



Brain science, addiction and drugs

An Academy of Medical Sciences working group report
chaired by Professor Sir Gabriel Horn FRS FRCP

The Academy of Medical Sciences

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Contents

Abbreviations	5
Summary	7
Objectives and scope of report	9
Background and objectives	9
Scope	9
Process	10
Review	11
Chapter 1 Introduction	13
1.1 Scientific background	13
1.2 Societal aspects	15
Part I: Recreational Drugs	
Chapter 2 Public engagement	17
2.1 Background and objectives	17
2.2 Implementation	18
2.3 Findings	19
2.4 Discussion	27
Recommendation	28
Chapter 3 Magnitude of the problem	29
Introduction	29
3.1 The nature of the problem	29
3.2 Trends in specific drugs	32
3.3 Future sources of psychoactive substances	35
3.4 Measuring the size and scale of drug use	37
Recommendation	41
Chapter 4 Neuroscience, addiction, pharmacology and treatment	43
Introduction	43
4.1 Neuroscience of addiction	43
4.2 Pharmacology and treatment	51
4.3 Brain science and future psychological therapies	56
4.4 Discussion	59
Recommendations	62
Chapter 5 Harm and regulation	63
Introduction	63
5.1 Philosophical principles concerning the regulation of illegal psychoactive substances	63
5.2 Regulatory strategy	66
5.3 Measuring the harm associated with the use of illegal psychoactive drugs	73
5.4 Discussion	88
Recommendations	90

Chapter 6 Risk factors and prevention	93
Introduction	93
6.1 Individual differences	93
6.2 Family social factors	104
6.3 Societal factors	106
6.4 Timing of substance misuse	110
6.5 Protective factors	113
6.6 Discussion	114
Recommendations	115
Part II: Medicines for mental health	
Chapter 7 Medicines for mental health	117
Introduction	117
7.1 Common mood disorders: depression and anxiety	118
7.2 Bipolar (manic-depressive) disorder	121
7.3 Schizophrenia	122
7.4 Personality disorders	123
7.5 Mental illness in childhood and adolescence	124
7.6 Benefits and limitations of current drugs	126
7.7 Brain sciences and mental health	128
7.8 The development of new curative and preventative treatments	133
7.9 Discussion	138
Recommendations	141
Part III: Cognition enhancers	
Chapter 8 Cognition enhancers	143
Introduction	143
8.1 Existing cognition enhancers	147
8.2 Cognition enhancing drugs of the future: theoretical pointers from basic research	152
8.3 Cognition enhancing drugs of the future: current strategies and indications	153
8.4 Ethical and regulatory issues	155
8.5 Discussion	157
Recommendations	159
Recommendations	161
Part I: Recreational drugs	161
Part II: Medicines for mental health	164
Part III: Cognition enhancers	165
Appendix I Report preparation	167
References	171

Abbreviations

5-HT	5-Hydroxytryptamine (serotonin)
5-HTT	5-Hydroxytryptamine (serotonin) Transporter
ACMD	Advisory Council on the Misuse of Drugs
AD	Alzheimer's disease
ADHD	Attention-Deficit Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
AMPA	α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid
AMRC	Association of Medical Research Charities
BAS	Behavioural Activation System
BCS	British Crime Survey
BIS	Behavioural Inhibition System
BNF	British National Formulary
BZP	Benzyl piperazine
cAMP	Cyclic Adenosine Monophosphate
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBI	Combined Behavioural Intervention
CBT	Cognitive Behavioural Therapy
COMT	Catechol-O-Methyl Transferase
CNS	Central Nervous System
CTC	Communities That Care
D2 receptors	Dopamine 2 receptors
DCSF	Department for Children, Schools and Families
DHI	Drug Harm Index
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual
ECT	Electro-Convulsive Therapy
EEG	Electro-Encephalography
EM	Experimental Medicine
EMDDA	European Monitoring Centre for Drugs and Drug Addiction
EPPE	Effective Pre-school and Primary Education
EU	European Union
FAS	Fetal Alcohol Syndrome
FDA	Food and Drug Administration (USA)
fMRI	Functional Magnetic Resonance Imaging
FSA	Food Standards Agency
GABA	Gamma-Aminobutyric Acid
GP	General Practitioner
GWA	Genome-Wide Association
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
IDU	Injecting Drug User
IOM	Institute of Medicine (USA)
IQ	Intelligence Quotient
ISD	International Statistical Classification of Diseases

LSD	Lysergic Acid Diethylamide
LTP	Long Term Potentiation
MAO	Monoamine Oxidase
MDMA	Methylenedioxymethamphetamine (Ecstasy)
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRS	Magnetic Resonance Spectroscopy
NMDA	N-methyl d-aspartate
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIDA	National Institute for Drugs and Addiction (USA)
NIHR	National Institute for Health Research
NNT	Number Needed to Treat
NTASM	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcome Research Study
OCD	Obsessive Compulsive Disorder
OCJS	Offending Crime and Justice Survey
OD	Overdose Death
ONDCP	Office of National Drug Control Policy (USA)
ONS	Office of National Statistics
OPM	Office for Public Management
OSCHR	Office for the Strategic Coordination of Health Research
PDU	Problem Drug User
PET	Positron Emission Tomography
PMSU	Prime Minister's Strategy Unit
PPRS	Pharmaceutical Price Regulation Scheme
PTSD	Post-Traumatic Stress Disorder
R&D	Research and Development
RNAi	Ribonucleic Acid Interference
SPET	Single-Photon Emission Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Substance Use Disorder
TCA	Tricyclic Antidepressant
TMS	Transcranial Magnetic Stimulation
UKATT	United Kingdom Alcohol Treatment Trial
WHO	World Health Organization

Summary

Understanding how the brain works, how drugs affect the brain's performance and in turn affect our behaviour, have been key challenges of 20th century science. The challenges of the 21st century will be to deepen this understanding and to use current and future knowledge for the benefit of individuals, their families and society.

The use of psychoactive drugs has been a feature of human society for much of recorded history. As shown in this report, all indicators point to a continued, and in some cases a growing, use of psychoactive substances, be they legal or illegal so-called 'recreational' drugs, medicines for mental health, or drugs called 'cognition enhancers', which can enhance brain performance in various ways. The use of psychoactive drugs brings both benefits and costs: while new drugs to treat mental illness or neurodegenerative disease are to be welcomed, there is a compelling need to reduce the burden of harms associated with drug misuse and addiction.

Although many outstanding research questions remain, major advances in genetics, neuroscience, pharmacology and psychology have already provided far-reaching insights into normal and abnormal brain function and how mental processes can be impaired and enhanced by psychoactive drugs. In this report we describe research showing that many drugs of abuse, for example cocaine, heroin or amphetamines, can 'highjack' certain brain processes, leading to dependency and addiction in some people. There is now evidence that most addictive drugs act on a common brain system and this evidence has given rise to several neurobiological theories of addiction that are currently under investigation. There is also a much deeper understanding of the brain changes that result from chronic drug use and the range of factors associated with vulnerability to drug misuse in children and adults, including genetic, psychological and environmental influences.

Yet this enhanced understanding appears to have had little impact on the development of new treatments for addiction. This situation is echoed in the fields of mental health and neurodegenerative disease, where there is an urgent need to translate research findings in basic science into new and improved therapies that not only relieve symptoms, and do so without debilitating side effects, but also cure or prevent the onset of established disorders.

Fulfilling this potential will require a greater prioritisation of research into addiction and mental health on the part of Government, research agencies, industry and the health and social services. For example, investment in large-scale genetic and epidemiological studies is needed to determine the interaction between genetic and environmental factors associated with substance misuse and mental illness. The full range of brain imaging technologies, such as functional magnetic resonance imaging (fMRI) and positron emission topography (PET), must also be exploited to identify brain changes associated with vulnerability, onset and progression to mental disorder or addiction. A more dynamic and multidisciplinary combination of brain imaging, neuroscience, genetics, experimental medicine and other fields holds real promise for the rapid development of new and better treatments for addiction and mental illness, but only if research is sufficiently resourced and appropriately coordinated.

In this report we show how research is leading to a more 'holistic' view of drug misuse and addiction, involving medical, genetic and neurobiological factors as well as individual factors and social context. This view has led some experts to characterise addiction as a chronic medical illness or, more specifically, as a chronic relapsing brain disorder. As with all disorders and illnesses, prevention is better than cure, and our knowledge of the individual, family

and social factors associated with substance misuse must now be utilised to reduce the impact of known risk factors and to inform public health interventions. This strategy will require more reliable information on the prevalence and harms of legal and illegal psychoactive drug use to formulate appropriate interventions and to target resources more effectively. Above all, in this report we seek to emphasise the importance of a health-based approach to reducing the harms associated with drug misuse, through providing treatments, identifying risk factors, formulating preventative measures and informing regulatory strategies.

In recent years, improvements in our understanding of cognition – internal mental processes such as attention, learning and memory – have led to the identification of several pharmacological agents that can enhance brain performance. These ‘cognition enhancers’ can potentially, for example, improve short-term memory or speed of thought, and could therefore bring significant benefits to patients with neurodegenerative

disease. However, these drugs will also be attractive to healthy people for use in non-medical contexts, perhaps to help them to pass an exam or to improve their performance at work, giving rise to complex questions about how such use should be regulated.

Engagement with the public on issues of brain science, addiction and drugs has formed a key component of this report and will be crucial in taking forward policy and regulation in these areas. The public’s ability to make informed choices requires the provision of accurate and balanced information about the potential benefits and harms of psychoactive drugs. Furthermore, an intelligent and appropriate approach to the regulation of psychoactive drugs requires deliberative and inclusive community debate. Continuing the type of public engagement activities carried out during this project can better inform regulators, allowing them to work with the grain of public opinion, and so develop policies that can achieve their desired objectives.

Throughout this report, and in our conclusions and recommendations, we emphasise the following five key messages:

1. Recent advances in brain science hold the promise of significant practical and therapeutic outcomes for treating mental illness and addiction. However, additional investment is needed to ensure that knowledge continues to be advanced and translated into benefits for patients.
2. The formulation of better prevention strategies requires enhanced efforts to understand and identify the factors that put particular individuals and population groups at risk of mental illness and drug misuse.
3. Improvements are needed in our information on the prevalence, duration and type of recreational drug use in the population, to enable more effective targeting of resources.
4. Regulation and policy require a more sophisticated index of the harms caused by the use of legal and illegal psychoactive drugs.
5. Regulation and policy around recreational drugs, medicines for mental health and cognition enhancers must move forward in a way that is informed by advances in research and the views of the public.

Objectives and scope of report

Background and objectives

The Government's Foresight report 'Drugs Futures 2025?' was launched in July 2005. The objective of the report was to consider 'how to manage the use of psychoactive substances in the future to best advantage for the individual, the community and society?'. The Foresight report was an independent analysis informed by 15 'state-of-the science' reviews, on topics including genomics, experimental psychology, neuroimaging, neuropharmacology, ethics and sociology. Informed by the science reviews, the Foresight project explored the likely impact of advances in the sciences and social sciences in relation to three types of psychoactive substance:

- Legal and illegal 'recreational' drugs.
- Medicines for mental health.
- Cognition enhancers.

These explorations led to the identification of several difficult and sensitive policy questions that were set out in the Executive Summary of the Foresight report. Following publication, the Government invited the Academy of Medical Sciences to take the Foresight report forward by considering the societal, health, safety and environmental issues raised in the project and to formulate recommendations for future research needs and public policy.

In early 2006, the Academy convened a working group, chaired by Sir Gabriel Horn FRS FRCP, to undertake this task. Membership of the working group and details on the preparation of this report are given in Appendix I.

The working group's terms of reference were to:

- Consider, in consultation with experts and the public, the societal, health, safety and environmental issues raised by 'Drugs Futures 2025?'.
Report to the Department of Health and other Government stakeholder departments

with recommendations for public policy and research needs.

- In the course of the consultation, to address the Government's policy priorities in this area.

This report is designed for policy-makers in Government, research funders, regulatory authorities, universities, NHS trusts, patient groups and other relevant bodies, as well as the public and all other interested parties.

Scope

As mentioned above, the Foresight report covered a wide array of topics and explored issues relating to three types of psychoactive substance (defined as a substance that affects brain function through its chemical neurotransmitters): 'recreational' drugs, medicines for mental health and cognition enhancers. The Academy was invited to follow the Foresight approach and consider issues relating to the same three categories in its own deliberations.

In considering the issues raised in the Foresight project, our report focuses on identifying firm actions to be undertaken by Government, research funders, regulatory authorities and others, as well as identifying research that needs to be carried out so that these agencies can be in a more informed position.

There are three parts to this report:

Part I 'Recreational' drugs (Chapters 3-6)

In Part I, we consider the use of so-called 'recreational' drugs such as cocaine, heroin and amphetamines. We discuss the magnitude of the problem; developments in the neuroscience of addiction in pharmacology and in treatment; how to identify and measure the harms caused by recreational drug use and how such use should be regulated; and risk factors

for substance misuse and addiction. Legal substances such as alcohol and tobacco are also discussed in these chapters. However, we emphasise our focus on *illegal* psychoactive substances: a detailed analysis of smoking and alcohol consumption is beyond the scope of this report. The Academy's 2003 report, 'Calling time: the nation's drinking as a major health issue', provides an in depth discussion of national levels of alcohol consumption, associated harms and opportunities for public health interventions.

Part II Medicines for mental health (Chapter 7)

In Part II, we explore the development and use of medicines for the treatment and prevention of mental illness in the context of recent and potential advances in cognitive neuroscience. It should be emphasised that, in considering medicines for mental health, we have focused on pharmacological therapies; psychological treatments such as cognitive behavioural therapy (CBT) are briefly considered in Section 7.8.3, but a detailed review is beyond the scope of this discussion. We also emphasise the importance of developing new and effective treatments for the age-related cognitive dementias, such as Alzheimer's disease. These diseases are becoming increasingly prevalent as life expectancy increases (Box 7.10), and were of major concern to many who participated in the public engagement programme. However, the general field of neurodegenerative diseases is vast. To do this field full justice, and in the light of the pressing need to develop new therapies, we recommend that neurodegenerative disease is the subject of a separate, dedicated review (Recommendation 17).

Part III Cognition enhancers (Chapter 8)

Finally, in Part III, we consider a new breed of psychoactive substance – the 'cognition enhancer'. These drugs can potentially enhance brain performance in specific ways, such as improving short-term memory, decision-making or speed of thought. We discuss their use both by patients and healthy people, and the associated ethical, safety and regulatory issues.

We emphasise that the final content of this report has been shaped by the discussions of the working group and by the priorities and interests that emerged from the public engagement programme (see below).

Process

Independence

The membership of the working group included Academy Fellows and external experts. It reflected the breadth of issues considered during the project; members were drawn from the fields of epidemiology, medicine, neuroscience, psychiatry, pharmacology, philosophy, psychology and law. The Chair and members of the working group were appointed as individuals and not as representatives of their affiliated organisations.

Although this study was initiated and sponsored by the Government, members of the working group were completely autonomous in their work and in reaching their conclusions. The Government is expected to give a written response to this report in due course.

Cross-Government advisory group

A dedicated cross-Government advisory group was convened for this study, including representatives from the Department of Health, the Home Office, the Department for Innovation, Universities and Skills (previously the Department for Trade and Industry), the Department for Children, Schools and Families (previously the Department for Education and Skills), the Department for Local Government and Communities and the Devolved Administrations. The remit of the advisory group was to: follow the progress of the project; advise on strategic direction; ensure relevance to Government as a whole; and contribute to the presentation and communication of the project outputs. The Chair and secretariat met with the advisory group on four occasions.

Interim reports on the deliberations of the working group were submitted to the Minister of Health in January 2007 and the Home Office in October 2007. The Government's strategy 2008-18, 'Drugs: protecting families and communities' (HM Government, 2008), was published during the final stages of production and has not been cited in this report.

Evidence gathering

The working group held monthly meetings during the course of the project, at which evidence from a wide variety of sources was considered, including:

- The 15 science reviews of the original Foresight project.
- Analysis and written contributions from working group members.
- Responses to the open call for submissions.

- Findings from the public engagement programme (below and Chapter 2).
- Reports and articles from the wider literature.

Public engagement programme

In accordance with the first of the project's terms of reference, the Academy commissioned a national programme of public engagement activities ('*drugsfutures*'), with funding from the Government's Sciencewise programme. Full details on the objectives, methods and outputs of this programme are given in Chapter 2.

Review

The draft report was reviewed by an external panel (Appendix I) appointed by the Academy Council and was amended by the Chair in light of the comments received.

Chapter 1 Introduction

In July 2005 the Government launched a Foresight project entitled 'Drugs Futures 2025?'. The aim of the project was to provide a challenging vision as to how scientific and technological advancement may impact on our understanding of addiction and drug use over the next 20 years.

The vision of the future was to be elaborated in two ways. Firstly through a series of reviews of present scientific knowledge in the relevant fields, and assessments of likely future developments of that knowledge; secondly by creating new networks of people across scientific disciplines and areas of business and policy-making. The range of disciplines covered by the project was enormous, extending from molecular genetics, through brain function and pharmacology to psychology, psychiatry, public health, education, economics and sociology. In the light of this wide range it is not surprising that when in 2007 the scientific reviews were published as a book, its title was not 'Brain science addiction and drugs', but 'Drugs and the future: brain science, addiction and society'.

An additional aim of the Foresight project was to identify the key challenges of the future and to engage those who can take them forward. The Academy of Medical Sciences was invited to accept these responsibilities. The deliberations and recommendations of the working group appointed by the Academy to undertake this task are set out in this report.

1.1 Scientific background

1.1.1 Advances in brain sciences

In his Foreword to the Executive Summary of the Foresight project, the then Chief Scientific Advisor to the Government, Sir David King, wrote:

'The greatest changes we will see in the twenty first century may be brought to us through developments in our understanding of the

brain. These advances may offer revolutionary treatments for the brain, and could see the end of neurodegenerative disorders such as Alzheimer's and Parkinson's Diseases. We should also see much improved treatments for addictions and other mental health disorders, and the development of new 'recreational' drugs some of which might lead to fewer harms and lower risks of addiction than the substances in use today.' (Foresight, 2005)

Thus one of the main reasons for initiating the Foresight project was the hope of future medical and social benefits that derive from our present and likely future understanding of the brain. Yet the understanding that we now have has come about through relatively recent advances. Less than 12 decades have passed since the nerve cell, or neuron, was first clearly recognised as the structural and functional unit of the nervous system, of which the brain is part. Since that time, the speed at which advances have been made in understanding the nervous systems of humans and other animals has been astonishing. We have learned much about the architecture of the human brain and the way that its 10-11 billion neurons are arranged; and how neurons in different regions of the brain function to process information about the world and to act on it through controlling our behaviour. Through recent developments in imaging techniques it has become possible to see the ways in which these different brain regions interact with each other during the performance of mental tasks so that we can, so to say, get a glimpse of the mind at work.

Among the many recent advances that have been made and that have a direct bearing on the Foresight project, are those that relate to the ways in which neurons communicate. For the most part, signals are transmitted from one neuron to the next at a special junction known as a 'synapse'. The terminals of the active neuron release a minute amount of a

chemical agent, a 'neurotransmitter', that binds to specialised receptors on the surface of the next neuron. There are many different kinds of neurotransmitter and many different kinds of receptor. Some neurotransmitters excite neurons and others reduce their excitability. The balance between increased and decreased excitability determines whether a signal is passed on through the nervous system, and even the route that the signal takes. Chemical synaptic transmission is under exquisitely sensitive control and a wide range of chemical substances may disturb this control. In doing so these substances may impair, or possibly even enhance, aspects of brain function. In this way they may influence our thoughts and perceptions, our capacity to learn and remember, our emotional reactions and mood, our capacity to make plans for the future and even our ability to function effectively in society. For these reasons, chemical agents that influence these functions of the brain are known as 'psychoactive substances' or 'psychoactive drugs'; in influencing the brain, they influence the mind.

The Executive Summary of the Foresight project identified three classes of use to which psychoactive substances are put (Foresight, 2005). Firstly, some such as cocaine and alcohol, are used for 'recreational purposes', to generate a feeling of pleasure and wellbeing, a 'buzz', and to act as a 'social lubricants'. However there is a negative side to this use. Use all too often leads to abuse, to dependence on the drug and, in the extreme, when the drug is not available, to craving. At that point the user's life becomes focused on the need to obtain a continuing supply of the drug whatever the cost in terms of personal ill health, harm to the user's family and to society at large. Secondly, some psychoactive substances have proved to be of value in treating mental ill health and certain degenerative disorders of the nervous system by relieving, for example, some of the symptoms of Alzheimer's disease. Thirdly, some psychoactive substances are used to enhance the mental performance of those suffering from this disease, as well

as that of healthy individuals. Used in these ways psychoactive substances are known as 'cognition enhancers'. Novel psychoactive drugs of many different sorts may emerge in the future, affecting for example the expression of complex social attributes, such as parental affection.

As a result of intensive research conducted over the past two or three decades it has become clear that several psychoactive substances, particularly drugs of addiction, 'highjack' the functions of specific types of neuron in particular regions of the brain. This knowledge has made it possible to develop medical treatments to offset the addictive effects of these drugs, although many of these treatments are only partially successful. Nevertheless there are realistic hopes of more effective medical and psychological treatments for addiction as we come to understand more about the normal functions of the brain regions on which the drugs act, how these drugs modify these functions and the psychological processes involved in drug abuse.

Mental ill health imposes an increasingly heavy burden on society. As life expectancy increases, the costs attributable to neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease will be added to this burden. Advances in neuroscience are likely to lead to new treatments for mental ill health and neurodegenerative conditions. However, for the promise of neuroscience to be realised, the subject must be seen in the wider context of genetics and the behavioural and social sciences.

1.1.2 Advances in behavioural, social sciences and genetics

For a long time, addiction has been regarded as a social or moral disorder. More recently it has come to be regarded by specialists who work in this field as a chronic medical illness. Viewed in this light, research not only focuses on treating the disorder once it has become established, but also seeks ways of preventing it from occurring in the first place.

Surveys of adults who misuse alcohol, tobacco and illegal substances have shown that such individuals are more likely than others to have several risk factors in their childhood. For example, they are likely to have exhibited high levels of impulsive behaviour, to have family members who have misused drugs, to have been mistreated as children, to have exhibited antisocial traits and more likely to have lived in neighbourhoods where there is high drug misuse. To be sure, not all people who misuse drugs fit into this picture. For some, the main reasons for use are likely to be societal, such as the availability of drugs, and permissive attitudes to their use.

To these largely 'environmental' factors must now be added genetic risks. For example, there is evidence that individuals who possess a variant of a particular gene get a much stronger buzz from some drugs and so, it is suggested, are more likely to repeat the experience than those who do not have this genetic variant. The gene encodes for a neurotransmitter receptor that is present in abundance in those brain regions that have been implicated in drug-seeking behaviour. There are fewer of these receptors in these brain regions in individuals that possess the genetic variant. With these studies we begin to see the interconnections among genetics, neuroscience and substance misuse. It is highly probable that research into the molecular genetics of mental ill health, including addiction, will continue to clarify this interrelationship and to clarify the interaction between genetic and environmental factors in affecting behaviour.

By identifying the range of risk factors for substance misuse, it becomes possible to formulate strategies for mitigating their effects. For example, ongoing work indicates that some of the effects of an adverse environment on a young child can be offset by skilled, non-judgemental advice to parents and by the provision of high-quality childcare. These and other interventions are more likely to be effective the earlier they are introduced into

the child's life. Where genetic predispositions have been identified, advice may be offered to susceptible young people about the risks they face in experimenting with psychoactive substances. However, the issue of identifying an individual's genotype for whatever purpose is fraught with ethical and legal difficulties and faces strong resistance from many members of the public whose views were sought as part of this study.

1.2 Societal aspects

Human beings have used psychoactive substances for much of recorded history. At various times and in various way societies have placed restrictions on their use, but it is at least questionable whether such use can wholly be eliminated. In the UK many psychoactive substances are subject to regulation. In the case of alcohol and tobacco, premises that sell these products must be licensed, their purchase is restricted to persons above a certain age, and smoking tobacco products in confined public places is now prohibited. Many other psychoactive substances are more rigorously controlled and are subject to the Misuse of Drugs Act 1971. This Act makes it an offence to possess or supply a controlled substance. It is also an offence to allow premises to be used for (illicit) drug taking. The aims of the legislation are to reduce the harm caused by drug misuse throughout the UK and, in particular, to protect young people from becoming drug users. Since the Act was introduced in 1971 much evidence has accumulated about the harms caused by the misuse of both licit and illicit psychoactive substances. If regulation is to be based on the best evidence, as it surely should be, then the post-1971 evidence should be taken into account in deciding how these substances are to be categorised for the purposes of legislation designed to impose restrictions on their use. Such legislation is, however, controversial for at least two related reasons. One is whether it is morally justified. The other is whether it is effective in achieving its aims.

On the question of justifiability, this legislation is wholly acceptable to some people. To others it is an unwarranted intrusion on their freedom as adults to act within a society that claims to be a liberal democracy. The justification for this second view is that, in such a society an adult should be free to act without interference from the state if their actions do no harm to others. The action might harm the individual, but that, the argument runs, should be of no concern to the state. Is this a viable position in respect of psychoactive substances, including cognition enhancers?

This question is a matter of deep concern to many members of the public; as well as philosophers, legislators and regulators. The question is difficult because we live in a complex, interconnected society. Should the drug misuser fall ill, abuse their family by neglect or by violence, or cause injuries to third parties through accidents, then others are harmed. If these consequences of drug misuse also involve the public services, the police, the social or health services, then the state and hence the taxpayer become involved. It is he or she that has to pay the taxes to meet the provision of these services; and the extent to which they pay more tax reflects a corresponding reduction in their freedom to spend the money they earn on the well-being of their children, on education, health, on charities and on their own well-being. That is, they are adversely affected. In our society it is difficult to harm oneself without bringing some

kind of harm to others, and this is the case whether the agent of harm is a legally available psychoactive substance or an illicit one. So the balance between protecting individuals and society from the harmful effect of these substances on the one hand, and protecting individual liberties on the other, is a very difficult one to strike.

In revising existing legislation, or in framing new legislation that restricts the liberties of individuals, it is important to take into account whether the legislation will be effective in achieving its aims, in the sense of generating general compliance. At the present time the question of the effectiveness of legislation in the UK in restricting drug possession and supply is controversial. Some argue that such legislation has been effective and there are far fewer drug addicts and users than there otherwise would be. Others point to the large-scale violation of such laws, the large numbers of users of illegal drugs and the resulting massive costs of policing and punishing drug possession and supply as evidence of the ineffectiveness of legislation. In contemplating changes to legislation it is essential to obtain the views of the public, as well as the police and drug workers, if the legislation is to be implemented effectively. Failure to consult in this way may lead to a failure to achieve the hoped-for objectives while placing a heavy burden on the criminal justice system, the social services, the health services, and ultimately on the exchequer.

Chapter 2 Public engagement

2.1 Background and objectives

To ensure that the final recommendations of the working group were informed both by scientific evidence and public concerns and aspirations, the Academy commissioned a national programme of public engagement activities (entitled '*drugsfutures*'), funded by the Department for Innovation, Universities and Skills' Sciencewise programme. The overall aim of the public engagement programme was 'to engage the public in a national conversation on the issues raised by the current and future use of drugs that affect mental well-being.'

The purpose of *drugsfutures* was to provide an opportunity for a broad cross-section of the public to discuss their aspirations and concerns about current and future issues related to brain science, addiction and drugs. Starting with the question 'what kind of drug culture do you want in the future?', the programme set out to identify areas of consensus, disagreement or uncertainty on a broad range of issues relating to the three categories of substance use covered in this report (recreational drugs, medicines for mental health and cognition enhancers).

The *drugsfutures* programme was designed and managed by a consortium of organisations led by the Office for Public Management (OPM). A comprehensive report of the findings, including a detailed analysis of participants' views on each of the three substance types, can be accessed at <http://www.acmedsci.ac.uk>. Information on the range of participants, the materials used during the activities and a separate report from the independent evaluator of the *drugsfutures* project are also available via the website.

The *drugsfutures* programme was an integral part of the Academy's study: working group members shaped the scope of the activities at the outset of the programme, participated in events and analysed feedback from the

activities during the course of their own discussions. There was a strong desire for the programme to involve a range of different audiences, particularly groups of young people, drug users and older adults who may have especially relevant views but are often excluded from debates on these topics. It should be emphasised that *drugsfutures* was designed to explore issues in-depth, rather than simply take a poll of opinions. As such, the activities were designed to explore both participants' initial views and their changes in opinion following dialogue with each other and with a range of 'experts' including scientists, ex-drug users, teachers, health professionals and members of the working group. From the outset the working group made a commitment to consider the findings from the public engagement programme when developing their recommendations. This commitment was relayed to participants at the start of each event.

The parameters of the programme were determined by the three categories of substances under consideration, together with five key themes (Table 2.1).

Structuring the content in this way meant that the same category of substance could be approached from different thematic perspectives and similar issues explored in different contexts. For example, recreational drugs were included in discussions of the law, society, young people and mental health. Similarly, medicines for mental health were discussed in terms of their role in society and their use by young people, as well as at a workshop dedicated solely to issues around medicines for mental health.

The stated objectives of the programme were to:

- Provide opportunities for members of the public to discuss and explore their aspirations and concerns about current

and future issues related to brain science, addiction and drugs.

- Identify areas of consensus, disagreement or uncertainty on a broad range of issues raised by current and possible future scientific developments, and explore both initial views and changes in opinion.
- Inform the final recommendations made by the working group for public policy and research needs.

2.2 Implementation

Over 500 participants, aged from 13 to 96, were involved directly in the programme, either through face-to-face events or through the website.

Participants at the workshops were recruited by a professional recruitment agency to include a diverse cross section of the population and were provided with a modest financial incentive. For the 'outreach' workshops (see below), participants were recruited on the basis of specific knowledge, experience or family situation, e.g. mental health service users, parents of children with attention deficit hyperactivity disorder (ADHD) and ex-drug users. Individual incentives were not given to participants in the outreach work, although a financial contribution was made to the several charitable, voluntary and public-sector organisations that provided assistance.

2.2.1 Face-to-face activities

Face-to-face activities took place between January and March 2007. The programme

launch event on 31 January 2007 was attended by 113 people, including participants recruited by the professional recruitment agency, people with a particular interest or experience in drugs and brain science, scientists, health care professionals, policymakers, media and other key stakeholders. After the launch event, 26 face-to-face events were held in eight locations across the UK (London, Birmingham, Liverpool, Exeter, Belfast, Glasgow, Merthyr Tydfil and Norwich), involving an additional 300 people. These events included:

- **Brainbox**, a reconvened deliberative workshop, taking place over 3.5 days in total, with a 1.5-day introductory session at the start of the project and a 2-day session at the end.
- **Five regional one-day workshops**, each of which was organised around a specific theme.
- **Smaller 'outreach' meetings**, with specific groups, e.g. teachers, students, ex-users, carers.

Brainbox was a model designed specifically for this project. It used a deliberative approach to involve a group of participants in an extended event, during which they were able to explore all the issues in some depth. Brainbox comprised an introductory 1.5-day event, held at the start of the programme, which introduced participants to the issues and provided an opportunity to gauge their initial attitudes, hopes and concerns. The follow-up 2-day event was held at the end of the

Table 2.1 Public engagement themes and categories

Categories of substance	Themes
Recreational drugs	Drugs and the law
	Drugs and society
Medicines for mental health	Drugs for a smarter brain
	Drugs and young people
Cognition enhancers drugs for a smarter brain	Drugs and mental health

drugsfutures programme. This second event provided expert input and built on the results emerging from the five regional workshops and outreach events. Before the follow-up event, participants were sent a summary of their initial Brainbox discussions and an overview of the findings from the regional workshops and outreach events, allowing them to measure their own views against those of the wider public and to consider those views when identifying their priorities.

2.2.2 On-line consultation

The on-line element of the programme ran between January and April 2007 and comprised a blog and a structured consultation. The on-line consultation was structured according to the five themes used in the face-to-face work. Participants were able to respond to any theme and could answer all questions or only those of most interest to them. The blog was designed to allow people to participate in the debate in a less formal way than the full on-line consultation. In total, 314 people registered on the website, with 125 people answering one or more questions. A total of 1,659 responses to questions were submitted.

2.2.3 Reporting and evaluation

The consortium commissioned to undertake *drugsfutures* wrote a comprehensive report on the findings. Information on the terminology

used in the full report, and in references to the public engagement programme included throughout this report, is provided in Box 2.1. The full public engagement report, along with a separate report from the independent evaluator of the *drugsfutures* project, is available at <http://www.acmedsci.ac.uk>.

2.3 Findings

Participants in *drugsfutures* came from a wide range of backgrounds, bringing with them different experiences of drug use and mental health and different attitudes to the issues discussed. Findings relating to specific themes are provided in the shaded boxes throughout this report. In the following sections, we outline some of the common themes that emerged from discussions of all the different substance types, including the benefits and costs of using psychoactive substances, drugs and young people and freedom of choice. We then highlight some of the main findings relating to each category of drug.

2.3.1 Common themes

2.3.1.1 The benefits and costs of using psychoactive substances

Across the programme of activities, participants expressed views on the acceptability and

Box 2.1 Terminology

Where the word 'people' has been used in this report, it should be read as meaning those people who took part in the *drugsfutures* programme. It is not intended to imply that the views expressed represent those of the wider population.

The term 'recreational drugs' was applied to illicit drugs currently falling under the Misuse of Drugs Act 1971, as well as licit drugs such as alcohol and nicotine. It could be argued that the term 'recreational' is not applicable to some of these drugs – or, at least, to the reasons for their use. However, this was the term used in the Foresight 'Drugs Futures 2025?' project and the terminology was retained. The term 'psychoactive substances' is used to capture recreational drugs, medicines for mental health and cognition enhancers.

Finally, although we recognise there is much debate about their use, terms such as 'participate', 'engage' and 'involve' have been used interchangeably.

benefits of using psychoactive substances.

- **'Recreational' drugs.** Many of the on-line participants talked about the pleasurable effects of using recreational drugs, such as feeling happier, more powerful or even invincible. Some people felt that a desire to experiment with changing the state of one's mind is part of human nature. Other participants felt that the excitement of doing something illicit and the challenge of not getting caught played a large part in making drugs attractive.
- **Medicines for mental health.** The value of medicines for mental health was largely unquestioned: people with experience of mental health problems recognised how valuable drugs had been in stabilising their condition; and people caring for relatives or friends with mental illnesses were aware that drugs were, at times, the only option.
- **Cognition enhancers.** Alzheimer's disease, as well as dementia more generally, was seen as a pressing social problem. The increase in incidence of Alzheimer's disease was cited as a reason for focusing research on its underlying causes and on developing more effective drugs to delay its progress in the early stages. People saw great benefits in the use of cognition enhancers to treat conditions such as dementia. Participants recognised that, when used appropriately, cognition enhancers also had a valuable role to play in the treatment of children with ADHD. Some participants, particularly students, saw some benefits to 'healthy' people using cognition enhancers to improve academic performance and to achieve better exam results.

Despite the perceived benefits, throughout the programme participants returned to the need to look at the costs of using drugs within a wider social, economic and environmental context. Participants discussed the danger of people using recreational drugs as a way to address their problems, for example to alleviate negative feelings, or to escape from pain, boredom, or the stresses of everyday life. Some

felt that a greater understanding about the risks of addiction and the other negative effects of drugs would deter people from using them. Others said that the feeling that 'it will never happen to me' meant that some people ignored the risks associated with drug use, even though they were aware of them. Many participants felt that the most effective way of discouraging the maximum number of people from using drugs was to address the social and environmental factors that might make a young person more vulnerable to drug use.

Similarly, despite the widely recognised value of medicines, there was a feeling that people often choose the 'quick fix' of pharmacological medication, in preference to seeking out longer-lasting solutions to their problems. More specifically, a great majority of participants felt that medication is used too early and too quickly in treating mental health problems. Many felt that an increasing number and range of 'mental states' are being seen as 'problems' and being treated with a greater number of drugs. Medication was also seen by many as a means of controlling those whose behaviour deviates from the perceived norm, that is, people we do not understand or find difficult to deal with.

2.3.1.2 Drugs and young people

Young people's use of drugs was viewed differently from adult drug use, regardless of the type of drug under discussion. A strong priority was placed on the need to protect the developing brain and to prevent the emergence of patterns of behaviour that might lead to addiction or mental health problems later in life:

- **'Recreational' drugs.** Participants' concern about young people's use of illicit and licit recreational drugs cannot be over-emphasised. Peer pressure was perceived as playing the biggest role in young people's use of drugs, but the media was also felt to play an important part in informing attitudes. Participants acknowledged that, while all young people were likely to be subject to peer pressure, their levels of resilience will vary. Some of the teachers who participated

in the project emphasised that peer pressure was a critical factor, in addition to the wider environmental and social features in a young person's background and the opportunities available to them in their social and educational life.

- **Cognition enhancers.** Many participants saw the use of cognition enhancers as valuable in helping young people to cope with ADHD, but there were concerns about the impact of a child growing accustomed to using drugs to control mood, and whether this heightens their risk of using recreational drugs. A small number of participants thought that healthy young people should be given the same freedom of choice as adults about using cognition enhancers.

Despite concerns about young people using drugs, many participants in both the on-line and face-to-face work thought that it would be impossible to prevent all young people from taking drugs (particularly 'recreational' drugs). Rebellion and experimentation with drugs were seen as part of growing up and the perception that some drug use was inevitable for most people was behind much of the support for a more health-based, rather than punitive, approach to drug use. Much of the discussion of young people's use of illicit recreational drugs was focused on education and prevention.

Throughout discussions on young people and drug use, participants identified what they felt to be a tension between the benefits of identifying young children at increased risk of, for example, illegal drug use or mental illness, and the disadvantages of 'labelling' young people. Many participants were resistant to the idea of identifying specific young people as particularly vulnerable, although others recognised the benefits gained from having additional information that could inform treatment decisions and the targeting of resources.

2.3.1.3 Freedom of choice

The implications of freedom of choice - for individuals, their families and wider society

- generated the most intense discussion. Participants debated the potential consequences of widening or narrowing the choice of drugs that individuals can legally consume, of changing the way drugs are distributed and the impact of improving their effectiveness.

Although many people expressed strong concern about the inappropriate use of psychoactive substances, there was strong support among participants for an individual's right to make their own decisions about whether or not to use 'recreational' drugs, medicines for mental health or cognition enhancers. For 'recreational' drugs, participants emphasised the importance of individual choice and several people argued that ensuring informed choice requires sufficient information for people to understand the risks they are taking.

Interventions that might reduce individual choice were generally rejected. For instance, most participants were against the idea that in the future it might be acceptable to vaccinate babies against addiction. However, the possibility of vaccines being used by adults was received more positively. The 'professional' use of cognition enhancers, for example in the military, shocked many participants, perhaps because of the association of drugs with loss of control. Participants rejected the idea that certain cognition enhancers might aid performance in certain jobs, for example through decreasing impulsive behaviour, and increasing focus and problem-solving skills, feeling that these benefits were outweighed by concerns over coercive use by employers.

