion of global population (%)	3.4	2.7	0.6	0.1	0.2	0.3	0.16
Proportion of population 15 years and above (%)	4.7	3.9	0.8	0.2	0.3	0.4	0.22

Source: reproduced from reference 5.

increases in the use of amphetamine-type stimulants among teenagers in Asia and Europe. Injecting substance use is also a growing phenomenon, with implications for the spread of HIV infection in an increasing number of countries (Box 1).

Burden of disease

There is now a developing tradition of estimating the contribution of alcohol, tobacco and illicit substance use to the global burden of disease (GBD). The first significant attempt at this was in the WHO project on the Global burden of disease and injury (6). Based on a standard of measurement known as disability-adjusted life years (DALYs), estimates of the burden imposed on society due to premature death and years lived with disability were assessed. The global burden of disease project showed that tobacco and alcohol were major causes of mortality and disability in developed countries, with the impact of tobacco expected to increase in other parts of the world.

Table 3 offers ample evidence that the burden of ill-health from use of psychoactive substances, taken together, is substantial: 8.9% in terms of DALYs. However, GBD findings re-emphasize that the main global health burden is due to licit rather than illicit substances.

Box 1.

Injecting substance use and HIV/AIDS

Globally, the percentage of persons living with HIV/AIDS who also inject psychoactive substances is 5% or 2.1 million people in more than 100 countries.

Globally, the proportion of adults living with HIV/AIDS who acquired HIV through injecting psychoactive substances is 5%, though this number varies greatly by region. It is as high as 50-90% in eastern Europe, Central Asia, East Asia, and the Pacific regions, and 25-50% in North America and western Europe.

Treatment and prevention of injection of psychoactive substances can help in the prevention of the spread of HIV infection.

HIV/AIDS prevention and care should be integrated into substance dependence treatment.

Table 3. Percentage of total global mortality and DALYs attributable to tobacco, alcohol and illicit substances

Risk factor	High mortality developing countries		Low mortality developing countries		Developed countries		World-wide
	Males	Females	Males	Females	Males	Females	
Mortality							
Tobacco	7.5	1.5	12.2	2.9	26.3	9.3	8.8
Alcohol	2.6	0.6	8.5	1.6	8.0	-0.3	3.2
Illicit drugs	0.5	0.1	0.6	0.1	0.6	0.3	0.4
DALYs							
Tobacco	3.4	0.6	6.2	1.3	17.1	6.2	4.1
Alcohol	2.6	0.5	9.8	2.0	14.0	3.3	4.0
Illicit drugs	0.8	0.2	1.2	0.3	2.3	1.2	0.8

Source: reproduced from reference 7.

Among the ten leading risk factors in terms of avoidable disease burden, tobacco was fourth and alcohol fifth for 2000, and remains high on the list in the 2010 and 2020 projections. Tobacco and alcohol contributed 4.1% and 4.0%, respectively, to the burden of ill health in 2000, while illicit substances contributed 0.8%. The burdens attributable to tobacco and alcohol are particularly acute among males in the developed countries (mainly Europe and North America). This is because men in developed countries have a long history of significant involvement with tobacco and

alcohol and because people in these countries live long enough for substance-related health problems to develop.

Adverse consequences of psychoactive substances and their mechanisms of action

Mostly, people use psychoactive substances because they expect to benefit from their use, whether by pleasure or by the avoidance of pain, including social uses. But using psychoactive substances also carries with it the potential for harm, whether in the short run or in the longer term.

The main harmful effects due to substance use can be divided into four categories (see Fig. 2). First there are the chronic health effects. For alcohol this includes liver cirrhosis and a host of other chronic illnesses; for tobacco taken in cigarette form, this includes lung cancer, emphysema and other chronic illnesses. Through the sharing of needles, heroin use by injection is a main vector for transmission of infectious agents such as HIV (see Box 1) and hepatitis B and C virus in many countries. Second there are the acute or short-term biological health effects of the substance. Notably, for drugs such as opioids and alcohol, these include overdose.

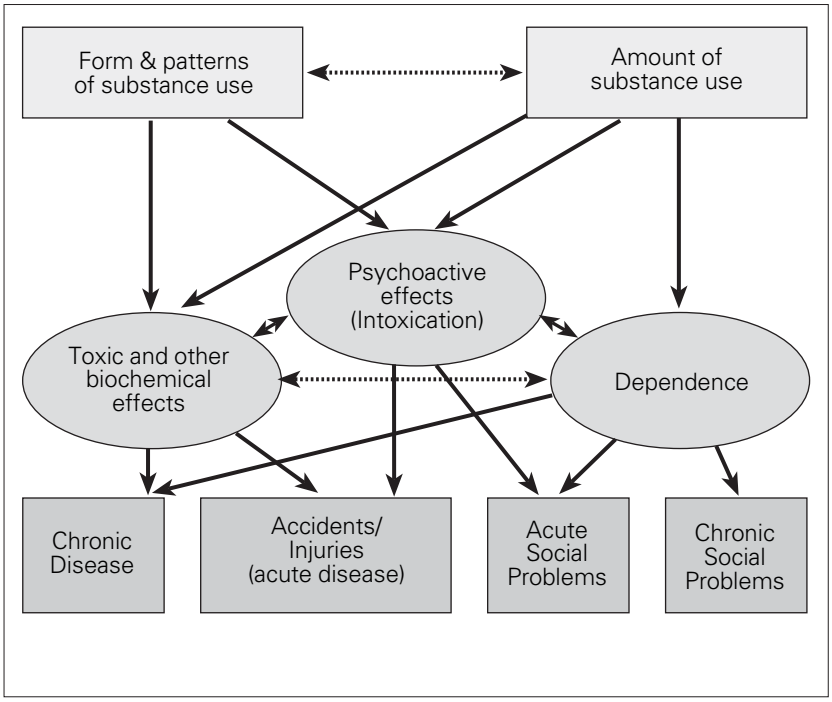
Also classed in this category are the casualties due to the substance's effects on physical coordination, concentration and judgement, in circumstances where these qualities are demanded. Casualties resulting from driving after drinking alcohol or after other drug use feature prominently in this category, but other accidents, suicide and (at least for alcohol) assaults are also included. The third and fourth categories of harmful effects comprise the adverse social consequences of the substance use: acute social problems, such as a sudden break in a relationship or an arrest, and chronic social problems, such as defaults in working life or in family roles.

Substance use and dependence in relation to neuroscience

As defined by ICD-10, substance dependence includes six criteria (see Box 2); a person with at least three of these is diagnosable as "dependent". The criteria used by the American Psychiatric Association are similar.

As can be seen from Box 2, the two criteria most easily measured biologically are the third and fourth: withdrawal – the occurrence of unpleasant physical and psychological symptoms when use of the substance is reduced or discontinued, and tolerance – the fact that increased amounts of the substance are required to achieve the same effect, or that the same amount produces less effect. The other four criteria for dependence include elements of cognition, which are less accessible to biological measurement, but are becoming measurable using improved neuroimaging techniques. It is also important to keep in mind that the criteria for dependence include health and social consequences.

Figure 2. Mechanisms relating psychoactive substance use to health and social problems



Source: adapted from reference 8.

Neuroanatomy, neurobiology, and pharmacology

Substance dependence is a disorder of altered brain function brought on by the use of psychoactive substances. These substances affect normal perceptual, emotional and motivational processes in the brain. However, as with any disorder specific to an organ or system, one must first understand the normal function of that organ or system to understand its dysfunction. Because the output of the brain is behaviour and thoughts, disorders of the brain can result in highly complex behavioural symptoms. The brain can suffer many types of diseases and traumas, from neurological conditions such as stroke and epilepsy, to neurodegenerative diseases such as Parkinson disease and Alzheimer disease, and infectious or traumatic brain injuries. In each of these cases, the behavioural output is recognized as being part of the disorder.

Similarly, with dependence, the behavioural output is complex, but is mostly related to the short-term or long-term effects of substances on the brain. The tremors of Parkinson disease, the seizures of epilepsy, even the melancholy of depression are widely recognized and accepted as symptoms of an underlying brain pathology.

Box 2.

Criteria for substance use dependence in ICD-10

Three or more of the following must have been experienced or exhibited at some time during the previous year:

1. A strong desire or sense of compulsion to take the substance;
2. Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. A physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms ;
4. Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses;
5. Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects ;
6. Persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to heavy substance use, or substance-related impairment of cognitive functioning. Efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Source: reproduced from reference 9.

Substance dependence has not previously been recognized as a disorder of the brain, in the same way that psychiatric and mental illnesses were previously not viewed as such. However, with recent advances in neuroscience, it is clear that substance dependence is as much a disorder of the brain as any other neurological or psychiatric illness. New technologies and research provide a means to visualize and measure changes in brain function from the molecular and cellular levels, to changes in complex cognitive processes that occur with short-term and long-term substance use.

Major advances in neuroscience research on substance dependence have come from the development and use of techniques that allow the visualization of brain function and structure in the living human brain, known as neuroimaging techniques. Using these techniques, researchers can see what happens from the level of receptors to global changes in metabolism and blood flow in various brain regions. Images can be observed when substances are administered, to see where they act in the brain, and also following long-term substance use to observe the effects on normal brain functions. One example of an imaging technique is magnetic

resonance imaging (MRI), which uses magnetic fields and radio waves to produce high-quality two- or three-dimensional images of brain structures (10-12). The brain can be imaged with a high degree of detail. Although MRI gives only static pictures of brain anatomy, functional MRI (fMRI) can provide functional information about brain activity by comparing oxygenated and deoxygenated blood.

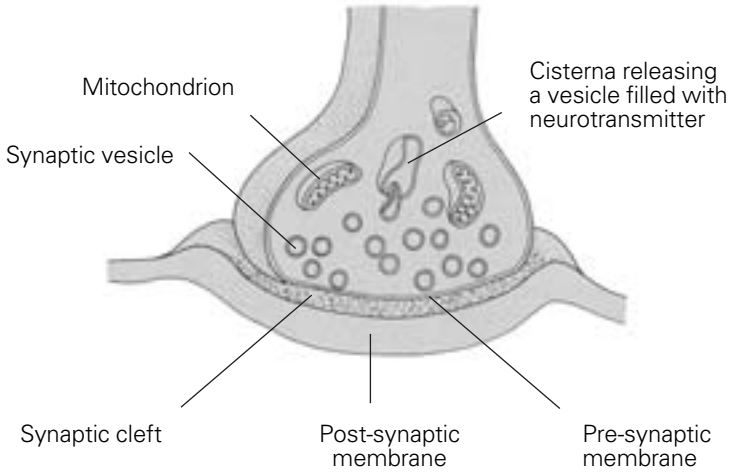
Another important and useful imaging technique is positron emission tomography (PET) (10-12). PET scans provide information about the metabolic activity in a certain brain region. Most commonly, a person is injected with a radioactive compound that can be followed through the bloodstream in the brain. This can be visualized as two- or three-dimensional images, with different colours on a PET scan indicating different levels of radioactivity (blues and greens indicating areas of lower activity, and yellows and reds indicating areas of higher activity). Using different compounds, PET scans can be used to show blood flow, oxygen and glucose metabolism, and drug concentrations in the tissues of the living brain.

Brain mechanisms: neurobiology and neuroanatomy

The brain is highly organized into a number of different regions with specialized functions. A region of the brain known as the hindbrain contains structures that are vital to the maintenance of life, such as centres that control breathing and wakefulness. The midbrain is a region that contains many areas that are important to a discussion of substance dependence, as these regions are involved in motivation and learning about important environmental stimuli, and reinforcing behaviours that lead to pleasurable and life-sustaining consequences, such as eating and drinking. The forebrain is more complex, and in humans the cerebral cortex of the forebrain is highly developed to give the ability for abstract thought and planning, and for associations of thoughts and memories. Specific regions of the forebrain have been shown by brain imaging techniques to be activated by stimuli that induce "cravings" in people with substance dependence, and other regions have been shown to function abnormally in people following acute or chronic substance use and dependence.

Communication in the brain takes place between the individual cells or neurons. The neurons communicate with one another through chemical messengers which are released at synapses (see Fig. 3). When one neuron is excited, an electrical signal is sent from the cell body, down an elongated process known as an axon, which can extend short distances to nearby neurons, or can extend long distances to other brain regions. At the end of the axon is a terminal button. To communicate the message from the terminal button of one axon, to the next neuron, a space must be crossed. This space is known as the synapse or synaptic cleft. Chemical messengers are released from the neuron sending the message, or presynaptic neuron, to the receiving, or postsynaptic neuron. These chemicals, or neurotransmitters have specific structures and functions, and which chemical is released depends upon the type of neuron. Some of the more well-studied neurotransmitters that are relevant to psychoactive substances are dopamine, serotonin, norepinephrine, GABA, glutamate and the endogenous opioids.

Figure 3. A terminal button and synapse
This figure shows the normal function of neurotransmitter release

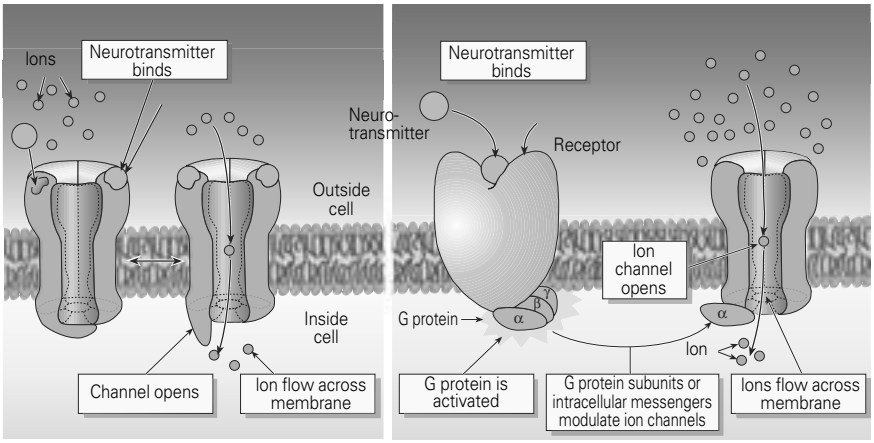


Source: Pinel JPJ (1990) *Biopsychology. Boston,* MA Allyn & Bacon.
Reproduced with permission from the publishers.

The brain contains dozens of different types of chemical messengers. Each specific neurotransmitter binds to a specific receptor, like a lock to a key (see Fig. 4). Binding of neurotransmitter to receptor can result in a number of different changes in the postsynaptic membrane. Receptors are named according to the type of neurotransmitter that they bind preferentially, for example, dopamine receptors and serotonin receptors. There are also many subtypes of each type of receptor. Psychoactive substances are able to mimic the effects of naturally occurring or endogenous neurotransmitters, or to interfere with normal brain function by blocking normal function, or by altering the normal storage, release and removal of neurotransmitters. One important mechanism by which psychoactive substances act is to block the reuptake of a neurotransmitter after it is released from the presynaptic terminal. Reuptake is a normal mechanism by which the transmitter is removed from the synapse by the presynaptic membrane. By blocking reuptake, the normal effects of the neurotransmitter are exaggerated. Psychoactive substances that bind and enhance the function of receptors are known as agonists, whereas those that bind to block normal function are known as antagonists.

Figure 4. Two types of chemical synapses

The first diagram shows binding to and opening of a ligand-gated ion channel. The second diagram demonstrates activation of a G protein-coupled receptor resulting in the opening of an ion channel via a second messenger.



Source: Rosenzweig MR, Leiman AL, Breedlove SM (1999) *Biological psychology*, 2nd ed. Sunderland, MA, Sinauer Associates.
Reproduced with permission from the publishers.

Psychopharmacology of dependence for different substance classes

The most common psychoactive substances can be divided into depressants (e.g. alcohol, sedatives/hypnotics, volatile solvents), stimulants (e.g. nicotine, cocaine, amphetamines, ecstasy), opioids (e.g. morphine and heroin), and hallucinogens (e.g. PCP, LSD, cannabis).