2.3.2 'Recreational' drugs

In the discussions on recreational drugs, participants tended to focus on illicit and addictive substances, such as heroin and cocaine. Using illicit recreational drugs was associated by many participants with economic and social deprivation and, in particular, with the attitudes and behaviour of parents. Many participants appeared to view problem drug use as more prevalent in people from less well-off

environments, or something that would happen to their own children only if they 'get in with the wrong types'. Some participants suggested that stereotyping drug users as being of a particular 'type' was incorrect and unhelpful.

2.3.2.1 Key themes

Of the on-line participants who answered the question of what limits should be placed on the right to use 'recreational' drugs, around half said there should be no limits if use has no impact on anyone else. However, since this was seen as unlikely, participants felt that limits need to be imposed to minimise harms. Some participants considered harms to include only the immediate risks to the user and others, such as accidents or injury resulting from intoxication, but more participants included the wider harms to the user's family, drug-related crime, violence and social problems resulting from family disruption and the economic cost of treating drug users.

In addition to discussions on 'harm', some of the themes raised during debates around recreational drug use were:

- **Education and prevention.** Most of the participants felt that scare tactics, moralising or 'just say no' approaches to drugs education were ineffective, primarily because they were often at odds with young people's own experiences. Many participants saw a good drugs education programme as one that provides balanced and honest information about the benefits, as well as the harms, associated with drugs. Teachers involved in one of the outreach events emphasised that young people are more likely to be influenced by their peers than by teachers or other adults. Delivering information and education in settings other than school was seen as likely to be more effective.
- **Regulation and control.** There was general agreement that some recreational drugs need to be controlled more strictly than others. How that control should work

was debated and further engagement activities will be important (Section 5.4). Many participants felt that the best way to address drug-related harm is to allocate more resources to providing support and help to addicts, and to ensure that general practitioners and other health providers are as knowledgeable about addiction and drug use as they are about other health problems. Providing safe environments for drug use and ensuring that users are aware of the wider health implications of their drug use were also seen as important. It was acknowledged that this approach would be resource-intensive, but nevertheless, participants considered this to be a more effective approach in the longer term than simply sending drug users to prison.

- **Users and ex-users.** Ex-users of drugs participated in several *drugsfutures* events. Much of the discussion raised by ex-users explored the place of children and young people in society today and the need to value and support them. It was suggested that a majority of people who use drugs do so to cope with childhood traumas. Investing in children's services and focusing on the prevention of these traumas was seen as the best way to minimise problem drug use in later life.
- **Illicit drugs and mental health.** Several participants in both the face-to-face and on-line activities raised the issue of the relationship between mental illness and illicit drug use. Some felt that self-medication with illicit drugs could at times be a positive alternative to prescribed drugs, although this view was not widely expressed. As might be expected, most participants focused on the negative aspects of this relationship. People using illicit drugs and people with mental health problems were more likely to see the relationship as circular: untreated mental health conditions could lead to self-medication with illicit drugs that may

in turn exacerbate the initial condition, leading to escalating drug use.

2.3.2.2 Future priorities

Looking to the future, effective drugs education was seen by participants as essential for the population as a whole. Several features identified by participants as essential for future education programmes were:

- Start drugs education at a much earlier age, with the information provided and approach tailored to different age groups.
- Ensure information is honest, open and clear about the benefits, as well as the disadvantages, of recreational drugs, including alcohol and nicotine.
- Provide information and education for drug users and addicts on the health implications of drug use and how to minimise harm.
- Include information on the effects of drug abuse on home, work and society, ensuring the dangers are properly understood.
- Involve ex-users and addicts in drugs education.
- Develop effective peer education programmes and drugs education for out-of-school venues.

Participants from a support group for ex-drug users suggested that resources should be targeted at removing the stigma and guilt associated with parental drug use. It was felt that having a parent with problematic drug use could deeply affect a child. Providing confidential support services for children and young people and helping families stay together were seen as crucial. Ensuring that social workers understand and are trained in how to provide this support was seen as a fundamental aspect of these services. Additional suggestions included having drugs liaison workers in 'high-risk' schools and having specially trained children's counsellors in schools to provide support in coping with difficult situations involving family, relationships, peer pressure, abuse, bullying and other personal issues.

For the regulation and control of 'recreational' substances, most participants supported continued prohibition, but favoured a more health-based approach in the future, with imprisonment only for dealers and traffickers.

Most participants felt that in the future we should:

- Reduce the dominance of legal sanctions against drug users.
- Have more areas where drug users can use safely without harming society.
- Acknowledge that it is impossible to eradicate the use of recreational drugs.
- Control the quality of drugs.
- Crack down hard on dealers and remove their assets.

2.3.2.3 Ongoing dialogue

As discussed above, although most participants supported continued prohibition, a range of attitudes towards how drugs should be controlled and regulated were expressed at the different workshops. A small minority of participants focused on what they considered would be the benefits of legalising the recreational drug market, arguing that quality could be assured and making it possible to gain more accurate information about the extent of drug use. They felt too that crime associated with use of illicit recreational drugs would decrease, as would the harms, because people would be less circumspect about seeking help and more likely to seek assistance at an earlier stage. This was seen as helping to prevent chaotic use, unemployment and family breakdowns that can be associated with drug use. Although the number of users might increase, it was seen as less likely to become problematic because it would no longer be hidden and would be compatible with living a stable life. Some respondents felt that removing the existing limits to people's enjoyment of currently illicit recreational drugs by legalising their use would lower the cost of drugs, remove dealers and therefore reduce drug-related crime and its consequences. However, very few participants felt that ending prohibition would be the most effective solution. Those who focused on the negatives of

legalising the recreational drugs market argued that the incidence of drug use would increase and that, even if legally available, people would still need money to buy them and hence would still commit crimes. With more people using drugs, some participants felt that the overall reduction in drug-related harm might be only minimal. In addition, they felt that more users might also lead to an increase in mental health problems associated with drug use.

2.3.3 Medicines for mental health

Throughout the face-to-face activities, participants recounted experiences of mental health problems suffered either by themselves or by family and friends. Some of the people who took part in the outreach work were recruited specifically because they had mental health problems, including bipolar disorder, schizophrenia, depression, generalised anxiety disorder and panic attacks. Two factors seemed to be important for these participants in determining what should count as a mental illness. The first was whether there was some underlying physical or chemical cause to which the symptoms could be attributed. The second factor relates to the consequences of the illness for the person affected.

2.3.3.1 Key themes

Participants identified a set of specific conditions that they felt should inform the appropriate use of medicines for mental illness.

- First, the decision about the type and dose of drug to be used should be made by both the doctor and the patient.
- Second, drugs should be used only if the particular medication has been proved effective in the treatment of the problem in question and other approaches have been exhausted.
- Third, on-going support should be available and accessible, to help the person come off medication as early as possible. Some participants felt that what they described as the 'sticking plaster' approach to medication could mean that the problem was seen as 'solved' once the prescription had been filled.

- Fourth, accessible information about the potential side effects and contra-indications of medicines for mental health should be available.

Other key issues identified by participants included:

- **Side effects.** Participants identified several disadvantages to drugs prescribed for mental illness. Those who had used these drugs, and people caring for others with mental health problems, tended to focus on the side effects. Their concern lay with both the immediate side effects and the possible impact of drugs on future health. When participants focused on priorities for future research, minimisation of side effects was high on the list.
- **Identification and diagnosis.** Participants debated the benefits and disadvantages of early professional diagnosis of mental health problems. They agreed that professional diagnosis was important and that early diagnosis would allow preventive steps to be taken and resources to be targeted where need was greatest. However, because of the stigma attached to mental illness (discussed below) there were also concerns about the possible negative impact of prematurely 'labelling' individuals.
- **Improved services.** Participants outlined several priorities for improved services. The cost implications of improving the range and quality of services were acknowledged but it was felt that, in the longer term, money would be saved because more people would be able to continue working and the need for long-term drug treatment would be reduced.

One of the strongest messages voiced during the discussion on mental health was the need for better and more varied non-pharmacological approaches to treat mental health problems. Participants considered that non-pharmacological approaches should be widely available on the NHS and should include: cognitive behaviour therapy; drop in centres; support groups; counselling; and back-to-work strategies. The view was

also expressed that mental health services and primary care should be integrated more effectively, with the suggestion that health centres should accommodate mental health facilities and that mental health nurses should be available in all doctors surgeries. Some participants also felt that GPs needed to be more informed about mental health problems and the range of support and services available in their area.

2.3.3.2 Future priorities

Throughout discussions on mental health, several priorities for future research emerged. These included:

- Developing a better understanding of the physical and social causes of mental illness and the factors involved in it.
- Giving priority to research into dementia and depression - focusing on the early stages and preventing progression.
- Conducting research into the relationship between mental health problems and recreational drug use.
- Conducting research to understand if and why any particular groups of people are more prone to mental illnesses.
- Focusing on developing drugs that are effective and have minimal or no side effects or long term effects on general health. Drugs that will prevent the emergence or progression of Alzheimer's disease were seen as crucial, given our ageing population.

2.3.3.3 Ongoing dialogue

Eliminating the perceived stigma that surrounds mental health problems was seen by participants as fundamental to improving the lives of people with mental health problems and those who care for them. Participants did not think that their own openness and honesty about mental health problems was reflected in wider social attitudes. Despite the prevalence of mental illness, the stigma was felt to leave people reticent to speak of their experiences and to make some sufferers feel ashamed, as if their condition was in some way a sign of weakness. The consequences of stigma, invisibility and a general lack of understanding

were described in a consistent manner by those involved in the outreach work and in the workshops. Some people saw the mental illness itself as less debilitating than the wider social consequences that can accompany the condition, such as isolation and being open to abuse and, at times, violence. They pointed to a lack of understanding among service providers – they mentioned the police in particular – as well as the public. To many participants, the wider understanding that might arise from a more open discussion of the impact of mental illness on the individual, their family, friends and the wider community was felt to be lacking. Participants proposed several ways to address the current situation:

- Making information on drug packaging easy to understand, free from technical terms and large enough for people to read.
- Initiating general awareness-raising campaigns to inform people of the range and nature of mental illness.
- Encouraging more sympathetic treatment of mental health problems in television programmes, soaps and dramas.
- Promoting positive mental health and awareness of problems through education in schools - for example, how to avoid depression or how to spot the early signs of dementia.
- Holding more workshops such as those run as part of this project to provide people with time to think about the issues.

2.3.4 Cognition enhancers

The term 'cognition enhancers' refers to a class of psychoactive substances with the potential to enhance cognitive performance, not only in patients with neurological or cognitive disorders (e.g. Alzheimer's disease), but also in 'normal', healthy people (Chapter 8). Four events were dedicated to discussing attitudes towards cognition enhancers. Issues around the use of cognition enhancers were also discussed at the launch event and Brainbox workshop.

Views on acceptable and unacceptable methods of enhancing cognition were complex; unlike

recreational drugs or medicines for mental health, few participants could draw on personal experiences of using such substances. For many people, attitudes towards cognition enhancers appeared to be influenced by two distinctions:

- **Treatment versus enhancement.** For many participants it appeared that the level of acceptable risk and side effects from using cognition enhancers depended on whether they are being used to treat a diagnosed medical problem or for enhancement of a 'normal' state.
- **'Natural' versus 'unnatural' forms of enhancement.** The use of vitamin supplements, a good diet and plenty of exercise, hiring a tutor or doing puzzles to improve memory were looked upon favourably by many participants and were perceived as 'natural' ways to enhance or maintain cognitive ability. In contrast, the use of pills to improve cognitive abilities in 'healthy' individuals was considered to be 'unnatural' and in the main was treated with suspicion.

Therefore, while there was wide support for use of cognition enhancers by people with recognised conditions such as ADHD and dementia, the use of the same drugs for enhancing the cognitive functions of 'normal' or 'healthy' people generated considerable debate.

2.3.4.1 Key themes

Several concerns were raised about the possibility of cognition enhancers becoming widely available for use by healthy adults:

- **Unwanted or unknown effects.** Participants felt that the current state of knowledge about potential side effects was not an adequate basis on which to make decisions about how this class of drug should be regulated for use by healthy people. The idea that long-term use of cognition enhancers might permanently change one's personality was one concern raised.
- **Devaluation of 'normal' achievements.** The effort and motivation involved in learning was seen as having an intrinsic value that would be reduced by use of

cognition enhancers. This argument was applied in particular to young people, but was also raised in relation to adult use.

- **Equality and control.** Participants were concerned that cognition enhancers might further increase existing social inequalities. Perhaps drawing on the media debate around the use of methyl phenidate (Ritalin) to control ADHD, participants expressed the fear that cognition enhancers might be used to control people's behaviour.
- **Pressure to use.** Participants felt that use of cognition enhancers by healthy adults would exacerbate what they saw as an already over-competitive culture, with people needing to use cognition enhancers, even if they preferred not to, to compete for jobs or qualifications.

There was also some debate about the use of cognition enhancers in particular circumstances. As described above, many participants predicted that competition to achieve at school and work might make people feel pressured to use enhancers. Participants were also split on whether it was acceptable for people in professions demanding high levels of concentration to use cognition enhancers. Despite disquiet about the potential social and individual consequences of cognition enhancer use by 'healthy' adults, a small majority wished to protect freedom of choice, with the proviso that a lot more research should be done before this class of drug could be made legally available.

2.3.4.2 Future priorities

Overall, participants emphasised the need for further research into the effects of cognition enhancers, including the effects of longer-term use, before policies are made that prohibit or permit their use among the 'healthy' population. The greatest concern, as with recreational drugs, was the use of these substances by young people, whose brains are still developing. The areas identified by participants as in need of further research give a clear indication of

their priorities. Participants prioritised more research into:

- The benefits of cognition enhancers for people with mental health problems, including dementia and ADHD.
- The effects on 'healthy' people of short term use, cessation of use and long-term use.
- The effects of abusive use of cognition enhancers and the impact of using cognition enhancers on the developing brain.
- The social and financial impact of widespread use of cognition enhancers.

2.3.4.3 Ongoing dialogue

The idea of healthy people using a drug to improve their cognitive capabilities was new to most participants. At the events on recreational drugs or medicines for mental health, participants were essentially explaining already-held views and debating the merits of particular positions. As the day progressed, they sometimes changed their positions after further thought or in the light of information from other participants or experts. In the discussions on cognition enhancers, participants were working out what they thought about this new class of drugs as much as explaining their thoughts to each other.

2.4 Discussion

Overall, some of the most strongly held hopes and concerns expressed by participants can be captured in the description of two possible 'futures'. Although not every element of each of these 'futures' was subscribed to by all participants, they do provide an indication of some of the priorities that were raised.

One possible future develops out of what participants think is wrong with our current attitudes and approaches to mental health problems, mental health drugs and recreational drugs, and their concerns about cognition enhancers. The main features of this more **negative future** are:

- Mental illness and addiction are stigmatised and largely invisible.
- The use of licit and illicit recreational drugs continues to increase.
- Society is infatuated by competition in education and employment, with cognition enhancers used to gain advantage in the race for success.
- Drugs are used to control older people and those with mental health problems, rather than to treat them.
- There has been little investment on understanding the origins, and preventing the occurrence, of addiction and mental illness.

The other possible future is more positive and reflects a different attitude towards drugs, their role in society and towards those who use them. The main features of the more **positive future** are:

- There is no stigma attached to mental health problems, drug use or addiction.
- Research has led to the development of drugs for mental illness that have minimal side effects and are prescribed only when necessary.
- Health, rather than punishment, is the framework for supporting those whose drug use becomes a problem, and the services are widely available and of high quality.
- Primary care and community health workers are experienced in working with addicts and people with mental health problems.
- All children receive age-appropriate, effective drugs education.
- Research on the causes of Alzheimer's disease and schizophrenia has given scientists a good understanding of their causes.
- Doctors and patients work together, with families and carers where necessary and beneficial, to work out the best course to take.

There are several similarities between the hopes and concerns expressed by participants in *drugsfutures* and the views that were articulated in the thirteen smaller workshops that were run as part of the original Foresight project. The Foresight 'public perspectives'

work was carried out two years earlier than *drugsfutures* and was also managed by the Office for Public Management.

For most participants in both projects, the strong belief that individuals should have the freedom to choose which 'recreational' drugs they use was offset by a high level of awareness of the harms associated with illicit and licit drugs. Mindful of the personal and social costs linked to drug use, participants in the Foresight programme considered preserving public health and protecting vulnerable people to be vital. Similarly, in the *drugsfutures* work, most participants also focused on the health of users, placing emphasis on the value of effective treatments for addiction, reducing drug-related illnesses and improving the quality of life of users and their families.

The use of psychoactive substances to alleviate suffering, whether physical or mental, was largely uncontroversial. Across both sets of workshops, most participants felt that it was essential that safe and effective treatments for mental illness were available and the overriding view on cognition enhancement was that it would be a positive development for those with cognitive impairment or dementia. However, with regard to both medicines for mental health and cognition enhancers, participants involved in *drugsfutures* and the Foresight work expressed concern that psychoactive substances should be used with care and, where appropriate, as part of a wider treatment regime. In all of the areas discussed, support for medical innovation and freedom of choice was often coupled with concerns that science might 'go too far', or that drugs and medicines might increasingly be used as a quick fix for wider social problems.

In making comparisons between the Foresight consultation and the *drugsfutures* programme, it is important to recognise the differences in the scale and design of the activities. In the 2005 Foresight project there were 13 workshops and 87 participants, with the same agenda and materials used for each event. In

contrast, during the *drugsfutures* activities, a total of 727 people participated and a different theme was covered at each of 26 different workshops. The approach taken for *drugsfutures* meant that although similar issues arose in different workshops, these issues were approached from different perspectives. In addition, more time was available at the 2007 events, allowing a more in-depth and complex debate. The findings from both the Foresight 'public perspectives' work and the *drugsfutures* activities demonstrate the capacity of the public to engage with the scientific and policy issues around drugs, addiction and mental health. Deliberative discussion of the benefits and disadvantages of specific new technologies, and of the general principles that might govern their use, will contribute to improved decision making. There is, however, a need for continued evaluation of the role of 'public engagement' activities and of the most appropriate methods for engaging the public in dialogue. This should include how to best make the transition from engaging small groups to more representative samples.

The hopes and concerns expressed during both projects indicate that the development of future policies should be guided by a principle of openness. Later in this report (Section 5.4) the importance of engaging the public in debates around the regulation and classification of illegal drugs is highlighted. As outlined above, there are many other issues that will also require discussion, and there will be an ongoing need to consider how increasing knowledge of the harms and risk factors associated with drug use can be applied to benefit individuals and society (Recommendation 26).

Recommendation

26. The Government and Advisory Council on the Misuse of Drugs (ACMD) should undertake further and continuing dialogue with the public on issues relating to brain science, addiction and drugs, including those topics identified in this report.

Chapter 3 Magnitude of the problem

Introduction

It is estimated that the Government spends in excess of £15 billion each year in meeting the costs of drug-related social and economic harms (Singleton *et al.*, 2006). To target these funds effectively, it is essential to have reliable estimates of the size of the drug-using population. Policies aimed at preventing and treating 'recreational' drug use need to be informed by accurate data on drug-related harm (e.g. blood-borne viruses, drug-related mortality and crime) and on dependable epidemiological information on the variation in frequency, duration and type of drug used by specific populations.

However, current information on population drug use is uncertain and complex. There is no single authoritative source of data; instead, there are multiple sources, providing a variety of information that relates to different aspects of drug use, its prevalence (the number of drug users in a population) and outcomes (the harms caused by the drug used). This chapter will set the scene for what follows within Part I of the report and focuses largely on the incidence (the number of new users) and the prevalence of drug use. The chapter will begin by presenting estimates of the scale and nature of current drug use in the UK. Data on the number of drug users and variations in use by specific populations (for example by gender or geographical area) will also be presented. This general overview will be followed in Section 3.2 with a review of trends in the use of tobacco, alcohol, cannabis, opiates and cocaine. These drugs have been selected to incorporate a range of the most frequently used or most harmful substances and serve to illustrate several issues around the limitations of existing data collection methods. Prevalence and incidence estimates for other drugs are more unreliable or in some cases unavailable.

Although it is difficult to predict whether the future 'recreational' use of psychoactive

substances will follow current trends, it is clear that the range of substances in use is increasing. In Section 3.3 possible future sources of psychoactive substances are identified. Because it is essential that future policies are informed by reliable estimates of the size of the drug-using population, we review the appropriateness of existing data collection methods and alternative indirect techniques for making such estimates. Despite not being the focus of the public engagement discussions, participants from across the various workshops did on occasion express views on the current scale of drug use and stated differing attitudes towards certain substances. These attitudes are presented in shaded boxes throughout the chapter.

3.1 The nature of the problem

3.1.1 General population

It is difficult to make reliable estimates of the number of people taking drugs in the UK. To date, estimates of drug use have largely relied on data provided by a range of population surveys. The shortcomings of these surveys are discussed in Section 3.4.1. Notwithstanding their limitations, population surveys currently provide the foundation for most drug use statistics (e.g. HM Government, 2007).

It is estimated that over 11 million people aged 16 to 59 in England and Wales have used illicit drugs in their lifetime, and just under 3.2 million (approximately 1 in 10) are estimated to have used one or more illicit drugs in the past year (Murphy & Roe, 2007). Of those people who have used an illicit drug in the past year, it is estimated that:

- Most users, over 2.6 million, used cannabis.
- Over 1 million people used a Class A drug: including over 800,000 people who took cocaine powder and over 550,000 people who took ecstasy (Murphy & Roe, 2007).

Young people in the UK are estimated to have some of the highest prevalence and consumption rates of legal and illegal drugs in Europe (Advisory Council on the Misuse of Drugs, 2006). The 2006-07 British Crime Survey (BCS) estimated that just under one in two (over 2.75 million) young people aged between 16 and 24 have used one or more illicit drugs at some point in their life. Just under one in four young people (over 1.5 million) used one or more illicit drugs in the past year, including:

- Over 1.3 million young people who used cannabis.
- Over 530,000 young people used a Class A drug; nearly 375,000 young people used cocaine powder and nearly 275,000 used ecstasy (Murphy & Roe, 2007).

The BCS (2006-07) also estimated that 11,000 people aged between 16 and 24 used heroin in the last year. Statistics on heroin use are often collated under the term 'problem drug use'. The term 'problem drug use' has been defined in several ways (for example, compare the definitions used by Singleton *et al.* (2006) and the European Monitoring Centre for Drugs and Drug Addiction (<http://www.emcdda.europa.eu>)). In this report, the term relates to the use of opiates and/or crack cocaine, and injecting drug use.

3.1.2 Gender

The prevalence of legal and illegal substance use varies between males and females by

age and type of drug (Table 3.1). For certain drugs, use is as prevalent among females as it is males: there are as many young girls and women who smoke tobacco as there are boys and young men; and roughly as many females as males currently use cannabis.

However, across the full range of illicit substances there are differences in the prevalence of use between men and women. The available data suggest that:

- 41% of men aged 16-59 have used an illicit drug during their lifetime, compared with 29% of women (Murphy & Roe, 2007).
- Nearly twice as many men have ever used a Class A drug (Murphy & Roe, 2007).
- Three times as many men attend specialist drug treatment services (NTASM, 2005).
- Four times as many men die from heroin overdose deaths as women (Morgan, 2006).

Gender variations in drug use have changed over time, and differences between males and females in the age of onset of drug use are generally narrowing. For example, data from the Offending Crime and Justice Survey (OCJS) show that differences between males and females in the age of first use of cannabis are narrowing over time (Hickman, 2007a). The reasons for gender differences and for their changes over time are poorly understood, and need to be explored in greater depth. So too do questions about differences in duration of use (Recommendation 11). For example, the ratio of males to females in specialist drug treatment is much higher for people aged 30 or over than

Table 3.1 Approximate male to female ratios for a variety of types of drug use

Type of Drug Use	M:F
Adolescent (11-15): tobacco	1:1
Adolescent (11-15): weekly alcohol	1:1
Ever used cannabis (aged 10-24)	1:1
Ever used amphetamine or ecstasy (aged 10-24)	1.2:1
Ever used cocaine (aged 10-24)	1.5:1
Ever used illicit drug (aged 16-59)	1.7:1
Ever used Class A (aged 16-59)	1.9:1

(Sources: ACMD, 2006; NTASM, 2005; Man & Roe, 2006)

for people aged under 30 (NTASM, 2005). The reasons for this difference are unclear.

3.1.3 Socio-economic group and geographical area

Differences in drug use by socio-economic group and geographical area have been the subject of several reports. The Advisory Council for the Misuse of Drugs (ACMD) concluded that 'deprivation, although far from being the sole cause of drug misuse, is on the balance of evidence significantly and causally related to problematic drug use' (ACMD, 1998). Neighbourhood deprivation and adverse social conditions are associated with high rates of drug misuse (Galea, 2004), and children from backgrounds of social disadvantage are more likely to use cannabis earlier in life (Daniel, 2007). Singleton *et al.* (2006) estimate that in England the prevalence of problem drug use varies from around 14.4 per 1,000 of the population in London, to 6.4 per 1,000 in the southeast region. Thus, geographical area and deprivation may be valuable independent predictors of drugs use. The perceptions of the members of the public consulted as part of this project are summarised in Box 3.1.

There are strong associations between deprivation and indicators of heroin use, and there are large differences in the number of overdose deaths and treatment presentations by area of deprivation. Thus drug misuse hospital admissions were 17 times higher in the most deprived geographical area of Glasgow compared with the most affluent (ACMD, 1998). Strong correlations between area deprivation

and overdose mortality have also been found in Spain and New York (Torralba, 1996; Galea, 2004). However, the cross-sectional studies used to measure such associations leave it uncertain as to what extent heroin users are more likely to live in deprived areas as a result of heroin use, or the extent to which people who live in deprived areas are more likely than others to become heroin users. To clarify this ambiguity longitudinal studies are needed that collect data on both early life disadvantage and heroin and other drug use (Section 6.7 and Recommendation 11).

3.1.4 Ethnic group

Population surveys find little or no difference in the prevalence of any drug use by ethnic group (Aust & Smith, 2003). However, there is a disproportionate arrest rate: members of the black population are seven times more likely to be arrested and 14 times more likely to be imprisoned for drug offences than are members of the white population (Aust & Smith, 2003). It has been suggested that the difference in arrest rate may reflect socio-economic factors or the concentration of police resources in disadvantaged neighbourhoods (Reuter & Stevens, 2007). A forthcoming study by the UK Drug Policy Commission, which will look at drugs issues within Black, minority ethnic (BME) and new migrant communities may help enhance understanding on this topic. However, the question of ethnic variation in drug use and treatment uptake cannot be properly investigated until reliable estimates or indicators of the prevalence of heroin and crack use by ethnic group are available (Recommendation 1).

Box 3.1 Public engagement: perceptions of use

Illicit recreational drug use was seen as ubiquitous throughout the UK, and the perception was that for anyone with a mind to buy them, the process was straightforward.

Participants who came from smaller villages suggested it was as easy to buy illicit drugs in rural areas as it was in the city. However, it was felt that drug use in rural settings was more likely to be hidden and more problematic because support services for drug users were less readily available.

3.2 Trends in specific drugs

The focus in this chapter is primarily to illustrate the difficulties and shortcomings of existing data collection techniques. As previously stated, data in this chapter are only provided for a selection of drugs because of the lack or unreliability of data for other psychoactive substances. The health and social harms associated with the substances reviewed below are discussed in Chapter 5.

3.2.1 Alcohol

In the UK, total recorded alcohol consumption doubled between 1960 and 2002, in contrast to several other EU countries where alcohol consumption has remained unchanged or even fallen (Leon & McCambridge, 2006). In 2000, between 40% and 50% of 15-year-old boys and girls in the UK were drinking weekly and nearly two in five young people aged 16-19 were drinking at least twice the recommended daily upper limit, at least once a week. Participants in the public engagement programme pointed to the easy availability of alcohol as one key factor contributing to what they described as an 'epidemic' of under-age drinking (Box 3.2). The average weekly consumption among boys and girls has doubled to over 10 units in the past decade (ACMD, 2006). In 2001 it was estimated that 19% of men and 7.4% of women aged 16-19 were dependent on alcohol (ONS, 2001). On average over one in three men and one in five women drink more than three or four units at a single sitting on a weekly basis (Academy of Medical Sciences, 2004).

Alcohol consumption causes many health and social problems (Edwards *et al.*, 1994; Room *et al.*, 2005), and increases the risk of over 20 causes of death. For example, chronic liver disease and cirrhosis are strongly associated with alcohol consumption (Academy of Medical Sciences, 2004). The annual number of deaths from chronic liver disease in the UK among people aged 25-54 has increased four- to five-fold in the past 30 years to over 3,000 deaths in 2000 (*ibid*, 2004). Over the last 10 years,

the rate of deaths from cirrhosis has doubled in Scotland and increased by over two-thirds in England and Wales (Leon & McCambridge, 2006). In contrast, in many other EU countries the rate of cirrhosis deaths over the same period has remained unchanged or fallen. The number of deaths directly attributable to alcohol increased two-fold from 4,144 in 1991 to 8,221 in 2004 (Health Statistics Quarterly, 2007). These figures count only those individual causes of death that are directly attributed to alcohol (such as alcoholic cardiomyopathy or alcoholic poisoning). The full range of alcohol-related deaths should include diagnoses where a proportion of the deaths may be related to alcohol (English, 1995). However, there is controversy about the proportion and the total number of deaths that are attributable to alcohol use. The controversy arises because moderate amounts of alcohol have been claimed to be protective against heart disease, though assessments of the biological plausibility of such claims are inconsistent (Davey Smith & Ebrahim, 2003; Ebrahim, 2008). Recently, it has been argued that the apparent protective effect of low levels of drinking compared with 'no drinking' is due to the misclassification of ex-drinkers and occasional drinkers among abstainers. If

Box 3.2 Public engagement: attitudes towards alcohol use

Teachers at one of the outreach workshops pointed to alcohol use by young people as the 'next big issue', arguing that alcohol was more socially acceptable and easily available than illicit drugs. In one workshop, participants described alcohol use as 'endemic', pointing again to its social acceptability and easy availability as key factors in what they saw as a growing problem of children drinking. Lax age checks in clubs and bars were, they suggested, allowing under-age drinking to increase, as well as the way in which alcohol is marketed. These views were raised by both parents and by young people themselves.

this misclassification is taken into account, it suggests that the risk of coronary heart disease is likely to increase with increased drinking rather than show a 'U'-shaped relationship (Fillmore, 2006). The implication is that studies that have assumed a protective effect are underestimating the harm caused by alcohol.

Uncertainty over what to consider an 'alcohol-related death' has resulted in a wide range of estimates. For example, Britton & McPherson (2001) estimated that in England and Wales there was an excess of alcohol-related deaths in young people (primarily because of accidents, suicides and other injuries). In contrast, by assuming that alcohol exerts a cardio-protective effect, they estimated that, for the population as a whole and across all ages, alcohol use actually saved lives. On the basis of this assumed protective effect, Britton & McPherson suggested that alcohol use was responsible for 10,000 fewer deaths, overall, in England and Wales than might otherwise have been the case. In contrast, a recent study, which ignored any cardio-protective effect, estimated that there were approximately

76,000 alcohol-related deaths, representing 15% of the total number of deaths in England and Wales in 2006 (North West Public Health Observatory, 2007).

Participants in the public engagement programme saw alcohol as the drug primarily responsible for aggression, in both young people and adults. Some of the younger people who took part at one workshop pointed out that adults fail to acknowledge fully the harms associated with alcohol.

Views expressed by participants in the public engagement program on nicotine and cannabis use are summarised in Box 3.3

3.2.2 Tobacco

Tobacco is the leading cause of premature death and preventable ill-health in developed countries (Department of Health, 1998; Royal College of Physicians, 2007). Tobacco is associated with over 40 individual causes of death. It is estimated to kill 120,000 people per year in the UK (one fifth of all deaths), and cause one third of all cancer and one seventh of cardiovascular

Box 3.3 Public engagement: attitudes towards nicotine and cannabis use

Given the wide scope of the project, relatively little time was given to discussing attitudes towards specific drugs. However, across the different workshops, participants drew on examples and expressed differing attitudes towards certain substances. Some of the more dominant views are mentioned below.

Nicotine

Most participants felt that attitudes towards nicotine were hardening, although smoking among young people was seen as a continuing problem, with adults worried about the age at which children began to smoke. As with alcohol, the ease of access to nicotine products was pointed out, with young people able to buy under age without any perceived difficulty.

Cannabis

The debate on cannabis was polarised between those who felt it should be legal to buy, under particular conditions, and those who felt that the reported trend towards higher levels of THC (the active ingredient in cannabis) – widely publicised in the media over the past year – meant that its reclassification as Class C needed to be rethought. As shown in Figure 3.1, the change in classification was not followed by evidence of an increase in use, in fact, use 'in the last year' amongst the general population appears to have declined.

disease (Wanless, 2004). In 1948, over 80% of men were smokers, 65% smoking cigarettes (Forey, 2002). The prevalence among women peaked at 45% in 1966. Cigarette smoking has declined steadily among both sexes since the 1970s, but the decline halted in the 1990s. In 2004 it was estimated that approximately 27% of adults in Britain smoke (Health Development Agency, 2004).

There has been no evidence of a decline in smoking among adolescents in England and Wales since the early 1980s (ACMD, 2006). It is estimated that, in 1984, 13% of boys and girls in England and Wales smoked; this percentage fell to 8% in 1988, but soon rose again to 13% in 1996 (ACMD, 2006). In 2005, one in four (26%) girls aged 15, and 21% (1 in 5) boys aged 15, smoked regularly. There is growing evidence that tobacco and cannabis smoking onset and persistence may interact (Ford, 2002; Amos, 2004).

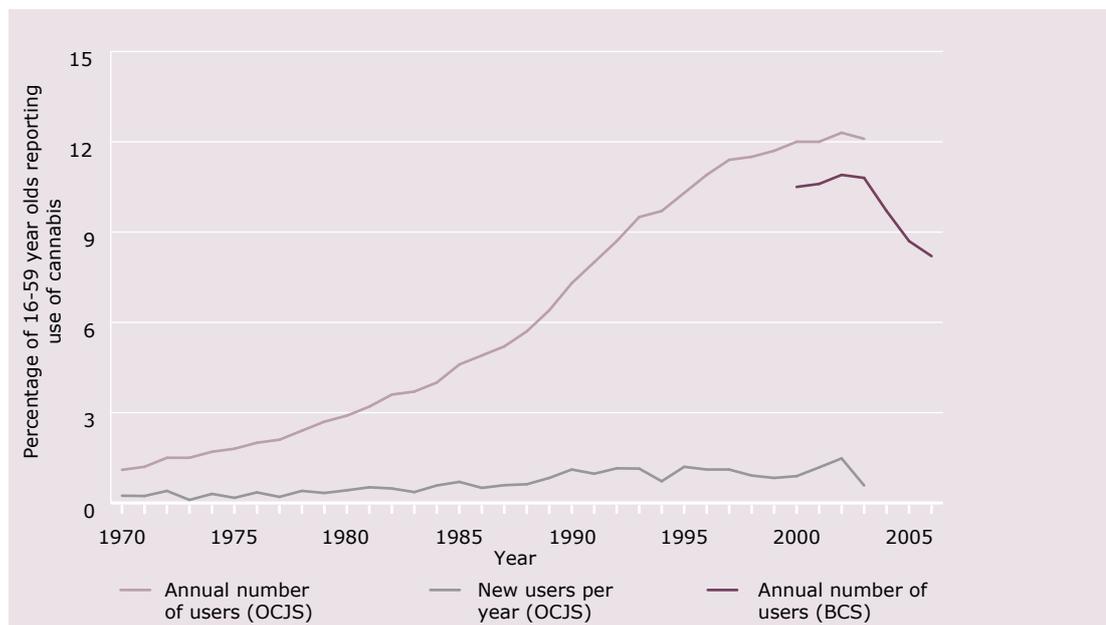
3.2.3 Cannabis

Estimates of the rate of cannabis use in England and Wales between 1970 and 2006 are shown in Figure 3.1. Although the Offending Crime and Justice Survey only

began in 2002, data on respondent's age when they first and last used cannabis can be converted to provide estimates of cannabis use during the preceding years. Estimates made from an analysis of the Offending Crime and Justice Survey suggest that from 1970 to 2002 there has been an approximate 6-fold increase in the number of new cannabis users per year (incidence) and greater than 10-fold increase in the annual number of cannabis users (prevalence) (Figure 3.1; see Hickman, 2007). In addition, first use of cannabis under the age of 18 was estimated to have increased by nearly 20-fold (Hickman, 2007).

An important policy question is whether there is evidence of an increase in cannabis use following changes in the law in 2004 that downgraded cannabis from Class B to Class C. Data on cannabis use between 1996 and 2007 have been published by the British Crime Survey (Murphy & Roe, 2007). Amongst the general population, use in the last year declined significantly between 2002 and 2007 (Figure 3.1). Use amongst 16-24 year olds also declined. These findings provide no evidence for increased cannabis use following changes to the law. From 2004 to 2007 estimates of cannabis

Figure 3.1 Estimated trends in cannabis use in England and Wales, 1970-2006



(Sources: Offending Crime and Justice Survey; British Crime Survey)

use are only provided by the British Crime Survey and it would have been valuable to also have had data from the Offending Crime and Justice Survey.