Different psychoactive substances have different ways of acting in the brain to produce their effects. They bind to different receptor types, and can increase or decrease the activity of neurons through several different mechanisms. Consequently, they have different behavioural effects, different rates of development of tolerance, different withdrawal symptoms, and different short-term and long-term effects (Table 4). However, psychoactive substances do share similarities in the way they affect important regions of the brain involved in motivation, and this is a significant feature with regard to the theories of the development of substance dependence.

Table 4. Summary of psychoactive substance effects

Substance	primary mechanism of action	tolerance and withdrawal	prolonged use
Ethanol	Increases the inhibitory effects of GABA and decreases the excitatory effects of glutamate. Reinforcing effects probably related to increased activity in mesolimbic dopamine pathway.	Tolerance develops due to increased metabolism in the liver, and changes to receptors in the brain. Withdrawal from chronic use can include shaking, perspiration, weakness, agitation, headache, nausea, vomiting, seizures, delirium tremens.	Altered brain function and structure, particularly in prefrontal cortex; cognitive impairments; decreased brain volume.
Hypnotics and sedatives	Facilitate the actions of endogenous inhibitory neurotransmitters.	Tolerance develops rapidly to most effects (except anti-convulsant), due to changes in brain receptors. Withdrawal characterized by anxiety, arousal, restlessness, insomnia, excitability, seizures.	Memory impairment.
Nicotine	Activates nicotinic cholinergic receptors. Increases dopamine synthesis and release.	Tolerance develops through metabolic factors, as well as receptor changes. Withdrawal characterized by irritability, hostility, anxiety, dysphoria, depressed mood, decreased heart rate, increased appetite.	Health effects due to smoking are well-documented; difficult to dissociate effects of nicotine from other components of tobacco.
Opioids	Activates receptors called mu and delta opioid receptors. These receptors are abundant in brain areas involved in responses to psychoactive substances, such as in the mesolimbic dopamine pathway.	Tolerance occurs due to short-term and long-term receptor changes, and adaptations in intracellular signalling mechanisms. Withdrawal can be severe and is characterized by watering eyes, runny nose, yawning, sweating, restlessness, chills, cramps, muscle aches.	Long-term changes in opioid receptors and peptides; adaptations in reward, learning, stress responses.

Table 4. (continued)

Substance	primary mechanism of action	tolerance and withdrawal	prolonged use
Cannabinoids	Activates cannabinoid receptors. Also increases dopamine activity in the meso-limbic pathway.	Tolerance develops rapidly to most effects. Withdrawal is rare, perhaps due to long half-life of cannabinoids.	Long-term exposure to cannabis may produce long-lasting cognitive impairment. Risk of exacerbation of mental illness is also present.
Cocaine	Cocaine blocks the uptake of transmitters such as dopamine, thereby prolonging its effects.	Perhaps short-term acute tolerance occurs. There is not much evidence of withdrawal, however, depression is common among dependent persons who stop using the drug	Cognitive deficits, abnormalities in specific regions of the cortex, impairments in motor function, and decreased reaction times have been found.
Ampheta-mines	Increases release of dopamine from nerve terminals and inhibits the reuptake of dopamine and related transmitters.	Tolerance develops rapidly to behavioural and physiological effects. Withdrawal is character-ized by fatigue, depres-sion, anxiety and intense craving for the drug.	Sleep disturbances, anxiety, decreased appetite; alterations in brain dopamine recep-tors, regional metabolic changes, motor and cognitive impairments (13, 14).
Ecstasy	Increased serotonin re lease and blockade of reuptake.	Tolerance may develop in some individuals. Most common withdrawal symptoms are depression and insomnia.	Damages brain seroto-nin systems, leads to behavioural and physiological conse-quences. Long-term psychiatric and physical problems such as impair-ments of memory, deci-sion-making and self-control, paranoia, depression and panic attacks (15, 16).
Inhalants	Most likely affects inhibitory transmitters, similarly to other sedatives and hypnotics. Mesolimbic dopamine activated.	Some tolerance develops, but is difficult to estimate. There is increased susceptibility to seizures during withdrawal.	Changes in dopamine receptor binding and function; decreased cognitive function; psychiatric and neurological problems.
Hallucinogens	Different substances in this class act on different brain receptors, such as serotonin, glutamate, and acetylcholine receptors.	Tolerance develops rapidly to physical and psychological effects. There is no evidence of withdrawal.	Acute or chronic psycho-tic episodes, flashbacks or re-experiencing of substance effects long after substance use.

Neurobiological and biobehavioural basis of the development of substance dependence

Dependence as a learning process involving key brain regions

The development of dependence can be seen as part of a learning process, in the sense that enduring changes in behaviour result from interactions with psychoactive substances and their associated environments. A person takes a substance and experiences the psychoactive effect, which is highly rewarding or reinforcing, and which activates circuits in the brain that will make it more likely that this behaviour will be repeated.

However, the rewarding effects of substances alone cannot account for why some psychoactive substances can lead to all of the behaviours associated with dependence (Box 2). Similarly, physical dependence on substances, as evidenced by withdrawal symptoms when substance use is discontinued, may contribute to substance use and dependence, but cannot alone explain why substance dependence develops and is maintained, especially after long periods of abstinence. What is it about psychoactive substances that causes people to lose their jobs and families in pursuit of these substances? What is the process by which substance-taking behaviour, in certain individuals, evolves into compulsive patterns of substance-seeking and substance-taking behaviour that take place at the expense of most other activities; and what causes the inability to cease substance-taking, that is, the problem of relapse? A complex interplay of psychological, neurobiological and social factors appears to be responsible.

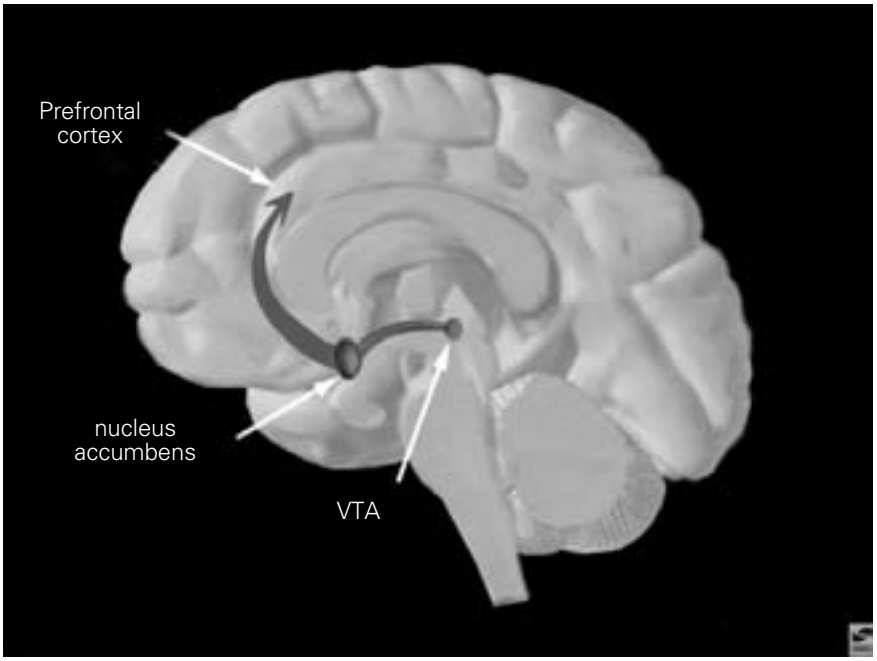
Biobehavioural processes underlying dependence

The brain has systems that have evolved to guide and direct behaviour toward stimuli that are critical to survival. For example, stimuli associated with food, water, and a mate all activate specific pathways, and reinforce the behaviours that lead to the obtaining of corresponding goals. Psychoactive substances artificially activate these same pathways, but very strongly, leading to enhanced motivation to continue this behaviour. Thus, according to this theory, dependence is the result of a complex interaction of the physiological effects of substances on brain areas associated with motivation and emotion, combined with "learning" about the relationship between substances and substance-related cues.

Mesolimbic dopamine pathway

Although each class of psychoactive substance has its own unique primary pharmacological mechanism of action (Table 4), many also activate the mesolimbic dopamine pathway (See Fig. 5), although through different mechanisms depending on the substance. The mesolimbic dopamine pathway resides in an area of the brain known as the midbrain**,** and is the system that is most strongly implicated in the dependence-producing potential of psychoactive substances (17). Two areas that are very important in substance dependence are the ventral tegmental area (VTA), and a region that it communicates with, known as the nucleus accumbens. The

Figure 5. Mesolimbic dopamine pathway



Source: NIDA website http://www.drugabuse.gov/pubs/teaching/largegifs/slide-9.gif.

ventral tegmental area is an area that is rich in neurons containing the neurotransmitter dopamine. The cell bodies of these neurons send projections to regions of the brain involved in emotions, thoughts, memories, and planning and executing behaviours. The nucleus accumbens is a very important brain area involved in motivation and learning, and signalling the motivational value of stimuli (18, 19). Psychoactive substances increase the release of dopamine in the nucleus accumbens, which is thought to be an important event in reinforcement.

Motivation and incentive

Motivation and incentive are important concepts with regard to substance dependence. The mesolimbic dopamine pathway of the brain has been shown to be closely involved in motivational processes: that is to say, stimuli that are recognized as being important to survival are given special importance in the brain. Motivation is the allotment of attentional and behavioural resources to stimuli in relation to their predicted consequences. Incentives are stimuli that elicit a response on the basis of their predicted consequences. For example, if a person is not hungry,

the visual and olfactory stimuli associated with food (incentives) will have little effect on his or her behaviour or attention (motivation). However, if the person is hungry, the sight and smell of food may cause him or her to pay attention, and to take steps to obtain food. If the person is starving and has no means of obtaining food, he or she might even steal or commit a crime to obtain it. This is known as incentive-motivational responding**,** or responding in terms of both the incentive value of the stimulus and the motivation to obtain the stimulus.

In substance dependence, psychoactive substances repeatedly activate the motivational systems of the brain that are normally activated by such important stimuli as food, water, danger, and mates. The brain is "tricked" by the substances into responding as if the substances and their associated stimuli are biologically needed. With repeated exposure, the association becomes stronger and stronger, evoking a larger behavioural and neurochemical response. This is known as incentive sensitization, whereby psychoactive substances and the stimuli associated with their use take on increasing motivational and behavioural significance (20). Through associative learning processes, the motivation to use psychoactive substances can be strongly activated by stimuli (environments, people, objects) associated with substance use, causing the desire or craving that can overwhelm people and cause relapse to substance use, even after long periods of abstinence. This also contributes to our understanding of why withdrawal symptoms alone are not enough to explain the full spectrum of substance dependence, because even people who have completely withdrawn from a particular substance can relapse to substance use in response to a variety of different situations.

In thinking about dependence, it is important to remember that over a lifespan many people experiment with a variety of potentially dependence-producing substances, but most do not become dependent. There are also individual differences in susceptibility to substance dependence due to environmental and genetic factors.

Genetic basis of individual differences in susceptibility to substance dependence

There are many individual, cultural, biological, social and environmental factors that converge to increase or decrease the odds that a particular individual will consume a psychoactive substance , and to what extent . Though the factors shown in Box 3 are more related to the initiation of substance use than to dependence, many of them are common to both phenomena.

One aspect of neuroscience research examines how psychoactive substances act in terms of the common biological inheritance shared by all humans. The counterpoint to this is the genetic research that focuses on the differences in action of the substances between one human and another that are attributable to different genetic inheritances. In addition to social and cultural factors, differences in genetic makeup explain a substantial proportion of the variation in psychoactive substance use and dependence among individuals. However, it is not a simple task to identify the genes that are involved.

Box 3. Risk and protective factors for substance use

Risk factors	Protective factors
Environmental	**Environmental**
• availability of drugs	• economic situation
• poverty	• situational control
• social change	• social support
• peer culture	• social integration
• occupation	• positive life events
• cultural norms, attitudes	
• policies on drugs, tobacco and alcohol	
Individual	**Individual**
• genetic disposition	• good coping skills
• victim of child abuse	• self-efficacy
• personality disorders	• risk perception
• family disruption and dependence problems	• optimism
• poor performance at school	• health-related behaviour
• social deprivation	• ability to resist social pressure
• depression and suicidal behaviour	• general health behaviour

Source: reproduced from references 21–24.

Although some illnesses are caused by a single gene, such as in Huntington's disease, other disorders, known as complex disorders, appear to be caused by the interaction of several genes with environmental factors. Substance dependence is one such complex disorder. Thus, exposure to psychoactive substances could have a much greater effect on somebody who carries a genetic vulnerability to substance dependence, than on someone who does not. This also makes the study of the genetics of substance dependence more complicated, although great progress has been made in recent years to identify the genes that may contribute to the development of dependence. Studies of patterns of inheritance in families, in identical and fraternal twins, and in adopted individuals, provide information on the extent to which inherited factors play a role in substance dependence. Other types of studies look at the inheritance of related traits, to try to identify *regions* of genes that

might be important. Candidate gene studies examine genes that might reasonably be thought to be involved in substance dependence, such as opioid receptor genes for opioid dependence.

There is evidence of significant heritability of tobacco use among different populations, sexes, and ages (25, 26). Studies suggest that there are likely to be many different genes that contribute to the development and persistence of smoking (27-29). Genes involved in nicotine metabolism may be important risk factors for smoking; and variation in these genes is likely to be a major determinant of brain nicotine levels and accumulation.

There is significant heritability of alcohol dependence, as well as heritability of frequency and quantity of alcohol consumed (30-37). Genes that may be important for this association are involved with alcohol metabolism (38), and receptors for the neurotransmitters GABA (38), serotonin (39), and dopamine (38). Genetic variations in alcohol metabolizing enzymes have also been identified as possibly underlying some of the variation in alcohol consumption (40-42). There is evidence from some studies that the heritability of opioid dependence is high, estimated at almost 70% (e.g. 43). This may be due to inherited differences in opioid receptors or opioid metabolizing enzymes.

There is also a genetic contribution to the use of and dependence on the combination of alcohol, tobacco and other substances together (30, 43-48). One estimate is that there is an eight-fold increased risk of substance dependence amongst relatives of people with substance dependence compared to controls, when applied to a wide range of substances including opioids, cannabis, sedatives and cocaine (49, 50).

The genetic findings provide an indication of the promise that genetic research offers. These genetic data can and have been used to improve our understanding of the origins of substance dependence, and variation in risk beween individuals. Once genes which alter the predisposition to dependence are identified, a major challenge will be to understand how the function of these genes interacts with the environmental influences on dependence (51). This information may form the basis for novel diagnostic tools as well as the basis of novel behavioural and pharmacological treatments.

Genetic screening, based on the research findings, can potentially identify subgroups of the population with a greater liability to dependence or harm from a particular psychoactive substance. However, this raises many ethical issues, as the identification is in terms of probabilities rather than certainties. Actions that could be taken on the basis of a positive screen might include notification of the affected person (or of the person's parents or guardian, in case of a child), and preventive interventions such as therapeutic education or other interventions targeted at reducing vulnerability to substance use and dependence. There are obvious ethical implications in terms of stigmatization, privacy, and consent to treatment.

Genetic differences may influence many aspects of substance use, for example, subjective pleasurable effects. Genetic factors may also greatly affect the toxicity of a substance, both in terms of overdose and of chronic health effects. Genetics may also

affect the intensity of psychoactive effects of a given formulation and dose of a substance, the development of tolerance, withdrawal, and craving. In addition, substance dependence may share neurobiological commonalities with several different forms of mental illness, suggesting that common treatment and prevention strategies may help both conditions.

Comorbidity of substance dependence and mental illness

There is an increased comorbidity, or co-occurrence, of substance dependence in individuals who have mental illness as compared to individuals without any mental disorder. This indicates either a shared neurobiological basis for both, or an interaction of effects at some level. Research on the origins of both mental illnesses and substance dependence will help to shed light on treatment and prevention strategies for both. There are several hypotheses as to why mental illness and substance dependence may co-occur:

1. There may be a similar neurobiological basis to both;
2. Substance use may help to alleviate some of the symptoms of the mental illness or the side effects of medication;
3. Substance use may precipitate mental illnesses or lead to biological changes that have common elements with mental illnesses.