3.2.4 Opiates and cocaine

Here we consider indirect estimates for the prevalence and incidence of heroin injecting in England and Wales, based in part on information on trends in opiate overdose deaths (De Angelis, 2004; Law, 2001). Opiate overdose deaths increased by over 80-fold between 1968 (9 deaths, 0.05 per 100,000) and 2000 (925 deaths, 4.4 per 100,000). In Figure 3.2 estimates of the incidence and prevalence of new heroin injectors are shown; the two lines each for prevalence and incidence show the range of uncertainty for these projections. This range is not a statistical confidence interval but is due largely to uncertainty over some of the key measures: uncertainty over the cessation rate (the average length of injecting drug use) and overdose mortality rate at different calendar periods. Nonetheless the projections show a consistent picture. Projections of the rate of new dependent heroin injectors (incidence) were estimated to have increased at a faster

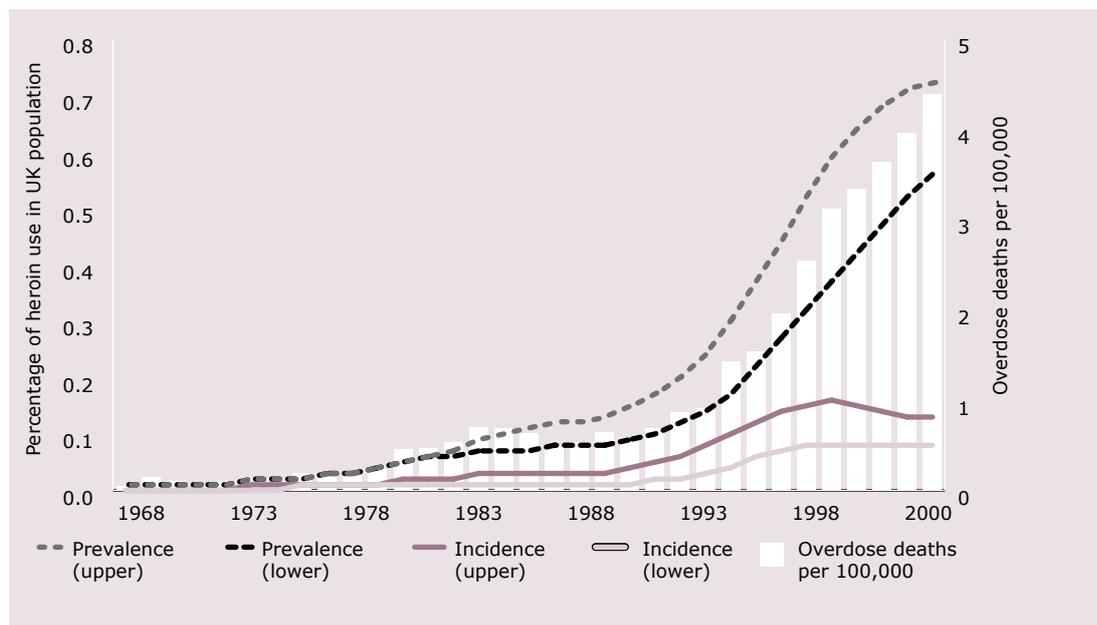
rate during the early 1990s, but may be declining since the late 1990s. However, these estimates need to be updated to clarify whether incidence has continued to decline. The total number of injecting drug users (prevalence) is estimated to have increased over 30-fold from 1970 to 2000.

We have analysed data from the Offending Crime and Justice Survey to estimate trends in cocaine use. The findings are shown in Figure 3.3 and suggest that from 1980 to 2002 the number of new cocaine users (incidence) per year has increased 13-fold and the total annual number of users (prevalence) has increased 15-fold. According to the British Crime Survey data, annual prevalence appears to have stabilised over the period 2002-05.

3.3 Future sources of psychoactive substances

It is difficult to predict whether the future use of psychoactive substances will follow the long-term pattern of increase that has been seen over the past two to three decades. However, the number of psychoactive substances available for

Figure 3.2 Back-calculation model estimates of prevalence and incidence of heroin use, and opiate overdose deaths in England and Wales, 1968-2000



human use has expanded at a growing rate and is likely to continue to increase. The manufacture and sale of illicit psychoactive drugs has become big business, with an increasing trend for manufacture to become focused in large factory-scale chemical plants. A United Nations report in 2003 estimated global annual manufacture of amphetamines at more than 400 tonnes, and ecstasy at 125 tonnes (United Nations, 2003). Amphetamine and methamphetamine were previously manufactured in small illegal, home laboratories. The centres for production of amphetamine, and especially the more potent methamphetamine, have shifted to Mexico and to Myanmar in South East Asia. In Myanmar, the precursor chemicals needed are easily obtainable from neighbouring China. Ecstasy production is focused on large-scale manufacturing centres in the Netherlands, again using illegal precursor chemicals imported from China (Iversen, 2006). The cultivation of cannabis has become the most important cash crop in California (Gettman, 2006) and in British Columbia. One consequence of this shift to factory-scale production has been to make certain drugs (e.g. methamphetamine and ecstasy) more widely available and cheaper.

The growth in the range of substances available is likely to occur through several routes including: the manufacture of new psychoactive substances; the diversion of prescription drugs for recreational use; and the increased sale of currently legal 'psychedelic' substances.

3.3.1 The manufacture of new psychoactive substances

The Foresight project concluded that new psychoactive substances are likely to emerge over the next 20 years. Although there may be unanticipated sources, these were considered likely to arise from:

- The refinement of the properties of known drugs.
- The synthesis of novel therapeutic compounds with abuse potential.
- The synthesis of drugs acting on newly identified molecular targets.

A review of possible chemical approaches to novel psychoactive drugs lists many little-explored avenues in the design and preparation of new psychoactive drugs (Cooper, 2003). Illegal chemistry laboratories will continue to use sophisticated techniques to explore the synthesis and marketing of novel psychoactive substances. A recent example is 1-benzylpiperazine (BZP) and related chemicals (Box 3.4). It is reported that the American husband and wife team Alexander and Anne Shulgin have alone been responsible for the synthesis and evaluation of almost 200 novel psychoactive amphetamine-like drugs, including 3,4-methylenedioxy-methamphetamine ('ecstasy') (Shulgin & Shulgin, 2000).

Box 3.4 Benzyl piperazines (BZPs)

These are amphetamine/ecstasy-like weak intoxicants currently legally available in the UK and many other countries. They were freely available and advertised as 'party drugs' in New Zealand until recently, when the government there controlled them under the Misuse of Drugs Act. Similar moves to control BZPs and related compounds have been proposed in the EU.

Despite attempts to restrict manufacture, for example through new patent laws with blanket-coverage of present and future amphetamine-like compounds, chemists can usually find a way to continue development. As a result, it has been predicted that the diversity of substances will continue to grow. One estimate is that around 2000 psychedelic compounds alone will be available by 2050 (Shulgin, 2004), more than double the number currently known.

3.3.2 The diversion of prescription drugs

The evidence from two recent examples suggests that there will be an increasing diversion of prescription drugs for recreational use and abuse, facilitated in part by the proliferation of on-line pharmacies.

Oxycodone

A sustained release formulation of this strong opiate painkiller was launched in the USA in 1996. Within a short time there were numerous reports of diversion of the prescription drug for recreational use, and a substantial number of emergency room admissions and deaths were attributed to oxycodone abuse. Many oxycodone abusers became addicted to the drug, and this addiction continues to pose a significant problem in terms of limited treatment facilities (Narconon, 2004; Hanson, 2002).

Drug-facilitated sexual assault

Drug-facilitated sexual assault has gained increasing notoriety in Europe, USA, Australia and New Zealand in recent years. In January 2006, the UK Home Secretary asked the Advisory Council for the Misuse of Drugs to review the factors surrounding it. The incidence of drug facilitated sexual assault is unclear and many victims fail to report the incident at the time for reasons that include: feelings of guilt or self-blame because of prior voluntary ingestion of alcohol and/or drugs; confusion and uncertainty, as a result of memory impairment due to the drug's effects, about what happened; and reluctance to make accusations without personal knowledge, or memory, of the circumstances leading to the assault (ACMD, 2007). Although by no means a new phenomenon, the practice is alleged to have become more widespread recently. This increase may be because of the availability of drugs that act as powerful sedatives or tranquillisers. These are often colourless, odourless and hard to detect when added to drinks. Although 'Rohypnol' (flunitrazepam) is the most well publicised agent, there is very little evidence for its widespread use. Several other substances have also been implicated, including other benzodiazepine tranquilisers and hypnotics, ketamine and gamma-hydroxybutyrate (GHB) (Drugscope, 2005).

3.3.3 The legal sale of unrestricted 'psychedelic' substances

There is also likely to be a growth in the legal sale of unrestricted 'psychedelic' herbs

and other substances in specialist shops and websites (e.g. 'magic mushrooms'). An increasing number of high street shops and websites specialise in the sale of drug-related accessories and legal herbal medicines with alleged psychoactive properties. A boom in the legal sales of 'magic mushrooms' (which contain the psychedelic compound psilocin) may have helped to kick-start the industry and a legal loophole (since plugged in 2005) led to a proliferation of vendors.

The UK's biggest on-line seller of such intoxicants lists more than 5,000 products including many types of drug: stimulant, visionary, relaxant, aphrodisiac. Customers give star ratings and can post reviews that are rapidly and widely disseminated, with intoxicants that do not work or have negative side-effects quickly disappearing from sale. The aim of the vendors is to find and isolate new psychoactive products from naturally occurring plants.

3.4 Measuring the size and scale of drug use**3.4.1 General population surveys**

Estimates of drug use in the UK are provided by a selection of population surveys. These include the British Crime Survey (BCS), the Offending Crime and Justice Survey (OCJS) and the Psychiatric Morbidity Survey.

Data from general population surveys must be interpreted with caution. As shown by the examples given below, different surveys give different estimates for the same substances. The divergence between surveys is not limited to the UK: two large US population surveys reported a two- to five-fold difference in estimates of any illicit drug use (Gruca, 2007). The variation in results is illustrated in Figure 3.3 (showing cocaine use) which compares estimates of annual prevalence from the BCS and the OCJS. As with Figure 3.1, estimates of annual prevalence of use prior to the start of OCJS in 2002 are calculated based on

respondent's answers when asked the age when they first and last used the drug. For cocaine, the BCS gives lower estimates of the prevalence of use than the OCJS, a pattern that tends to be repeated for other substances (Figure 3.1). In turn, the OCJS survey reports lower estimates of any drug use for young people compared with the Schools Survey. For example, the OCJS estimated that 6.2% of young people aged 11-15 in 2002-03 used cannabis compared with 12.5% from the Schools Survey (Pudney, 2006).

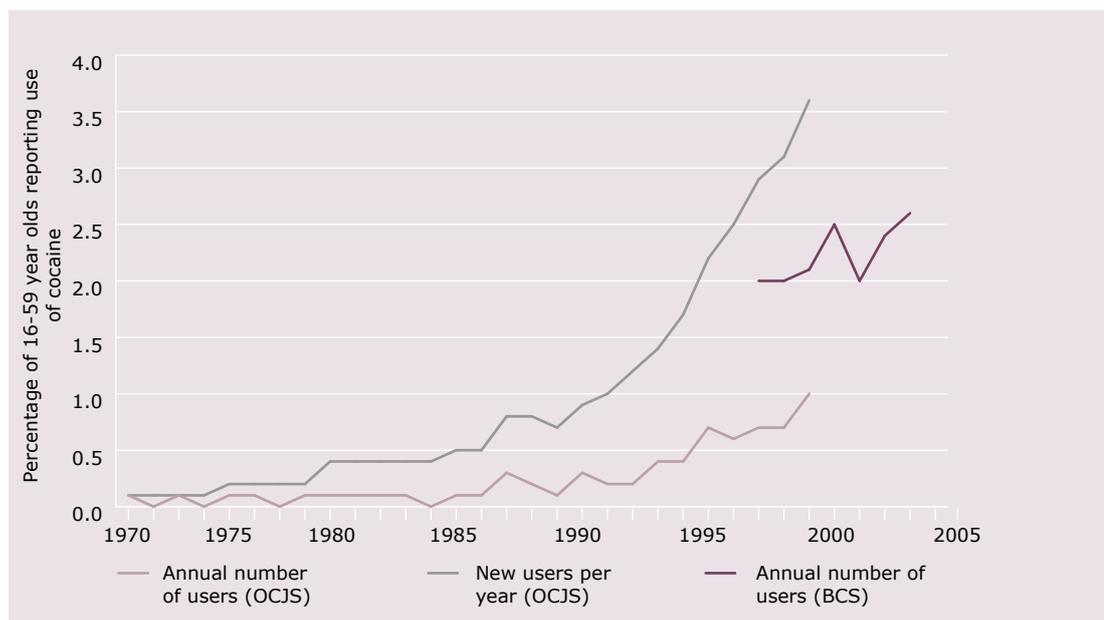
Differences in the focus of each survey also contribute to variation in the results and make comparison difficult. The BCS covers experiences of crime using separate 'victim' and 'non-victim' questionnaires, with the drug misuse module asking about drug use over the respondent's lifetime, in the past year and in the past month. In contrast, the OCJS covered the respondents offending behaviour. Different methods will also result in differences in self-reporting of drug use. The OCJS was conducted in the individual's home, which for a young person may feel less anonymous than the Schools Survey, which was conducted in a classroom.

The reliability of data from population surveys becomes even more questionable the less

frequent the use of a drug, making surveys of heroin or crack use more inefficient and inaccurate (Gfroerer & Brodsky, 1992; Hickman & Taylor, 2005). Sampling errors will be larger for drugs such as cocaine and heroin where frequency of use is lower than, for example, cannabis. The unsuitability of population surveys for measuring problem drug use is illustrated by the paradox that the number of individuals estimated by the BCS to use heroin is less than the number presenting for treatment (Hickman & Taylor, 2005).

Additional uncertainties in the suitability of population surveys as the sole measure of drug use arise because of the number and type of respondents that are included in the surveys. The BCS and OCJS only reach people resident in private households. The numbers that complete each survey are adequate only for the more common drugs. For example, in 2005-06, 29,232 individuals completed the BCS drugs module, and the OCJS involved fewer than 5,000 interviews. In addition to the problem of selection bias, the methods chosen to collect confidential and sensitive data on drug use also contribute to the unreliability of the data. Population surveys are solely dependent on respondents' self-reporting drug use.

Figure 3.3 Estimated trends in the incidence and prevalence of cocaine use, 1975-2005



(Sources: Offending Crime and Justice Survey; British Crime Survey)

There is strong evidence that some individuals approached fail to respond and some of those who do respond give false responses (Manski, 2001; Grucza, 2007). As a result, interpreting changes in substance misuse over time is fraught with difficulties when non-responders comprise a substantial minority of those sampled in the survey. Manski and colleagues have suggested that without information on type of non-response there may be insufficient evidence to determine whether drug use has fallen, increased or remained stable over time.

3.4.2 Indirect estimates

In an attempt to address the recognised limitations of population surveys for measuring illegal drug use, several alternative indirect estimation techniques have been proposed for some drugs. Indirect methods, using a variety of statistical techniques and based on a range of assumptions, relate data sources on drug users (such as people in drug treatment or overdose mortality statistics) to the total number of drug users in the population (Hickman, 2005; Singleton *et al.*, 2006). The value of indirect methods is largely dependent on having data sources available, in addition to population survey data, that identify a reasonable proportion of the target population.

However, indirect estimates and population survey estimates can be widely divergent. For example, indirect estimates suggested that the prevalence of use of crack-cocaine in London was over 1%, four times higher than the BCS estimate (Hope *et al.*, 2005); and BCS estimates suggest that 0.1-0.2% (approximately 50,000) adults are heroin users, which is lower than the number in specialist treatment (Hickman, 2003). It is also uncertain which indirect estimates of prevalence may be more reliable, and whether differences in the prevalence estimates over time can be interpreted as changes in the number of problem drug users, or as differences in methodology. For example, indirect estimates of the prevalence of problem drug use have ranged from 1 in 100,

to 1 in 150 adults (approximately 225,000-325,000), and indirect estimates of the prevalence of injecting drug use range from 1 in 175, to 1 in 350 (approximately 95,000-190,000) (see Sweeting, 2005; Fisher 2006; Singleton *et al.*, 2006).

Calculated over different periods and often using different methods and data sources, indirect methods make many assumptions about the relationship between the number identified by data sources and the total number of problem drug users in the population. These assumptions may not be testable by the method itself, and if violated may give biased results (Bishop, 1975; Cormack, 1999). The difficulty of using indirect estimates is illustrated by the information on numbers of opiate users presented in Figure 3.2. Numbers of opiate users were projected using a back-calculation model, which works on the basis that trends in an outcome are related through an incubation period to trends in incidence (De Angelis *et al.*, 2004). Thus, trends in opiate overdose deaths (ODs), and information and assumptions on the risk of opiate overdose deaths and the duration of injection (which comprise the incubation period between onset and overdose death) were used to estimate trends in incidence and prevalence of use (De Angelis *et al.*, 2004). The different lines on the graph (two lines each for incidence and prevalence) reflect the range of uncertainty generated by the models.

To obtain more reliable estimates, better data are required on the overdose mortality rate and injecting duration, both of which will require investment in longitudinal studies of opiate users (Recommendation 11).

3.4.3 Monitoring trends in use

There is a continuing need to monitor trends in psychoactive drug use through Customs and Excise, police seizures and the British Crime Survey. In addition to the data based on seizures, the ACMD regularly monitors potential trends in new psychoactive drug use and examines each case in detail to assess the harmfulness of the

drug and to make recommendations to the Home Secretary about illicit drug classifications. In 2005-06 the ACMD reviewed methamphetamine, khat, magic mushrooms, buprenorphine and the use of sleeping drugs and tranquillisers in drug-facilitated sexual assault. The reviews of khat, magic mushrooms and methamphetamine were completed and the Home Secretary accepted the advice given (to make no changes in the law for khat; to control the sale of magic mushrooms under the Misuse of Drugs Act 1971; and to move methamphetamine from Class B to A). This monitoring system appears to be working effectively, although a closer integration of the national surveillance scheme with the broader European scheme operated by the European Monitoring Centre for Drugs and Drug Addiction is to be encouraged.

3.5 Discussion

Valid estimates of the size of the drug-using population are needed to inform drug policy, to determine the scale of drug-related harms and to monitor the effect of interventions designed to reduce the prevalence and incidence of drug misuse. Marked differences in the size of estimates from different methods in similar years, and the correct interpretation of changes in the size of the drug-using population over time, need to be resolved.

Evidence synthesis is one approach that may offer a solution to the problem of combining multiple data sources and assumptions to generate consistent prevalence estimates (Ades & Sutton, 2006; Goubar, 2006). The difference between evidence synthesis and other indirect methods is that an 'all available information' approach is taken that formally tests whether information and assumptions on the size of drug use are consistent (and seeks to resolve any inconsistencies). Critically, evidence synthesis can also simultaneously estimate the size of specific outcomes or harms (such as HIV or hepatitis C viral (HCV) infection, or drug-related overdose or crime) and test whether

information on the prevalence of drug use is consistent with information on the amount of harm in the population. For example, the number of injecting drug users and the overdose mortality risk largely determines the number of opiate overdose deaths in the population. Similarly, the number of problem drug users and their rates of crime determine the amount of drug-related crime in the population. Because these quantities relate to each other, information on the different measures - drug use prevalence, risk of harm and total harm - in the population should be consistent with each other. Furthermore, we have some information on each of these different aspects e.g. on the number of problem drug users (PDU); rate of infection, crime or overdose by problem drug users; and total number of infections, crimes, or overdose deaths in the population. However this information is often partial and uncertain. So far, studies have often simply multiplied one quantity by another to generate a third quantity (see Singleton *et al.*, 2006). This approach assumes that the information used in the calculation is accurate and that the uncertainty is adequately measured, and ignores information that may be available on the sum.

Recent examples of the use of the evidence synthesis approach are given by projects that estimated the number of HIV and HCV infections in England and Wales (Goubar *et al.*, 2006; De Angelis *et al.*, 2008; Sweeting *et al.*, 2008). The method takes an 'all available evidence' approach incorporating information from multiple sources including those that measure the same quantity. The method builds a model that explicitly relates and links different sources of information to each other to simultaneously estimate both the size of the population at risk and the size of the outcome or harm. If the information sources and resulting estimates are consistent with each other (so that information on the size of the population at risk and amount of harm are consistent) this adds strength and validates the outcome. If one or other information sources are inconsistent or in conflict (e.g.

that information on the risk of HIV infection among pregnant women is not consistent with information on the number of HIV infections and population at risk) then the modelling process can seek to resolve the inconsistency by identifying and incorporating further information (e.g. information on selection bias). Thus, evidence synthesis models can provide a framework for identifying parameters or quantities that need better measurement because they generate the greatest amount of uncertainty in the outcome estimate (such as the size and duration of injecting of ex-injecting drug users) and for incorporating new information as it becomes available to improve the evidence base.

In the US, researchers have recognised the need to adjust population surveys with other information to estimate the prevalence and incidence of cocaine use. These estimates have provided the raw material for models of the number of dependent and recreational users over time, and estimates of the amount of money users spend on cocaine (Everingham & Rydell, 1994; ONDCP, 2002; Caulkins, 2004). The reason for combining indirect (such as information on cocaine use among arrestees) and direct information sources (population surveys) is that each of these sources provides only a partial estimate of total drug use. Population surveys, on the one hand, are likely to underestimate the numbers of problematic cocaine users, but can provide information on the numbers of general or occasional users. On the other hand indirect estimation techniques, based on criminal justice data, are likely to under-count occasional use but can provide information on problematic cocaine use. A study similar to those undertaken in the USA has recently been conducted in the UK to estimate the amount and cost of cocaine and other drug consumption (in Singleton *et al.*, 2006). However, the revised estimates generated through combining indirect and direct data sources are not formally (i.e. statistically) validated and may still rely upon unverified assumptions. The difference with evidence

synthesis modelling is that all assumptions of how data sources relate to each other are made explicit and tested for whether information on the size of the population is consistent with information on other outcomes. The UK Government has invested in the collection of information from multiple sources on different aspects of drug use and harm. It is possible to combine this information to generate single estimates of drug use and drug harm respectively. The opportunity to do this work should be taken and greater use made of direct and indirect estimation techniques. It will be important to test the validity of the combined estimates because the assumptions made by these techniques and the potential for bias are considerable (Recommendation 1).

Recommendation

To target resources for treatment and prevention of drug use accurately and cost effectively, and to test whether such interventions affect the prevalence and incidence of drug use, improved methods for estimating the scale of substance misuse and drug-related harm in the UK are needed.

1. The Government should appoint a single body, such as the Office of National Statistics (ONS), to work in partnership with academic institutions to:
 - Review and improve the accuracy and reliability of existing population surveys that seek to measure the prevalence, duration and type of drug use. When assessing the variation in drug use attributable to factors such as gender, age, geographical regional, ethnicity and socio-economic class, account should be taken of potential inequalities in treatment access and involvement with the criminal justice system.
 - Develop 'evidence synthesis methods' that combine information from police, health, social and other services to provide more accurate estimates of

the scale of substance misuse, the amount of drug-related harm, and the relationship between harm and misuse.

Chapter 4 Neuroscience, addiction, pharmacology and treatment

Introduction

The field of addiction neurobiology has seen major advances in the past 30 years. The primary molecular sites of action of many addictive drugs - the receptors - have now been identified and mapped to specific regions of the brain. Information on how these receptors regulate behaviour, and how the brain responds to chronic drug use is also rapidly accruing. However, this knowledge appears to have had little impact on the discovery and development of new medicines for addiction. Indeed, even the concept of pharmacological treatments for addiction is a relatively recent development.

In this chapter we discuss recent developments in the neuroscience of addiction, including research into the brain circuitry and neural processes involved in drug abuse and the evidence for a common addiction system. We explore the various theories of addiction, and analyse evidence for brain changes that occur as a result of chronic drug use and the factors associated with vulnerability to addiction. We identify several important questions that demand further research. Later sections review current and potential future pharmacological and psychological treatments for addiction.

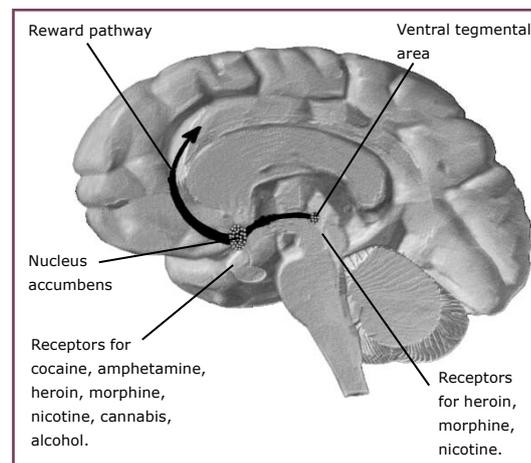
4.1 Neuroscience of addiction

4.1.1 The brain circuitry and neural process involved in addiction

There have been major developments in our understanding of the neural bases of addiction in recent years. These have resulted from research into the main drugs of abuse, including psychomotor stimulants such as cocaine and amphetamine, opiates such as morphine and heroin, alcohol, nicotine, MDMA (ecstasy), cannabis and benzodiazepines such as diazepam (see Koob & LeMoal, 2005; Robbins *et al.*, 2007). Most of the initial work was performed in experimental animals (mainly

rats and non-human primates), but more recent studies using neuroimaging techniques have shown that many of the findings from animal experiments also apply in humans. Indeed, we are now at a stage where the effects of chronic drug abuse on brain structure and function have been widely documented both in animals and humans. Since the identification of the specific nerve-cell receptors on which many drugs of abuse act, perhaps the most striking finding has emerged from studies that have mapped these receptors within the brain. Although there are differences in the subjective effects and primary receptors of different drugs of abuse, it is now understood that many of them act on receptors located in the same neural system in the base of the forebrain, which includes a structure called the nucleus accumbens (Figure 4.1).

Figure 4.1 Activation of a common reward pathway by addictive drugs



The activity of the nucleus accumbens is influenced by nerve cells (neurons) that contain the chemical messenger (neurotransmitter) dopamine. Many drugs of abuse work directly or indirectly by affecting the transmission across dopaminergic junctions, or synapses, in this nucleus. Studies in experimental animals have shown that the administration and withdrawal of psychoactive substances (including opiates,

alcohol and nicotine) lead to changes in dopamine function, as measured directly in the nucleus accumbens (e.g. DiChiara, 1998; Nestler, 2005). Reductions in dopamine (D2) receptors have been found in the brains of non-human primates after chronic cocaine self-administration, in experiments performed using neuroimaging techniques including ligand-based position emission tomography (PET) (Nader *et al.*, 2002). Neuroimaging techniques have also shown reductions in D2 receptors in the brains of humans who chronically use heroin, cocaine, methamphetamine or alcohol (e.g. Volkow *et al.*, 2001).

It has been possible to quantify the chronic effects of most drugs of abuse in terms of their actions on nerve cell receptors and on the associated intracellular biochemical changes. These biochemical changes may influence gene expression and thereby produce long-term modifications of brain function. Nestler (2005) discusses the molecular changes that occur after chronic treatment by several drugs

of abuse. The changes, which occur in nerve cells within the ventral tegmental area-nucleus accumbens axis, include: the induction of enzymes such as tyrosine hydroxylase, which is involved in the biosynthesis of dopamine; the regulation of glutamate receptor function; and the induction of transcription factors such as calcium receptor element binding protein (CREB). These factors bind to specific elements of DNA and so modify gene expression.

4.1.2 Evidence for a common addiction system

As described above, a key development has been the demonstration that many drugs of abuse act on a common neural system, despite different modes of action in terms of initial receptor targets. Furthermore, the action of some legal drugs (e.g. alcohol and nicotine) and the reinforcers of behavioural addictions (e.g. money in the case of gambling), can all be understood within the same general scheme, with strong commonalities in terms of underlying brain systems.

Box 4.1 Similarities between gambling and drug addiction

Several pieces of evidence combine to illustrate the affinities between gambling and drug addiction. The basic phenomena of addiction apply to gambling: euphoria on winning, tolerance on repetition, compulsion, withdrawal and craving. Expectancy of monetary reward in humans activates the same part of the brain, the nucleus accumbens, as is activated by the administration of drugs (Knutson *et al.*, 2001). A recent imaging study reported diminished responsiveness to monetary winnings in the nucleus accumbens of compulsive gamblers, compared with 'normal' controls (see Reuter *et al.*, 2005). As the authors acknowledge, the small amounts of money used in the task may have been less salient to the gamblers than to the control group of subjects, and so may have led to a reduction in the response of the nucleus accumbens. However, the finding does suggest that compulsive gamblers strive to activate the neural system linked to reward and so bring the activation to normal levels (Reuter *et al.*, 2005).

Impaired dopamine function is implicated in reward (drug) seeking behaviour in addiction, and there is anecdotal evidence for such impairment in gamblers. Dopamine neurons degenerate in Parkinson's disease and, in some patients, dopamine replacement therapy reportedly triggered remarkable compulsive gambling, even in the absence of significant prior experience of gambling (Dodd *et al.*, 2005). The opiate antagonist naltrexone is effective in treating certain forms of alcoholism (Mann *et al.*, 2004) and a recent study found evidence that a long-acting version of naltrexone promoted abstinence from gambling. However, the drug was very poorly tolerated (Grant *et al.*, 2006).

The neural systems involved in drug addiction and natural motivation in experimental animals may be involved in behavioural addictions in humans including: compulsive sexual behaviour; incentive motivation for preferred food, and compulsive gambling for monetary reward (Box 4.1). As with the administration of illegal psychoactive substances, 'natural' rewards such as food and sex also lead to changes in dopamine function.

4.1.3 Theories of addiction

As a result of the advances described above, several plausible theories of addiction are now being actively investigated (see below). This research has been aided by the development of behavioural models in rodents and non-human primates that predict the potential for drug abuse in humans and provide a basis for analysing human addiction (see Koob & LeMoal (2005) for an historical account of the animal behavioural models of addiction and their validation as models of human addictive behaviour). A recent trend has been to develop animal models that more closely replicate aspects of human drug abuse based on definitions in the 'Diagnostic and Statistical Manual of Mental Disorders' (4th edition) as criteria for drug dependence, e.g. in terms of the intoxication/binge cycle (Ahmed & Koob, 1998) and compulsivity (Vanderschuren & Everitt, 2004).

Most theories of addiction have focused on the role of the nucleus accumbens, which provides an interface between parts of the brain mediating motivation and reward and those producing behavioural output. One element common to most theories is that addiction is due, in part, to the ability of addictive drugs to 'hijack' brain mechanisms involved in learning and memory, causing aberrant learning patterns to be established. This common theme of learning explains the propensity to relapse: behavioural conditioning triggers memories of drug-related experiences that elicit further drug-seeking and drug-taking behaviour.

Learning theory, based on animal and human studies, has recently been invoked to understand and treat addiction (Everitt & Robbins, 2005). A central concept of this theory is that the addicted user comes impulsively to prefer small, immediate rewards to potentially larger, but delayed, rewards. In simple terms, an addicted user might seek the 'rush' that follows the use of a substance and ignore the longer-term risk of serious ill health and premature death. Bechara (2005) reviewed recent advances in our understanding of the brain systems implicated in impulse control and decision-making in humans, including a recent study of dual neural systems mediating immediate choices and prospective choice of reward outcomes (McClure *et al.*, 2004). There is considerable evidence that drug addicts discount other forms of reward in an impulsive manner, suggesting hyperactivity in those neural mechanisms of impulsive choice (Bickel *et al.*, 2006). This recent focus on relapse and reinstatement has re-awakened interest in neural systems mediating impulsive choice and processes of memory consolidation, reconsolidation and extinction. This renewed interest, and the recent experimental evidence, may lead to plausible treatments of addictive behaviour (Lee *et al.*, 2005; Shaham & Hope, 2005).

4.1.4 Brain changes associated with drug misuse

As our understanding of the neural basis of addiction has improved, drawing on a wide range of evidence (some of which is described in the previous sections and in Chapters 5 and 6), addiction has come to be viewed as a chronic mental illness (see McLellan *et al.*, 2000). More specifically, addiction is now considered to be a 'chronic relapsing brain disorder' (Leshner, 1997). This perspective contrasts with earlier views of addiction, which emphasised factors such as individual responsibility, rather than medical, genetic and neurobiological factors. Most views expressed during the public engagement programme

focused on the social and environmental context of drug use, but also acknowledged the highly addictive nature of specific substances (Box 4.2).

The harmful effects of drugs on the central nervous system are considered in the Foresight review on 'Neuroscience and drugs' (Robbins *et al.*, 2007) and are reviewed in Chapter 5 of this report. Overall, there is clear evidence that prolonged use of drugs results in neurotoxic changes that occur at cellular, brain systems and behavioural levels in experimental animals and in humans (Section 5.3). However, many problems arise when interpreting these studies (see Rogers & Robbins, 2003). For instance, it is difficult to know whether drug-related changes in nerve cells and neural systems result in persistent impairments in cognitive and neurological functions. Investigation of such impairments requires integrated studies involving psychological and clinical assessment, as well as the use of brain imaging techniques and neuropathological methods in laboratory settings. Such studies are expensive to conduct and require well-integrated professional services (including those of psychologists, clinicians, biologists and neuropathologists). It can also be difficult to determine the causes, or aetiology, of a condition in humans. For example, the reduced binding of striatal dopamine D2 receptors in cocaine addicts might be a result of cocaine abuse; but the reduced binding might equally have been present before the subject was exposed to any psychoactive substance. That is, low D2 receptor binding might be a consequence of cocaine abuse, or it could predispose to cocaine abuse. It is important to resolve this ambiguity to develop effective treatments.

A further problem occurs if several drugs have been used: which - if any or all of them - is responsible for a pathological change?

Experiments in animal models may suggest answers to this question, since drug exposure and early environment can be more easily controlled in animals than in humans (Sections 5.3.2 and 5.3.3). However, the use of animals is not free of difficulties, not least because of the issue of cross-species comparisons. For example, the assessment of higher cognitive functions may require the use of non-human primates as well as rodents. The absorption, distribution and metabolism of drugs can also vary enormously across species and caution is needed when extrapolating results to humans. Ultimately, any potentially important findings derived from animal studies can serve to inform human studies.

4.1.5 Vulnerability to drug abuse

Social science and clinical studies have generated considerable evidence for the existence of predisposing factors to human addiction, including social experience and context (Chapter 6). A rich neurobiological literature, based on human and animal studies, links changes in self-administration behaviour to influences such as stress and early social experience (see Robbins *et al.*, 2007). One significant perspective relates vulnerability to drug abuse to stress (Piazza & LeMoal, 1998). A particularly important study with non-human primates, with clear links to human drug abuse, concluded that low D2 receptor number might be a vulnerability marker for cocaine abuse (Morgan *et al.*, 2002) (Box 4.3).

A detailed account of the role of genetic factors in addiction is provided in the Foresight review on 'Genetics' (Ball *et al.*, 2007). In Box 4.4, research techniques that have contributed to current understanding, or are likely to facilitate future advances in the genetics of addiction, are briefly described. In Section 6.2.2 we consider the role that improved understanding of the genetics of addiction is likely to play in the future.

Box 4.2 Public engagement: reasons for using recreational drugs

Participants identified a wide and varied number of reasons for using recreational drugs, but focused predominately on environmental, economic or social factors including peer pressure, boredom, social isolation and youthful experiment. Many participants highlighted what they perceived to be increased use of drugs in areas of economic and social deprivation. Emphasis was also placed on the role of parental attitudes and behaviour.

It was clear that most people saw starting and stopping the use of recreational drugs as a choice. There was much discussion across the different workshops about whether addiction could be considered a 'mental illness'. Many people saw it as self-inflicted and the result of bad choices. Some participants discussed drug use as a way to address problems – for example to alleviate negative feelings, and to escape from unpleasant things such as pain, boredom and the stresses of everyday life. The focus on social reasons that may lead to the use of illicit drugs was consistent throughout both the face-to-face and on-line responses.

However, although few participants talked explicitly of addiction as a medical illness, the difficulty of overcoming addiction, particularly heroin addiction, was acknowledged by nearly all participants. It was felt that people may 'choose' to start using drugs, but once they become addicted the users will have, or feel they have, less of a choice about their drug use.

Box 4.3 Dopamine D2 receptors

Using neuroimaging techniques, Morgan *et al.* (2002) showed that socially subordinate monkeys had lower levels of striatal dopamine D2 receptors than their socially dominant peers. After these observations had been made, the two groups were allowed to self-administer cocaine. The subordinate monkeys had a greater propensity to self-administer cocaine than their socially dominant peers. These studies suggest that low D2 receptor number may be a vulnerability marker for cocaine abuse, although further studies are needed to elucidate whether altered levels of dopamine activity or some other factors are responsible for the vulnerability.

These studies are relevant to parallel studies of 'normal' human subjects. Drug-naive human volunteers with relatively low striatal D2 receptors exhibited more euphoric reactions to an intravenously administered psychomotor stimulant, methylphenidate, than normal volunteers with higher striatal dopamine D2 receptors (Volkow *et al.*, 2004). The hypothesis, derived from animal and human studies, is that low striatal D2 receptors may be a risk factor for stimulant abuse (Section 6.2.1.2 and Box 6.3). This factor may operate as a tendency to optimise the functioning of the dopamine D2 system through self-medication (see Koob & LeMoal, 2005).

Box 4.4 Genetic research techniques

Inherited genetic make-up contributes to sensitivity to psychoactive drugs and their effects, and to behavioural traits that may predispose to compulsive drug taking (Ball *et al.*, 2007 and Chapter 6).

The traditional starting point for genetic studies has been to carry out family or twin studies to establish whether a particular disorder is to some extent influenced by genetic factors. Adoption studies, twin studies and 'high-risk studies' with family members of substance misusers, have all confirmed the existence of important genetic effects on substance misuse (Section 6.2.2). Research strategies noted above quantify the proportion of population variance accounted for by genetic and environmental factors and these need to lead on to molecular genetic studies that examine the effects of individual susceptibility genes. The two main types of measures are linkage and association studies. For a more detailed discussion of these methods, including the limitations of such approaches see Heath *et al.* (2008) and Thapar & Rutter (2008).

Linkage studies

In linkage studies the inheritance of a particular trait or disorder is tracked through family pedigrees in an attempt to identify a co-inheritance between a genetic marker and a condition. If linkage is identified, this implicates a gene, in the broad region around the marker, in the development of the disorder.

The chromosomal regions identified by linkage studies can be large and such studies may require the estimation of several unknown parameters, including the proportion of individuals carrying a particular variation of a gene that then express a particular trait (Ball *et al.*, 2007). While there have been many successes for disorders involving single genes of large effect, linkage studies are generally less useful for identifying the multiple, relatively modest individual genetic contributions that are anticipated in complex behaviours such as drug dependence.

Association studies

Association studies focus at the molecular level by identifying specific genetic alleles that occur more frequently in people with the disorder, compared to those without the disorder. Candidate genes may be selected according to their position in the genome or their function (for further discussion see Thapar & Rutter, 2008).

Reproducing the findings from some of the earlier genetic association studies has proved difficult. However, advances in genotyping technology now make it possible to test thousands of genetic markers simultaneously. Large-scale studies of common genetic variation across the human genome (genome wide association studies) will make it possible to search the whole genome for susceptibility genes of small effect size (Carlson *et al.*, 2004). Large sample sizes will be needed to avoid the problem of generating false positives. Collecting these large samples will require a sophisticated level of coordination among research agencies, universities, health providers and others (Recommendations 2, 11 and 17).

Other approaches

Complementary studies in animals selectively bred for addiction-related traits have confirmed the importance of inheritance in addiction, and have identified a number of chromosome regions and specific genes that are associated with selected traits (for example, see Lovinger & Crabbe, 2005).

Gene expression analysis allows the influence of drug taking on gene function to be investigated. Human and animal studies reveal that drug taking is associated with the change in expression of dozens or hundreds of genes (for example, see Nestler *et al.*, 1999). The pattern of change may vary with the tissue studied or between brain regions. It will take several years before we understand the complexity of drug influences on gene expression, and the implications for neuronal and behavioural plasticity that may contribute to future addictive behaviour (Ball *et al.*, 2007).