There is some evidence for all of these hypotheses. It is interesting that the effects of many psychoactive substances can produce psychiatric-like syndromes. For example, amphetamines and cocaine can induce psychotic-like symptoms. Hallucinogenic substances can produce hallucinations, which are an aspect of some psychoses. Furthermore, psychoactive substances regularly alter mood states, producing either euphoric and happy feelings, or inducing depressive symptoms, especially during substance withdrawal. Psychoactive substances can alter cognitive functioning, which is also a core feature of many mental illnesses. These factors all suggest common neurobiological substrates to both mental illnesses and substance dependence.

Some studies in the US have reported that more than 50% of the people with any mental disorder also suffer from substance dependence compared to 6% of the general population; and the odds of exhibiting substance dependence are 4.5 times higher for people with any mental disorder than for people without mental disorder (52). Clearly, there is a substantial overlap in these disorders.

The lifetime prevalence of alcohol dependence is 22% for individuals with any mental disorder compared to 14% for the general population, and the odds of having alcohol dependence if a person also has any mental disorder is 2.3 times higher than if there is no mental disorder (52). Studies in the United States over the last 20 years indicated that lifetime rates of major depressive disorder were 38-44% in people with alcohol dependence compared with only 7% in non-dependent individuals (35, 53-61). Further, approximately 80% of people with alcohol dependence have depressive symptoms (52, 62-64). An individual with alcohol dependence is 3.3 times more likely to also have schizophrenia, while a person with schizophrenia

is 3.8 times more likely to exhibit alcohol dependence than the general population (52).

Higher percentages of people with mental illness, particularly people with schizophrenia, smoke tobacco compared to the general population. Depending on the particular mental illness, it has been reported that 26-88% of psychiatric patients smoke, compared to 20-30% of the general population (65-67). There are several close links between a major depressive disorder and tobacco smoking. In the US, up to 60% of heavy smokers have a history of mental illness (67, 68), and the incidence of major depressive disorder among smokers is twice that of non-smokers (65). Moreover, smokers who had a history of clinical depression were half as likely to succeed in quitting smoking than smokers without such history (14% versus 28%) (65). Epidemiological data indicate that the lifetime rates of major depressive disorder were 32% in cocaine users, and only 8 - 13% among non-cocaine users (52, 54, 56, 58, 69).

There is also a high degree of comorbidity of schizophrenia with psychostimulant use. Psychostimulant use is 2-5 times higher among patients with schizophrenia compared to people without schizophrenia, and more prevalent than in other psychiatric populations (70). Thus, it seems clear that substance dependence shares a considerable link with mental illness. Although most of the research on comorbidity has been carried out in only a few countries and the cultural validity of the data is unknown, neuroscience research into the treatment and prevention of one disorder will be beneficial to the other.

Treatment and prevention: links with neuroscience, and ethical issues

Research in neuroscience has led to the development of a number of pharmacological and behavioural interventions for the treatment of substance dependence. Many have been very successful, while some remain controversial for ethical reasons. New treatments are on the horizon, and with more research, improved treatments are likely. The combination of pharmacological and behavioural therapies appears to be the most effective in treating dependence. One question that arises concerns the measures of success: is a treatment considered successful only if complete abstinence is obtained? Or, is a reduction in the amount, frequency or harmful use of a substance sufficient as a measure of success? Current pharmacological therapies are presented in Table 5.

Types of treatment

There are a variety of pharmacological and behavioural treatments available with proven efficacy. In terms of pharmacological interventions, one choice is of substances or procedures that interfere in one way or another with the action of the substance in the body, taking away the positive rewards from using the substance or making its use aversive. For example, the opioid receptor blockers naloxone and naltrexone, reduce the rewarding effects of opioids and alcohol (see Table 5).

Table 5. Pharmacological treatments for substance dependence

Substance	Treatment	Efficacy
Alcohol	Acamprosate is a synthetic substance with structural similarity to a naturally occurring amino acid. Restores the normal activity of neurons, which become hyperexcited as a result of chronic exposure to alcohol.	Overall, patients treated with acam prosate exhibit a significant increase in rate of completion of treatment, time to first drink, abstinence rate and/or cumulative duration of abstinence, compared with patients treated with placebo (73).
	Naltrexone: Blocks opioid receptors.	Naltrexone is effective in reducing relapse and in helping people to remain abstinent and to decrease alcohol consumption (74).
	Disulfiram interferes with the normal metabolism of acetyaldehyde, a metabolite of alcohol. High acetaldehyde levels produce an unpleasant reaction that is intended to render the consumption of alcohol aversive (75).	The efficacy of disulfiram is variable, and is confounded by the need to carefully titrate the dose, and by the need for a high degree of compliance (75).
Nicotine	Nicotine substitution with nicotine patch or gum.	All nicotine-replacement therapies are equally effective in helping people to quit smoking, and, combined with increased public service announcements in the media about the dangers of smoking, have produced a marked increase in successful quitting
	Bupropion: A weak norepinephrine and dopamine reuptake inhibitor, and a nicotinic receptor blocker.	Bupropion improves the abstinence rates of smokers, especially if combined with nicotine replacement therapy (76, 77).
	Immunotherapy: Vaccines that can prevent nicotine from acting on the brain have been proposed.	Vaccines are not yet ready for clinical trials. Trials with mice show promising results.
Heroin	Methadone (synthetic opioid agonist).	Methadone maintenance treatment is safe, and very effective in helping people to stop taking heroin, especially when combined with behavioural therapies or counselling and other supportive services.
	Buprenorphine: Partial agonist at the mu opioid receptor and a weak antagonist at the kappa opioid receptor.	Relatively long duration of action and good safety profile.

Table 5. (continued)

Substance	Treatment	Efficacy
	Levo-alpha-acetyl-methadol (LAAM): a synthetic opioid.	Long-acting synthetic opioid that can be used to treat heroin dependence, but it needs only be taken three times per week, thus making it even easier for people to use this therapy.
	Naltrexone blocks the effects of morphine, heroin and other opioids by acting as antagonist at the opioid receptors.	This therapy begins after medically supervised detoxification, because naltrexone does not protect against the effects of withdrawal, and can in fact precipitate withdrawal symptoms in dependent people. Naltrexone itself has no subjective effects or potential for the development of dependence. Patient noncompliance is a common problem. Therefore, a favourable treat ment outcome requires that there also be a positive therapeutic relationship, effective counselling or therapy, and careful monitoring of medication compliance.
Cocaine	GBR 12909 is an inhibitor of dopamine uptake that antagonizes the effects of cocaine on mesolimbic dopamine neurons in rats (78), and blocks self-administration of cocaine in rhesus monkeys (79).	Clinical trials of this substance are in the planning stage.
	Immunotherapies: cocaine is sequestered in the bloodstream by cocaine specific antibodies that prevent its entry into the brain.	Clinical trials are underway.
Sedatives/ hypnotics	Slow tapering of substance dose combined with behavioural therapy.	Effective.

Another example is disulfiram, which interferes with the metabolism of alcohol, making its consumption aversive. However, these medications are effective only insofar as people take them. Extensive experience suggests that the main problem with such substances is patient compliance: that those with a history of extensive use of a substance are often unable to keep a commitment to continual use of the pharmacological therapy.

The other choice for pharmacological treatment options is of substances that mimic the effects of the psychoactive substance in some ways, without some of the more harmful effects of that substance. This is referred to as substitution treatment, or maintenance treatment. This choice has been most widely explored and used for

opioids, with codeine, methadone, buprenorphine and other substances substituted for heroin or other opioids, to reduce illegal opioid use and the crime, death, and disease associated with substance dependence. Methadone and buprenorphine, the two medications most commonly used, are also prescribed on a short-term basis to detoxify those dependent on opioids. Many substance users who only detoxify, however – no matter what method used – lapse into heavy substance use. Substitution therapy seeks to reduce or eliminate illicit opioid use by stabilizing people for as long as is necessary to help them avoid previous patterns of substance use and associated harms, including sharing of injection equipment. The most common treatment, methadone maintenance, has been shown in hundreds of scientific studies to be effective in reducing substance-related harm without negative health consequences. Compared to illegal users of opioids, people who undergo methadone maintenance treatment spend less time in jail and in hospital, have better social integration and lower rates of HIV infection, commit fewer crimes, and live longer (71).