Gene-environment interactions

Using a number of different research tools, future studies should provide a clearer understanding of the genetics of addiction and the interplay between genes and the environment. Well characterised longitudinal samples are needed to examine the interplay of environmental factors with genes during the development of dependence. Further research will be needed to develop the methods used and to help understand the relevance of the large amounts of data that will be generated.

Much of this knowledge derives from studies into the genetic basis of the propensity for alcohol preference (Lovinger & Crabbe, 2005). Recent evidence for genetic factors in addiction in a neurobiological context is summarised by Kreek *et al.* (2005). One key study, conducted in non-human primates, investigated the effect of early experience (separation from the mother) on excess alcohol consumption. It was found that functional polymorphisms of the 5-hydroxytryptamine (5-HT) transporter promoter region could moderate this effect. In these experiments, animals who were serine/leucine heterozygotes showed greater self-administration than leucine/leucine homozygotes (Barr *et al.*, 2004). This study is important because the serine alleles of this polymorphism have been associated with reduced 5-HT function and depression in humans, including depression following chronic ecstasy abuse (Rosier *et al.*, 2005). Functional single nucleotide polymorphisms in both the 5-HT transporter promoter and in the COMT gene (which encodes a dopamine metabolising enzyme), have also been shown to influence the cognitive enhancing effect of amphetamine in humans (Mattay *et al.*, 2003).

There is compelling epidemiological evidence that developmental factors are important in vulnerability to drug abuse in adulthood (Chapter 6). However, the neurobiological basis for this vulnerability is not understood. There is a general assumption that drugs are likely to

have a greater adverse effect on the developing than on the adult brain. One reason for this view is that nerve cells in the brains of young animals and children are forming connections more extensively than are nerve cells in adult brains. From this evidence, it is inferred that the young brain is more vulnerable to toxic insult than the adult brain. However, this conjecture needs to be tested more directly. Some of the pertinent evidence on the effects of prenatal exposure to drugs is surveyed briefly in the Foresight 'Neuroscience and drugs' review (Robbins *et al.*, 2007). There is no doubt that prenatal exposure to drugs such as cocaine, heroin, alcohol and nicotine in experimental animals can adversely affect subsequent brain and behavioural development (*ibid.*), although the detailed behavioural effects of drug intake have not yet been studied in detail. Exposure to drugs during adolescence when parts of the brain that are implicated in addiction (such as the prefrontal cortex) are still undergoing maturation, may produce comparable effects (see Robbins *et al.*, 2007). A key question of clinical significance is whether exposure to methylphenidate treatment during treatment for ADHD during adolescence reduces the propensity for adult drug-taking (Wilens *et al.*, 2003; Section 6.2.4.2).

4.1.6 Outstanding questions in addiction research

Although most research into drugs and addiction is conducted in the USA, it is worth

emphasising the significant contribution made by UK laboratories (Box 4.5). The UK is thus in a strong position to progress work in this field and to address the many unanswered scientific and clinical questions that remain (Section 4.4; Box 4.12 and Recommendation 2).

The key issues to be addressed include:

- Determining whether specific molecular changes within defined neural regions can be identified during the course of addiction and whether the changes may be targets for therapeutic drug development.
- Testing the validity of several theories of learning and addiction. For example, one theory places emphasis on the importance of drug taking to escape from the aversive 'withdrawal syndromes' (including both physical and psychological symptoms) (Hutcheson *et al.*, 2001; Koob & LeMoal, 2005). Another theory places emphasis on the incremental effects ('sensitisation') of repeated drug experiences leading to addiction (Robinson & Berridge, 2001). Still another theory likens drug addiction to pathological habit formation analogous to obsessive-compulsive disorder (Everitt & Robbins, 2005).
- Determining the possible roles of the prefrontal cortex, dorsal striatum and nucleus accumbens in addiction. The ability of an addict to control behaviour is impaired by chronic drug abuse. One hypothesis proposes that this impairment results from an interference with the way in which the prefrontal cortex controls other brain regions, including the nucleus accumbens and the dorsal striatum (see Everitt & Robbins, 2005). Little is known about the mechanisms by which chronic drug abuse might interfere with this control.
- Understanding the neurobiological basis of 'drug craving' and its role in promoting drug relapse.
- Understanding the precise relevance of chronic drug self-administration in experimental animals to patterns of drug use in humans.
- Understanding how the concept of 'memory reconsolidation' might be used in developing medications designed to eliminate disruptive drug-associated memories. Reconsolidation refers to a process by which existing memories may be modified and even erased as a result of interfering with the neurochemical changes underlying memory (see Przybylski *et al.*, 1999). Animal studies have shown that cue-induced cocaine seeking and relapse can be reduced by disruption of drug memory reconsolidation (Lee *et al.*, 2006). It is too early to evaluate the likely success of this approach for human drug addiction. However, interventions with existing agents such as β -blockers might theoretically exert therapeutic effects in humans; β -blockers have been used experimentally in post-traumatic stress disorder to reduce the impact of the negative memories associated with an event (Nader, 2003).
- Better understanding of the concept of 'self-medication' and its use for understanding the aetiology and maintenance of drug abuse. 'Self-medication' refers to a theory of drug abuse that suggests that individuals self-administer drugs to regulate a perceived deficit in mood or performance.
- Determining the bases of individual differences in propensity to abuse drugs in terms of genetic and environmental factors and the way these factors interact.
- Knowing how best to interpret changes in brain indices, whether at the molecular, cellular or neural systems level, in terms of potential harms caused by psychoactive substances.

Box 4.5 UK contributions to addiction research

The UK has made substantial and original contributions to advancing knowledge in addiction research, including:

- The discovery and isolation of enkephalins (Waterfield *et al.*, 1976). Nerve cells in the brain have specific receptors for opiates such as morphine. In addition, neurons synthesise their own opiate-like compounds, the enkephalins, which act as natural endogenous opiate neurotransmitter substances that bind to these opiate receptors.
- Early analyses of the behavioural and neurochemical effects of nicotine (Stolerman *et al.*, 1973; Benwell & Balfour, 1992); formulating the scientific case that nicotine is addictive (Stolerman & Jarvis, 1995).
- Elucidating the neural basis of stimulant drug action in the nucleus accumbens and related structures in the brains of experimental animals; establishing that these structures are part of a more general 'reward' system (Everitt & Robbins, 2005).
- Developing novel theories of learning that have been applied to the neurobehavioural basis of drug addiction (Everitt & Robbins, 2005).
- Identifying new candidate mechanisms for the treatment of addiction (e.g. Pilla *et al.*, 1999).
- Inventing and developing neuroimaging methods (including fMRI - see Garavan *et al.*, 2007) and using them to study the brains of drug abusers (Lingford-Hughes *et al.*, 1998; Mehta *et al.*, 2000; Kumari *et al.*, 2003).
- Pioneering assessments of the cognitive and behavioural impact of chronic ecstasy abuse (Morgan, 1998), including a determination of genetic predisposing effects to depression following chronic ecstasy abuse (Roiser *et al.*, 2005).

4.2 Pharmacology and treatment**4.2.1 Current treatments for addiction**

Pharmacological treatments for addiction are a relatively recent development and are reviewed in the Foresight review on 'Pharmacology and treatment' (Iversen *et al.*, 2007). Table 2 in that review (from Lingford-Hughes *et al.*, 2004) lists all the currently available medicines.

Virtually all existing medicines for addiction are based on the principle of harm reduction - replacing the addictive drug with another that has similar effects on the brain, but is less harmful. Examples include nicotine patches or chewing gum for cigarette smokers (Hughes & Carpenter, 2005) and, for heroin addicts, the slow-acting and weaker opiates such as methadone or buprenorphine (Uchtenhagen, 2004; Law *et al.*, 2004). Heroin itself has been provided to addicts in Germany and Switzerland as part of a harm reduction programme. Results over the short term (several months) have been

promising for addicts that have been resistant to other forms of treatment. The authors, Fischer *et al.* (2007) conclude that '*studies have demonstrated in several different contexts that the implementation of heroin assisted treatment for otherwise treatment resistant addicts is feasible, effective and safe as a therapeutic intervention. This demonstration should not be seen as a conclusion that could be taken for granted, since many observers had expected disastrous consequences from the provision of medical heroin prescription.*' Similar trials are under way in the UK (Lintzner *et al.*, 2006) (Recommendation 8).

Where effective, addicts who receive available treatments show reduced drug use and drug harms (crime), compared with those receiving minimal or no treatment (Prendergast *et al.*, 2002; Gossop, 2006). However, this apparent improvement could simply reflect the likelihood that those not receiving treatment have more severe problems. The UK National Treatment

Outcome Research Study (NTORS) showed that, overall, between one-third and two-thirds of the initial opiate-using sample remained abstinent over four to five years of follow-up, with best results for residential rehabilitation (Gossop *et al.*, 2001). Nevertheless, around half the NTORS sample continued using heroin and, in general, about two thirds of those in treatment had received previous treatment. Substitution of heroin by methadone or buprenorphine had a success rate of 50-60% after three months in maintaining subjects heroin-free. There is clearly a large unmet need for better ways of promoting abstinence. This is the great potential benefit of insights into molecular and brain mechanisms of addiction and its component psychological processes.

Attitudes towards drug treatment expressed during the public engagement programme are outlined in Box 4.6. Rather than focusing on 'curing' addicts, many participants highlighted the importance of treatment in terms of reducing harm and improving quality of life. The importance of non-drug based approaches to treatment, such as exercise and counselling, were also emphasised by participants.

The European Union ban on the sale of 'snus' (a moist snuff product) is an example where regulation appears to have prevented access to an effective treatment for cigarette smoking.

Snus has become widely used in Sweden, and has been attributed to causing a drop in cigarette smoking: only 17% of Swedish men smoke, whereas 19% of adult men are daily users of snus (Fagerstrom & Schildt, 2003). The use of snus has helped Sweden to become the only European country to reach the WHO goal of less than 20% daily smoking prevalence among adults by 2000.

Concerns about links between snus and increased risk of oral cancer or cardiovascular disease have not been confirmed by a large-scale epidemiological study (Luo *et al.*, 2007). However, their data suggested that snus may be associated with an increased risk of pancreatic cancer - with an odds ratio of 2.0, suggesting a lifetime risk increased from 1% to 2% (Luo *et al.*, 2007). In 2004 the number of new cases of pancreatic cancer in the UK was 7,398 (Cancer Research UK, 2008). This increase is still much lower than the 15-fold increase in the risk of lung cancer attributable to cigarette smoking (38,313 new cases in 2004) (*ibid*).

4.2.2 Future addiction medicines

Several approved and potential treatments for addiction have already arisen from neuroscience research. The development of more sophisticated models of addiction is allowing the targeting of drug-induced euphoria, cue-induced craving or drug seeking. For example:

Box 4.6 Public engagement: the importance of treatment

Many participants emphasised the value in providing drug users with effective treatments. The perceived benefits of providing treatment to addicts included:

- Reducing drug-related illnesses and the spread of diseases.
- Reduction in costs associated with abuse (for individuals and society).
- Improving the quality of life of users and re-introducing the users into society.

The specifics of existing drug treatment services were not discussed in great detail, primarily because most participants had very limited awareness of what was available. Most people placed a priority on ensuring that effective health and support services are widely available and accessible for all drug users. During this discussion, many people did acknowledge the resource implications, but it was felt that treatment services that focus on harm reduction would have significant benefits in terms of reducing the health and social costs of drug use.

- Naltrexone, an opiate receptor antagonist and a promising treatment for certain forms of alcoholism (Dackis & O'Brien, 2005), was originally found to extinguish alcohol self-administration in rhesus monkeys (Altshuler *et al.*, 1980). This application of naltrexone was also rationalised by findings that alcohol acutely increases opioid activity and that opiate μ -receptor knockout mice fail to self-administer alcohol (Roberts *et al.*, 2000). The efficacy of naltrexone in the treatment of alcohol abuse is greater in a subgroup of alcoholics with polymorphisms affecting the affinity of the μ -opioid receptor (Oslin *et al.*, 2003).
- In rodents (as in humans) drug-seeking behaviour is maintained by cues that are associated with drug taking (Everitt & Robbins, 2005; Koob & LeMoal, 2005). Recent studies of rodents found that treatment with a novel dopamine D3 receptor partial agonist reduced cocaine-seeking behaviour maintained by drug-associated cues. The treatment did not impair drug-taking behaviour (i.e. self-administration) *per se* (Pilla *et al.*, 1999). Subsequent analysis has focused on the possible effects of D3 receptor antagonists on similar measures of drug seeking behaviour. Such studies make the D3 receptor a viable target for research and development by pharmaceutical companies: the outstanding question is whether the regulation of dopamine activity itself can be a plausible target for therapeutic strategies in addiction.
- Further research is asking whether other neurotransmitter receptors that play important roles in the neural 'reward' system could be therapeutic targets. Research on cannabinoid receptors has suggested that rimonabant, a cannabinoid CB1 receptor antagonist, might be an effective treatment for drug abuse (LeFoll & Goldberg, 2005). Cannabinoid receptors have also been implicated in nicotine, opioid and perhaps food-related addictions (e.g. Bifulco *et al.*, 2007).
- Potential treatments might also be developed from research into GABA-B agonists, which have proved efficacious in animal models of cocaine self-administration (Roberts, 2005) and reinstatement (Kalivas & McFarland, 2003).
- Experimental treatments for addiction include modulation of the NMDA receptor by such agents as d-cycloserine. Such modulation has been shown to facilitate fear extinction in experimental animals (Walker *et al.*, 2002). In humans, d-cycloserine has also been shown to enhance the extinction of the fear of heights in phobic individuals when used in conjunction with behavioural desensitisation therapy (Ressler *et al.*, 2004).

4.2.3 Products in development

To review industry activity in this area, an internet-based survey of pharmaceutical addiction treatments that are in development worldwide was undertaken for this report. Although an internet search of company websites will not comprehensively identify all products in development, the results provide a clear indication of the limited scale of commercial activity. It is possible that several additional early stage R&D projects focused on developing addiction treatments may already be under way, but have not yet reached the public domain (Breitstein, 2002). However, in our survey only 46 novel products in development were identified. This compares unfavourably with other fields of R&D, for example, over 600 compounds are currently being evaluated as treatments for neurodegenerative disorders (Kwon & Herring, 2005).

Those 46 compounds in development identified by the internet survey involve 33 different commercial companies, 24 of which are small biotechnology start-up companies that have no existing portfolio of products. Ten major pharmaceutical companies have declared an active interest in addiction and most have focused their attention on novel treatments

for cigarette smoking or alcoholism. The 46 development candidates largely fall into the traditional category of harm reduction - replacing the drug of abuse with a less harmful substance that has similar actions in the brain. Even the proposed use of monoamine uptake inhibitors for cocaine addiction merely seeks to stimulate dopaminergic receptors in the brain by acting on the same molecular target as cocaine (the dopamine transporter). Less than a quarter of the proposed novel treatments make use of the new knowledge that brain science has generated on the molecular mechanisms underlying addiction (Recommendations 2 and 3).

Nevertheless, some of the products under development could offer important practical advances in the treatment of addiction. In particular, the development of depot-injectable formulations of the opiate antagonists nalmofene, naltrexone and the partial agonist buprenorphine, should allow enhanced compliance with treatment regimes, because these products can provide up to a month's-worth of treatment in one injection. The ability to treat addicts in out-patient clinics or GPs' surgeries on a once-a-month basis should make treatment cheaper and more widely available, although such a regime may only be practical for the long-term maintenance of addicts who have already successfully been detoxified.

Developments in this field also suggest a possible change of attitude by the pharmaceutical industry to addiction research. Some major new products have been launched on the US market in recent years, including acamprosate (Forrest Laboratories) for the treatment of alcoholism, and buprenorphine (Schering-Plough/Reckitt-Benckiser) for the treatment of heroin addiction. Both of these drugs involve novel pharmacological mechanisms (acamprosate is a weak glutamate NMDA receptor antagonist; buprenorphine is a partial agonist at opiate receptors). They are non-scheduled drugs and thus widely available in doctors' surgeries as prescription medicines.

In 2006 Pfizer launched a new anti-smoking medicine, varenicline (@'Chantix'), a substance that selectively targets the receptors in brain that are activated by nicotine. Sales exceeded \$150 million in 2006 and are predicted to be in excess of \$1 billion annually. Indeed the entire addiction treatment market, currently dominated by nicotine replacement products for cessation of cigarette smoking, is already valued at annual sales of \$2 billion, and is predicted to double within the next five years. This development may well help to awaken interest from other pharmaceutical companies.

4.2.4 Vaccines

A particularly innovative approach to the treatment of addictions is the development of drug-specific vaccines. The principle behind this approach is to link a psychoactive drug to a larger protein molecule in order to generate a vaccine that will stimulate the immune system to make antibodies. These antibodies would then recognise and neutralise the psychoactive drug. This principle could be applied to any psychoactive drug, but research has so far focussed on vaccines for cocaine and for nicotine. Three companies have variations of a nicotine vaccine in development, including Cytos Biotechnology in Switzerland, Xenova (now Celtic) in the UK and Nabi Biopharmaceuticals in the USA. All these vaccines function by triggering the immune system to produce circulating antibodies. The antibodies bind to nicotine to form a large molecule, the antibody/nicotine complex. This complex cannot cross the blood-brain barrier and so cannot gain access to the central nervous system. The vaccines are therefore intended to prevent the nicotine-induced 'rush' that is sought by smokers.

Preliminary clinical trial results of nicotine vaccines show some promise (Box 4.7), but there are many hurdles still to overcome. There are likely to be considerable individual variations in antibody response and a need for sustained treatment with repeated vaccine

injections. Long-term relapse rates for cigarette smoking are notoriously high and it remains to be seen how well the vaccines will perform against other methods of treatment (e.g. nicotine replacements, bupropion, or the newly introduced synthetic nicotine agonist varenicline).

It is hard to envisage vaccines as an effective treatment for addictions to psychoactive drugs such as cocaine or heroin. In these cases, the addict is likely to be tempted to increase drug dose to overcome the effects of the vaccine, or simply to switch to an alternative drug. It is also difficult to see how a nicotine vaccine could come into widespread use as a prophylactic to prevent children becoming addicted to cigarette smoking. The practical and ethical difficulties could prove too great; the views expressed during the public engagement exercise focussed on the disadvantages of developing vaccines (Box 4.8).

4.2.5 Drug Testing

Drug testing plays a vital role in the important task of monitoring compliance with addiction

treatment programmes. There are also forensic needs: the police need drug testing for application of the criminal law, as well as for testing in association for example, with road traffic accidents. Drug testing is also used to monitor drug abuse in the work place, although the distinction between the detection of 'use' as opposed to 'abuse' is not always clearly drawn. Drug testing in schools can be used to identify drug users at an early stage and guide them into treatment. Considerations around testing in schools are discussed in relation to cognition enhancers in Chapter 8 (Section 8.4.1).

Sophisticated methods already exist for on-the-spot identification of a range of illegal psychoactive drugs from readily available body fluids such as saliva. Easily portable kits are available that use selective antibodies as reagents with samples of saliva. In this way, a quick 'yes-or-no' test can be followed up by more rigorous laboratory analysis. Analysis of hair can be useful in determining long-term compliance with addiction treatment programme. An increasing application of miniaturisation of technologies and new

Box 4.7 Vaccines for drug addiction

In June 2005, Cytos Biotechnology reported findings from the largest clinical trial so far of a vaccine for cigarette smoking. The placebo-controlled, double-blinded trial involved 341 cigarette smokers. Two thirds received injections of the vaccine, at varying doses, over four months. The other third received placebo. All patients received cessation counselling. The results showed that 40% of smokers receiving the vaccine gave up smoking for nearly six months of follow-up; the highest smoking cessation rate (57%) was associated with the highest antibody response. These results are better than those seen in most nicotine replacement trials, but it is interesting that an unusually high proportion (31%) of the smokers receiving placebo also quit smoking for up to six months (Holman, 2005). Cytos formed a partnership in 2007 with the Swiss pharmaceutical company Novartis to develop the nicotine vaccine CYT002NicQb, which is expected to be available by 2010.

Nabi Biopharmaceuticals has also reported positive results from a phase II study in smokers receiving its vaccine 'NicVAX'[™]; and Celtic is due to start a phase II trial of its nicotine vaccine in 2007. In the trials of the Nabi vaccine, significant benefits were seen only in those patients who had the highest antibody responses. In these subjects, 16% remained abstinent after 12 months, versus only 6% of the placebo group consider using NABI website (NABI, 2007).

analytical methods will make drug testing even simpler and more widely available.

4.3 Brain science and future psychological therapies

4.3.1 Current approaches

The primary aim of psychological and medical treatments for addiction is to promote abstinence and reduce harmful drug intake (Box 4.9). Many psychosocial treatment programmes aim to prevent the harmful effects of continuing abuse use on:

- Social and family functioning.
- Employment, debt and crime.
- Psychological health e.g. depression.
- Physical health e.g. HIV, cardiovascular disease.

In the short-term, abstinence can be achieved through drug-withdrawal and detoxification until symptoms abate, if necessary treating the addict as an inpatient. However, without a follow-up programme, relapse can follow rapidly. Addictions are chronic, relapsing conditions and the harms described above can maintain pressure for relapse and continuing use. Some psychological therapies, such as brief motivational interventions, focus on acceptance of help and promoting treatment adherence. As discussed in Box 4.1, affinities

between problem gambling and drug addiction are increasingly recognised and similar cognitive and behavioural principles are being applied across treatment programmes.

4.3.2 Effectiveness of current psychotherapies

Widely used psychological approaches to treatment are described in the Foresight review on 'Psychological treatments of substance misuse and dependence' (Curran & Drummond, 2007). There is clear evidence that these approaches are effective in promoting abstinence in most forms of substance abuse compared with detoxification alone and with standard non-drug treatment (Lingford-Hughes *et al.*, 2004; Curran & Drummond, 2007).

However, treatments vary considerably in:

- The clinical problems, behavioural processes and mechanisms that they target (e.g. craving, social skills, relapse prevention).
- Their intended outcomes (abstinence, clean urine, harm reduction).
- Their targeted group (in- or out-patients, recent onset or chronic).
- How the therapy is delivered (at home, in groups or individually).

There is also a lack of agreement about what objective measures of outcomes should be used and what the standard comparison (or control) group should be. These factors make

Box 4.8 Public engagement: attitudes towards anti-addiction vaccines

When discussing anti-addiction vaccines most participants envisaged a future where vaccines might be used on babies identified as vulnerable to addiction. The great majority of participants saw no benefits in this possibility. For some people, the key factor underlying this view was the belief that starting and stopping the use of recreational drugs was a choice, and most participants felt that this choice should remain open.

The possibility of vaccines being used by adults was received more positively, because of the feeling that older people would be able to make an informed choice based on the available information. Participants raised several questions about the nature of possible vaccines, including whether it would be a one-off or repetitive treatment, and what the side effects might be. The view of some participants was that the answers to these questions would impact on their attitudes towards the acceptability of anti-addiction vaccines.

it difficult to identify the effective ingredients of therapy. Overall, there is little consistent evidence that psychotherapies either: differ in their effectiveness (Miller & Wilbourne, 2002; Lingford-Hughes *et al.*, 2004; Berglund, 2005; Curran & Drummond, 2007); add substantially to the effects of drug treatment (Anton *et al.*, 2006); have long-term benefits; or work by their intended mechanism.

It is notable that most of the clinical trial evidence around psychological treatments comes from the USA, particularly from the National Institute for Drug Addiction, which actively solicits and sponsors clinical trials. In the UK only four small studies are currently funded by the major grant giving bodies (Box 4.10). However, the UK is capable of organising excellent psychotherapy trials in addiction. The UKATT study (United Kingdom Alcohol Treatment Trial; UKATT Research Team, 2005) funded by the MRC is a good example (Box 4.10). Important multi-centre studies of acamprosate and naltrexone in alcoholism

have also been conducted by clinicians in collaboration with industry (e.g. the COMBINE study, see Anton *et al.*, 2006).

Most trials take a strong pragmatic approach: what works and is it worth it? However, there have been very few mechanistic studies that seek to understand how therapies work: through which psychological processes or behaviours does the treatment work and what are the effective elements of the treatment? Both 'pragmatic' and 'mechanistic' studies require many participants because of high drop-out rates and variability in outcomes. Mechanistic studies may additionally require behavioural and psychological measures taken during treatment to understand the mechanism of change. For reasonably well-established treatments, such as motivational interviewing or cognitive behaviour therapy (CBT), there would seem to be little point in conducting further small-scale trials that do not address the mechanisms of action or synergies with other treatments.

Box 4.9 Approaches to psychological treatments

Behavioural and cognitive therapies are based on theories of learning as applied to addictions. The core elements of cognitive therapies are:

1. Learning to recognise and cope with situations where there is a danger, or an actual occurrence, of relapse into drug use.
2. Providing a standard toolkit for skills training, based on therapist instruction and performance by the client such as modelling, role-plays, behavioural rehearsal and practical real-world exercises (Morgenstern & Longabaugh, 2000).

It can be difficult to determine the key effective ingredients of different psychological treatments because of the many components involved and the differing skills of the therapist in formulating individually tailored treatment programmes. Morgenstern & Longabaugh (2000) point out the lack of evidence that any benefits of cognitive therapy are due to an enhancement of coping skills.

Other behavioural approaches aim to change behaviour by extinguishing or unlearning automatic responses to environmental cues that trigger relapse, and rewarding desired behaviours such as producing clean urines (i.e. urine free of a drug or its metabolic products) or engaging in normal social recreation such as sport. Rewards can vary, but might include vouchers or housing provision.

Studies from the USA have shown that large-scale multi-centre studies can be highly informative when multiple treatment groups are combined and compared. For example, the COMBINE treatment study of alcoholism is outstanding because of its size and the number of treatments compared (Anton *et al.*, 2006). The study evaluated the effects of acamprosate, naltrexone and their combination versus placebo in over 1,300 patients. All groups received medical management and half of each group also received combined behavioural intervention (CBI), which included elements of CBT, 12-step facilitation and motivational interviewing. The results indicated that patients receiving medical management with naltrexone, CBI, or both fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination of treatments produced better efficacy than naltrexone or CBI alone in the presence of medical management (Anton *et al.*, 2006).

4.3.3 Future psychotherapies

It seems unlikely that new, effective and stand-alone psychosocial treatments are imminent. Existing psychological approaches show similar partial efficacy and their effects do not

appear to be additive. Although much is being achieved through increasing the accessibility of current treatments (see National Treatment Organisation, <http://www.nta.nhs.uk>), more mechanistic trials would help to focus existing treatments and improve their efficiency. The best prospect for substantial advance in the effectiveness of psychological treatments may lie in a more experimental medicine approach (for a full description of this approach, see Section 7.9.4). Evidence reviewed in the Foresight report 'Drug Futures 2025?' and in previous sections of this report shows how preclinical studies in experimental animals, many conducted in the UK, have identified dissociable neural systems that underlie addiction, such as drug-seeking, drug-wanting, drug-withdrawal and reinstatement of drug self-administration. It is now important to translate these insights into humans, to apply them to the development of new treatments and to incorporate them into assessments of the individual patient and monitoring of treatment (Recommendation 2).

Many studies have demonstrated that stimuli (cues) associated with drug exposure acquire control over drug seeking behaviour in animals

Box 4.10 UK psychotherapy trials

The MRC and the Wellcome Trust each fund a single trial, one using genotype to predict adherence to nicotine replacement therapy, and the other motivational interviewing to reduce drug-related risk in students. The NHS funds two further studies in drug users: one investigates the effect of referral to a liaison worker, and the other, use of carbamazepine to assist withdrawal from benzodiazepines. Some small-scale psychological studies are funded by charities such as the Alcoholism Education and Research Council (<http://www.aerc.org.uk>) and Action on Addiction (<http://www.aona.co.uk>). The MRC funds one clinical research programme (Neurotransmitters in Opiate and Alcohol Addiction) involving brain imaging and psychopharmacology.

UKATT study (UKATT Research Team, 2005)

This study, funded by the MRC, compared the effectiveness of a new therapy - social and network therapy - with the more established motivational enhancement therapy in 700 patients. The treatments lasted 2-3 months and were equally effective in increasing alcohol-free days from 30% to 46%. Equivalence was also shown in a rigorous cost-effectiveness analysis. Nevertheless, most patients continued to drink heavily, although at reduced levels and at lower frequency.

(Koob & Le Moal, 2005). There is increasing laboratory evidence in humans that such cues automatically engage attention, to the exclusion of other normally salient stimuli, and elicit the drug seeking response (Lubman *et al.*, 2000; Robbins & Ehrman 2004). Some psychological therapies aim to extinguish or cope with cue-evoked craving (Box 4.11). Recent fMRI studies have visualised the brain pathways that are engaged by drug-related cues. In one study, five recently detoxified alcoholic participants who showed the greatest brain responses to viewing images of alcoholic drinks were the five who relapsed most rapidly. Importantly, their subjective craving for alcohol did not predict time to relapse (Grusser *et al.*, 2004). Kosten *et al.* (2006) reported a similar finding in cocaine

users. These results suggest that imaging techniques could enable rapid screening of psychological and drug treatments to identify the most effective in correcting attentional or motivational biases underlying drug-seeking behaviour. The most effective treatments could then be tested for clinical effectiveness in larger trials in which brain imaging could be validated as a marker or predictor of success.

4.4 Discussion

In this chapter we have reviewed some of the major advances made in the field of addiction neurobiology over the past three decades.

There is now a much greater understanding

Box 4.11 Cue exposure therapy

Cue-exposure therapy aims to unlearn (extinguish) the association between cues (for example, a picture of a syringe) and the drug state by repeated exposure of the addicted individual to the cues without the drug. This type of therapy has been combined with rehearsal of strategies to cope with the urge to take drugs in situations previously associated with drug use. Despite experimental and some clinical evidence of efficacy, cue-exposure therapy has not been widely adopted (Drummond & Glautier, 1994; Rosenhow *et al.*, 2001).

Wiers *et al.* (2005) describe 'new' psychological approaches that tackle attentional biases and implicit cognitions, for example in an alcohol attentional control training program. Essentially, these approaches tackle cue-evoked responses. The main problem with cue-exposure therapy is that extinction/unlearning in a laboratory situation may not generalise to contexts in which the drug is taken. Indeed, a general principle of Pavlovian learning is that extinction of conditioned responses to cues is specific to the context in which the non-reinforced cues are presented (Bouton, 2002). Reinstatement of responses (e.g. craving) occurs if cues that have been extinguished in one context, such as a hospital, are encountered in the context in which the association was originally learned, i.e. where drugs were taken.

There is considerable interest in the possibility of using cognition enhancers to facilitate the extinction of cue-drug associations. This interest is based on the evidence that extinction of conditioned responses to cues is a form of new learning rather than the unlearning of old cue association (Myers & Davis, 2002). Ressler *et al.* (2004) determined whether pre-treatment with the glutamatergic drug cycloserine, a putative cognition enhancer, would cause a long-term reduction in cue-evoked fear in patients with a fear of heights. Patients were re-tested at one week and then three months after two sessions of virtual reality exposure to views from a lift. Two sessions of cue exposure reduced cue-evoked fear, but only in the cycloserine-treated group. The findings raise the possibility that glutamatergic drugs could accelerate and magnify the effectiveness of cue-exposure therapy in the addictions.

of the brain circuitry and neural processes involved in addiction, with evidence that most drugs of abuse (and indeed some behavioural addictions) act on a common neural system. Several theories of addiction are currently under investigation, aided by animal models of human drug abuse and addiction. We also have a much deeper understanding of the brain changes that result from chronic drug use and the factors associated with vulnerability to addiction in children and adults. Yet many outstanding research questions remain (Section 4.1.6) and this enhanced understanding appears to have had little impact on the discovery and development of new addiction medicines.

The survey of products in development for the treatment of addiction (see Section 4.2.3) suggests that at the current rate of development there is unlikely to be a substantial number of new treatments available by 2025. The Foresight review on 'Pharmacology and Treatments' (Iversen *et al.*, 2007) considers the general scientific principles that might determine the development of future addiction treatments. The Foresight document 'Drugs futures 2025: perspective of the pharmaceutical industry' discusses some of the reasons underlying the reluctance of major pharmaceutical companies to invest in the development of addiction treatments. Briefly, these reasons include: a perceived paucity of scientific targets, limited size of the market and difficulties in conducting clinical trials in subjects with notoriously poor compliance. The pool of products currently in development is small, a problem that is worsened by the significant probability of failure at each stage of the drug development process, and the long lag time between laboratory discovery and marketed product.

Research into the medical, genetic and neurobiological aspects of addiction has led many scientists and clinicians to view addiction as a chronic mental illness - a view that will be key to developing rational, novel approaches to treatment. This perspective

challenges earlier judgemental views of addiction. Views expressed in the public engagement programme emphasised the role of social and environmental context of drug use and individual choice in drug taking. However, participants also acknowledged the highly addictive nature of some substances and the involvement of 'physical' dependency. Looking forward, we emphasise the need to integrate psychological and social factors with neurobiological knowledge to achieve a deeper and more profound understanding of addiction. Ensuring ongoing public dialogue will also be important as potentially more radical treatments, including anti-addiction vaccines, are developed.

Given the substantial cost of substance misuse to both individuals and to society, there is a pressing need to develop preventative and restorative treatments for addiction; there are several promising avenues for investigation (Section 4.2.3). UK research agencies must look to support further research into the underlying mechanisms of addiction, as well as specific funding to translate research findings, particularly in the field of neuropharmacology, into a wider and more effective range of new treatments (Recommendation 2). Examples of the value of translational research are considered in Section 5.3.2 and also in Section 7.8.4 when discussing experimental medicine. Translational studies should make full use of the resources of the NHS, including the new NIHR Research Programmes, Biomedical Research Centres and the Mental Health Research Network. Studies should include the development of biomarkers to measure psychological and neurochemical responses to treatment to allow prediction of the clinical effectiveness of new psychological and pharmacological therapies.

Despite having a narrow research base in terms of relatively few dedicated UK investigators or laboratories, the UK has made substantial and original contributions to addiction research and is well positioned to address the many scientific

and clinical challenges that exist in this field. Some of the areas in particular need of further research are outlined in Box 4.12. Other centres in the EU have also made significant contributions to addiction research. Advances in the neuroscience of addiction and of treatment would be facilitated by improved co-ordination of research, training and translational studies across Europe. UK research funders and institutes undertaking research on neuroscience and addiction should be encouraged to work with their European partners. Improved co-ordination and the formation of collaborative links would facilitate activities such as large-scale genetic and epidemiological studies. Although a more detailed consideration of the exact remit and financial costs is needed, the creation of a European Institute for Addiction Research could potentially establish a critical mass of

research and enable the pooling of expensive technological facilities (Recommendation 4). The productivity of the US NIDA in the clinical evaluation of treatments for alcohol and stimulant abuse is testament to the value of a coordinated large-scale translational effort. The EU might chose to make a special contribution to the global problem of opiate abuse given its prevalence in the EU and the emphasis on stimulant abuse in US studies (Recommendation 4). The US NIDA 'Medications Development Program' also offers a valuable example of how government can facilitate the development of new medicines in an otherwise neglected field through partnerships with academia and industry. Government might help to encourage research and innovation, and incentivise the pharmaceutical development of new addiction medicines by taking a flexible approach to pharmaceutical drug pricing

Box 4.12 Areas in need of further research

Despite recent advances in the neuroscience of addiction there are many areas that require further research. These include:

- The neural circuits of addiction and craving in humans and animals, including the functional interactions both within these circuits and with other neural systems.
- The molecular targets of psychoactive substances.
- The neural bases of predisposition to addiction.
- The long-term behavioural and neural effects of chronic drug exposure in humans and animals.
- The vulnerability of the developing brain to psychoactive substances and adverse social environments.
- The molecular genetics of people who misuse drugs and the relationship between gene expression and neural function in both humans and animals.
- Genetic and epidemiological studies (both small and large scale) to advance understanding of the interaction between genetic and environmental factors in substance misuse in humans.
- The relationship between substance dependence and behavioural dependence (e.g. gambling), in terms of both brain mechanisms and behaviour.
- The pharmacological interaction of common forms of poly-drug use (such as effects of opiates and alcohol, and opiates and crack-cocaine) on overdose, dependence, relapse and recovery.
- The impact of maternal drug use on the developing embryo. The research should include: the molecular mechanisms conveying vulnerability or immunity to the effects of toxins during pregnancy; and whether prevalence of drug misuse among children is affected by the level of support received by mothers during pregnancy.

taking account of the value to society that such medicines could bring (Recommendation 3).

Recommendations

2. UK research agencies, including the Medical Research Council (MRC) and National Institute for Health Research (NIHR), should work with the Office for the Strategic Coordination of Health Research (OSCHR) to:
 - Enhance basic, translational and multidisciplinary research into the neuroscience of addiction; create additional academic and clinical posts, including new training fellowships, and invest in state-of-the-art brain imaging and other technological facilities.
 - Expand translational studies in humans, including proof-of-concept studies, to test and screen possible pharmacological and psychological treatments for addiction, making full use of the resources of the NHS.
 - Facilitate collaborations with industry to identify novel approaches to developing new pharmacological treatments for addiction and to bring successful compounds into clinical use.
3. The Government could encourage research and innovation, and incentivise the pharmaceutical development of new addiction medicines, by adopting a flexible approach to the Pharmaceutical Price Regulation Scheme, taking account of the overall societal value of such medicines.
4. Advances in the neuroscience of addiction and in the development of new treatments will be facilitated by improved co-ordination of research, training and translational studies across Europe. UK research funders and institutes should be encouraged to work with European partners. Improved co-ordination and the creation of a European Institute for Addiction Research would create a critical mass of research, enable the pooling of expensive technological facilities and facilitate activities such as large-scale genetic and epidemiological studies.

Chapter 5 Harm and regulation

Introduction

In this chapter we review current knowledge about the spectrum of individual and social harms associated with recreational drug use, and examine a range of philosophical and legal principles concerning the regulation of illegal psychoactive substances.

We start by briefly discussing the underlying goals of a national drugs strategy, as well as philosophical principles of liberalism, risk and harms to self and others. We then look at regulatory strategy, including the legitimacy and effectiveness of regulation, why regulatory interventions can fail and how future regulation may increasingly look towards technological solutions. The final sections draw on data from clinical and epidemiological research, social surveys and experimental animal studies to examine the current evidence base around the harmfulness of illegal psychoactive drugs, together with how this evidence might be improved and used to inform classification and regulation.

5.1 Philosophical principles concerning the regulation of illegal psychoactive substances

5.1.1 The underlying goal of a drug strategy

To understand how drug use should be regulated it is essential to determine the underlying goal of drug strategy. This will differ between countries and jurisdictions. For example, since the 1980s, the USA has adopted the goal of a 'drug free society' (Hall & Pacula, 2003), whereas since 1986 Australia's national drugs strategy has been '*to minimize the harmful effects of drugs on Australian society*' (*ibid.*). The stated aim of the UK Drug Strategy is '*to reduce the harm that drugs cause to society: to communities, individuals and their families*' (Home Office, 2006).