Substitution therapy has often been controversial, with the argument stated in ethical terms. On the one hand, it is stated to be unethical for the State or a treatment professional to contribute to the continuation of the dependence, even if on a substitute regime. On the other hand, the counter-arguments of the demonstrated reductions in harm to society (e.g. criminal activity) or the individual (e.g. HIV infection) from the substitute regime, are also ethical at their core.

With therapies that interfere with the psychoactive effects or that are aversive, the main ethical issue is the consent of the patient to the treatment, and the ethics of coerced treatment. The use of immunotherapies, such as for cocaine dependence (see Table 5), particularly to the extent that they are irreversible, would raise difficult ethical issues. The neuroscience findings that the use of psychoactive substances shares many pathways in the brain with other human activities also raises the question of what other pleasures or activities might be adversely affected by a treatment. The application of genetic modifications would raise many of the same ethical issues regarding potentially permanent changes.

In addition to pharmacological treatment, behavioural therapies are employed in treating substance dependence. It is interesting to relate these therapies to the learning processes that were discussed with respect to the effects of psychoactive substances on the brain. Motivational and cognitive therapies are designed to work on the same motivational processes in the brain that are affected by psychoactive substances. These therapies try to replace the motivation to use substances with the motivation to engage in other behaviours. Note that these therapies rely on the same principles of learning and motivation that are used to describe the development of dependence. For example, contingency management uses the principles of positive reinforcement and punishment to manage behaviour. Cognitive behavioural therapies and relapse prevention help the person develop new stimulus-response associations that do not involve substance use or craving. These principles are employed in an attempt to "unlearn" the dependence-related behaviour and to learn more adaptive responses. Thus, similar neurobiological mechanisms are involved in

the development of dependence, as are involved in learning to overcome dependence.

The information in Box 4 is a summary of types of psychotherapies and behavioural interventions (72).

Ethical issues in neuroscience research on substance dependence

The rapid pace of change in the field of neuroscience research brings with it a host of new ethical issues in both research and treatment, which will need to be addressed. An influential set of moral principles guide the ethics of biomedical research (80, 81). These are the principles of autonomy, non-maleficence, beneficence, and justice (82).

The principle of respect for autonomy is usually taken to require informed consent to treatment or research participation, voluntariness in research participation, and maintenance of confidentiality and privacy of information provided to a researcher. The principle of non-maleficence simply means, "do no harm", and requires researchers to minimize the risks of research participation. Positive beneficence requires us to perform actions that result in a benefit. The benefits to society of the research should outweigh its risks to participants, and the benefits to individual participants in research should exceed the risks. Distributive justice refers to the equitable distribution of the risks, as well as the benefits of research participation.

Perhaps the most urgent ethical issues arise around the issue of genetic screening, which is already on the horizon. A person identified by a genetic screen as vulnerable or at risk is potentially disadvantaged by that identification in a number of ways. In the first place, the person's own self-esteem may be reduced. The person's financial and status interests may be adversely affected if the identification is available to anyone else: an insurance company may refuse insurance, an employer may choose not to employ, a lover may refuse to marry. At present, in many countries, these adverse effects of such identification are not at all theoretical: for instance, insurance companies may have routine access to health records, or may require such access as a condition of applying for insurance (thus coercing consent).

Ethics and types of neuroscience research on substance dependence

There are many types of research on substance dependence, all of which have both unique and common ethical issues that will have to be dealt with. These include animal experiments, epidemiological research, human experimental studies, and clinical trials of therapies for substance dependence.

Clinical trials compare the effects of different drug or behavioural treatments, and sometimes placebos, on the substance use, health, social adjustment and well-being of persons with substance dependence (80). Clinical trials differ from experimental studies in one key respect: participants in clinical trials have some chance of benefiting from their participation in the study (80). The criteria for good clinical trials agree in requiring that a representative sample of the population at risk is

Box 4. Types of psychotherapies and behavioural interventions

Cognitive behavioural therapies

Cognitive behavioural therapies focus on:

(a) altering the cognitive processes that lead to maladaptive behaviours of substance users;
(b) intervening in the behavioural chain of events that lead to substance use;
(c) helping patients deal successfully with acute or chronic substance craving;
(d) promoting and reinforcing the development of social skills and behaviours compatible with remaining substance free.

The foundation of cognitive therapy is the belief that by identifying and subsequently modifying maladaptive thinking patterns, patients can reduce or eliminate negative feelings and behaviour (e.g. substance use).

Relapse prevention

An approach to treatment in which cognitive behavioural techniques are used in an attempt to help patients develop greater self-control in order to avoid relapse. Specific relapse prevention strategies include discussing ambivalence, identifying emotional and environmental triggers of craving and substance use, and developing and reviewing specific coping strategies to deal with internal or external stressors.

Contingency management

A behavioural treatment based on the use of predetermined positive or negative consequences to reward abstinence or to punish (and thus deter) substance-related behaviours. Rewards have included vouchers awarded for producing substance-free urine samples that can be exchanged for mutually agreed upon items (e.g. cinema tickets) and community reinforcement in which family members or peers reinforce behaviours that demonstrate or facilitate abstinence (e.g. participation in positive activities). Negative consequences for returning to substance use may include notification of courts, employers, or family members.

Motivational enhancement therapy

This brief treatment modality is characterized by an empathetic approach in which the therapist helps to motivate the patient by asking about the pros and cons of specific behaviours; by exploring the patient's goals and associated ambivalence about reaching these goals; and by listening reflectively. Motivational enhancement therapy has demonstrated substantial efficacy in the treatment of substance dependence.

recruited into such studies (80). An ethical issue of increasing significance, given the extent of pharmaceutical company funding of clinical trials, is ensuring public confidence in the results of clinical trials (83, 84). Additional policy recommendations have been made that have not so far been implemented. These include: independent monitoring of compliance with the study protocol, especially with reporting of any adverse events experienced by participants; and a requirement that investigators and the sponsors of a trial commit to publishing its results within two years of completing data collection, as a condition of the study protocol being approved by an ethics committee (85).

The outcomes of neuroscience research for the treatment of substance dependence will bring ethical issues to the fore. One such issue is ensuring equal access to treatment for all those who may need it. Economic and social costs of treating people with substance dependence with publicly subsidized substance treatment, as opposed to the criminal justice system will also be relevant (86, 87). As well, the potential use of a pharmacological treatment for substance dependence or a substance immunotherapy under legal coercion needs to be considered (88-90).

Conclusion and implications for public health policy

This report has summarized the advances in our understanding of the neuroscience of psychoactive substance use and dependence in recent decades, and has considered some of the ethical issues which are connected with these advances. The developments in neuroscience have greatly increased our knowledge about substance use and dependence, and the new knowledge poses substantial challenges for us to make ethical choices in applying the fruits of this knowledge, both globally and locally. Relevant organizational and professional bodies should play a leading role in meeting these challenges at global and regional levels.

A substantial portion of the global burden of disease and disability is attributable to psychoactive substance use. In turn, a substantial portion of the burden attributable to substance use is associated with dependence. Tobacco and alcohol use are particularly prominent contributors to the total burden. Measures to reduce the harm from tobacco, alcohol and other psychoactive substances are thus an important part of health policy.

Neuroscience is a fast growing field of scientific research. Though the knowledge base is far from complete, there is a considerable amount of useful data with enormous potential for influencing policies to reduce the burden of disease and disability associated with substance use. The following recommendations are made to facilitate greater openness and assist all stakeholders in mobilizing action:

- All psychoactive substances can be harmful to health, depending on how they are taken, in which amounts and how frequently. The harm differs between substances and the public health response to substance use should be proportional to the health-related harm that they cause.
- Use of psychoactive substances is to be expected because of their pleasurable effects as well as peer pressure and the social context of their use. Experimentation does not necessarily lead to dependence but the greater the

frequency and amount of substance used, the higher the risk of becoming dependent.

- Harm to society is not only caused by individuals with substance dependence. Significant harm also comes from non dependent individuals, stemming from acute intoxication and overdoses, and from the form of administration (e.g. through unsafe injections). There are, however, effective public health policies and programmes which can be implemented and which will lead to a significant reduction in the overall burden related to substance use.
- Substance dependence is a complex disorder with biological mechanisms affecting the brain and its capacity to control substance use. It is not only determined by biological and genetic factors, but psychological, social, cultural and environmental factors as well. Currently, there are no means of identifying those who will become dependent - either before or after they start using drugs.
- Substance dependence is not a failure of will or of strength of character but a medical disorder that could affect any human being. Dependence is a chronic and relapsing disorder, often co-occurring with other physical and mental conditions.
- There is significant comorbidity of substance dependence with various other mental illnesses; assessment, treatment and research would be most effective if an integrated approach were adopted. Treatment and prevention insights from other mental illnesses or substance dependence can be used to inform treatment and prevention strategies in the domain of the other. Attention to comorbidity of substance use disorders and other mental disorders is thus required as an element of good practice in treating or intervening in either mental illness or substance dependence.
- Treatment for substance dependence is not only aimed at stopping drug use - it is a therapeutic process that involves behaviour changes, psychosocial interventions and often, the use of substitute psychotropic drugs. Dependence can be treated and managed cost-effectively, saving lives, improving the health of affected individuals and their families, and reducing costs to society.
- Treatment must be accessible to all in need. Effective interventions exist and can be integrated into health systems, including primary health care. The health care sector needs to provide the most cost-effective treatments.
- One of the main barriers to treatment and care of people with substance dependence and related problems is the stigma and discrimination against them. Regardless of the level of substance use and which substance an individual takes, they have the same rights to health, education, work opportunities and reintegration into society, as does any other individual.
- Investments in neuroscience research must continue and expand to include investments in social science, prevention, treatment and policy research. The reduction in the burden from substance use and related disorders must rely on evidence-based policies and programmes which are the result of research and its application.

Finally, emerging technologies and therapies to prevent and treat dependence and related problems pose difficult ethical issues. These issues should be addressed by national and international scientific and policy communities as a priority.

References

1. Room R et al. (2001) Cross-cultural views on stigma, valuation, parity and societal values towards disability. In: Üstün TB et al., eds. *Disability and culture: universalism and diversity*. Seattle, WA, Hogrefe & Huber:247–291.

2. Mackay J, Eriksen M (2002) *The tobacco atlas*. Geneva, World Health Organization.

3. WHO (1999) *Global status report on alcohol*. Geneva, World Health Organization.

4. Room R et al. (2002) *Alcohol and the developing world: a public health perspective*. Helsinki, Finnish Foundation for Alcohol Studies.

5. UNODC (2003) *Global illicit drug trends 2003*. New York, NY, United Nations Office on Drugs and Crime.

6. Murray CJ, Lopez AD (1996) *Global health statistics. Global burden of disease and injury series. Vol. 2*. Geneva, World Health Organization.

7. WHO (2002) *The world health report 2002*. Geneva, World Health Organization.

8. Babor T et al. (2003) *No ordinary commodity: alcohol and public policy*. Oxford, Oxford University Press.

9. WHO (1992) *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva, World Health Organization.

10. Aine CJ (1995) A conceptual overview and critique of functional neuro-imaging techniques in humans. I. MRI/fMRI and PET. *Critical Reviews in Neurobiology*, **9**:229–309.

11. Volkow ND, Rosen B, Farde L (1997) Imaging the living human brain: magnetic resonance imaging and positron emission tomography. *Proceedings of the National Academy of Sciences of the United States of America*, **94**:2787–2788.

12. Gatley SJ, Volkow ND (1998) Addiction and imaging of the living human brain. *Drug and Alcohol Dependence*, **51**:97–108.

13. Volkow ND et al. (2001a) Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry*, **158**:2015–2021.

14. Volkow ND et al. (2001b) Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *American Journal of Psychiatry*, **158**:377–382.

15. Kalant H (2001) The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *Canadian Medical Association Journal*, **165**:917–928.

16. Montoya AG et al. (2002) Long-term neuropsychiatric consequences of "ecstasy" (MDMA): a review. *Harvard Review of Psychiatry*, **10**:212–220.

17. Wise RA (1998) Drug-activation of brain reward pathways. *Drug and Alcohol Dependence*, **51**:13–22.

18. Robbins TW, Everitt BJ (1996) Neurobehavioural mechanisms of reward and motivation. *Current Opinion in Neurobiology*, **6**:228–236.

19. Cardinal RN et al. (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews*, **26**: 321–352.

20. Robinson TE, Berridge KC (2000) The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction*, **95**(Suppl 2):S91–S117.

21. Schmid H (2000) Protektive faktoren. [Protective factors.] In: Uchtenhagen A, Zieglgänsberger W, eds. *Suchtmedizin: konzepte, strategien und therapeutsches management.* [*Addiction medicine: concepts, strategies and therapeutic management.*] Munich, Urban & Fischer Verlag:226–234.

22. Lloyd C (1998) Risk factors for problem drug use: identifying vulnerable groups. *Drugs: Education Prevention and Policy*, **5**:217–232.

23. Uchtenhagen A (2000a) Determinanten für drogenkonsum und –abhängigkeit. [Determinants of drug use and addiction.] In: Uchtenhagen A, Zieglgänsberger W, eds. *Suchtmedizin: konzepte, strategien und therapeutsches management. [Addiction medicine: concepts, strategies and therapeutic management.*] Munich, Urban & Fischer Verlag:193–195.

24. Uchtenhagen A (2000b) Risikofaktoren und schutzfaktoren: eine übersicht. [Risk and protective factors: an overview.] In: Uchtenhagen A, Zieglgänsberger W, eds. *Suchtmedizin: konzepte, strategien und therapeutsches management.* [*Addiction medicine: concepts, strategies and therapeutic management.*] Munich, Urban & Fischer Verlag:195–198.

25. Cheng LS, Swan GE, Carmelli D (2000) A genetic analysis of smoking behavior in family members of older adult males. *Addiction*, **95**:427–435.

26. McGue M, Elkins I, Iacono WG (2000) Genetic and environmental influences on adolescent substance use and abuse. *American Journal of Medical Genetics*, **96**:671–677.

27. Bergen AW et al. (1999) A genome-wide search for loci contributing to smoking and alcohol dependence. *Genetic Epidemiology*, **17**(Suppl.1):S55–S60.

28. Straub RE et al. (1999) Susceptibility genes for nicotine dependence: a genome scan and follow up in an independent sample suggest that regions on chromosomes 2, 4, 10, 16, 17 and 18 merit further study. *Molecular Psychiatry*, **4**:129–144.

29. Duggirala R, Almasy L, Blangero J (1999) Smoking behavior is under the influence of a major quantitative trait locus on human chromosome 5q. *Genetic Epidemiology*, **17** Suppl 1:S139–S144.

30. Carmelli D et al. (1992) Genetic influence on smoking: a study of male twins. *New England Journal of Medicine*, **327**:829–833.

31. Enoch MA, Goldman D (2001) The genetics of alcoholism and alcohol abuse. *Current Psychiatry Reports*, **3**:144–151.

32. Han C, McGue MK, Iacono WG (1999) Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses. *Addiction*, **94**:981–993.

33. Heath AC et al. (1997) Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychological Medicine*, **27**:1381–1396.

34. Johnson EO et al. (1998) Extension of a typology of alcohol dependence based on relative genetic and environmental loading. *Alcoholism: Clinical and Experimental Research*, **22**:1421–1429.

35. Kendler KS et al. (1994) A twin-family study of alcoholism in women. *American Journal of Psychiatry*, **151**:707–715.

36. Prescott CA, Kendler KS (1999) Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *American Journal of Psychiatry*, **156**:34–40.

37. Prescott CA, Aggen SH, Kendler KS (1999) Sex differences in the sources of genetic liability to alcohol abuse and dependence in a population-based sample of US twins. *Alcoholism: Clinical and Experimental Research*, **23**:1136–1144.

38. Long JC et al. (1998) Evidence for genetic linkage to alcohol dependence on chromosomes 4 and 11 from an autosome-wide scan in an American Indian population. *American Journal of Medical Genetics*, **81**:216–221.