Different strategies generate different approaches to the regulation of drugs. A policy of aiming for a drug-free society is principally measured in terms of its effects on drug use. By contrast, a policy of harm minimisation generally starts from the assumption that, whether or not it is desirable to eradicate drug use, it is not a practical possibility. On this view, policy should aim to reduce the harmful effects of drug use insofar as this is possible. This could mean, for example, allowing addicts easy access to clean syringes for injecting their drugs, or providing machines in nightclubs to analyse drugs for their strength or purity.

The policy question, therefore, is whether drug use is rightly considered so seriously wrong that it should be eradicated, as far as this is possible, whatever the costs are elsewhere, or whether drug use is merely one harm among others, and its reduction should be balanced against other social harms and benefits of various policy options. Whichever approach is favoured, for a balanced debate it is essential to consider the harms that drugs cause, the benefits that individuals may derive from them, and the potential harms and benefits of different policy options.

5.1.2 The liberal position

The philosophical question faced here is that of the justified limits of state power over the freedom of choice of the individual. One powerful and popular approach to this issue is that of John Stuart Mill, in 'On liberty' (in Warnock, 1962), which sets out the classical liberal position, in terms of the 'liberty' or 'harm' principle. According to Mill, '*[T]he only purpose for which power can be rightfully exercised over any member of a civilised community against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant*' (in Warnock, 1962). That is, if people do harm only to themselves, then society has no right to

interfere. It is important to note that Mill states that this is a principle to regulate the behaviour of rational adults and hence it does not apply to children or to those who are not in control of their rational faculties.

According to the liberal view, the first step in an argument for prohibition of an activity is to show that it causes harm to third parties. There is no doubt that the production, sale and use of drugs have enormous social costs in terms of crime, and the costs of law enforcement and health and social services. However, it is important to try to factor out the harms that may be the result of the criminalisation, from the harms that naturally follow from the production, sale and use of drugs, whatever their legal status. A substantial proportion of the financial costs associated with drugs are costs of law enforcement, and there are significant financial and social costs of the criminalisation of people for drug offences (Barry, 2005). Nevertheless, it seems clear that drug use can cause harm to third parties independently of the effects of its criminalisation. The behaviour of addicts, and those who lose self-control while using drugs, can cause substantial harm (Section 5.3 onwards).

However, the liberal position is that, although actual or threatened harm to others is a reason for considering whether there should be prohibition, it is not in itself a conclusive reason for prohibition. There is no absolute rule that actions that cause or threaten harm to others must be prohibited, for it is possible that potentially harmful actions may also have beneficial consequences that outweigh the harm. A good example is driving, which can cause harm to third parties including other drivers and pedestrians. Although steps are taken to reduce or mitigate the harms associated with driving (for example speed limits and mandatory wearing of seat belts), road deaths are reluctantly tolerated as an unavoidable consequence of a valuable form of activity.

5.1.3 Harm and paternalism

The liberal position prevents governments from interfering with the free choices of adults. Governments, however, might make more pessimistic assumptions about human nature and rationality than liberal philosophers such as Mill and assume that, for reasons of miscalculations, misinformation, temptation, impulse and failure of rationality, human beings cannot always be expected or trusted to make the best decisions for themselves, even by their own standards of rationality. Hence a principle of 'rational paternalism' is often applied, which allows governments to consider regulation or prohibition of activities to protect people from themselves. Once again, however, there can be reasons for allowing certain activities, even if they threaten or cause harm to the individual involved. Arguments from freedom of choice, self-development, pleasure, convenience and other values will also often be relevant. For example, most societies allow some forms of dangerous sports, such as hang-gliding, believing that the value people find in them outweighs the increased risk of death or injury.

However, potentially dangerous activities are typically heavily regulated, for example, motorcyclists are required to wear helmets, which appears to indicate that governments are prepared to engage in rational paternalism, and indeed feel that they have a duty to do so. Alternatively, it could be suggested that society regulates dangerous activities because those who are seriously injured in accidents risk becoming a burden to society, who will have to pay for their health care needs. In the face of this argument the distinction between 'harm to self' and 'harm to others' can break down.

In Section 5.3 we show that drugs can cause a range of harms to the individual user, including acute effects, long-term health effects and dependency. However, a significant number of people regularly take illicit psychoactive drugs (Chapter 3), at some financial cost and with the risk of acquiring a criminal record. It therefore seems reasonable to suppose that such people

strongly desire the experiences provided by the drugs, and in the sense of achieving what they desire, derive benefit from drug use (Box 5.1). Against this it could be argued that, to the extent that drug use is harmful, such people are making a mistake and that they in fact derive a net harm from drug use.

However, different drugs vary significantly in their harms (Section 5.3), and these harms will vary from person to person. Although it is plausible that a proportion of drug users are mistaken about the total effects of their drug use, it is hard to assess a general claim that there is more cost than benefit for each occasion of drug use. An important argument is that, once a person is addicted to a drug, the decision to consume more of the drug is not evidence that the person derives benefit from the experience. However, this argument does not apply to non-addicted users.

Even if it is thought prohibition is justified to prevent users harming themselves, outside of drug legislation, it is now rare for an activity to be penalised through a prison sentence if the point of its regulation is to protect people from self-harm. Although it was once possible to be imprisoned for attempted suicide, this law has been repealed, and its undesirability seems evident. Seat-belt offences, while driving, are punishable by fine only. The philosophical case for providing severe punishments for people who engage in activities which might harm only themselves remains obscure (Husak, 2005). Of course, harming oneself may have indirect

costs for others, for example the societal costs of using scarce resources to help drug users. Yet the costs of punishment are not trivial either. Leaving aside such indirect effects, it can be argued that punishing people who engage in actions leading to self-harm has the rather perverse effect of harming people in one way for attempting to harm themselves in a different way.

Nevertheless, arguments can be found to justify such a practice, for example using the idea of deterrence. If the form of self-harm is extremely severe and only threatening imprisonment would be effective as a deterrent, then a prison sentence may be acceptable. However, each of the premises of this argument is uncertain. It has been argued that, for drugs such as heroin, the health risks for children are so severe as to justify entirely prohibiting their production, sale, possession and use. This argument, however, still falls short of an argument for punishing adults who possess drugs for their own use, as distinct from suppliers and dealers (de Marneffe, 2005). The current law distinguishes between users and dealers; a distinction that was supported by the participants in the public engagement programme (Box 5.2).

5.1.4 Is taking drugs intrinsically wrong?

As will be seen (Section 5.3.4) there are some recreational drugs the use of which can, in some circumstances, risk harm to third parties. Others are known or suspected to present serious health risks to the users. Nevertheless, some sectors of the public might feel that it is morally acceptable

Box 5.1 Public engagement: drugs and the law

Participants expressed several reasons to explain why people use illicit recreational drugs despite the risk of punishment. These included a lack of respect for the law, a feeling that the risk of getting caught is low, and a feeling that punishments are lenient and do not act as a deterrent. In fact, the illicit status of drugs and the penalties attached to use were viewed as contributing to the harms arising from recreational drug use. Prison was seen as likely to exacerbate rather than curtail drug use. Most participants did not see sending people to prison for possession and use of illicit recreational drugs as effective and thus a majority saw little point in introducing harsher punishments.

to punish people who use drugs, whatever the facts about the harmfulness of those drugs. People who feel this way might believe that all illegal drugs have been shown to be greatly harmful, but would change their minds if presented with contrary evidence. Or it could be that they feel that taking drugs is somehow wrong, even if it is harmless, and punishment is necessary to express society's outrage at such wrongful behaviour. This view remains, however, highly problematic.

In summary, in thinking about the ethical principles underlying the regulation of drugs, it is possible to distinguish three general approaches. First, an attempt to eliminate drug use is most likely to be based on the moralistic idea that drug use is bad in itself and so should be prohibited in all circumstances. Second, a harm reduction strategy takes as its foundation the idea that a chief responsibility of governments is to protect the life and health of its citizens, and therefore its drug regulation should be adjusted to minimise harm. Third, a liberal approach would be to put the autonomy of individuals ahead of their health and well-being, and to allow drug use unless it can be shown to harm third parties. Whatever the underlying philosophical arguments, the UK Drug Strategy is one of harm reduction (Section 5.1.1). In adopting such a strategy, the Government has implicitly rejected both the moralistic elimination approach and the permissive liberal approach. However, to

implement the harm reduction strategy it is necessary to come to a firm view of first, the regulatory strategies available, together with their costs and benefits, and second, the harms different drugs can cause. We examine these questions in the remainder of this Chapter.

5.2 Regulatory strategy

Given the diversity of drugs, and of their effects, careful studies are needed to understand the degree to which any drug causes harm, and its seriousness and frequency (Section 5.3). It is also possible that very widespread use could have a detrimental effect on a society's economic performance. Where the use of a drug has clear harm to third parties, most notably to the children of addicts, there is a case for regulation, including prohibition, of production, sale and use. The case for punishment of adults who possess drugs for their own use is weaker, unless such possession and use has effects that are so harmful that criminalisation is thought appropriate. Where no harms have been identified, then there seems no case for prohibition, still less for punishment.

The choice of regulatory intervention to be used will depend on how serious and common these harms are likely to be, but it is also necessary to take into account any benefits the users obtain from taking drugs, as well as the likely effects of prohibition, and the necessary

Box 5.2 Public engagement: a distinction between 'users' and 'dealers'

Many participants felt that there was a distinction to be made between 'users' and 'dealers'. It was felt that any crime committed by a drug user should be dealt with in the same way as the same crime committed by a non-drug user and that the punishment for large-scale dealers and traffickers should be long prison sentences and sequestration of assets. Most participants felt that in the future we should:

- Reduce the dominance of legal sanctions against drug users.
- Have more areas that drug users can use safely without harming society.
- Acknowledge that it is impossible to eradicate the use of recreational drugs.
- Protect users by introducing measures to check the quality and purity of drugs.
- Crack down hard on dealers and remove their assets.

means of enforcing such prohibition. There is, unfortunately, no agreed formula by which we can determine whether the harms outweigh the benefits, and in the end a political decision will be needed. However, we emphasise that these decisions must be informed by a full appreciation of both the costs and the benefits of the activity (Recommendation 6).

5.2.1 Supply-side and demand-side regulatory interventions

If government decides that the recreational use of a particular psychoactive drug is contrary to public policy, then what kind of regulatory approach should be used? One option is to target the 'supply-side', i.e. to prevent the drug in question from reaching the market by detecting and deterring its production, transit, storage, or supply. This might involve acting against producers, importers, carriers, coordinators or those who supply directly to users. The UK Government's drug strategy, 'Tackling drugs, changing lives', places considerable emphasis on such supply-side intervention (Home Office, 2006). Indeed, it is generally agreed that supply-side intervention is an important element in any attempt to reduce drug use (see Brown *et al.*, 2003). Conversely, where the intervention is targeted at the 'demand-side', the idea is to reduce the volume or intensity of demand. If people decide to give up smoking, consuming alcohol or using cocaine, there is less urgency about disrupting the supply-side network.

Where the intervention, whether on the supply or demand side, is of a criminal justice kind, government relies on the deterrent effect of the criminal law coupled with the activities of the law enforcement agencies and the corrective effects of penal sanctions. However, government might also, or alternatively, focus on a non-criminal justice approach. This might include policies that aim to identify children and young people at risk of later substance misuse and to take steps to mitigate those risks (Chapter 6), or policies that adjust the tax and

benefit regime so as to introduce appropriate financial incentives and disincentives.

In the following sections, we discuss two key regulatory dimensions, namely regulatory effectiveness and regulatory legitimacy. We examine the range, capacities, and limits of possible regulatory instruments, identifying why, when and how such instruments can fail. We then look at legal modes of intervention alongside other regulatory modes, particularly increasingly technological strategies, and examine the significance of 'phasing' regulation. As a result of this review, we make recommendations for intelligent regulatory decision-making, not on the substance of the decisions that should be made, but on the overall nature of a rational regulatory approach.

5.2.2 Regulatory effectiveness and regulatory legitimacy

In this section we consider questions of:

- **Regulatory legitimacy:** whether the purpose that guides a regulatory intervention is appropriate or, failing that, whether the processes that led to the adoption of that purpose were fair.
- **Regulatory effectiveness:** whether a regulatory intervention achieves its intended purpose.

These are not entirely discrete questions; on one view, perceived regulatory legitimacy is a necessary (if not always a sufficient) precondition for regulatory effectiveness. Nevertheless, each question sets in motion important inquiries about the general limits of law.

5.2.2.1 Regulatory legitimacy

Characteristically, regulatory interventions are guided by particular standards or values and/or are designed to achieve a particular purpose. Sometimes, regulators will be able to offer a substantive (or 'on the merits') justification in support of a particular regulatory intervention. On other occasions, regulators might instead offer a procedural justification in support of their intervention. In such cases, regulators will

claim that the process leading to the adoption of the regulation was reasonable, or inclusive, or in line with democratic principles. That is to say, regulators will argue that, irrespective of one's view of the merits of the regulation, it was arrived at in the right kind of way.

As discussed in Section 5.1.2, according to the Millian liberal tradition, in a freedom-loving society, the governing principle is that no conduct should be criminalised unless it is harmful to others: harm to others sets a threshold requirement. Although it may not always make good regulatory sense to penalise conduct that is harmful to others, where the threshold requirement is met, the intervention of the criminal law can be considered legitimate.

The context in which government pursues a supply-side policy of confinement or reduction of recreational drug use might be more or less conducive to its regulatory efforts, with regulatees being more or less receptive and responsive to the intervention in question. The most resistant context will be one in which:

1. The use of the drug for recreational purposes is socially embedded.
2. Such use is not unlawful.
3. Such use is regarded as perfectly acceptable by most of the community.
4. Use of the drug is addictive.
5. Lawful suppliers of the drug are significant employers.
6. Government itself relies on the usage as a source of revenue.

To a great extent, this is the case in relation to both tobacco and alcohol. Even if supply and use of the drug is illegal, this does little to improve the context if large numbers regard the use of the drug as perfectly acceptable, or if enforcement sends out mixed messages, or if the supply chain is controlled by professional criminal classes.

The least resistant context is one in which the drug is not yet available and where there is not yet a significant interest in supply or demand. However, for most recreational drugs, government will be acting in a context where regulatees are neither receptive nor responsive to its interventions, and the only question will be just how resistant and refractory that context proves to be. Importantly, where a significant number of persons see no wrong in using a particular drug for recreational purposes, supply-side regulatory intervention is liable to be seen as lacking legitimacy.

5.2.2.2 Regulatory effectiveness

In a general sense, regulatory effectiveness concerns whether a particular regulatory intervention is achieving its intended purpose, i.e. does the regulation work? Regulatory audit will also look at efficiency (whether regulators are achieving the optimal ratio between resource input and achieved output) and economy (whether the resource input is minimised). Three of the key factors that bear on the limits to legal and regulatory effectiveness are described below.

Box 5.3 Public engagement: attitudes to drugs use

Most participants felt that eliminating the use of recreational drugs is neither possible nor desirable. Many participants took the attitude of 'I don't mind as long as it doesn't harm me'. However, this view does not capture participants' attitudes towards the drug user or how society and the law should respond to problem drug use. These were topics of passionate and sometimes heated debate. For many participants, the primary concern for the future was to reduce the personal cost of drug use.

A public health based approach to users was seen as more effective than 'locking them up'. Participants acknowledged that this approach would be resource-intensive initially but felt it would be more economically efficient over the longer term.

First, at some level, because the politico-legal system is based on a social contract, laws will lack public support where they push beyond the terms of the contract. It follows that, where this happens, the laws in question will be ineffective. For instance, experience (especially in the USA) of regulatory prohibitions on alcohol suggests that legal interventions that overstep the mark will not only be ineffective, but can also have significant corrupting and secondary criminalising effects. The use of marijuana (cannabis) as a recreational drug is also a textbook example. Thus:

'The fact remains...that marijuana use continues to be illegal in most parts of the world, even as people continue to break these laws with apparent impunity. And there is no resolution in sight. The persistence of marijuana use remains a prime example of how our legal system is based on an implicit social contract, and how the laws on the books can cease to matter when a large percentage of people decide they want to do something that may not be acceptable under the law' (Biegel, 2001).

Second, law has a better chance of being effective when both the issues and the boundaries of the problem are localised (in

the sense that the source of the problem is not located beyond the regulating state's geographical boundaries). As Dorn *et al.* (2003) have remarked in relation to the supply of drugs, the fact that there is a supply-push from countries and regions of the world affected by weakness, corruption or collapse of the state remains a significant factor.

Third, unless resources for law enforcement are unlimited, it is just not feasible to suppose that the law can control everything and everyone: total control is not an option. Moreover, as discussed above, the law will often need to rely on the co-operation of other legal regimes to achieve effective enforcement. So, for example, even though in 2004-05, 54 tonnes of cocaine were seized en route to the UK and a further 11 tonnes seized on mainland Britain, it is estimated that some 60 tonnes reached the market for sale (Ford & O'Neill, 2006). The average street price of cocaine powder has fallen consistently in the past five years, from £65 per gram in 2000 to £49 in December 2005 (SOCA, 2006). Putting all this rather bluntly, we can say that, where the law is pushing at an open door, there is a predisposition to compliance. The tougher question is what impact the law has where it is not pushing at an open door (Jenkins, 1980). Here, an

Box 5.4 Public engagement: approaches to regulation

Some participants believed that, other than age restrictions, drugs - particularly 'softer' drugs such as cannabis - should be legal and available to use by competent adults. However, most were not in favour of ending prohibition. Participants could not reach an agreement on the age at which drug use might be allowed: suggestions ranged from over-16s, over-18s to over-21 year olds.

Some participants suggested a controlled market, for instance with access restricted to small amounts of a particular drug. Some of those who argued for adults' rights to use drugs for enjoyment specified that this should not be actively promoted or used for commercial gain. A few of people felt that drugs of any kind should only be allowed on prescription, and for medical rather than enjoyment purposes. A very few felt that ending prohibition was the most sensible and effective solution. Even then these participants emphasised the need for some form of regulation, for instance in the form of licensed outlets, restrictions on quantity, or age limits for purchasing and using.

intervention might be counter-productive or have unintended negative effects. We need to know more about why legal interventions sometimes fail, where (in the regulatory cycle) they fail and how they do so.

5.2.3 Why, where and how legal interventions fail

Legal interventions are pitched at regulatees in several ways. Regulators might appeal to the prudential interests of regulatees, whether as suppliers or consumers of recreational drugs, i.e. to their desire to avoid the stigma that goes with criminalisation, to their financial interests, to their interest in avoiding the negative effects of custodial sentences and so on. Regulators also might appeal to the sense that regulatees have of what is right, running from the sense that compliance is appropriate simply because it is mandated by the law through to the sense that the particular legal provision is justified.

Some regulatees will not attend to the legal pitch at all. For example, some might be so habituated to a certain life style that the law is never any part of their practical calculation. One of the key factors that will determine the penetration of a law is whether there is any economic resistance: quite simply, if regulatees are rational economic actors, they will tend to view law as a 'tax' on certain kinds of conduct. If non-compliance is the better economic option, the logic for such regulatees is to disobey and (sometimes) pay. For instance, in the days when Sunday trading was illegal, it made good business sense for large-scale DIY enterprises to open for business on Sundays and occasionally pay a £2,000 fine. If Sunday trading had damaged the reputation of these businesses, this would have been factored into the economic calculation; but, generally, the public supported the vanguard Sunday traders, and so there was no such risk. Putting the point rather generally, we can say that, where people believe that compliance makes economic sense, they will comply; but, where compliance does not make economic sense, they will be less ready to comply (Mundy, 2001).

Does the logic of this strategic economic approach apply equally in the illicit drug trade as it does in other legitimate trades? According to Dorn *et al.* (2003), it seems likely that '*only interventions causing traffickers to perceive a significant risk of capture leading to imprisonment have a worthwhile deterrent effect, lower-impact interventions providing for traffickers no more than the expected 'costs of doing business'.* So, regulators should assume that the rational economic person operates on both the licit and the illicit sides of the regulatory fence.

Regulatory failure can occur at different stages of the regulatory cycle (Box 5.5). With regard to the response of regulatees (Box 5.5, stage 3), failure may take more than one form. For instance, regulatees might:

- Simply not comply. For example, where enforcement against the transfer of drugs across borders becomes more intensive, the drugs barons exploit vulnerable persons to act as 'packhorses' and take the risk.
- Go through the motions of compliance while seeking to circumvent or undermine the regulation. For instance, producers of recreational drugs might comply with a legal prohibition against advertising the product but, at the same time, they might sponsor research that is designed to challenge the view that the drug is harmful, or they might employ lobbyists to press for a more congenial regulatory environment.
- Comply, but with unintended negative consequences. For instance, landlords might comply with laws that require them to introduce bans on smoking in their pubs, but the pub trade may suffer as a result and jobs are lost. Similarly, breweries and landlords might decide that the business is no longer viable and pubs are closed, leading to a genuine social loss in some areas (although there are likely to be gains in the health of the community).

It is important, too, to recognise that legal interventions might be counter-productive even as regulators are celebrating a degree

of success. For example, if a more intensive enforcement effort succeeds in restricting the availability of recreational drugs (crops are destroyed, large seizures are made, and so on), this might simply result in an increase in street prices, leading to an increase in secondary crime rates. Similarly, a successful crack-down on today's suppliers might prompt a more ruthless breed of supplier, armed and ready to kill: if a decrease in the availability of recreational drugs leads to an increase in gun carrying and shootings, this might make one wonder whether this is a step forward or a step backward.

5.2.4 Regulatory modes: smart regulation and techno-regulation

In 'Code and other laws of cyberspace', Lessig (1999) identifies four regulatory modes: the law, social norms, the market and architecture. The use of seat belts is one of his illustrative examples, thus:

'The government may want citizens to wear seatbelts more often. It could pass a law to require the wearing of seatbelts (law regulating behaviour directly). Or it could fund public education campaigns to create a stigma against those who do not wear seatbelts (law regulating social norms as a means to

regulating behaviour). Or it could subsidize insurance companies to offer reduced rates to seatbelt wearers (law regulating the market as a way of regulating behaviour). Finally, the law could mandate automatic seatbelts, or ignition-locking systems (changing the code of the automobile as a means of regulating belting behaviour). Each action might be said to have some effect on seatbelt use; each has some cost. The question for the government is how to get the most seatbelt use for the least cost.'

So-called 'smart regulators' will consider direct and indirect strategies, choosing and combining strategies in whichever way promises to deliver most effectively the desired regulatory output (Gunningham & Grabosky, 1998). Reflecting this kind of thinking, in 'The culture of control', Garland (2001) describes several new crime prevention strategies in very similar terms:

'The key phrases of the new strategy are terms such as 'partnership', 'public/private alliance', 'inter-agency co-operation', 'the multi-agency approach', 'activating communities', creating 'active citizens', 'help for self-help', and the 'co-production of security'. The primary objective is to spread responsibility for crime control onto

Box 5.5 Five stages of the regulatory cycle

Broadly speaking, there are five key points in the regulatory cycle at which failure or success can be tested:

- Stage 1: the identification of a recognised or authoritative regulator.
- Stage 2: the issuing of 'guidance' by a recognised regulator.
- Stage 3: the response of regulatees to the guidance issued; that is, whether or not regulatees act on, or comply with, the guidance.
- Stage 4: the monitoring of compliance and the detection of non-compliance.
- Stage 5: the response made by regulatory agencies if regulatees do not act on or comply with the guidance; that is, whether remedial steps are taken (whether by way of enforcement or by making adjustments to the guidance).

So stated, these key stages leave a great deal to be unpacked. In particular, it is implicit in Stage 2 that the guidance issued (whatever its particular content) is at least clear and intelligible, that it coheres with other guidance that has been issued, and that it is properly communicated to regulatees.

agencies, organizations and individuals that operate outside the criminal justice state and to persuade them to act appropriately.'

Smart regulators will also be aware of the importance of the phasing of a regulatory intervention, be it 'first phase', 'second phase' or 'third phase', etc. Where regulation is first phase, its purpose is to control, confine and channel ex ante the particular aspect of practice that is its target. This would apply to a new recreational drug or one not previously used for such purposes. Where first phase regulation is successful, practice operates (largely) in accordance with the rules laid down by the regulatory order.

Where regulation is second phase, no attempt is made to control, confine or channel the given aspect of practice; regulators have abandoned such ex ante first-phase intervention. Instead, second phase regulation operates ex post, endeavouring to compensate for, or adjust in response to, the consequences of a practice (e.g. recreational drug use) that cannot be controlled by first phase regulation. In this way, much of modern criminology can be understood as an adaptive response to the fact that criminal activity is something we must live with. In the case of recreational drugs, the point is that we might do far better with a second phase approach that focuses on regulating the ex ante effects (see Stock, 2002). Indeed, in some places, without admitting as much, law enforcement might already be geared to containing recreational drug use (so that it does not exceed an 'acceptable' level), without altogether eliminating it.

Where regulators persist in seeking first phase regulatory solutions, we might imagine an approach that resorts increasingly to a technological fix. In this context, the question of genetic profiling at birth might be revisited in the future. Although the Human Genetics Commission (2005) has advised against such a step at present - for reasons to do with both

costs and consent - a different view might be taken in ten years or so, if the cost factor is not such an inhibition and if significant drug-disposing genetic markers have been identified. Regulators may also look to the potential applications of the new brain sciences. According to Green (2006):

'Compared with genetics, forensic neuroscience is in its infancy. But the promise or threat is obvious. Research on the use of neuroimaging for lie detection, drug abuse monitoring, or the diagnosis of insanity and other brain states relevant to criminal prosecution is actively underway and, in some cases, is supported by interested governmental agencies... It is an irony of genetics and neuroscience, but a further consequence of their informational density, that research begun to provide means for improving human health may eventually come to be known best for its contribution to social control.'

A full discussion of the ethics of smart and techno-regulation, including considerations about the displacement of crime, discrimination against certain groups, privacy as well as deeper questions about virtue and dignity, are outside the scope of this report (but see Von Hirsch *et al.*, 2000; Brownsword, 2004; 2005; 2008).

We emphasise that, to pursue a philosophically and legally robust regulatory strategy for drugs, we must be clear about the harms that using drugs can cause. Likewise, evidence on the harms caused by different drugs is necessary to make decisions on whether some drugs should be controlled more strictly than others - an approach that was favoured by most participants in the public engagement programme (Box 5.6). In the following sections we review current evidence on the range of individual and social harms associated with the use of different drugs.

5.3 Measuring the harm associated with the use of illegal psychoactive drugs

The use of illicit psychoactive drugs is associated with a range of physical, psychological and social harms, which can include deaths from overdose, long-term adverse effects on health, dependency liability, and harms to family, community and society. Several attempts have been made to capture the range of health and social harms of illegal recreational drug use. Table 5.1 presents a summary of major health and social harms and the main drugs responsible, as cited in Levitt *et al.* (2006) and reports from the Institute of Medicine (1996) and Prime Minister's Strategy Unit (2003). We emphasise that the strength of evidence of the association between a harm and a drug will vary in each case.

The harmfulness and danger of psychoactive substances are key considerations for their

regulation, including their classification within the framework the Misuse of Drugs Act 1971. Since the Act was introduced, an abundance of information not then available has accumulated on the diverse harms of individual drugs. In the remainder of this chapter we set out what is currently known of these harms and propose a way of using this knowledge as a guide to the classification of drugs and the regulatory measures to control their use. Understanding the harms associated with the use of individual drugs, for example the risk of addiction, the toxicity of a drug or the potential to cause mental and physical health problems, also has important implications for specialist drug treatment and the provision of support for drug users and their families.

Under the Misuse of Drugs Act 1971, there are three classes of illegal psychoactive substances - A, B and C - with substances in Class A considered to be the most harmful. Some of the members of these classes are listed below.

Table 5.1 Examples of major health and social harms of illegal recreational drug use

Harm	Main drugs/route
Overdose and other drug-related deaths	Heroin (especially if administered by injection), other opiates, cocaine, ecstasy and amphetamines
Infections by blood borne viruses (HIV, hepatitis B, hepatitis C); bacterial infections (botulism, severe systemic sepsis, endocarditis, tuberculosis)	Injecting drug use (IDU)
Dependence syndrome	Opiates/heroin, cocaine, amphetamines, cannabis
Psychosis	Amphetamines, cocaine, (cannabis?)
Respiratory disorders/ cancer	Smoking drugs: cannabis, crack, heroin
Adverse effects on fetal and child development	Opiates/heroin, cocaine, cannabis
Road traffic accidents and other injury	All drugs
Adverse impacts on school and work performance	All drugs
Family adversity, deprivation, and inter-generational substance misuse	Early onset of cannabis use or use of other substances, including heroin, cocaine
Crime	Heroin and cocaine

(adapted from IOM, 1996; PMSU, 2003; Levitt *et al.*, 2006; HPA, 2008)

The Advisory Council on the Misuse of Drugs (ACMD) was formed to keep the classification under review in the light of new scientific/medical knowledge and experience. In the following sections we examine a range of harms associated with the use of illicit psychoactive drugs, and how these harms can be measured. We have grouped these harms according to:

- Drug-related deaths: poisonings.
- Long-term health effects.
- Dependency.
- Harms to family, community and society.

It should be noted that the use of alcohol and its associated harms is not analysed in depth in this report. In 2004, the Academy published the report 'Calling time: the nation's drinking as a major health issue', which reviewed some of the harms associated with alcohol use and

warned of the increasing danger to individuals' health from the growing consumption of alcohol and the spiralling costs of alcohol-related illness to the NHS. Several of the recommendations made in 'Calling time' remain timely and we recommend that these should be taken forward (Box 5.7 and Recommendation 9).

5.3.1 Drug-related deaths: poisonings

Information on drug-related deaths is important both as a measure of population health and as an indicator of drug-related harm (ACMD, 2000). The ONS database of deaths from drug-related poisonings was initiated in 1993. For each death, the database includes every mention of a substance recorded on the death certificate or mentioned by the coroner. It is important to emphasise that there are a

Class A drugs	Class B drugs	Class C drugs
Heroin, cocaine LSD, ecstasy Psilocin Methamphetamine	Amphetamine Barbiturates Codeine Methylphenidate	Cannabis Benzodiazepines Anabolic steroids GHB, ketamine

Box 5.6 Public engagement: the classification system

There was general agreement that some drugs need to be controlled more strictly than others. Most participants felt that the drug classification system should be revised to reflect more accurately the harms associated with each drug.

The overall view of most participants was that the current drug classification system is confused, inconsistent and arbitrary. Although the specific rationale behind the system was not explored in any detail, initial discussions showed that most participants thought that it had been developed on the basis of the harms associated with particular drugs. However, after further discussion and consideration of the harms arising from use of 'recreational' drugs the underlying rationale became increasingly unclear. The reclassification of cannabis and more recent coverage in the media about 'skunk' furthered the confusion.

Many people argued that currently illicit recreational drugs should remain classified and focused on how to improve the social and health support provided to people who continue to use and on how to make use as safe as possible. Some bolstered this argument by pointing out that alcohol and nicotine have been legally available for many years and are now recognised as being among the most harmful of all recreational drugs, with alcohol in particular having clear economic and social costs and rising use by young people.

number of difficulties in using these data to measure the number of deaths attributable to drug use and the figures need to be treated with caution (Box 5.8).

The data in Figure 5.1 represent deaths related to drug misuse, which are defined as '*deaths where the underlying cause is poisoning, drug abuse or drug dependence and where any of the substances controlled under the Misuse*

Box 5.7 'Calling time: the nation's drinking as a major health issue'

The Academy's 'Calling time' report reviewed scientific evidence on the relationships between levels and patterns of population drinking on the one hand, and degree of population-level harm on the other. The report concluded that to address the challenge of alcohol-related harm in individuals, society has to address general levels of alcohol consumption in the community as a whole; it is not sufficient to target heavy drinkers.

Several recommendations were put forward to reduce per capita alcohol consumption:

- Increasing taxes on alcoholic beverages to restore the affordability levels of 1970, when they were more expensive relative to disposable income.
- Reducing EU alcohol allowances for travellers.
- Reviewing the advertising and promotion of alcoholic beverages, particularly to young people.
- Improving education and enhancing medical research on the damaging effects of excessive alcohol consumption.
- Lowering the statutory blood alcohol concentration for drivers from 80mg to 50mg; with a zero statutory blood alcohol level for drivers under 21.
- Establishing an interdepartmental alcohol policy research programme to contribute to the evidence-base and further develop UK alcohol policy.

These recommendations remain timely and where they have not already been acted upon, should be taken forward (Recommendation 9).

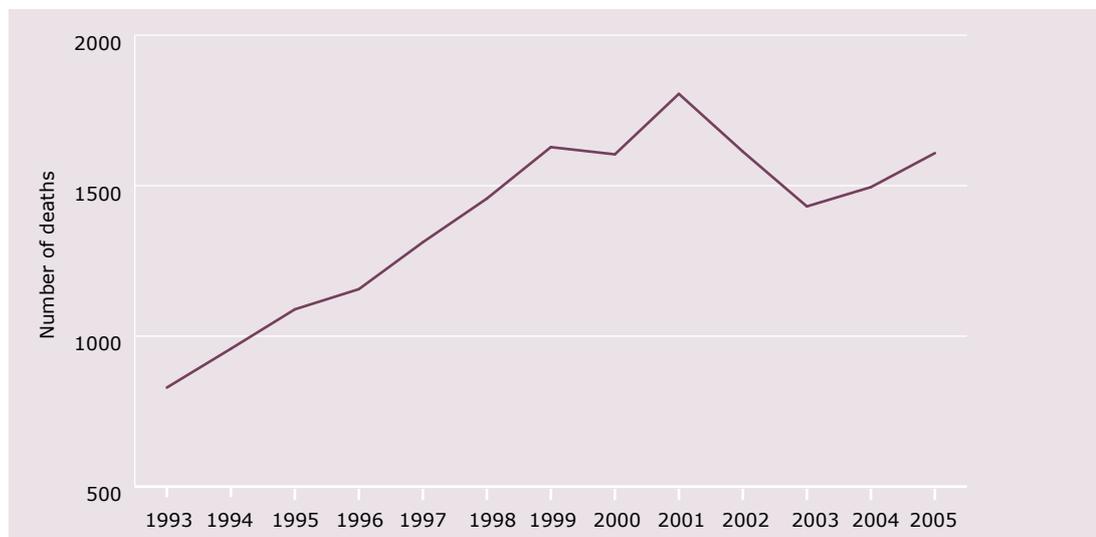
Box 5.8 Difficulties in measuring deaths attributable to drug use

Death certification and poly-drug use

Not all substances detected at post mortem may be cited on the death certificate (Gossop *et al.*, 2002). It is also important to distinguish between total mentions of a substance on a death certificate and the number of deaths that may be caused by a specific substance or combination of substances. Deaths can often involve multiple substances (poly-drug use), making it difficult to ascribe some drug-related poisonings to a single drug or even a combination of drugs. For example, in a study of 150 drug-related poisonings in London there were over 69 different combinations of drugs detected by toxicology and only 10% involved one drug (Hickman *et al.*, 2007a). In part, the difficulty of interpreting the toxicological evidence is that the levels of drugs detected at death may not be unusually high, and have been shown in some studies to be lower than levels found in living drug users (Tagliaro *et al.*, 1998; Darke & Hall, 2003).

Long-term effects

As discussed in Section 5.3.2, the use of certain substances is associated with several serious long-term health effects, some of which may be fatal. Some of these long-term effects may not yet be fully explicated or quantified (Hickman *et al.*, 2003).

Figure 5.1 Deaths related to drug misuse in England and Wales 1993-2005

(HSQ, 2007)

of Drugs Act (1971) are involved' (Health Statistics Quarterly, 2007). Deaths increased steadily from 1993 to 1999, then stabilised in the region of the 1999 figure (with some variation around it). It is also possible to look at the number of drug-related poisonings where selected substances were mentioned on the death certificate. However, again we emphasise the need for caution in interpreting the data, and the following factors should be taken into consideration:

- In around 10% of deaths, only a general description, such as 'drug overdose' is recorded on the death certificate; these deaths do not contribute to the count of specific substances.
- Some deaths may be counted in more than one category. For example, if heroin and cannabis are recorded on the death certificate, the death will be recorded once under heroin and once under cannabis.

There are differences in the total number of times selected substances are mentioned on a death certificate. For example, in 2005, heroin and morphine were mentioned 842 times, compared with 14 mentions of barbiturates and 176 mentions of cocaine (Health Services Quarterly, 2007). This figure of 176 for cocaine is the highest number of deaths

where cocaine was mentioned since records began in 1993, when 11 deaths mentioned cocaine (Health Services Quarterly, 2007). This difference is probably due, in part, to poly-drug use and the increased use of crack cocaine by heroin users in many UK cities (Hope *et al.*, 2005; Morgan *et al.*, 2006). It should also be noted that the risk of heroin-related overdose is substantially higher in the period immediately after prison release or treatment discharge/drop out (Seaman *et al.*, 1998; Farrell & Marsden, 2005; Davoli *et al.*, 2007) (Recommendation 6).

In addition to the stated difficulties around routine mortality statistics, to understand and interpret these data we require information on the mortality risk (i.e. the risk of death among drug users). However, apart from a few small studies, there has been no large-scale or ongoing monitoring of the mortality risk associated with opiate use in the UK since 1993 (Ghodse, 1998; ACMD, 2000; Hickman *et al.*, 2003). Indeed, no large-scale cohort studies have investigated the mortality risk associated with exposure to any recreational drug.

The variation in the acute toxicity of individual drugs can also be illustrated by comparing the narrowness of the window between

the dose used to procure a desired effect ('pharmacological dose') and the dose that might result in death from overdose ('lethal dose'). The ratio of the lethal dose to the pharmacological dose is called the safety ratio: the lower the safety ratio, the greater the risk of overdose. Gable (2004) reviewed 3,000 publications to obtain the human safety ratios for a range of psychoactive substances. Safety ratios ranged from 6 to over 1000. In accordance with the data on drug misuse deaths, heroin and cocaine were at the most harmful end of the scale, with safety ratios of 6 and 15 respectively. Methamphetamine, GHB and alcohol also had some of the lowest safety ratios (10, 8 and 10 respectively). The safety ratio of cannabis was stated at more than 1000. We emphasise that several considerations should be borne in mind when considering these data: individuals vary in their sensitivity to drugs; taking more than one drug at any one time can increase toxicity; and repeated use can lead to tolerance.

Gable and others have also emphasised that establishing accurate safety ratios for different drugs in humans remains difficult because of the paucity of reliable data. Safety ratios can be obtained from animal studies and, when appropriately adjusted for differences in body weight and species, can provide a prediction of human safety ratios (Gable, 2004). An estimate of the human 'pharmacological dose' can also be obtained in animals allowed to self-administer a drug (see Koob & LeMoal, 2005). However, care must always be taken when extrapolating results between animals and humans.