39. Lappalainen J et al. (1998) Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in two populations. *Archives of General Psychiatry*, **55**:989–994.

40. Agarwal DP (2001) Genetic polymorphisms of alcohol metabolizing enzymes. *Pathology and Biology* (Paris), **49**:703–709.

41. Li TK (2000) Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. *Journal of Studies on Alcohol*, **61**:5–12.

42. Ramchandani VA, Bosron WF, Li TK (2001) Research advances in ethanol metabolism. *Pathology and Biology* (Paris), **49**:676–682.

43. Tsuang MT et al. (2001) The Harvard Twin Study of Substance Abuse: what we have learned. *Harvard Review of Psychiatry*, **9**:267–279.

44. Daeppen JB et al. (2000) Clinical correlates of cigarette smoking and nicotine dependence in alcohol-dependent men and women: the Collaborative Study Group on the Genetics of Alcoholism. *Alcohol and Alcoholism*, **35**:171–175.

45. Hopfer CJ, Stallings MC, Hewitt JK (2001) Common genetic and environmental vulnerability for alcohol and tobacco use in a volunteer sample of older female twins. *Journal of Studies on Alcohol*, **62**:717–723.

46. Reed T et al. (1994) Correlations of alcohol consumption with related covariates and heritability estimates in older adult males over a 14- to 18-year period: the NHLBI Twin Study. *Alcoholism: Clinical and Experimental Research*, **18**:702–710.

47. Swan GE, Carmelli D, Cardon LR (1996) The consumption of tobacco, alcohol, and coffee in Caucasian male twins: a multivariate genetic analysis. *Journal of Substance Abuse*, **8**:19–31.

48. Swan GE, Carmelli D, Cardon LR (1997) Heavy consumption of cigarettes, alcohol and coffee in male twins. *Journal of Studies on Alcohol*, **58**:182–190.

49. Merikangas KR et al. (1998) Familial transmission of substance use disorders. *Archives of General Psychiatry*, **55**:973–979.

50. Bierut LJ et al. (1998) Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. *Archives of General Psychiatry*, **55**:982–988.

51. Swan GE (1999) Implications of genetic epidemiology for the prevention of tobacco use. *Nicotine and Tobacco Research*, **1**(Suppl. 1):S49–S56.

52. Regier DA et al. (1990) Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiological Catchment Area (ECA) Study. *Journal of the American Medical Association*, **264**:2511–2518.

53. Myers JK et al. (1984) Six-month prevalence of psychiatric disorders in three communities, 1980 to 1982. *Archives of General Psychiatry*, **41**:959–967.

54. Robins LN et al. (1984) Lifetime prevalence of specific psychiatric disorders in three sites. *Archives of General Psychiatry*, **41**:949–958.

55. Rounsaville BJ et al. (1982) Heterogeneity of psychiatric disorders in treated opiate addicts. *Archives of General Psychiatry*, **39**:161–168.

56. Rounsaville BJ et al. (1987) Psychopathology as a predictor of treatment outcome in alcoholics. *Archives of General Psychiatry*, **44**:505–513.

57. Rounsaville BJ et al. (1991) Psychiatric diagnoses of treatment-seeking cocaine abusers. *Archives of General Psychiatry*, **48**:43–51.

58. Robins LN, Regier DA, eds (1991) *Psychiatric disorders in America: the Epidemiologic Catchment Area Study*. New York, NY, The Free Press.

59. Miller NS et al. (1996b) Prevalence of depression and alcohol and other drug dependence in addictions treatment populations. *Journal of Psychoactive Drugs*, **28**:111–124.

60. Schuckit MA et al. (1997a) Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *American Journal of Psychiatry*, **154**:948–957.

61. Schuckit MA et al. (1997b) The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. *Addiction*, **92**:1289–1304.

62. Schuckit MA (1985) The clinical implications of primary diagnostic groups among alcoholics. *Archives of General Psychiatry*, **42**:1043–1049.

63. Roy A et al. (1991) Depression among alcoholics: relationship to clinical and cerebrospinal fluid variables. *Archives of General Psychiatry*, **48**:428–432.

64. Kessler RC et al. (1996) The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *American Journal of Orthopsychiatry*, **66**:17–31.

65. Glassman AH et al. (1990) Smoking, smoking cessation, and major depression. *Journal of the American Medical Association*, **264**:1546–1549.

66. Breslau N (1995) Psychiatric comorbidity of smoking and nicotine dependence. *Behavior Genetics*, **25**:95–101.

67. Hughes JR et al. (1986) Prevalence of smoking among psychiatric outpatients. *American Journal of Psychiatry*, **143**:993–997.

68. Glassman AH et al. (1988) Heavy smokers, smoking cessation, and clonidine: results of a double-blind, randomized trial. *Journal of the American Medical Association*, **259**:2863–2866.

69. Kessler RC et al. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry*, **51**:8–19.

70. Le Duc PA, Mittleman G (1995) Schizophrenia and psychostimulant abuse: a review and re-analysis of clinical evidence. *Psychopharmacology*, **121**:407–427.

71. Subata E (2002) Injecting drug users, HIV/AIDS treatment and primary care in Central and Eastern Europe and the former Soviet Union: results of a region-wide survey. http://www.eurasianet.org/health.security/presentations/emilis.ppt

72. American Journal of Psychiatry (1995) Practice guidelines for the treatment of patients with substance use disorders: alcohol, cocaine, opioids. *American Journal of Psychiatry*, **152**:1–59.

73. ason BJ et al. (1996) A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *Journal of the American Medical Association*, **275**:761–767.

74. Streeton C, Whelan G. (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. *Alcohol and Alcoholism*, **36**:544-552.

75. Kranzler H.R (2000) Pharmacotherapy of alcoholism: gaps in knowledge and opportunities for research. *Alcohol and Alcoholism*, **35**:537–547.

76. Hurt RD et al. (1997) A comparison of sustained-release buproprion and placebo for smoking cessation. *New England Journal of Medicine*, **337**:1195–1202.

77. Jorenby DE et al. (1999) A controlled trial of sustained-release buproprion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine*, 340:685–691.

78. Baumann MH et al. (1994) GBR12909 attenuates cocaine-induced activation of mesolimbic dopamine neurons in the rat. *Journal of Pharmacology and Experimental Therapeutics*, **271**:1216–1222.

79. Rothman RB, Glowa JR (1995) A review of the effects of dopaminergic agents on humans, animals, and drug-seeking behavior, and its implications for medication development: focus on GBR 12909. Molecular Neurobiology, **11**:1–19.

80. Brody BA (1998) *The ethics of biomedical research: an international perspective*. Oxford, Oxford University Press.

81. Jonsen AR (1998) *The birth of bioethics*. Oxford, Oxford University Press.

82. Beauchamp TL, Childress JF (2001) *Principles of biomedical ethics*. Oxford, Oxford University Press.

83. Davidoff F et al. (2001) Sponsorship, authorship, and accountability. *New England Journal of Medicine*, **345**:825–827.

84. de Angelis CD, Fontanarosa PB, Flanagin A (2001) Reporting financial conflicts of interest and relationships between investigators and research sponsors. *Journal of the American Medical Association*, **286**:89–91.

85. Reidenberg MM (2001) Releasing the grip of big pharma. *Lancet*, **358**:664.

86. Gerstein DR, Harwood HJ (1990) *Treating drug problems. Vol. 1. A study of effectiveness and financing of public and private drug treatment systems.* Washington, DC, National Academy Press.

87. National Research Council (2001) *Informing America's policy on illegal drugs: what we don't know keeps hurting us.* Washington, DC, National Academy Press.

88. Cohen PJ (1997) Immunization for prevention and treatment of cocaine abuse: legal and ethical implications. *Drug and Alcohol Dependence*, **48**:167–174.

89. Hall W (1997) The role of legal coercion in the treatment of offenders with alcohol and heroin problems. *Australian and New Zealand Journal of Criminology*, **30**:103–120.

90. Spooner C et al. (2001) An overview of diversion strategies for drug-related offenders. *Drug and Alcohol Review*, **20**:281–294.