A more cross-disciplinary approach would do much to improve information and understanding on drug-related poisonings, as well as to inform more effective prevention measures. Such an approach could also help to explain the causes of overdose death. Several hypotheses have been put forward in this area:

- Alcohol and other depressants, such as benzodiazepines, interact pharmacologically to increase the risk of opiate overdose (see

Warner-Smith *et al.*, 2001; Darke *et al.*, 2006).

- A concurrent illness, such as hepatitis C or heart disease, increases the risk of drug overdose (see Warner-Smith *et al.*, 2001; White & Irvine, 1999).
- Risk of heroin-overdose is reduced during methadone treatment because methadone confers some protection against the acute (respiratory depressant) effects of heroin (Ward *et al.*, 1999).

These hypotheses cannot be tested by observational studies, such as mortality audits, or by comparing those drugs used by living drug users with those cited on the death certificates of deceased drug users. Opportunities for clinical trials to test these and other hypotheses concerning overdose are also severely limited. For example, in the case of poly-drug use, trials would be limited by the need to allocate different drugs and combinations of drugs to different heroin users selected on a random basis. Trials are also limited by the need to withhold interventions that have other benefits and may have an impact on overdose. Animal models, therefore, may be helpful where they can replicate human patterns of consumption, for example poly-drug use. This evidence could then be further corroborated by data from epidemiological and clinical studies.

5.3.2 Long-term health effects

Repeated use of a drug over long periods can lead to a variety of adverse effects on health. However, it can be difficult to identify and measure these effects. Although some effects may be well established, for example liver damage caused by alcohol, others are more contentious, for example the possibility of psychiatric illness precipitated by amphetamines or cannabis (Box 5.9).

Apart from these direct adverse effects of a drug, there may be a variety of secondary adverse effects on health associated with the manner in which the drug is used. These include:

- The harmful long-term consequences of smoking cigarettes and other tobacco products that are mainly due to the carcinogens and other noxious chemicals contained in the smoke inhaled into the lungs (Hecht, 2006).
- Injecting Drug Users (IDUs) are at risk of transmitting and acquiring a range of infections, including HIV, hepatitis C (HCV), hepatitis B (HBV), and bacterial infections at the injection site. All of these infections can contribute considerable morbidity and mortality (Health Protection Agency, 2006a; 2006b).

Although there are secondary adverse effects associated with several drugs, the dangers

associated with injecting drug use are particularly shocking (Recommendation 8). As shown in Table 5.2, in the UK the burden of HCV is largely determined by the number of people with an injecting history. There are estimated to be 1800 HIV and 150,000 HCV infections that are attributable to injecting drug use in England and Wales (Goubar *et al.*, 2006; De Angelis *et al.*, 2008). In 2000, the hepatitis and HIV infections due to injecting alone were estimated to cost the NHS £80 million per year (Godfrey *et al.*, 2002).

The harmful effects of long-term exposure to psychoactive drugs can be assessed in detail in animals. This approach brings the advantage that clear 'pre-drug' baselines can

Table 5.2 Relationship between injecting drug use and certain infectious viral diseases in England and Wales

	Percentage of cases attributable to IDU	Percentage of injecting drug users infected with virus
HIV	6%	1%
Hepatitis B	40%	20%
Hepatitis C	80%	40%

(Department of Health (2002); Health Protection Agency (2007))

Box 5.9 The relationship between cannabis and schizophrenia

The relationship between cannabis use and schizophrenia illustrates the problem of determining the long-term health effects of drug use. Evidence from observational studies suggests an increased risk of schizophrenia or psychotic illness in adults who used cannabis earlier in life (Macleod *et al.*, 2004; Fergusson *et al.*, 2005; ACMD, 2006; Hall, 2006; Moore *et al.*, 2007). However, data from Australia indicate that the number of cannabis users and cases of schizophrenia over time did not establish a simple cause and effect relationship, (Degenhardt *et al.*, 2003). Caspi *et al.* (2005) found evidence that regular use of cannabis by adolescents puts some genetically predisposed individuals at risk of developing psychotic symptoms. However, the number of such individuals was small, and these findings continue to be the subject of debate (Zammit *et al.*, 2007). The ACMD (2005) considered it prudent to recommend that young people be warned of this possible risk of cannabis use.

Further longitudinal studies, with detailed information on vulnerabilities to psychosis, molecular genetic approaches and better routine data on consumption patterns, are required to elucidate and quantify the potential harm of cannabis use and to guide policy in this important area (Recommendation 11).

be measured and any effects can reliably be attributed to one particular drug administered at precisely known dose levels (see for example Dalley *et al.*, 2005a; 2005b). Such reliability is not generally possible in human subjects because of 'uncontrolled' poly-drug use (see Rogers & Robbins, 2003 for a review of the difficulties of assessing the deleterious effects of drugs of abuse on human cognition and brain function).

It is also possible to measure subtle and persistent neuropsychological deficits after the chronic exposure of animals to psychoactive drugs. Using sensitive psychological assessment techniques, there is evidence for persistent and profound cognitive deficits following exposure to alcohol, amphetamine, cocaine and heroin (see Robbins *et al.*, 2007). These deficits involve changes in attention, motivation and impulsivity (Dalley *et al.*, 2005a; 2005b; 2007). However, more research is required on the long-term behavioural and neural effects of chronic drug exposure in experimental animals, both before and after abstinence. Such studies should ideally be informed by parallel studies of human drug users, using a diversity of methods to assess neurotoxicity. These include non-invasive brain imaging (Box 5.10), sensitive neuropsychological tests to provide measures of cognitive function and of behaviour, and social and epidemiological studies to measure the scale of harm in the population (Section 4.1.6; Box 4.11 and Recommendations 2 and 11).

Toxicity can be assessed on peripheral organs, but for most psychoactive substances, attention has naturally been paid to their harmful effects on the brain. Biochemical markers can be used to assess alterations or damage to a variety of chemical neurotransmitter systems (e.g. Wilson *et al.*, 1996). Several studies have shown consistent evidence for long-lasting changes in dopamine- and serotonin-containing neurons in the brains of animals after exposure to high doses of amphetamine, particularly methamphetamine (see Fumagalli *et al.*, 1998 for review), or in serotonin-containing neurons, in the case of high doses of ecstasy (De Souza *et al.*, 1990). Whether these effects are relevant to the much smaller doses of these drugs taken by human users remains controversial (Iversen, 2006). In this respect, Fantegrossi *et al.* (2004) found no change in serotonin neurons in animals self-administering lower doses of ecstasy.

Histopathological studies make it possible to identify overt brain damage, as in the case of chronic alcoholism (Wilson *et al.*, 1996). There is substantial evidence for the association of chronic drug abuse with structural brain pathology, particularly following stimulants such as cocaine and methamphetamine (see review by Chang *et al.*, 2007). Both white and grey matter changes have been reported in the cerebral cortex in cocaine abusers (Franklin *et al.*, 2002; Matochik *et al.*, 2003). There is parallel evidence for changes in alcoholics (see O'Neill *et al.*, 2001) and some limited evidence

Box 5.10 Brain imaging techniques

Several brain imaging techniques ('modalities') can be used to assess the impact on the brain of chronic drug abuse (e.g. Garavan *et al.*, 2007; Robbins *et al.*, 2007). Structural magnetic resonance imaging (MRI) can provide measures of alterations in both brain grey (i.e. nerve cells) and white (i.e. nerve cell fibres) matter. Neurotransmitter function can be assessed using positron emission tomography (PET) and single photon emission tomography (SPET) (Volkow *et al.*, 2001; 2003); and brain activity can be monitored in different regions using a variety of imaging modalities. Drug-dependent individuals can be compared with groups of healthy, normal subjects to assess whether their patterns of brain activation are abnormal, or relate to impairments measured using cognitive testing procedures (see Garavan *et al.*, 2007).

for opiate-dependent individuals (see Lyoo *et al.*, 2006) and smokers (see Brody *et al.*, 2004). There is also growing evidence that chronic drug abuse is associated with changes in brain function that can be assessed by brain imaging (Box 5.10).

However, several factors remain unclear: whether some of the changes could have been present before drug exposure; whether the changes are likely to be permanent; and whether they can be related to long-term adverse functional outcomes – a clear marker of ‘harm’. Some of these uncertainties may be resolved by animal experiments and, in humans, by studying large, carefully selected samples of chronic drug abusers and groups of abstinent individuals, in which changes in brain function and behaviour are related to reliable measures of cognitive performance, long term functional outcomes and quality of life. The various methods of brain imaging, despite their cost, will continue to provide important, objective information on the possible harmful effects of drugs on brain function.

5.3.3 Dependency

Many drugs used for recreational purposes have pleasurable effects that are rewarding to users. However, in addition to long-term adverse effects on health, nearly all of the drugs covered in the Misuse of Drugs Act 1971 classification can lead to dependence on repeated use. ‘Substance dependence’ or ‘addiction’ is defined by several diagnostic features in the ICD-10 (2007) and DSM-IV (2000) diagnostic manuals. Dependence essentially means that the user’s life becomes focussed on the need for a continuing supply of the drug and its repeated use. In extreme cases, dependent users may ultimately lose interest in their own well-being, as well as the well-being of their families and others.

The existence of dependence *per se* is not necessarily damaging to the individual user or others. For instance, many habitual coffee or cola drinkers may become dependent on the caffeine these drinks contain. They

show the features of dependence in terms of withdrawal symptoms if denied the stimulant (e.g. headache, nervousness) and they need to maintain a constant supply of caffeine to prevent these symptoms recurring. However there is little evidence that caffeine dependence is harmful. On the other hand, the heroin addict or alcoholic are clearly damaging their own health and their addictions carry a range of secondary social harms.

Although it is clear that different psychoactive drugs differ in their potential for giving rise to dependent use, the term ‘dependence’ is not easily quantified. A factor that contributes to dependence is the presence and severity of withdrawal symptoms, both physical and psychological, when drug use is stopped after prolonged use. These symptoms provide a measure of the negative potential of a drug for the user. It is also possible, with greater difficulty, to measure the effects of dependence on the family of the user and to society at large.

One way of measuring the potential for creating dependent use is to measure the ‘capture ratio’ of the substance. This ratio measures the proportion of people who try a drug who will become dependent on its continuing use, to the extent that the use of the drug is no longer under their voluntary control. Attempts to compare psychoactive drugs in this way place nicotine (tobacco) at or near the top of the list (Kozlowski *et al.*, 1989). Surveys that measure lifetime use and dependence indicate different dependence risks for different substances (Warner *et al.*, 1995). For example, the US National Comorbidity Survey suggests that almost 33% of people who had ever used tobacco became dependent, in contrast to 23% of heroin users, 17% of cocaine users, and 15% of alcohol users (Warner *et al.*, 1995).

The ONS Psychiatric Morbidity Survey (2000), a UK survey of the general population, estimated that, overall, approximately four in every 100 respondents had at some stage in their lives been drug dependent, with most (two-thirds)

of them having been dependent on cannabis. However, there is little information on the duration or natural history of many forms of dependent illicit drug use. Even for heroin, which has been studied longitudinally, there is uncertainty over the duration of dependent use. Studies in Switzerland have assessed the mean duration of heroin use to be as long as 25 years (Nordt & Stohler, 2006), and studies in Holland and Australia give a figure of 20 years (Law *et al.*, 2001; Termorshuizen *et al.*, 2005). In contrast, some estimates, based on studies in the US, suggest that the mean duration of heroin use is 8-12 years (Kaplan, 1989; Pollack, 2001). Analyses that include 'occasional' heroin users suggest that up to 35% of heroin users cease within one year (De Angelis *et al.*, 2008). Furthermore, although it is well known that dependent heroin use is a chronic relapsing illness (McLellan *et al.*, 2000), its characteristics, like those of many other such illnesses, need continually to be refined (IOM, 1996). One US study suggested that, after four years of follow-up, 70% of heroin

users may have one drug free cessation period of three months, but within a year 75% of them will have relapsed into dependent heroin use (Shah *et al.*, 2006). High rates of relapse and long duration of use are also features of tobacco dependence (Hughes & Carpenter, 2005).

Knowledge of the potential duration and natural history of dependence on illicit substances is important for several reasons (Recommendation 11). It is necessary to have reliable estimates of the duration of dependency to project reliable estimates of the number of drug users in the population, to inform the classification of harms of drug use and to provide adequate support services. Animal studies offer one way to achieve this (Box 5.11). Better data on the natural history of dependence will improve the reliability and utility of models of the dynamics and harms of drug use. At the moment, the unreliability of the data means that these models often make unfounded assumptions about the duration of drug use.

Box 5.11 Animal studies for drug dependency

Much of our understanding of the neurobiological mechanisms underlying drug addiction has come from animal studies conducted over several decades (Everitt & Robbins, 2005; Koob & LeMoal 2005; Olmstead, 2006). Animal models of drug dependence can help in the comparison of the dependence liabilities of psychoactive drugs. Animals can be trained to self-administer most of the psychoactive drugs of abuse, and continued exposure often leads to the development of tolerance and dependence (see Koob & Le Moal, 2005). Animals differ in the ease by which they can be trained to self-administer different drugs, and the extent to which self-administration, when established, is pursued at the expense of other activities. For example, rats given free access to cocaine will self-administer the drug to the detriment of virtually all other activities, including eating, sleep and sex (see Koob & Le Moal, 2005).

These factors may offer one way of assessing the human dependence potential of different drugs. Dependence in animals is often assessed by provoking a withdrawal syndrome and measuring its severity. Animal models of withdrawal may involve the administration of a drug that acts as an antagonist at the receptors on which the psychoactive drug acts. Thus antagonists of opiate receptors, benzodiazepine receptors or cannabinoid receptors can be used to precipitate models of heroin, benzodiazepine or cannabis withdrawal respectively (Koob & Le Moal, 2005). Animals trained to self-administer a particular drug will also self-administer other similar drugs. This 'drug discrimination' ability can be used to assess novel drugs to determine which of the existing classes of psychoactive drugs they most closely resemble (Koob & Le Moal, 2005).

5.3.4 Harms to family, community and society

Many of the harms referred to in the preceding sections have focussed on harms to the individual user, but this gives only part of the profile of 'harmfulness' of substance misuse. For a more complete picture it is necessary to know, for a particular drug, what damage repeated use or dependence might do to others. Habitual use of some psychoactive drugs can clearly have adverse effects on the family, in terms of domestic violence, loss of family income and poor role models for children, all of which may be consequences of dependence. In wider terms, drug use may be associated with criminal activity to provide the means for continuing the supply of drugs.

Estimates of the cost to society of illicit drug use are dominated by the costs of crime, attributed largely to crimes committed by dependent heroin and crack users (Godfrey, 2002; Singleton *et al.*, 2006). The economic and social costs of Class A drugs (including heroin, cocaine, LSD, amphetamine) in 2003-04 were estimated at £15.4 billion (Singleton *et al.*, 2006). The greatest part of this sum was accounted for by drug-related crime (90% or £13.9 billion). Health and social care costs absorbed £557 million, and the costs of drug-related deaths were estimated to account for £923 million. However, these costs were not uniformly distributed across all Class A drugs: the use (including injecting drug use) of heroin, other opioids and crack cocaine accounted for 99% (£15.3 billion) of the total.

Drug users in the UK are estimated to spend £5.3 billion annually on recreational drugs (estimates range between £4 - 6.6 billion (Singleton *et al.*, 2006)). This sum represents roughly one third of the amount spent on tobacco (£16 billion) and two-fifths of the amount spent on alcohol (£13 billion).

Estimates of the proportion of crime that may be drug-related are provided by surveys of

arrestees (Holloway *et al.*, 2004; RDS, 2006; Singleton *et al.*, 2006). These surveys estimate that over one in six arrestees were positive for cocaine and one in five were positive for opiates; and that over 70% of those arrested for 'acquisitive' crime were regular heroin or crack users. The proportion testing positive for opiates contrasts with the national prevalence estimate (England and Wales) of approximately 1 in 100 (Singleton *et al.*, 2006). Similarly, Home Office data for 2006-07 indicate that 2.6% of 16 to 59-year-olds had used cocaine in the past year (Home Office, 2007). Intoxication may also lead to public disorder and violence as seen, for example, with alcohol and amphetamines. It should be noted, however, that estimates of the costs of crime and drug consumption make a considerable number of assumptions on the size of the drug-using population (dependent and non-dependent) and their levels of consumption and behaviour (such as crime), which need to be further tested and developed (Recommendation 1).

Social harm is difficult, but not impossible to assess. The Home Office has developed the 'Drug Harm Index' (DHI) as way of quantifying social harm, taking into account numerous health and crime statistics that relate to illegal drug use (MacDonald *et al.*, 2005; 2006). The DHI takes into account the harms that individuals and society suffer because of drug-related crime, the health impacts arising from drug use, and the impact of drug use and dealing on communities. In its current form this index seeks to measure the overall harm caused by the use of illegal psychoactive drugs. Currently, the DHI does not formally link information on the number of drug users and the number of harms. However, this could be done and could form the basis for future assessment of the harm attributable to all psychoactive substances. The index does not, currently, include the impact of illegal drug use on educational attainment, financial stability and homelessness, on productivity,

unemployment and absenteeism, on the welfare of children of drug users, or on family stability. There is a compelling need to quantify these harms and so extend the value of a harm index (Section 5.3.6, Table 5.4 and Recommendations 5 and 6).

Measuring the overall social harm attributable to psychoactive drug use is made more difficult by the fact that some drugs are far more widely used than others. A recent survey of alcohol and tobacco use by young people in the UK concluded that the damage caused by these two agents was far greater than that caused by all illegal drugs (ACMD, 2006) (Box 5.12). Furthermore, self-reported drug consumption is often unreliable: population surveys often miss the most dependent drug users and those with greatest social problems; and people may under or over estimate their consumption. Quantification studies gather evidence on the risk of specific causes of death associated with a drug and information on the prevalence of its use. Such studies have been used to quantify the effects of smoking. Studies in Australia and the USA have compared the number of drug-related deaths due to smoking, alcohol and the use of illegal drugs (English *et al.*, 1995; McGinnis & Foege, 1999; Ridolfo & Stevenson 1998); fewer data are available to quantify deaths and morbidity attributable to illegal

drug use than for smoking and alcohol. For illegal drugs, apart from direct causes such as overdose poisonings, the US study attributed a proportion of deaths to infectious diseases and injury, but none to other potential harms such as suicide, problems associated with low birth weight or potential respiratory illnesses. The Australian study derived estimates for suicide (9% associated with illegal drugs and 30% associated with alcohol), low birth weight (2-3% for cocaine or opiates) and road traffic accidents, but not for other injuries or mental illness.

The lack of evidence for the full range of harms is due partly to the problems of separating interactions among tobacco, alcohol and illicit drug use, for example in relation to low birth weight and fetal problems (Section 6.2.1), or cancers associated with smoking cannabis (or other drugs). There is also a lack of follow-up studies that can determine the contribution that exposure to specific drugs makes to morbidity and mortality (Section 4.4; Box 4.11 and Recommendations 2 and 11).

5.3.5 Towards a classification of harm

Nutt and colleagues devised a scheme for assessing the harmfulness of different recreational drugs (Nutt *et al.*, 2007b). The scheme used nine parameters to measure physical harm, dependence and social harm of

Box 5.12 Public engagement: harms to children

The use of illegal and legal substances by children was a significant concern for participants in the public engagement programme:

- Alcohol was identified as one of the most harmful recreational drugs for young people, more harmful, than cannabis, nicotine and heroin.
- Teachers in the outreach work in Exeter pointed to alcohol use by young children as the 'next big issue' – '*Kids around here are drinking younger and younger*'.

These concerns are compounded by a lack of guidance on whether small amounts of alcohol – perhaps given under parental supervision – are harmful to children. Continuing vigilance will be needed in monitoring minors' access to illegal and legal substances (Recommendation 10). Where necessary, improvements should be made in enforcing existing laws that place restrictions on selling or giving psychoactive substances to minors, and in more effectively implementing current child protection laws and practice.

illegal drugs, together with alcohol and tobacco (cigarettes). Under this scheme, two groups of experts were asked to score each substance for each of the nine parameters (Table 5.3). One group comprised British consultant psychiatrists who were specialists in addiction, while the second group comprised other scientists and experts on psychoactive drugs. A four-point scale (0-3) was used, with 0 being 'no risk' and 3 'extreme risk'. For each substance, the scores were combined as a 'mean harm score', to provide an overall index of harm. The correlation between scores for the two groups was excellent ($r = 0.89$).

Figure 5.2 shows the mean harm score for each substance. Although category A drugs heroin and cocaine were given the highest harm scores, another Category A drug, ecstasy, had nearly the lowest harm score. In general, there was little relationship between harm scores and the A, B and C Classes of the Misuse of Drugs Act 1971.

The respective classification, where appropriate, under the Misuse of Drugs Act is shown above each bar. Class A drugs are indicated by dark red bars, B by pink and C by black. Unclassified substances are shown as white bars. Since the Nutt *et al.*, paper was published ketamine has been classified as a Class C substance.

The approach of Nutt *et al.* (2007b) is a valuable step forward, but it relies on the

subjective judgement of experts. It therefore makes only indirect use of advances in knowledge of brain science, measurements of the clinical and social impact of drugs on individuals and populations and the economic and social costs of drug misuse. Furthermore, it is restricted to a few categories of harm, and it is arguable whether all of the most important factors are included.

Nonetheless, this ranking, particularly at the upper end of the scale, is consistent with the financial costings referred to in Section 5.3.4 and in the PMSU Report (2003). In this report (Phase 1) the cost of drug-motivated crime was considered for several drugs; heroin and/or crack cocaine, cocaine, ecstasy, LSD, methadone (all Class A), amphetamines (Class A and B) and cannabis (a Class B drug in 2003). Users of heroin and/or crack cocaine were responsible for 87% of the cost of drug motivated crime.

As noted, problem drug users of heroin, other opioids and/or crack cocaine are estimated to account for 99% of the total economic and social costs of all Class A drugs. The obvious corollary to this finding is that the remaining Class A drugs, including ecstasy and LSD, incur 1% of these costs. It does not, however, follow that such drugs are without harm; in the absence of warning signs of immediate harm there may be adverse effects on the user that only declare themselves after a long time (Sections 5.3.2 and 5.3.3). Some of the

Table 5.3 Assessment parameters

Category of harm	Parameter	
Physical harm	1	Acute
	2	Chronic
	3	Intravenous injection harms
Dependence	4	Intensity of pleasure
	5	Psychological dependence
	6	Physical dependence
Social harms	7	Intoxication
	8	Other social harms
	9	Healthcare costs

(Nutt *et al.*, 2007b)

difficulties of establishing a causal link between substance use/abuse and later ill health are illustrated in seeking to determine the role of smoking in the aetiology of lung cancer (see Peto, 1994), and whether or not cannabis use plays a role in the aetiology of schizophrenia (Box 5.9). Furthermore, some of the harms to others, to families and especially to the children of users - socially important as they are - have proved difficult to quantify and so may not appear in estimates of the economic and social costs of the harms incurred by the misuse of psychoactive substances (see MacDonald *et al.*, 2005 and Section 5.3.4).

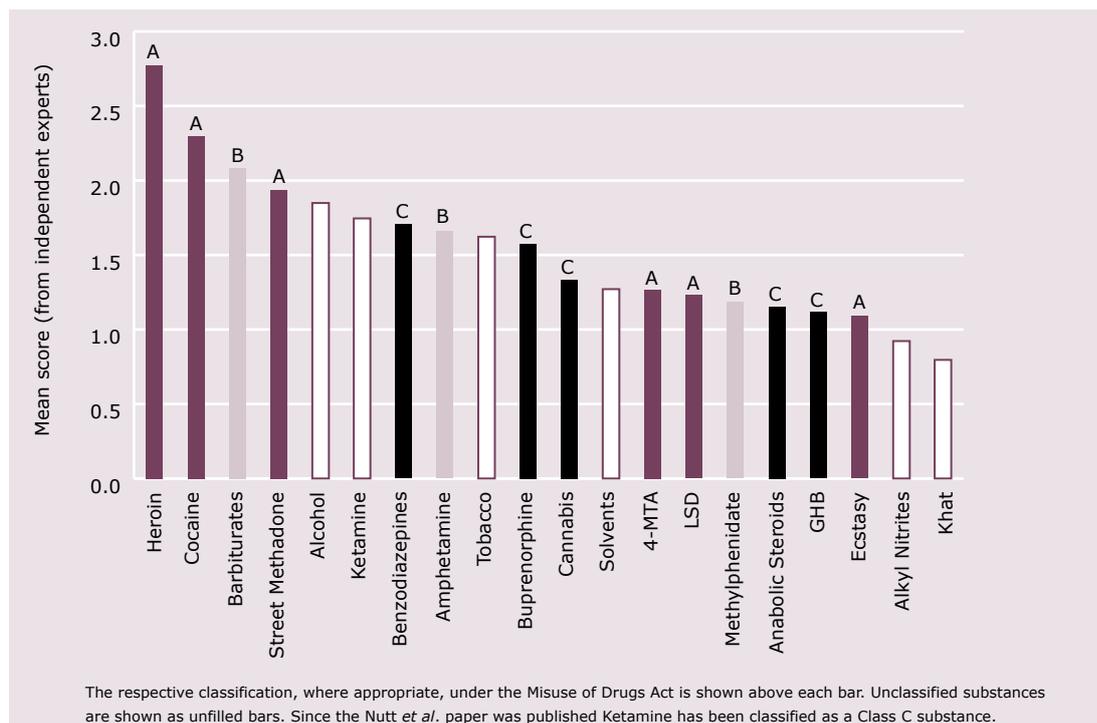
Although many of the harms attributable to alcohol and cigarette smoking, and to the misuse of Class A drugs, particularly heroin and crack, have been subject to detailed analysis and financial costings, few Class B and Class C drugs have been subject to the same scrutiny. In the absence of such information, it is difficult to establish an evidence-based system of classification of the harms of individual drugs for the purposes of regulation or for the purposes of estimating their economic

costs. We recommend that, wherever possible, this information is obtained and propose a scheme for doing so (Section 5.3.6 and Recommendation 5).

5.3.6 A scheme for measuring and comparing the harms and associated economic costs of individual drugs: developing an evidence based classification procedure

The scheme shown in Table 5.4 provides a list of the factors that could be considered when developing an evidence-based system for measuring the harms of drug use. The scheme would provide an objective means of ranking drugs, or groups of drugs, according to their harmfulness and dangers – the basis of classification under the Misuse of Drugs Act 1971 (Callaghan, 1970). The scheme, which can of course be further developed and refined, also allows comparisons to be made of the harmfulness of illicit drugs against a baseline of harms caused by legally available psychoactive substances, including tobacco, alcohol and herbal products (e.g. *Salvia divinorum*, betel nut and St John's Wort).

Figure 5.2 Mean harm scores for different substances



(Nutt *et al.*, 2007b)

The scheme specifies different aspects and types of harm mentioned in this and previous chapters grouped in line with the assessment parameters used by Nutt *et al.* (2007b) (Table 5.3) according to acute and chronic physical harm, mental health, and social harms. These harms are further segregated into whether they affect or are measured at the individual or population level, or whether they operate by affecting measures of behaviour or brain function. Information on these different harms may be generated from clinical or epidemiological studies, social surveys or routine statistics, as well as from experimental animal studies.

As far as possible, we have proposed ways in which evidence can be quantified, and the relative impact of different drugs compared in a transparent fashion. For example, routine mortality statistics and animal studies can provide information on the proportion of deaths caused by specific drugs and lethality in terms of the ratio of a therapeutic or recreational dose compared with a fatal dose; clinical and animal studies can provide information on the potential

risk of addiction and whether dependence develops over the potential duration of use; and social and epidemiological surveys can provide information on arrests that may be drug-related and of family adversities that are related to drug use. The table also highlights other harms caused by drug misuse, such as the potential to harm the fetus, the risk of transmitting blood-borne viruses and the potential to cause mental and physical health problems. Sources of information about these harms are also given in the table. All of this information can be used to measure, that is to provide an index of, the harmfulness of a drug or group of drugs. The proposed harm index is inclusive because drugs can cause a range of harms, and some harms need to be measured in multiple ways.

In some cases, quantitative measures are not available for specific harms and specific drugs. Further clinical, epidemiological, sociological or animal studies will be needed to provide these measures. The scheme will make it possible to classify and compare drugs for different purposes, such as estimating the costs of drug

Table 5.4 A scheme for assessing the harmfulness of individual drugs or groups of drugs

Acute physical harm			
Classification - type of harm			Type/source of information
	Risk to individual	Population %	
Overdose	Acute toxicity i.e. difference or ratio between therapeutic or recreational and lethal dose		Behavioural toxicity (pre-clinical/animal)
	Overdose risk i.e. number of drug users that die annually per 100 person years or per 1,000 uses of the drug	Number (and %) overdose deaths	Epidemiological/longitudinal studies and ONS mortality statistics
Other injury	Intoxication i.e. degree of capacity after consumption of recreational/therapeutic dose		Behavioural toxicity (pre-clinical/animal) and clinical literature
	Suicide (risk of suicide among drug users)		ONS mortality statistics and epidemiological/ longitudinal studies
	Risk of other injury associated with drug use (including homicide)	Road traffic accidents (RTAs) caused by drug use	ONS mortality statistics and epidemiological/ longitudinal studies, ONS and police statistics

Chronic physical harm			
Classification - type of harm			Type/source of information
	Risk to individual	Population %	
Chronic mortality and ill health	Risk of chronic disease and organ damage due to persistent use	Number (and %) of non-acute deaths attributable to drug use	Behavioural toxicity - chronic effects - animal models and ONS mortality statistics and epidemiological/longitudinal studies
Chronic - secondary	Risk of acquiring blood-borne or other infection	Infections associated with drug use/injecting/ route of administration	ONS/HPA and epidemiological studies
	Fetal problems associated with drug consumption during pregnancy		Behavioural and other toxicity (pre-clinical/ animal)

Mental health			
Classification - type of harm			Type/source of information
	Neurochemical	Behavioural & individual risk	
Dependence and addiction	Pharmacokinetics - speed of effect/delivery on brain	Self-administration - likelihood of developing and strength of dependence	Application of brain imaging, neurological animal models and behavioural animal models
	Risk of acquiring blood-borne or other infection	Average duration of dependence	Behavioural animal models and epidemiological studies
		Risk of relapse	Behavioural animal models and clinical and epidemiological studies
		Severity of withdrawal	Behavioural animal models and clinical studies
Brain damage and cognitive deficit	Physical brain damage	Cognitive deficits (during use and after cessation)	Application of brain imaging, neurological animal models and behavioural animal models, and clinical studies
Psychiatric/ psychological ill health		Co-morbidity (other mental health problems) associated with drug use	Clinical and epidemiological studies

Social harms			
Classification - type of harm			Type/source of information
	Individual	Family and society	
Deprivation and family adversity	Risk of unemployment/loss of income	Risk of family adversity/deprivation	ONS, social services and epidemiological and social science studies and surveys
		Family neglect and risk of abuse	Social services and social science studies
		Loss of working days due to drug use	ONS and social surveys
Crime	Criminality – problems associated with having a criminal record	Arrests associated with drug use including public disorder	Home Office/Police drug testing
		Estimated frequency of crimes due to drug use	Home Office/epidemiological
		Estimated number of imprisonments due to drug use	Home Office/epidemiological
Drug treatment and social services		Estimated frequency of drug treatment events and social service assessments and accident and emergency attendances	NHS/Social services statistics and surveys

misuse to health services, social services and to the criminal justice system respectively.

5.4 Discussion

In this chapter we have discussed the philosophical principles underlying drug strategy, the opportunities and limitations of different regulatory interventions and the evidence base for the harmfulness of psychoactive substances. All of these considerations will inform the development of public policy around the use of drugs for recreational purposes.

From the discussions set out in Section 5.1 and 5.2 of this chapter, we emphasise that, in a liberal democracy, an intelligent and appropriate approach to the regulation of recreational drug use presupposes a prior deliberative and inclusive community debate. To be sure, any

debate about the kind of recreational drug culture that the community wishes to have should be informed by an appreciation of what regulators can and cannot achieve. However, it is only after the deliberative debate has taken place that our regulatory intelligence can be applied to best effect. Government should therefore continue to engage in a sustained conversation with the public to develop a position that commands real support (Recommendation 7). The public engagement activities undertaken as part of this study started with the question: what kind of recreational drug culture is it that the country wants? The views expressed during the activities, and summarised in the boxes throughout this report, do not present a 'wish list', but provide a clear indication of the thinking and priorities of the participants.

Overall, we emphasise that continuing the type of public engagement activities performed

during this project can only better inform regulators, allowing them to work with the grain of public opinion and to develop regulation that can achieve its desired objectives (Box 5.13). To this end, we recommend that the ACMD takes the lead in maintaining a continued, informed dialogue between policy makers and the public to maintain trust and ensure credible regulation (Recommendation 7).

Most participants in the public engagement activities considered the current drug classification to be 'confused, inconsistent and arbitrary' and argued that it should be revised to reflect more accurately the harms associated with each drug. Given this view and the issues discussed in previous sections of this chapter, we propose that a closer relationship needs to be established between the harms associated with individual drugs and the sanctions imposed for infringing the regulations controlling their use. This principle needs to underpin future changes to the classification system and the regulation and control of 'recreational' drugs more broadly.

In Section 5.3.6 we list the factors that could be considered when developing a scheme for comparing the harms associated with different substances. New indices of harm, together with any other relevant evidence, should be used by the ACMD to provide advice on the harmfulness and dangers of individual substances, the appropriate class to which a substance should be assigned, whether or not it should be assigned and whether the present three category system is too fine, or indeed too coarse, to 'capture' the different levels of

harm. Because the adverse effects of drug misuse have a major impact on the health and wellbeing of individuals and their families and on society, as well as incurring massive costs through the criminal justice system, there would be merit in the ACMD being responsible to both the Home Office and the Department of Health. We also propose that the ACMD reports annually to an inter-departmental Government committee including representatives from the Departments for Children, Schools and Families; Universities, Innovation and Skills; and Communities and Local Government as well as the Department of Health and Home Office (Recommendation 7).

On the issue of control and regulation, participants in the public engagement programme emphasised a view that the primary objective of UK legislation on psychoactive substances should be to reduce the harmful effects of their misuse:

'For a majority, the primary concern for the future was to reduce the personal cost of drug use. This would mean bringing problematic drug use within a framework of public health and harm reduction. There would be a more open approach to drug use and drug users, including effective education, safe environments for consumption, quality control, and widely available and accessible health and support services for all drug users who wanted them' (drugsfutures, Academy of Medical Sciences, 2007).

This view resonates with the evidence considered in this chapter about the dangers to the health of individuals and to the societal

Box 5.13 Public engagement: the need for ongoing dialogue

Participants recognised that many groups will seek to influence the direction of policies to regulate illegal and legal drugs: the police, health services, scientists and scientific institutions, government, drug companies, recreational drug users and people with mental health problems. Continuing the conversation with a broad cross-section of audiences - and developing policies that take account of their views - was seen as fundamental to reducing the harms associated with drug use.

costs of drug misuse, with the evidence of Chapter 4 on the urgent need to develop new treatments for addiction, with the evidence to be set out in Chapter 6 about the factors that put young people at risk for later substance misuse, and with the stated goal of the UK drugs strategy of the UK Government 'to reduce the harm that drugs cause to society: to communities, individuals and their families' (Section 5.1.1). Our recommendations are made in the context of this strategy.

Recommendations

5. The Advisory Council on the Misuse of Drugs (ACMD), together with the Home Office, the Department of Health, Office for National Statistics and other relevant bodies, should develop new, quantitative indices of all harms attributable to individual illegal and legal psychoactive drugs.
6. In developing effective measures to regulate the use of illegal psychoactive substances, it is recommended that:
 - The framework of classification, and the place of each drug in that framework, should be based on evidence of harm and should be reviewed in the light of new evidence, including information provided by the proposed new indices of harm (Recommendation 5).
 - A balance is struck between individual freedom and the harms of substance misuse to individuals, families and society; that account is taken of the long-term harms of criminalising individuals for infringing current legislation for possessing drugs for personal consumption; and that regulatory measures are related to the harmfulness of individual drugs.
 - Dependent users given custodial sentences should be offered treatment both while in detention and on release.
7. On the basis of the proposed new indices, the ACMD should continue to provide advice on the classification of drugs and on the category into which individual substances are placed. As part of its remit, the ACMD should:
 - All regulatory measures are reviewed five years after implementation for effectiveness in reducing harm.
 - So far as possible, be responsible to both the Home Office and the Department of Health.
 - Report annually to an inter-departmental Government committee including representatives from the Department of Health, Home Office, and Departments for Children, Schools and Families; Innovation, Universities and Skills; and Communities and Local Government.
 - Take the lead in maintaining a continued, informed dialogue between policy makers and the public to maintain trust and ensure credible regulation.
8. To mitigate the serious consequences of injecting drug use, and subject to positive outcomes from current pilot studies, supervised injecting facilities for treatment-resistant addicts who use this method of drug delivery should be introduced on a wider scale.
9. The Government and the NHS should continue to communicate to the public the dangers of legal psychoactive substances, for example tobacco and alcohol. The recommendations in the Academy of Medical Sciences' report 'Calling time' (2003) should be taken forward.
10. The Government should continue to monitor, and where necessary improve, the enforcement of restrictions on selling or giving tobacco and alcohol to minors. Minors' access to tobacco and alcohol should be restricted by more effective use

of existing laws forbidding sale and gift, and by the use of child protection laws and practice. The health effects of children using small amounts of alcohol should be investigated.

Chapter 6 Risk factors and prevention

Introduction

Epidemiological and clinical studies have identified a range of factors associated with an increased risk of substance misuse, as well as factors that protect against risk. Potential risk factors can operate at the individual, family, community and societal level. Individual factors include genetic predisposition, personality characteristics such as impulsiveness, and psychopathology such as conduct disorder. Examples of family factors are neglect and abuse, whereas community factors include the availability and affordability of drugs and the attitudes and practices of the peer group. Broader societal influences, such as media attitudes and the legal regime, are also likely to be risk factors.

This chapter reviews current knowledge about risk factors arising from within the individual person, those related to the immediate and family environment, and those that are part of the broader environment – the neighbourhood and society at large (Scheier & Newcomb, 1991; Hawkins *et al.*, 1992; Tinzmann & Hixon, 1992). We consider the strength of evidence for particular risk factors and how this evidence can be used to design public health interventions to reduce and prevent drug use. We also identify areas where additional research is needed to disentangle the role played by different factors associated with drug misuse. Throughout the chapter the focus is largely on a developmental perspective and the discussion of interventions concentrates predominately on childhood and adolescent interventions that may reduce risks of later substance misuse.

When considering the evidence it is important to acknowledge two key issues. First, given that some degree of substance use occurs among so many young people, it should not necessarily be seen as pathological behaviour in itself. Some individuals cope with these experiences more effectively than others: successful coping

with the availability of, and pressure to use, illicit psychoactive substances is a phase of development, which if adequately negotiated, determines a good deal of an individual's future. The importance of research identifying particular individual, family and wider environmental risks should not obscure the fact that many young people who drink excessively, smoke or use illegal drugs, do not share any of these risk factors. Thus, although it is important to base targeted interventions on knowledge of risk factors, it will also be important to develop and offer universal interventions throughout childhood.

Second, in this chapter as in most of the literature, the risks factors associated with abuse of all kinds of psychoactive substances are considered together, the assumption being that individuals who misuse one substance either actively use or have misused other drugs. Although more research is needed to draw conclusions about the generality and specificity of risk and protective factors, most of the genetic and shared environmental risk factors identified so far appear to be largely non-specific (Box 6.1).

6.1 Individual differences

6.1.1 Prenatal exposure

There is evidence that fetal exposure to psychoactive substances taken by the mother is likely to have an adverse effect on postnatal development and on psychological adjustment. The influences of maternal drug use are of two main types:

1. Those that damage the fetus (prenatal teratogenic effects) and are evident at birth or emerge during development.
2. Those that exert their effects on the mother postnatally and adversely affect her parenting behaviour.

Substances taken by a pregnant mother may cross the placenta and affect the development

Box 6.1 Evidence that risk factors are largely not specific to particular drugs

Kendler *et al.* (2003) investigated the use and misuse of six classes of illicit substances by male twin pairs to examine whether genetic and shared environmental risk factors are substance-specific or non-specific in their effect. The study found that one common genetic factor had a strong influence on risk for illicit use and abuse/dependence for all six substance classes. Environmental experiences unique to the individual were found to largely determine whether predisposed individuals will use or misuse one class of psychoactive substances rather than another. The question of whether risk factors are specific to each substance, or whether there are factors that predispose an individual to use of illicit substances in general, has also been examined in several large-scale studies. For example:

- A study of female twin pairs in the USA found that genetic and environmental factors were entirely non-specific in their effect (Karkowski *et al.*, 2000).
- The Collaborative Study on the Genetics of Alcoholism found some specificity of familial transmission for cannabis and cocaine dependence, but most of the variance still came from risk factors that predicted misuse of both these substances (Bierut *et al.*, 1998).
- The Drug Clinic Family Study found evidence for non-specificity of familial effects, with elevated rates of both 'soft' and 'hard' drug use in the relatives of individuals with opiate, cocaine, and cannabis dependence (Merikangas *et al.*, 1998).

The one discordant note comes from the Vietnam Era Twin Registry (Tsuang *et al.*, 1998), in which there were specific genetic risks for heroin use. However, this study should be viewed in the particular context of conscription into the Vietnamese armed forces and exposure both to combat and cheap heroin.

of the fetus. Although the risk extends through much of fetal development, these substances may exert their adverse effects before the mother is aware that she is pregnant. Numerous complications are attributable to illicit drug use, including pre-term delivery, low birth weight, smaller-than-normal head size, miscarriage, genital and urinary tract deformities, and

damage to the nervous system (Brown *et al.*, 1995). At birth, there is a higher incidence of HIV and of symptoms that indicate drug withdrawal for those infants who have been exposed *in utero* to heroin, methadone or cocaine (Frank *et al.*, 1988; Finnegan & Kaltenbach, 1992). The damage caused by maternal use of several individual substances is discussed in Box 6.2.

Box 6.2 Fetal exposure to specific drugs**Alcohol**

Children with the distinctive physical signs of fetal alcohol syndrome (FAS) are very much at risk of psychological impairment. FAS, which affects about 1.9 in 1,000 live births (Abel, 1990) is one of the common causes of generalised learning disability. It has been found that the physical signs of FAS (including growth deficiencies and organ and skeletal deformities) are present in proportion to the degree of alcohol taken in pregnancy; physical signs of FAS are also negatively correlated with IQ and are related to alcohol intake after allowing for other substances used (Streissguth *et al.*, 1984; Graham *et al.*, 1988). For an overview of the fetal effects of prenatal alcohol exposure see review by Gray & Henderson (2006). High levels of alcohol exposure, which fall short of causing the physical signs of FAS, may still be harmful to psychological development (see for example Barr *et al.*, 1990). However, there are few studies that have

sufficient statistical power to detect small effects of small doses, and the major public health question of the 'safe' level of drinking during pregnancy remains unanswered.

Smoking

Research into the influence of smoking on the developing fetus is often problematic because of the difficulty of separating the direct effect of parental smoking from indirect effects of factors associated with smoking, e.g. social adversity and personality traits in the parents (Ramsay & Reynolds, 2000). Nevertheless, epidemiological studies have shown that smoking during pregnancy is associated with mental changes in the offspring:

- A case-control study of 280 cases of ADHD found a two-fold increase in rates of maternal smoking during pregnancy for those with ADHD, even after adjusting for familial psychopathology, social adversity, and co-morbid conduct disorder (Mick *et al.*, 2002).
- A large UK birth cohort study found that the children of mothers who smoke were three to five months behind in reading, mathematics and general ability, after allowing for a range of possible social confounders (Butler & Goldstein, 1973).

In both of these studies, the number of cigarettes smoked was linearly related to the degree of ADHD-like behaviour in the offspring; there was no sign of a safe level.

Cocaine

Maternal use of cocaine is well known to produce 'neonatal abstinence syndrome' characterised by jittery, unresponsive infants. Maternal cocaine use is also associated with a high rate of spontaneous abortions (Chasnoff *et al.*, 1985) and fetal growth retardation (Bingol *et al.*, 1987), suggesting that the direct effects of the drug are severe and damaging. One study that analysed the earliest stools of infants for the presence of cocaine found that the drug was present in four times as many babies than was expected on the basis of the mother's admission to drug use (Ostrea *et al.*, 1992).

However, it is particularly difficult to disentangle the direct effects of cocaine from the social and psychological problems that typically affect parents who are dependent upon cocaine. Quantification of the degree of fetal exposure to cocaine has been too uncertain to allow any reliable dose-response conclusions to be drawn about the harmful effects of the drug to the fetus. In general, little is known about the possible effects of exposure to psychoactive drugs on later behaviour. However, a large prospective cohort study has now been established in the USA to investigate the effects of toxins on early development (Berkowitz *et al.*, 2002).

Prenatal exposure to substances such as alcohol, cocaine and nicotine can have enduring effects on subsequent behaviour in later childhood (Fergusson, 1999; Taylor & Rogers, 2005). For instance, studies of cocaine-exposed children suggest a pattern of small deficits in intelligence and moderate deficits in language (Lester *et al.*, 1998), as well as deficits in academic skills including poor attention and lower abstract reasoning ability (Richardson *et al.*, 1996; Delaney-Black *et al.*, 1998; Leech *et al.*, 1999). Adverse effects that appear during childhood include learning

problems, conduct problems, ADHD and depression, all of which are themselves risk factors for substance misuse.

6.1.1.1 Genetic factors

Fetal exposure to both alcohol and cigarettes are common enough for simple association studies to examine whether any psychological impairment is associated with specific genetic variants (alleles). Studies have shown that dizygotic (non-identical) twins can be discordant for the effects of fetal alcohol syndrome (FAS) (Christoffel & Salafsky, 1975;

Chasnoff, 1985), suggesting that the level of maternal drinking is not the sole determinant. However, this does not necessarily imply that the other influences are genetic, since there was no comparison between identical and non-identical twins (for a further discussion of twin studies see Section 6.1.2).

One study has suggested that girls who develop FAS lack the enzyme aldehyde dehydrogenase-2 (which was present in their mothers), but the numbers in the study were low and the findings have not been confirmed (Tsukahara *et al.*, 1986). If it is true, it suggests that either the genetic factors leading to the enzyme deficiency may cause an increased vulnerability of the fetus to alcohol, or that long-term suppression of the enzyme may result from early exposure to alcohol. Surveys based on children with ADHD suggest that the exposure to cigarette smoke as a fetus is a significant risk factor only in children with a particular genetic constitution, specifically children who were homozygous for a variant of the dopamine transporter (Kahn *et al.*, 2003). The suggestion is that fetal exposure to cigarette smoke, and possibly other risk factors, may be particularly damaging in genetically vulnerable subgroups.

6.1.1.2 Mechanism of action

The studies described above of human pregnancy and drug misuse are mainly correlational (i.e. studies that looked at associations, rather than case-control experiments). However, studies using experimental animals have demonstrated a causal relationship between fetal exposure to drugs and an increased risk of later dependence. For instance, the offspring of pregnant rats that received alcohol in pregnancy were more likely than the offspring of controls to prefer alcohol to water when offered the choice (e.g. Bond & di Guisto, 1976).

Research using animal models has also clarified some of the developmental mechanisms through which fetal exposure to specific substances may produce behavioural changes in their adult life. For instance,

animal experiments have shown that alcohol enhances the migration of embryonic nerve cells and interferes with the production of neuroendocrine hormones, both of which could interfere with brain growth (Pratt, 1984). Studies in mice have shown that nicotine administration causes alterations in adult levels of nicotinic receptors and that smoking may also lead to increased levels of carboxyhaemoglobin, and therefore to reduced oxygenation of the fetus (Eriksson *et al.*, 2000). Studies in rats have indicated that the ability of cocaine to block the reuptake of neuroactive amines could lead to long term effects, such as dopamine receptor down regulation, in fetuses that are exposed to this drug (Dow-Edwards, 1989). An increased risk of later dependence has also been associated with a down regulation of dopamine D2 receptor levels in a particular brain region - the striatum - that mediates reward mechanisms (Robbins *et al.*, 2007). It is not clear whether such down regulation occurs in humans, but such a mechanism is one way in which the known link between fetal exposure and later substance misuse could be mediated.

There is ongoing research in the USA and Norway designed to increase understanding of chemical influences on the human fetus (e.g. Moe & Slinning, 2002). Such research, coupled with appropriate animal experiments, is likely to provide a basis for designing methods to block the toxic effects of chemical exposure during pregnancy. However, given the birth complications and adverse effects on child development associated with maternal drug use, there is a need for UK research funders to support further work into understanding of the impact of maternal drug use on the developing fetus (Box 4.11, Recommendation 2 and Section 4.1.5).

6.1.1.3 Interventions

The outcomes of drug testing during pregnancy are not centrally collated, and the full extent of substance misuse by pregnant women in the UK is therefore unknown. Data from the

USA estimate that, in 1999, the numbers of births affected by maternal use of illicit drugs, tobacco and alcohol were respectively 134,110, 694,220 and 544,330 (Lester, 2004). This represents a substantial public health issue both during and after pregnancy. The figures for tobacco and alcohol are important in that approximately one third of those who use illicit drugs during pregnancy also use alcohol and tobacco (Wenzel *et al.*, 2001), compounding the potential adverse influences on the fetus.

At present, antenatal services rely on pregnant women who misuse substances to identify themselves. Evidence suggests that simple enquiry to expectant mothers may be insufficient. In one UK study, urine screening for amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, methadone, opiates and alcohol was performed in 150 women who attended antenatal clinic (Sanaullah *et al.*, 2006). A total of 16 women (10.7%) tested positive, all of whom had denied use of any substance. It is more likely that pregnant women would self-identify as using alcohol or smoking during pregnancy and put themselves forward for services designed to reduce or stop alcohol or tobacco intake. They are much less likely to volunteer the fact that they are using illicit substances because of the associated stigma, or child protection issues. There is certainly scope to improve systems to enhance the identification of substance use during pregnancy, taking into account the risk that women may be put off antenatal treatment if they know tests of urine or hair are to be performed (Recommendation 12).

The Nurse Family Partnership intervention is designed to reduce the use of licit and illicit substances, to enhance maternal nutrition and to provide potentially vulnerable young women with coping skills to manage stress during pregnancy and after birth (Olds *et al.*, 1986). The scheme is currently being piloted in ten sites in England, as part of the Social Exclusion Strategy (Social Exclusion Unit, 2001). There is a valuable opportunity to use these pilot

studies to further understand the risk factors of substance misuse and it is important that the children of mothers taking part in the studies are followed up to determine effects on the prevalence of drug misuse. Overall, much more should be done to emphasise the hazards of drug use during both pregnancy and breast-feeding (Recommendation 12). Established support systems for pregnant women known or thought to be at risk of drug addiction should be expanded. Evaluation should assess the effectiveness of these support systems, their benefits and the possibility that women may be put off antenatal treatment if they know tests are to be performed; and assessment of different methods of engaging mothers and their partners.

6.1.2 Genetic influences

Inherited genetic make-up contributes to sensitivity to drugs and their effects, and to behavioural traits that may predispose to compulsive drug taking (Ball *et al.*, 2007). In the future, technological developments are likely to permit advances in the genetics of addiction. Through using genome-wide association studies, it is now possible to test thousands of genetic markers simultaneously. These studies will help to inform our understanding of genetic risk factors that influence susceptibility to addiction. Furthermore, advances in genetics should help to clarify the biological underpinning of reward mechanisms, the genes involved in drug metabolism and facilitate the development of much needed novel treatments (Chapter 4).

A brief overview of genetic research techniques is provided in Box 4.4. The following section draws on current understanding and considers the important role that improved understanding of the genetics of addiction is likely to play in the future.

6.1.2.1 Twin, family and adoptive studies

Evidence that genetic factors influence the risk of drug addiction is provided by natural experiments in the form of family, twin

and adoption studies. Such studies have provided clear evidence of the importance of genetic factors, while also recognising the contribution of environmental and other influences on the development of addiction.

Adoption studies have shown that an individual's substance misuse tends to reflect misuse by their biological, rather than their adoptive, parents (Cadoret *et al.*, 1986). These studies have, for example, found that broadly defined substance dependence (largely meaning alcohol and cannabis dependence) in adoptees is significantly correlated with alcoholism in biological fathers and uncorrelated, or weakly correlated, with alcoholism in adoptive parents (see Heath *et al.*, 1994).

Findings from adoption studies must be interpreted with caution: results will be dependent on the samples from which they were taken and may be influenced by the adoptees age at the time of adoption. Environmental risks such as parental mental health problems may themselves have a substantial genetic component. Nevertheless, many adoption studies agree on a genetic contribution to vulnerability to, for example, nicotine addiction (Osler *et al.*, 2001), alcohol addiction (Yates *et al.*, 1996) and illegal drug use in general (Cadoret *et al.*, 1996).

Evidence from twin studies has illustrated the importance of genetic factors in the familial transmission of alcohol dependence risk (Heath *et al.*, 1997; Knopik *et al.*, 2004) and provides support for genetic influences on nicotine dependence (Lessov *et al.*, 2004). A number of small twin studies provided evidence in favour of heritability of addiction to other substances (see Ball *et al.*, 2007). These findings have been supported by studies with large-scale samples of twins (Kendler *et al.*, 2003; Agrawal *et al.*, 2004). It has been suggested that some 45% of the variability between people in the misuse of psychoactive substances can be attributed to the interaction of multiple genetic influences (Kendler *et al.*, 2003).

Results from family and twin studies are consistent with the idea that addiction has a heritable component, while recognising that occurrence of a trait within a family can be caused by shared genetic effects, environmental factors, or a combination of genetic and environmental factors and their interactions. Such quantitative studies have traditionally served as pre-cursors to linkage and association studies. Linkage studies 'map' a putative gene variant that is contributing to a disorder to a particular chromosomal region. Association studies attempt to detect variation in the distribution of a particular allelic variation between a sample of unrelated individuals with a particular phenotype and matched controls.

6.1.2.2 Genome wide association studies

To date, candidate gene association studies have implicated alleles of several genes in alcohol dependence, including genes of the γ -aminobutyric acid (GABA), opiate, dopamine and 5-HT systems (see Ball *et al.*, 2007). Genes of the dopamine system have also been implicated in opiate addiction. Much attention has focused on variations in the DRD2 gene that encodes the dopamine D2 receptor (Box 6.3). However, the findings from some of the earlier genetic association studies have not been reproduced. Much of this inconsistency can be attributed to inadequacies in study design and implementation – many studies were under-powered in terms of sample numbers involved and did not exclude other candidate genes, leading to a high probability of generating false-positive genetic associations (Thapar & Rutter, 2008).

More systematic approaches, guided by linkage findings, are now beginning to replicate previous genetic associations (Edenberg & Faround, 2006). New technologies that enable thousands of genetic markers to be tested simultaneously are likely to lead to advances in this field and using genome-wide association (GWA) studies it has become possible to test thousands of genetic markers across the genome.

There is increasing evidence that genome-wide association (GWA) studies provide a highly effective approach for exploring the genetics of common complex diseases (The Wellcome Trust Case Control Consortium, 2007). A number of GWA studies of DNA from individuals dependent on a variety of addictive substances have already been completed (see Uhl *et al.*, 2008). Data from these studies provide an important insight into the genetics underpinning addiction. Genetic markers have been identified with allelic frequencies that distinguished addicts from matched controls. In addition, convergent data from GWA studies of individuals addicted to different substances support the idea that many genes contribute to dependence on a variety of legal and illegal substances. These findings provide promise for illuminating the features that are common to human addictions in ways that could facilitate efforts to enhance prevention and treatment strategies for debilitating addictive disorders.

Using a number of different tools, future studies should provide a clearer understanding of the genetics of addiction and the interplay between genes and the environment. Information from GWA studies will inform our understanding of predictors or risk factors for addiction and substance misuse, will help identify new targets for drug development and improve the likelihood of selecting compounds that will ultimately prove successful in treating addiction.

6.1.2.3 Pharmacogenetics

Pharmacogenetics is the study of how genetic variation affects our response to medicines, including our capacity to metabolise drugs and the effects of drugs on individuals. The potential benefits of pharmacogenetics include: improving the safety of medicines by identifying genetic variants associated with adverse reactions; and enhancing the efficacy of treatments by prescribing medicines only to those patients most likely to respond. New medicines could

Box 6.3 The role of dopamine in substance misuse

The neurotransmitter dopamine is used by parts of the brain that are selectively active when responding to rewards. Nerve cells contain several kinds of receptor for dopamine. One of these, the D2 receptor, is coded for by a gene that is sometimes present in a variant form (the DRD2 A1+ allele) that results in a low density of this receptor. People with this variant gene get a stronger 'buzz' from a self-administered drug so may be more likely to repeat the experience (Volkow *et al.*, 1999). The same variant gene is more common in people who misuse drugs than in ordinary controls, a finding that suggests how excess substance use might develop in genetically susceptible people. Conversely, animal studies have shown that over-expression of D2 dopamine receptors is associated with reduced alcohol self-administration (Thanos *et al.*, 2001).

A meta-analysis has been conducted on 64 published studies that examined the relationship between DRD2 A1+ allelic status and substance misuse. Data from substance misusers were compared with data from healthy controls who were screened to remove any who had used any substances (i.e. a 'super normal' control group). A statistically significant association was found between DRD2 A1+ allelic status and substance misuse (Young *et al.*, 2004).

One group of studies, which compared clinically confirmed drug misusers with controls who had not been screened for drug misuse, found that the DRD2 A1+ allele was significantly more likely to be found in the clinical samples than in the control groups (effect size = 1.425; 95% confidence interval 1.010–2.010, $P < 0.05$). This result is interesting because, even though the control group may have used some drugs, they had not developed misuse.

also be designed on the basis of genetic information about the cause of disease.

An example of how genetic variation at a single genetic locus may affect an individual's response to a psychoactive substance is provided by the association between alcoholism and the ALDH2 (aldehyde dehydrogenase) genotype. A single point mutation in the gene for ALDH2 leads to an inactive enzyme and makes it impossible for individuals to convert alcohol into acetic acid, resulting in alcohol intolerance and a characteristic flushing response (Wall *et al.*, 1997). It should be noted however that this polymorphism is found almost exclusively in Asiatic populations and the association has been less consistently reported in other populations (Borras, 2000).

One further insight into how pharmacogenetics could have implications for clinical practice is provided by preliminary data that suggest individuals with a certain genotype may respond better to naltrexone, an opioid receptor antagonist that has shown to be beneficial for the treatment of alcohol dependence (Oslin *et al.*, 2003). The OPRM1 susceptibility gene is the primary site of action of most commonly used opiates, including heroin, morphine, and most drugs to treat opiate dependence (Rutter, 2006). In a randomised, placebo controlled clinical trial, Oslin *et al.* (2003) found that naltrexone-treated subjects carrying the A118G allele in the OPRM1 susceptibility gene showed significantly longer time to relapse.

The emergence of technologies that permit rapid screening for specific polymorphisms, as well as increasing knowledge of the genetic sequences of target genes such as those coding for enzymes and receptors involved in drug response, will facilitate future advances in pharmacogenetic research. To date, genetic data have pointed to genes involved in drug abuse and addiction, which in turn have begun to elucidate genetic variants that may be helpful in identifying treatment medications for different individuals. Incorporating

genetic data that are reliably consistent into the clinical setting will be an important next step. Initiatives such as the NIDA Genetics Consortium, which has collected over 20,000 samples from individuals with smoking, cocaine, opioid and polysubstance addictions, will be crucial to increasing understanding of addiction vulnerability and addiction treatment response.

6.1.2.4 Interventions

Evidence suggests that some genes such as DRD2 are likely to influence all types of psychoactive substance use. Further research is needed to clarify individual differences in genetic traits that increase the risks of starting hazardous activities such as drug-taking (Recommendation 11). In the future, it is conceivable that individual differences in the pleasurable response to substances could be modified by medical/pharmaceutical interventions that make the response to the substances less attractive. Animal research is also likely to allow a deeper understanding of the underlying neural and behavioural processes of impulsivity and response to reward.

Advances in genetic understanding and DNA technology can be expected to define groups of young people who show a specific risk. For example, Caspi *et al.* (2005) reported that regular cannabis use put some genetically susceptible individuals at an increased risk of developing psychotic symptoms (Box 5.9). However, the attributable risk of genetic variants to substance misuse (at present unknown) would need to be high for genetic testing or counselling to be useful and there are many ethical issues to consider. Some of these ethical issues were discussed during the public engagement programme: assuming that the accuracy of a test was high and that the genetic change identified was strongly predictive, participants could see both benefits and disadvantages (Box 6.4).

Further research is needed to examine gene-environment interactions in relation

to substance misuse (Section 6.6 and Recommendations 11). There should also be continuing research and public consultation, especially with young people, about the likely effects of knowing one's particular biological susceptibilities on drug taking behaviour. Participants in the public engagement activities conducted during this project emphasised that giving information to susceptible young people about the particular 'risk' they face may well deter them, but that general injunctions to abstain are often ineffective. There is also a need for a continuing dialogue with the public about the more general issues raised by identification of genetic risk factors and the potential use in children of vaccines against the

effects of dangerous drugs (Section 4.2.4, Box 4.7 and Recommendation 25).

6.1.3 Personality differences

Longitudinal research has shown the importance of personality traits such as impulsivity and novelty-seeking for substance misuse (see for example Acton, 2003). It has been suggested that a weak behavioural inhibition system (BIS) and a strong behavioural activation system (BAS) may contribute to the development of substance misuse (Fowles, 1980; 1988). The neural structure of the BAS is thought to relate to the dopaminergic 'reward circuit' that has been associated with substance misuse. This suggestion has been supported by findings of

Box 6.4 Public engagement: genetic testing for addiction

In looking towards the future, participants discussed the possibility of a diagnostic test for genetic predisposition to addiction. Participants raised several questions, for example: how accurate would the test be, would it identify whether someone was predisposed to use a specific substance, or more broadly as having an 'addictive personality'? Many participants felt their attitudes towards a test would differ depending on the answers to these questions. Participants identified several advantages and disadvantages of having a genetic test, which are summarised below.

Benefits of genetic testing

- Tests could provide parents with an opportunity to intervene in a more direct manner and to inform them about environmental and social factors that might lead to the expression of the genetic predisposition.
- The development of genetic tests and increased understanding of genetic factors linked to addiction could lead to new treatments.
- Tests could contribute to a greater social acceptance of - and more sympathetic attitudes towards - people with addiction problems.

Disadvantages of genetic testing

- Tests could generate concerns around the disclosure of information and the discrimination of those with a 'positive' result.
- Tests could lead to anxiety about how friends and family would respond to news of a 'positive' test.

In general, most participants felt that for a test to have any value it would have to be considered in the context of the support available and the clinical use of the test results. Overall, participants felt that there would be more value in understanding drug use within a social context than could be gained by focusing on genetic factors.

autonomic hypo-reactivity among young (and adolescent) men and women with substance use disorders (Iacono *et al.*, 2000; Taylor *et al.*, 1999; 2004).

Personality characteristics associated with a family history of substance use disorders are found even in adolescent offspring who have not yet developed these disorders themselves, suggesting that personality might be one indicator of familial risk. Elkins *et al.* (2004) selected 479 subjects from a larger investigation called the Minnesota Twin Family Study. Of these 479 teenagers, 257 had parents without an alcohol or substance-use disorder, 160 had parents with an alcohol disorder, 21 had parents with a drug-abuse disorder, and 41 had parents who had both alcohol and drug abuse disorders. The results showed that parental history of alcohol dependence was associated with greater negative emotionality, as measured by scales of stress reaction (e.g. easily upset, irritable, alienation, and aggression); parental history of drug disorders was associated with lower 'constraint' (e.g. lower propensities to endorse traditional values, act in a cautious manner, avoid thrills and avoid harm).

6.1.4 Psychopathology

Another set of important risk factors includes the various forms of psychopathology found in people who heavily use psychoactive substances. Of course, many heavy users have no evident psychopathology at all, and although 'harmful' or 'dependent' use is itself classified as a form of psychopathology, it is not necessarily accompanied by any other form. Nevertheless, the coexistence of substance misuse and mental disorder is much greater than could be predicted from the community prevalence of either (e.g. Brook *et al.*, 1998, Kandel *et al.*, 1999). Mental health problems, especially conduct disorder and ADHD, are also effective predictors of later substance misuse (see below). The question is how best to understand this connection: is one causing the other, or do both result from a common set of risks?

6.1.4.1 Conduct disorder and anti-social adjustment

The risk of substance misuse associated with conduct disorder (a persistent condition of antisocial traits) is probably the highest of all types of psychopathology (Robins, 1998). There will be several reasons for the coexistence of conduct problems and substance misuse. For example, people using drugs may steal to obtain the money for the habit, and antisocial children who reject the rules may gravitate into an antisocial and drug-using peer group. The Belfast Youth Development Study, a longitudinal study of adolescent drug use, found that children attending special units for emotional and behavioural disturbance consistently reported higher levels of licit and illicit drug use throughout adolescence, as well as behaviours predicting more drug use including antisocial behaviour and disaffection with school (McCrystal *et al.*, 2007). However, this inter-relationship between conduct problems and substance misuse should not be taken too far. It may be obvious that, for instance, drunkenness will lead to the 'conduct disorder' symptom of fighting, but a study of USA veterans indicated that alcohol-dependent veterans did not fight when drinking unless they had also fought excessively as children, before alcohol use appeared (Robins, 1998).

Furthermore, it is quite possible that the association of the two conditions, substance abuse and conduct disorder, stems entirely from shared risk factors. Both are more common in males and in individuals whose parents were themselves substance abusers; school failure is also common to both and both are becoming more common in successive generations (Collishaw *et al.*, 2004; Maughan & Kim-Cohen, 2005). Yet these relationships would also be seen if one were primary and the other a secondary consequence. In theory, it should be simple to examine whether the association is still there after controlling for the associated factors; indeed the association usually does remain after controlling for age and sex and social status (Robins, 1998).

However, there are always unmeasured factors in the tangle of adversity that have not been controlled for. Longitudinal and genetic research designs carry the highest promise of disentangling the developmental mechanisms of psychopathology and substance misuse (Recommendation 11).

6.1.4.2 Attention deficit hyperactivity disorder

It has been suggested that attention deficit hyperactivity disorder (ADHD) has a specific neurochemical basis (Taylor, 1999). The underlying pathology, at least for some individuals, is argued to be an over-expression of dopamine transporter in the brain as a result of an altered section of the DNA (present on chromosome 5) that is responsible for making the protein. The suggested consequence is a down-regulation of dopaminergic systems, in the striatum and frontal lobes of the brain, which mediates the capacity to inhibit inappropriate reactions and the response to reward. There is some neuroimaging evidence for this suggestion (Rubia & Smith, 2005) and good evidence that the therapeutic effect of the ADHD treatment methylphenidate is brought about by inhibition of the dopamine transporter and consequent magnification of the dopamine signal (Volkow *et al.*, 2003). This finding in turn leads to a possibility that the abuse of stimulant drugs might be more common in people with ADHD, perhaps representing a form of self-medication, and would be reduced by the prescription of stimulant drugs before the age of illegal drug use. Clearly, this possibility needs careful investigation.

Epidemiological and therapeutic investigations have supported the idea that the presence of ADHD predicts later substance misuse, the risk being raised about five-fold (Levin and Kleber, 1995). This increased risk applies to tobacco and alcohol, as well as for stimulants such as amphetamines and cocaine. A good deal of the risk, perhaps most of it, can be accounted for by the association of ADHD with conduct disorder: a follow-up study of London boys aged from 7 to 17 suggested that ADHD was only a

significant risk for substance misuse if conduct disorder was also present (Taylor *et al.*, 1996).

The treatment of conduct disorder and ADHD usually includes measures intended to alleviate family, peer and school difficulties that are considered to play a role in the development of behaviour problems. Treatment is often effective for reducing these behaviour problems (Schachar & Tannock, 2002; Dretzke *et al.*, 2005). However, rigorous experimental evidence that this treatment will prevent later substance misuse for some individuals is lacking. The best evidence that ADHD is a risk factor for substance use comes from the finding that people with ADHD who have been treated with stimulants are less likely than untreated people with ADHD to misuse tobacco, alcohol or illicit drugs (Wilens, 2003). It must be noted, however, that treatment with a drug will achieve more than a neurochemical change. Treatment may lead to an alteration in parent-child relationships and improve school achievement; it may be that these changes are crucial to reducing the risk. In addition, the evidence for treatment leading to lower substance misuse has been derived from survey studies rather than from experimental trials. It is also possible that those people who seek treatment for their ADHD are a lower-risk group than those who are not treated.

In summary, the possibility that ADHD constitutes a direct and reversible biological risk for substance misuse cannot be excluded, but direct evidence is lacking. In any case, ADHD is still important because it is a risk factor for the development of conduct disorder, which is a well established risk factor for substance misuse, particularly if it is present at a young age (Schachar & Tannock, 2002).

6.1.4.3 Depression

Some authorities have argued that a significant proportion of substance use is an attempt at self-medication of miserable feelings, and that much drug misuse is a consequence of

depression (Weiss *et al.*, 1992). This view was also expressed by participants in the public engagement programme (Box 4.2).

Certainly it is clear that depression and substance misuse frequently occur together (Weissman *et al.*, 1999). In UK studies, however, follow-up of children diagnosed with depression into adult life has suggested that the risk for substance use consequent to depression is greater if conduct disorder accompanied depression (18%) than if only depression was present (1%) (Fombonne *et al.*, 2001). That is, as with conduct disorder, much of the association between depression and substance misuse is likely to be due to the risk factors that are common both to drug use and to mental health problems, and substance abuse may only emerge if depression is co-morbid with conduct disorder (Rutter, 2002). Thus, it may be that the main focus for prevention should be on conduct disorder, not depression.

6.1.4.4 Interventions

Children with mental health problems are a high-risk group for developing substance misuse, at least in part because they share risk factors with those 'healthy' children who will become substance misusers. Several targeted early intervention programmes, some starting during pregnancy (Olds *et al.*, 1986), and others initiated during the preschool years (Ramey *et al.*, 2000; Schweinhart *et al.*, 1993; 2005) have been shown to reduce the risks associated with various forms of psychopathology. Schools, together with the health and social care services, should provide a comprehensive service for young people with mental health disorders, which includes the provision of focussed advice on the hazards of substance misuse. Children and young people who are misusing drugs, particularly those in young offender institutions, should be assessed for depression and conduct disorder, so that the individuals can be treated for these conditions in conjunction with any substance misuse or addiction (Recommendation 14).

6.2 Family social factors

In general, adversities in the home and family environment are pervasive and complex and their effects cannot be separated easily. Potentially harmful factors tend to occur together and are associated not only with substance misuse, but also with psychopathology (especially conduct disorder) that may itself be a risk for substance misuse. Many harmful factors - particularly poverty, poor parenting and living in a disadvantaged neighbourhood - can follow from the parents' own problems, such as mental health problems, criminality, or their own substance misuse. A child's early psychological environment plays a crucial role in development. The consistency, responsiveness and availability of the primary caregiver, as well as the provision of perceptual stimulation are also important factors (Melhuish *et al.*, 2008).

6.2.1 Home environment and parenting

Box 6.5 summarises research that illustrates the importance of the home environment and parenting. The role of parental support was also considered during the public engagement programme (Box 6.6). The parenting risk factors involved in the development of substance misuse are similar to those implicated for children with mental disorder. At the extreme, overt abuse - physical, sexual or emotional - carries a substantially increased risk for substance misuse (Roberts *et al.*, 2004). Short of abuse, there are associations with 'negative' adversities such as neglect, lack of warmth from parents and lack of supervision; and with the 'positive' adversities of disciplinary aggression, hostility and domestic violence; as well as with permissive family attitudes towards substance use (Runyan *et al.*, 2002). These problems of parenting often coexist, and often generate other mental health problems in children.

There are strong associations between the tendency to misuse drugs and the prior presence of adverse parenting. The risk for

the child is particularly high when a parent is both misusing substances themselves and has an antisocial disposition (Langbehn *et al.*, 2003). However, it is more difficult to show prospectively that poor or inconsistent parenting leads to substance misuse, and to determine the extent of risk that it represents. It has been suggested that family factors are more relevant to experimentation with drugs than to the development of abuse or dependence, which may be more strongly related to genetic risks (Kendler *et al.*, 1999).

Although it is unlikely that the relevance of poor parenting in the development of substance misuse is due to the effects of a single type of early damage, such as the failure to establish maternal bonding in infancy, animal research has emphasised that periods of separation from parents or from peers can give rise to enduring alterations of learning and social interaction (Hinde & Spencer-Booth, 1971; Robbins *et al.*, 2007).

It is also true that early extremes of neglect, such as those experienced by children brought up in a harsh institutional environment, can cause long-lasting mental damage even after the neglect has been corrected (Rutter *et al.*, 2007). Severely adverse experiences during early childhood can to some extent lead to a biological programming, with persisting abnormalities of social development for a small proportion of children suffering these experiences. However, most children who have been rescued even from severe deprivation will develop normally (Rutter *et al.*, 2007); it is often continuing adversity that causes persistent problems in the child. This is encouraging for the success of interventions based on reducing current adversity. Similarly promising evidence from the literature on animal research indicates that individual characteristics that are risks for drug dependence and addiction (e.g. sensation seeking) can be manipulated by alterations in the type of care-giving experienced. (Robbins *et al.*, 2007)

Box 6.5 The importance of the home environment and parenting

The Effective Pre-school and Primary Education (EPPE) Project is a UK longitudinal study of child development. The project has collected a wide range of information on 3,000 children, their parents, their home environments and their pre-school and primary schools, to investigate influences upon intellectual and social development. The research uses a range of instruments including standardised assessments, interviews and observational schedules to build a developmental trajectory for each of the 3,000 children. Multilevel modelling is used to assess the influences of home, neighbourhood, preschool and school factors upon development. At age 10, medium to high quality pre-school provision still exercised an influence upon development (Sammons *et al.*, 2007), but the strongest influences were from the home, in particular the home learning environment (Melhuish *et al.*, 2008).

Box 6.6 Public engagement: parental support

Many participants focused on the need to provide support for parents of young people who may be more vulnerable to drug use or abuse, additional to the general education and information that all parents would need. This support might include parenting classes or mentors for families and young people. As with many other questions raised in the project, people returned to the need to address the wider issues around the drug use – including housing, education, social inequality and employment opportunities – in addition to the drug use itself.

6.2.2 Interventions

Family interventions that focus on strengthening parenting where it is inadequate are probably the most promising of the psychosocial interventions in reducing substance misuse (Dretzke *et al.*, 2005; Petrie *et al.*, 2007; see Box 6.7 for further evidence for the value of family interventions). Such interventions are most promising where they are applied to high-risk groups, including: the children of alcoholic and other substance-dependent parents, or mentally ill parents; children already showing the associated mental health problems at a stage before substance misuse has occurred; and children already starting to misuse drugs. The National Institute for Health and Clinical Excellence (NICE) recommends the use of family-based interventions to reduce substance misuse among vulnerable and disadvantaged people (NICE, 2007). Their key recommendations for vulnerable children aged 11-16 include:

1. At least three brief motivational interviews each year aimed at the parents/carers.
2. Assessment of family interactions.
3. Offers of parental skills training.
4. Encouragement to parents to monitor their children's behaviour and academic performance.
5. Inclusion of feedback.
6. Continuation even if the child or young person moves schools.

However, these recommendations do not relate to children below the age of 11, an age when the risk factors for later substance misuse already exist.

Family-based interventions usually involve broad-based support including teaching parents focused skills to control their child's behaviour, encouraging reading, clear supervision of the child, and encouraging the parents and child to engage in joint activities. The Cochrane review by Petrie *et al.* (2007) made a systematic analysis based on 20 trials. There were statistically significant self-reported reductions of alcohol use by young people

in 6 of 14 studies, of drugs in 5 of 9 studies and tobacco in 9 out of 13 studies. The most effective interventions were those that shared an emphasis on active parental involvement and on developing skills in social competence. Furthermore, the effect size appears to be greater when the intervention is directed at the child and parents together, than when only parenting is addressed (Love *et al.*, 2002).

Overall, there is an important need to introduce trials of interventions that encourage positive parenting and community support, especially in high-risk groups, and that examine the impact of interventions on resilience to the development of substance misuse. Evidence-based family support programmes should be introduced before substance misuse has developed (Recommendation 13) and should involve a broad based support package including:

- Providing community and family level interventions that encourage positive parenting and community support, especially in high-risk groups.
- Promoting joint parent/child activities, in particular encouraging reading.
- Teaching parents skills to supervise and control their child's behaviour.
- Increasing parental sensitivities to the child's needs and interests.
- Providing high quality child care and early education for children under three years old.
- Enhanced pre-school provision, parental support and education for children over three years old.
- Enhancing provisions for identifying and supporting pupils with low ability and low educational achievement and those at risk of dropping out of school. These provisions should include support for parents.

6.3 Societal factors

The environment outside the family has an impact both on family functioning and on the individual child. The neighbourhood in

which a child lives can have a great influence on exposure to illicit substances, as well as substances such as tobacco and alcohol. Part of this influence relates to the culture within the community, to the acceptability of using these substances, to their availability, and to opportunities to become involved in illicit drug culture from a young age. The community context often interacts with peer influences, particularly peers a child may meet in school or in the local neighbourhood.

6.3.1 Neighbourhood context

A study of a nationally representative UK sample has shown that mental health problems in childhood and adolescence are associated with poor social circumstances (Meltzer *et al.*, 2000). However, focusing too narrowly on family poverty fails to take into account the wider context in which the family lives. Deprivation and its sequelae are caused not only by insufficient personal resources, but also by unsatisfactory community resources such as dilapidated schools, remotely-sited shops or poor public transport, which reinforce and perpetuate the effects of household poverty (Robson *et al.*, 1995).

Substance misuse is more common in, though not confined to, deprived communities and poor families (Jencks & Meyer, 1990). Some of this disadvantage is transmitted by the destructive effects of poverty on family life and parenting. Also key to the community context are the relationships between residents, and the values they hold. The relationship between community social disorganisation (lack of shared values, lack of intervention to prevent problems in the community), parenting problems and child behaviour problems is well established (Sampson, 1997). The processes that lead to a higher risk of child abuse, delinquent behaviour and crime are also likely to lead to greater substance abuse in children living in such communities. In the local community, which may differ from the society at large, the availability of drugs, their price and their image, conveyed by social attitudes, advertising (and perhaps parts of the media) are very likely to play their part in encouraging the use of psychoactive substances. For example, young people may use as role models individuals in the community who openly sell and use drugs. The level of antisocial behaviour locally will

Box 6.7 Social interventions and drug misuse

In 2006 a Cochrane review surveyed 17 non-school studies that evaluated the effects of various social interventions on drug misuse among young people (Gates *et al.* 2006). Four types of intervention were evaluated: motivational interviewing or other brief focussed intervention on an individual basis; education or skills training; family interventions; and multi-component community interventions. A preliminary analysis of the review suggests that motivational interviewing for people already using psychoactive substances, and support packages for parenting, were the most effective interventions. A further Cochrane review (Petrie *et al.*, 2007) has concluded that around half of the family interventions assessed have turned out to be statistically significant compared with control groups.

Further evidence of the effectiveness of family interventions is provided by Gates *et al.* (2006), who reviewed the effectiveness of various social interventions on drug misuse among young people (involving a total of 1,230 participants). Most of the major intervention programmes had received only one evaluation in randomised controlled trial design, so the results could not be replicated. Nevertheless, a preliminary analysis of the review found that two family interventions may have beneficial effects in preventing cannabis use: Iowa Strengthening Families Program (Molgaard, 1994); and Preparing for the Drug-Free Years (Spath, 2004). These interventions were statistically significant ($P < 0.01$ and $P < 0.01$ respectively).

also be relevant, and indeed the risk factors for delinquency and for substance use are similar (Lee *et al.*, 2004).

6.3.1.1 Interventions

There is some evidence that local neighbourhood interventions may be an effective way to reduce the level at which the community 'accepts' the presence of illicit drug sales and public drug use; such illicit activities decline in the community as community cohesion and collective efficacy improve (Sampson *et al.*, 1989; 1997). The Communities That Care (CTC) programme, which targets a range of social risks, is an example of a community level intervention that builds a coalition of key leaders and decision makers (Box 6.8). The effects of broader, society-wide interventions are less well documented. However, successful interventions in reducing substance misuse will

need to investigate prevailing beliefs and values surrounding substance use and, in particular, focus on the views of young people, in conjunction with more targeted prevention and intervention measures (Recommendation 15).

6.3.2 School and education

The Foresight report emphasised the importance of risk factors associated with school, including failure at school and the influence of a 'deviant' peer group. With regard to the last of these, there is a danger that unsuccessful children may group together and form a view that ordinary society has little to offer them (McKeganny *et al.*, 2007).

Outside the UK, school projects intended to dissuade children from experimenting or continuing to use illicit substances have been implemented and evaluated in several countries. These projects have been reviewed

Box 6.8 Communities That Care

The Communities That Care (CTC) programme is a holistic, multi-agency approach that was originally developed in the USA in the 1980s (Hawkins *et al.*, 1992). The programme is based on a public health intervention model used to prevent a range of physical illnesses and social difficulties (Roussos & Fawcett, 2000). CTC is a comprehensive community-wide and community-focused initiative designed to deal with a range of problems faced by teenagers, particularly crime, anti-social behaviour and substance misuse. It establishes partnerships between local people, agencies and organisations and implements local action plans to create safer communities with better outcomes for young people. It represents an attempt to combine the involvement of community members in planning and deciding what actions to take with the provision of evidence-based approaches to crime and substance abuse prevention (France & Utting, 2005).

CTC involves building a community coalition of key leaders and decision makers who are brought together to form a community prevention board, the members of which are provided with training on risk and protective factors for drugs and other problems affecting teenagers. They are also informed about evidence-based prevention programmes. The board commissions a needs-assessment in the local community, and based on this assessment, a range of initiatives and strategies are put into place. CTC has been implemented in several countries including the UK, Australia, Ireland and the Netherlands (France & Utting, 2005) and evaluations are underway in some of those settings (e.g. Williams *et al.*, 2005). It is still too early to establish clear evidence of the impact of CTC and it will be important to monitor these types of interventions to see if they achieve their desired impact.

by Faggiano *et al.* (2005), who found 32 studies that were good enough to include in a Cochrane review. The studies involved 46,539 subjects and 19 evaluated programmes (such that most programmes received only one evaluation). Faggiano *et al.* concluded that: skills-based programmes in schools are more effective than standard teacher-delivered classroom teaching in persuading children to avoid using illicit substances; skills-based programmes are probably more effective than knowledge-based or affect-based techniques; and peers and external educators are more effective than teachers.

Skills-based interventions can be successful when they aim to increase drug knowledge, decision-making skills, self-esteem, the ability to resist peer pressure, and ultimately to resist cannabis and hard drug use. However, Faggiano *et al.* (2005) emphasised the limitations of many of the studies in this area and caution must be used in interpreting the findings. These limitations include: unsystematic reporting across series, so that meta-analysis is difficult; failure to allow for cluster effects in the statistical analyses; and difficulties in comparing different types of intervention.

Nevertheless, these studies suggest that there is scope for encouraging a wider use in schools of skills-based education delivered by peers or ex-users, and that interventions of this type should receive more systematic research evaluation, both to extend knowledge of their value in UK settings and to indicate how improvements in effectiveness might be achieved (Recommendation 15). In this regard, promising results have been found in a randomised trial of a peer-led intervention in UK Schools (ASSIST). This trial was successful in both recruiting and retaining peer supporters, and salivary nicotine analysis indicated that smoking was 18.2% lower in intervention schools (Starkey *et al.*, 2005; Audrey *et al.*, 2006). The evaluation of the Government's 'Blueprint' drugs education programme will shortly be complete and the

results will offer an important opportunity to reconsider the role and content of drugs education (Recommendation 15).

6.3.3 Media and culture

The availability of drugs, their price and their image conveyed by advertising and the media are likely to influence the extent to which children and adolescents misuse psychoactive substances (Hickman, 2002; Blackman, 2004). For some time there has been a counter-culture - in part represented in film, music, clothes, advertising, and the reporting of 'celebrity' activities - associating illicit drug use with being fashionable (Box 6.9). It has been suggested that the perception of drugs is influenced by those who are seen to be the consumers. Thus, if individuals who are portrayed as users of substances are held in high esteem they are likely to be taken as role models by young people; conversely, if such individuals are held in low esteem they are less likely to serve as role models (McKegany *et al.*, 2007). In some sociological literature, drug users (especially males) are described as self-determining individuals, willingly choosing that lifestyle (one that just happens to be deviant), especially if they are from disadvantaged backgrounds (Hanson *et al.*, 1985; Williams, 1990). Participants in the public engagement programme emphasised the role of the media in establishing perceptions about drug use; it is clear that the media has an important role to play in discussions about public health strategies (Recommendation 16).

The media redefine and normalise the concept of addiction by using it in conjunction with shopping and eating, and by incorporating its language into labels given to 'glamorous' products (Berridge & Hickman, 2007). When illicit drug use and abuse is portrayed in television or film as typical or normal, then it is likely that young people will consider it acceptable for themselves (Gerbner *et al.*, 1980) (Box 6.10). Advertising strategies using drug names (e.g. Opium) to advertise non-drug products (in this case perfume) may

also alter the prevailing culture, normalising the concept of such substances and indirectly promoting their use.

In addition, there are thought to be more direct influences of advertising, leading children and youngsters to misuse both legal and illegal substances. A recent survey from the USA showed that teenagers aged 11 to 16 demonstrated a high degree of knowledge about prescription and over-the-counter medications, as well as illicit drugs (PDFA, 2005). Teenagers were familiar with brand names of a wide variety of medications and accurately described their effects - knowledge that the researchers concluded had been gained by exposure to advertising material. Furthermore, it was found that teenagers were more likely to have abused a prescription painkiller to get high, than to have experimented with illicit drugs such as ecstasy, cocaine, crack or LSD. The authors concluded that the knowledge of over-the-counter drugs (aided by advertising) had been instrumental in increasing the likelihood that these drugs would be used for experimentation, as new ways to get high.

6.4 Timing of substance misuse

6.4.1 Early onset of drug use and experimentation

There are suggestions in the epidemiological literature that an early entry into substance

use is a particularly significant factor, and that those who take this route are at especially high risk of persistent and escalating misuse. For example, Hingson *et al.* (2006) reported, from a survey of adults in North America, that the earlier the age at which people started to use alcohol, the greater the lifetime risks of alcohol dependence and the greater the severity and duration of dependence. There are similar findings from surveys by Pitkanen *et al.* (2005) and Fergusson *et al.* (1995). Evidence from several different forms of natural experiments (e.g. twin studies) suggests that the correlation found between early alcohol consumption and later dependence may reflect a shared genetic liability and not causation (Rutter, 2007). Early tobacco use has also been shown to predict dependence on nicotine (Hu *et al.*, 2006) and use of illegal drugs (e.g. Lynskey *et al.*, 2003). A birth cohort study showed that those children who had smoked or drunk alcohol by the age of 12 had a greatly increased likelihood of using cannabis by the age of 14 (Fergusson *et al.*, 2006). Children in the ALSPAC birth cohort who had smoked by the age of eight or drunk alcohol by the age of 10 had a nearly ten-fold rise in the likelihood of using cannabis by the age of 12 (Bowen, 2006). Furthermore, they had very high rates of other personal problems (e.g. a five-fold increase in being bullies) and a higher rate of family adversity.

There are several possible reasons to explain the risk of early exposure to substance use.

Box 6.9 Public engagement: the role of the media

For most public participants, attitudes towards cocaine were largely informed by media reports of celebrity use of the drug. They were very critical of what they saw as 'double standards', with celebrities making the papers, being castigated for a brief period and reappearing a short time later as if nothing had happened. They felt this was in sharp contrast to the treatment an 'ordinary person' was likely to receive. Participants accused the media of depicting celebrity drug users as glamorous and decadent, occupants of a glittering world far removed from the reality of cocaine addiction. Celebrities and the wealthy were also not thought to be subject to the same legal regime that applies to 'ordinary' users, especially those in difficult financial straits; after a brief fall from grace, the celebrity cocaine users are soon able to reclaim their position and continue with their lives.

For instance, those individuals who experiment with substances at a younger age are likely to have a more vulnerable style of behaviour, typified by risk-taking and rejection of rules or authority. There could also be a 'gateway' effect, where using one type of substance makes a child directly more vulnerable to misusing other substances. If this is the case, then restricting access to legal and illegal substances by young people should become a high social priority. Alternatively, it could be that early use and later heavy use arise from the same blend of risk factors. The evidence is not conclusive, but is strengthened by studies using genetic twin designs. These studies have shown that, after shared risk factors have been taken into account, early cannabis use still predicts the later use of 'harder' drugs. (Lynskey *et al.*, 2003; Agrawal *et al.*, 2004; Fergusson *et al.*, 2006; Lynskey *et al.*, 2006) (Recommendation 11).

Importantly, there are indications that individuals who experiment with drugs at an early age show high rates of other risk factors such as conduct problems and family adversity (e.g. Fergusson *et al.*, 2006). Early use therefore needs to be considered in conjunction

with early evidence of conduct problems.

Those children who are identified with conduct problems at an early stage - before the age of four years - are the most likely to persist, escalating to delinquency in later years and criminality in adult life (Moffitt *et al.*, 1996). There is evidence to suggest that early onset is more likely to be a proxy indicator of some important liability, rather than a cause of persistent antisocial behaviour in its own right (Rutter, in press) Both early substance use and early emergence of conduct problems are risks for substance misuse. These findings highlight the importance of taking preventive measures during the preschool years, rather than waiting until the problems emerge in childhood or adolescence (Box 6.11 and Recommendation 11). It is possible that misuse of psychoactive drugs at different stages of life may result from different risks. Initial experimentation with drugs is an essential 'first step' in a career of substance use. The probability of initial experimentation occurring, however, will be affected by availability of the drug as well as individual risk. Some young people, without having any predisposing characteristics or risk factors, may experiment because the drug is simply there. Most young people have drunk

Box 6.10 Drugs in popular film and music

A detailed examination of popular films and music from the years 1996 and 1997, conducted for the US Office of National Drug Control Policy, found that almost all the films studied depicted some form of illicit drugs, alcohol, tobacco or over-the-counter/prescription medicines (Roberts *et al.*, 1999). The most commonly featured substances were alcohol and tobacco, but illicit drugs appeared in 22% of the films studied, and one quarter of these appearances contained explicit and graphic portrayals of their preparation and/or ingestion. Few films specified motivations for drug use and only a minority portrayed consequences, either short or long term. Similar results were obtained in the analysis of popular music, although the type of song was relevant, with almost two thirds of rap music mentioning illicit drug use.

There is a need to test further the implicit assumption that exposure to ideas related to substance use, or portrayals of people misusing drugs, will increase the likelihood that youngsters will develop these behaviours. In one study it was found that teenage smoking was influenced by the extent to which it was seen more or less often in films, where the prevalence of ever trying smoking increased with higher exposure (Sargent *et al.*, 2001). Research of a similar kind needs to be undertaken with illicit substances.

alcohol at some time. By the age of 17 about 40% of the young people describing their use in an Edinburgh study, had tried cannabis and about 13% had used other illegal drugs (ACMD, 2006a).

6.4.2 Regular use

A further stage to consider is that of the progression from occasional to regular use. Such progression is likely to be influenced by the nature of the physiological reaction to the substance, but there is no evidence about whether knowledge of one's own response characteristics could moderate one's intake. Smoking cigarettes seems to have a particularly high continuity over time (i.e. for initiation to turn into regular use) and this sequence may well reflect the potency of smoking in giving rise to dependence (Nutt *et al.*, 2007).

Attitudes to substance use and the social context will also be influential on young people's decisions to make frequent use of

drugs. Certain transition points in development may be particularly important - moments when the risk can be increased or reduced depending on other factors. The time of leaving school and starting in work appears to be an important opportunity for prevention because this transition may be associated either with stopping smoking or taking it up. In one qualitative study, interviewees aged 16 to 19 described how moving from school to work, further education or unemployment, had an impact on their smoking (Wiltshire *et al.*, 2005). Smoking was perceived to be an important 'lubricant' for social relations, and a marker of an acceptable identity in familiar and new contexts which acted to reinforce and increase smoking. In contrast, smoking restrictions at home, work and/or educational settings were considered by some to moderate their consumption. These findings have interesting implications for prevention: the changes in older adolescents suggest that they might be a good target group; and smoke-free

Box 6.11 Pre-school interventions

Several targeted early intervention programmes, some starting during pregnancy (Olds *et al.*, 1986) and others initiated during the pre-school years (Ramey *et al.*, 1984; 1998; in press; Schweinhart *et al.*, 1993; 2005) have been shown in trials to reduce the risks of substance misuse in children.

In the Ypsilanti Perry Preschool study, disadvantaged children with very low IQ aged three to four were randomly assigned to a programme or a no-programme group (Schweinhart *et al.*, 1993; 2005). The programme group was provided with high quality early education for one to two years in addition to support for their parents through home visits. The no-programme group was not enrolled in any pre-school programme. Throughout school and into adult life, better outcomes have been recorded for the 'intervention' children, including higher scores on cognitive development tests, less grade-retention or special education, less school drop-out, more employment, fewer arrests (including arrests for drug-related offences) and less dependence on welfare.

The Abecedarian Project (Ramey *et al.*, 1984) was initiated during infancy and lasted throughout pre-school. Similar to the Ypsilanti programme, the project offered a mix of high quality group experiences for the children and one-to-one support for their parents. Most of the effects of this intervention are related to enhanced cognitive development and academic achievement, which would be protective against substance use.

Box 6.12 Public engagement: experimentation and prevention

Many participants in both on-line and face-to-face work thought that it would be impossible to prevent all young people from taking drugs. Rebellion and experimentation were seen as part of growing up; for some young people this would mean using drugs. The inevitability of drug use by some people, whether as young people or adults, was behind much of the support for a health based or harm reduction, rather than punitive, approach to drug use.

Many participants felt that the most effective way of discouraging the maximum number from using drugs was to address the social and environmental factors that might make a young person more vulnerable to drug use. Some participants in the on-line work characterised this in terms of support from parents and the wider community, providing positive role models, teaching personal responsibility, reducing inequality, tackling gangs and providing a creative and loving environment.

policies in their workplaces and leisure areas are likely to be an obstacle to the transition from social to regular smoking.

The later stages of transition into dependent and harmful use are harder to summarise. At this point, cumulative disadvantage from the effect of regular and heavy use will complicate the picture. This disadvantage and the associated risky lifestyle (e.g. using crime to obtain substances, experiencing health problems) may make some individuals more motivated to enter a stage of desistence, but for many it may be too late for preventive measures.

6.5 Protective factors

Risk factors alone may be insufficient to understand and limit drug-related behaviours. Protective factors - those aspects of a person's biology, psychology and environment that mitigate the impacts of risk factors - could be significant for the aetiology and prevention of substance use and misuse.

Most research into protective factors has addressed the development of psychopathology in general (Werner & Smith, 1982; Garmezy & Devine, 1984; Rutter, 2006), rather than substance use and abuse in particular. However, Brook *et al.* (1990) focused on protection against adolescent drug abuse and identified

two models to explain how protective factors operate. In the first 'risk/protective' model, protective factors such as strong parental attachment or high intelligence act to limit the impact of imposed risks, such as those from drug-using peers. In the second 'protective/protective' model, one protective factor, such as intelligence or having an adult to confide in, strengthens the effect of others.

Protective factors can be seen at an individual level, e.g. positive self-esteem, personal and social competence, independence and autonomy, commitment to societal norms, positive social bonding. Family characteristics can also be protective, e.g. family cohesion and intactness, emotional support for children, strong parent-child attachments, and clearly-defined family norms about substance use (McIntyre *et al.*, 1990). Few community level protective factors have been discussed in the literature and the effects of community support groups on the individual or the family, and moral development, are poorly understood at present. These factors may operate differently for males and females, and may depend on ethnicity or community context. However, it has been demonstrated that a high level of social support in the community is associated with lower levels of child abuse and neglect and less delinquency (Sampson *et al.*, 1997), both of which are associated with (risk factors for) substance abuse (Recommendation 13).

6.6 Discussion

Further research is needed to more accurately determine the relationship between drug misuse and different individual, family, and contextual variables. The ongoing ALSPAC study can examine early drug use and has many strengths (a large sample size compared with other birth cohorts, drug use measured from age 10, regular data collection and investigation of maternal behaviour during pregnancy) and could be used to establish important drug using phenotypes at 17, i.e. what proportion of adolescents are dependent at 17 and what are the predictors of dependence. However, the children involved in the study are now past the age when early drug use can be examined. The Millennium Cohort Study (MCS) is another large-scale longitudinal study that will provide valuable data about children, their family circumstances and the broader socio-economic context in which the children grow up. Begun in 2001, the MCS provides data about children living and growing up in each of the four countries of the UK. The sample design was intended to ensure a proper representation of the total population, while at the same time having sufficient numbers of key subgroups (such as those living in disadvantaged circumstances, and ethnic minorities) for analysis. It has gathered information from the parents of 18,818 babies (aged 9 months) born in the UK over a 12-month period. The MCS is a multi-purpose study and the children will already be 7 years old at the fourth round of the study, with data collection beginning in April 2008. It is important that other existing and new longitudinal studies specifically collect information about drug misuse and the associated risk factors, before drug misuse occurs (Recommendation 11).

Further research is also needed to:

- Clarify the routes of entry into substance misuse and its persistence.
- Test more rigorously the possibility that different risk factors are involved for different stages of drug use, misuse and dependence.
- Identify the early stages and risk factors that differentiate children who experiment with drugs from those who become heavy users.
- Disentangle the developmental mechanisms of psychopathology and substance misuse.
- Integrate genetic, behavioural, and family information to predict risks separately for conduct disorder and substance misuse or addiction.
- In diagnosed groups, particularly for ADHD, disentangle the relationship between being brought for treatment by parents, the drug treatment itself, and associated changes in relationships and school success.

The aims of prevention strategies are to remove or reduce risks, convey protection against risks that are already present, limit the availability of substances, encourage people to decide against misuse of substances, encourage them to quit, or apply methods to mitigate the harmful consequences of substance misuse. 'Universal' methods apply preventive techniques to whole communities or populations; 'targeted' methods focus on high-risk groups. Targeted methods, which are more appropriate if the intervention is costly, depend upon efficient definition of high-risk groups. For this reason, targeted prevention methods are not suitable for assisting the very many young people who do not show any of the risks described earlier in this chapter and yet misuse psychoactive substances. Both population-based and focussed interventions need to be used for prevention as appropriate.

Recent attention has been directed to the importance of the first years of life because of the high rate of brain development at that time (McCain & Mustard, 1999; Shonkoff & Phillips, 2000). Interventions offered early in life have, on the whole, the chance of making a greater difference to life course development in relation to their cost, than those offered in the teenage years or in

early adulthood (Heckman, 2006; 2007). Although Heckman concentrates for the most part on interventions designed to enhance cognitive ability, his argument is relevant to the likelihood that children and adolescents will begin using tobacco, alcohol or illicit substances. He has shown that investment in early interventions has the potential to provide much greater gains in terms of cognitive ability, reducing the likelihood of learning difficulties and special educational needs, than intervention in the adolescent years. Heckman studied the cost benefit ratio of intervention in the early years. He found that much of the cost saving to society is related to the reduced likelihood of incarceration, not to increased opportunities for entering higher education or employment. Delinquency and criminality are closely linked to the use of both legal and illicit substances. Their use is also linked with cognitive ability. For example Heckman and colleagues (Heckman *et al.*, 2006) found that the probability of smoking is almost twice as high for the lowest quintile of cognitive ability compared with the top quintile. Thus an important way to reduce drug abuse in the teenage years is to offer relatively low-cost interventions that will reduce the likelihood of several risk factors for later drug problems, including learning difficulties, school failure, peer problems, conduct problems and lack of employment once leaving school.

A number of targeted early intervention programmes, some starting during pregnancy (Olds *et al.*, 1986), and others initiated during the preschool years (Ramey *et al.*, 1998; Schweinhart *et al.*, 1993), have been shown in trials to reduce the risks described above. At a later stage of development, psychological interventions targeted at individual children become feasible. Approaches intended to sustain and promote healthy attitudes to drug misuse are likely to be more effective if they are focussed on individuals for whom such approaches are particularly relevant (Recommendations 12-16).

Recommendations

Epidemiological and clinical studies have demonstrated that a range of individual, family and social factors are associated with substance misuse. Although there is a need for a deeper understanding of these factors, action must be taken now to reduce the impact of the known risk factors and to use current knowledge to inform public health interventions.

We emphasise that all of the interventions described below should be evaluated according to best practise, using randomised controlled trials and long-term follow-up whenever possible. Such evaluation should assess the effectiveness of the interventions in reducing risk factors and substance misuse. Failure to evaluate in this way may waste human and financial resources and result in a failure to achieve objectives.

11. Longitudinal and cohort studies are needed to clarify the routes of entry into substance misuse and dependence, and to determine more accurately the relationship between drug use/misuse and a range of genetic, individual, family, social and environmental variables. It is recommended that:
 - Information collection begins at an early age, before drug use and misuse occurs.
 - Information about drug misuse is incorporated into appropriate existing longitudinal studies.
12. The Department of Health and NHS should emphasise the hazards to both mother and fetus of taking legal or illegal drugs before and during pregnancy and breast-feeding. Established support systems for pregnant women known or thought to be at risk of drug misuse should be expanded and systems developed to enhance the identification of substance use during pregnancy. Support given to women using legal and/or illegal drugs should be non-judgemental and provided by skilled professionals.

13. The Government, led by the Department for Children, Schools and Families (DCSF), should increase investment in evidence-based family support programmes targeted at children identified as at increased risk of substance misuse. Programmes should be introduced before substance misuse has developed and should involve a broad-based support package.
14. Children and young people with mental health problems are a high-risk group for developing substance misuse, partly because they share risk factors with 'healthy' children who may become substance misusers. Interventions should target common risk factors (e.g. in family life and school failure) as well as the relief of their mental health problems. It is recommended that:
- Health and social care services should work with schools to provide a comprehensive service for young people with mental health disorders, as well as for their families.
 - Interventions should include the early identification and treatment of children with conduct disorder and attention deficit hyperactivity disorder (ADHD), including measures to discourage harmful drug use.
 - Young people who are misusing drugs should be assessed for mental health problems so that they can be treated for these conditions in conjunction with treatments for substance misuse.
15. Trials of skills-based school education, delivered by peers and ex-users, should be extended in both primary and secondary schools. The outcomes of promising schemes, including 'Communities That Care' and the 'Blueprint' drugs education programme, should be evaluated by Government for their effectiveness in reducing risks of substance misuse.

Chapter 7 Medicines for mental health

Introduction

Approximately 450 million people worldwide suffer from a mental disorder such as unipolar or bipolar depression, schizophrenia or Alzheimer's disease, representing nearly 10% of the global adult population (WHO, 2001). In the UK, it is estimated that one in six people between the ages of 16 and 74 experience a mood or anxiety disorder, which in 2000 equated to approximately 7 million people (ONS, 2001). Importantly, all forms of mental illness are associated with increased rates of suicidal thoughts and attempts (ONS, 2002) and research indicates that 5-13% of patients with schizophrenia die from suicide (Pompili *et al.*, 2007). Studies of suicide deaths have shown that around one in four individuals had been in contact with mental health services in the year before death, and half had been in contact with mental health services in the preceding week (Appleby *et al.*, 1999).

The cost of all mental illness is estimated at £77 billion per year in England alone. Much of this sum reflects indirect costs to the economy through lost productivity, costs to the criminal justice system and to society more broadly (Sainsbury Centre for Mental Health, 2003).

However, over £600 million per year is directly spent on medication (Sainsbury Centre for Mental Health, 2006). As with all medicines, there has been a steady increase in the prescription of antidepressant and antipsychotic drugs in recent years (Department of Health, 2007). For instance, the number of prescription items for antidepressant drugs rose by 36% between 2000 and 2005, to approximately 29 million (*ibid*). Similarly, drugs used to treat psychoses and related disorders increased by 7% from 2002 to 2003 to reach 6.4 million prescription items (Department of Health, 2007).

In this chapter we explore the development and use of medicines for the treatment and prevention of mental illness in the context of recent and potential advances in cognitive neuroscience. It should be emphasised that, in considering medicines for mental health, we have focused on pharmacological therapies; psychological treatments such as Cognitive Behavioural Therapy (CBT) are briefly considered in Section 7.8.3, but a detailed consideration is beyond the scope of this discussion. We also emphasise the importance of developing new and effective treatments for the age-related cognitive dementias, such as Alzheimer's disease. These

Box 7.1 Public engagement: views on mental illness

The results of the public engagement activity emphasised that most participants felt that eliminating the stigma attached to mental health was fundamental to improving the lives of people with mental health problems and those who care for them. The wider understanding that might arise through a more open discussion of the impact of mental illness seemed to be lacking. Some participants explained that the mental illness itself was less debilitating than the wider social consequences of the disorder, including isolation, vulnerability to abuse and sometimes violence.

Participants also considered that the stigma attached to mental health problems and lack of obvious external manifestations contributed to the 'invisibility' of these problems. Participants felt that this stigma can leave people feeling ashamed of their condition or reticent to speak of their experiences.

diseases are becoming increasingly prevalent as life expectancy increases (Box 7.10), and were of major concern to many who participated in the public engagement programme. However, the general field of neurodegenerative diseases, of which Alzheimer's disease is one, is vast. To do this field full justice and in the light of the pressing need to develop new therapies, we recommend that neurodegenerative disease is the subject of a separate, dedicated review (Recommendation 17).

In this chapter we show how drugs can provide effective treatments for mental illness that can transform lives. However, we also describe the limitations of current drug treatments, characterised by partial efficacy, side effects, poor treatment adherence, sub-optimal diagnosis and sub-optimal drug dosing. Later sections of this chapter set out the compelling need to develop new and better medicines for mental health. We review research into the neuroscientific processes underlying mental illness and discuss how a better understanding of the pathology of functional disorders may give rise to new and more effective treatments.

Overall, it is clear that our understanding of brain processes and structure and how these impact on mental health has evolved in recent years. Neural systems mediating many of the key information processing activities have been known for some time, including the neural systems involved in the specific drives of sex, hunger and thirst, and the more general drives of fear and reward (pleasure). Brain imaging in humans is leading to a more subtle understanding of the interaction of perception, thinking, reasoning and emotion and thus to a more realistic understanding of the experience of mental illness. In short, modern psychiatry sees functional mental disorders as disturbances of information processing performed by increasingly well mapped inter-connected systems in the brain. It is in this context that we have explored issues around medicines for mental health. We start by briefly reviewing the most common mental disorders.

7.1 Common mood disorders: depression and anxiety

7.1.1 Diagnosis and prevalence

By far the most common mental illnesses in adults are depression and anxiety - frequently occurring together. In 2003 it was estimated that these disorders affected approximately 6.3 million people, or 15% of the UK population, and accounted for one-third of days lost from work because of ill health and one-fifth of all GP consultations (ONS, 2003). Depression also has a major influence on risks and outcomes of many medical disorders such as cardiovascular disease (Prince, 2007). Anxiety disorders include panic disorder, agoraphobia, generalised anxiety disorder and post-traumatic stress disorder (PTSD); co-occurrence of these disorders with depression is very common (NICE, 2004).

The symptoms of depression and anxiety are familiar to all of us - sadness, worry, loss of sleep and gloomy thinking. In patients who suffer from such illnesses, these symptoms are usually triggered by adversity, just as they are in individual members of the general population who are not ill. There is no clear dividing line between a normal response to adversity and clinical illness. The degree of suffering, the severity and persistence of the symptoms, and a disproportionate response to the adversity, are all important considerations in reaching a medical diagnosis and predicting the likely effectiveness of drug treatment. A key question in diagnosis is whether there is significant impairment of function: can the patient work, look after themselves, enjoy leisure, have a social life? The difficulties of diagnosing mental illnesses were raised by participants during the public engagement activities (Box 7.2).

Studies in the 1970s and 1980s identified four filters that determine the treatment received by the community population who have depression (Goldberg & Huxley, 1980). These filters are as follows:

1. Only 60% of community cases present to the GP.
2. About 60% of those presenting are recognised (diagnosed) by the GP.
3. The GP initiates medical or psychological treatment in about 33-50% of those recognised.
4. About 10-20% are referred to community psychiatric services (reviewed in NICE, 2004).

These filters vary widely in their stringency, depending on social and cultural factors, individual GPs' detection and referral rates, as well as the communication skills of both the doctor and patient. However, these data on potential under-diagnosis of depression must be viewed

in the context of increases in the total number of prescriptions for antidepressants and recent concerns that anti-depressants are being prescribed for mild cases of depression where they do not work (Section 7.1.2).

7.1.2 Current treatments

All antidepressant drugs work by increasing the synaptic actions of one or more of the monoamine neurotransmitters: 5-hydroxytryptamine (5-HT or serotonin), noradrenaline and, to a much lesser extent, dopamine (Box 7.3). Between 1993 and 2002 the total number of prescriptions for antidepressants rose from approximately 10 million to 26 million items per year, including a seven-fold increase in the use of the selective

Box 7.2 Public engagement: diagnosis of mental illness

The results of the public engagement activity indicated that some participants' knowledge of mental illness would not enable them to identify whether somebody was developing a mental health disorder. Participants' opinions were divided over the benefits and disadvantages of professional diagnosis. Some thought that a professional diagnosis made too early could lead to labelling or a kind of 'fatalism'. However, others argued that early diagnosis would enable preventative measures to be taken and would enable treatment to be targeted where the need was greatest.

Box 7.3 Anti-depressants: mode of action on monoamine neurotransmitters

Synaptic transmission involves the release of neurotransmitter from the presynaptic nerve terminal into the synaptic cleft. The neurotransmitter then acts on specific receptors in the membrane of the postsynaptic nerve cell. A re-uptake or transporter mechanism terminates the synaptic actions of monoamine neurotransmitters by taking most monoamine molecules back into the presynaptic nerve terminal. These molecules are then broken down by the enzyme monoamine oxidase (MAO). The most commonly prescribed antidepressant drugs work to inhibit the uptake and metabolism of monoamines, allowing monoamines to persist and accumulate in the synaptic cleft.

There is evidence that the most commonly used antidepressant drugs work through their ability to increase the neurotransmitter serotonin (5-HT) at the synapse. In a classic study, patients whose symptoms had recently resolved after treatment with SSRIs experienced a transient relapse of symptoms (lasting a few hours) after a simple dietary manoeuvre that depletes the circulation of tryptophan, the dietary precursor of 5-HT (Delgado *et al.*, 1999). The depletion of tryptophan causes a temporary impairment of brain 5-HT release and the clear inference is that antidepressants require intact 5-HT functioning to work.

serotonin reuptake inhibitors (SSRI) class of drug (Health Statistics Quarterly, 2004).

There is evidence from a substantial number of studies that 5-HT neurotransmission is impaired in episodes of depression (Deakin *et al.*, 1990; Cowen, 1994; Sargent *et al.*, 2000). Despite these findings, the nature of the impairment, or whether it is located within 5-HT neurons or 5-HT receptors, is not yet clear. It is essential to resolve these uncertainties about the pathogenesis of depression to develop treatments that are more effective.

In moderate and severe depression, four to six weeks of treatment with SSRIs has been shown to double the chance of recovery (from 25 to 30% on placebo to 50 to 65% on drug) (Anderson *et al.*, 2000). Importantly, the response to placebo in published trials of antidepressant drugs is variable, but often substantial (Walsh *et al.*, 2002). A recent meta-analysis of data submitted to the USA Food and Drugs Administration (FDA) relating to four SSRIs – Fluoxetine, Venlafaxine, Nefazodone and Paroxetine – showed that the main problem in interpreting findings from trials of these drugs is the very high placebo response rate in anything other than the more severe varieties of depression (Kirsch *et al.*, 2008). A key concern raised in this report is the proportion of studies by drug companies in which there were negative findings that were not published (for a general discussion of this issue see Avorn, 2006; for a discussion of publication bias see the Academy of Medical Sciences 2007 report 'Identifying the environmental causes of disease: how do we know what to believe and when to take action?').

As discussed above, most antidepressant drugs act to increase 5-HT function, and a few act through noradrenaline systems. However, no new mode of drug action to treat depression has been discovered for decades. A significant improvement can be induced in about 20% of patients

who are resistant to treatment by using antidepressants with mixed actions, combinations of different antidepressants, or the addition of other agents such as lithium (Austin *et al.*, 1991; Thase *et al.*, 1997; Lin *et al.*, 2006; reviewed in Anderson *et al.*, 2000). Recovery can sometimes be achieved by switching or combining drugs, but there is very little controlled trial evidence to guide treatment options.

A substantial proportion of prescriptions for antidepressant drugs are never collected and patients often stop a course of drugs before they have had a chance to work. The problem was much worse with older antidepressants, the tricyclic antidepressants (TCAs), probably because of their greater burden of side-effects than the newer SSRIs, rather than to any difference in efficacy. Common side effects of TCAs include dry mouth, blurred vision and constipation. Patients are much more likely to persist with the newer SSRI antidepressants, which have far fewer side effects (NICE, 2004) and have been associated with fewer drug-related deaths (Health Statistics Quarterly, 2004). In addition, the lower burden of side effects associated with SSRIs means that the starting dose for treatment is usually the recommended effective dose. Treatment at sub-therapeutic doses of SSRIs is much less of a problem than for older antidepressant drugs, which frequently never reached therapeutic levels.

The most effective long-term treatments for anxiety disorders are antidepressants. Short-term relief (NICE recommend no more than 2 weeks) from anxiety disorders can be provided by benzodiazepines and related drugs that enhance the effect of the neurotransmitter GABA at GABA-A receptors. Each benzodiazepine possesses, to greater or lesser extent, five important pharmacological effects: anxiolytic, sleep-inducing, muscle-relaxant, anticonvulsant and memory impairing effects. Their use is limited by tolerance, dependence and withdrawal reactions (Baldwin *et al.*, 2005).

Concerns about the side-effects of medicines for mental illness were raised by participants throughout the public engagement activities (Box 7.4).

7.2 Bipolar (manic-depressive) disorder

7.2.1 Diagnosis and prevalence

Bipolar disorder is a more severe form of mood disorder in which periods of elation, hyperactivity, rapid speech and diminished sleep occur in addition to periods of depression. Between 1% and 2% of the general UK population will develop bipolar disorder at some point in their lives, at an estimated annual societal cost of £2 billion (NICE, 2006). Onset most frequently occurs in late adolescence or early adulthood, with approximately equal numbers of males and females affected. In some cases, depressive and manic symptoms can reach psychotic intensity where there is loss of contact with reality. Between episodes, patients may be entirely normal. However, mild symptoms of depression can be very persistent and many patients with bipolar disorder suffer chronic depression.

7.2.2 Current treatments

Symptoms of bipolar disorder (and other mental disorders) can be treated with mood stabilising drugs, which are generally divided into two classes:

1. Lithium is effective in treating mania and reducing the risk of relapse into mania or depression. It is a well-known and effective treatment for bipolar and unipolar disorders: a meta-analysis of 22

studies of bipolar and unipolar patients demonstrated that suicide was 82% less frequent in patients taking lithium (Tondo & Baldessarini, 2000). At the cellular level, the lithium ion has several actions, including competition with sodium ions for the sodium pump, increased synthesis and release of serotonin and increased uptake of catecholamines into nerve terminals. However, the mechanisms by which these actions mediate the drug's properties are poorly understood.

2. The anticonvulsant mood stabilisers, sodium valproate, carbamazepine and lamotrigine, are effective in treating mania and preventing further episodes in bipolar disorder. They exert their effects by increasing GABA neurotransmission in the brain, although this mechanism is also poorly understood. Lamotrigine is thought to work by decreasing glutamate release as an indirect effect of its primary action in blocking one of the many varieties of sodium channel.

Tolerability and adherence with these drug treatments are generally poor. In one study, only one-third of patients starting lithium continued it for five years. This is unfortunate because 43% of patients had no recurrence and 88% halved the time they spent in hospital while they were taking the drug (Maj *et al.*, 1998). Low adherence compounds the debilitation associated with bipolar disorder because each episode that occurs increases the likelihood of another. For instance, after a first episode of bipolar disorder the average interval until recurrence is four years, but after a fourth episode it is 18 months (Kessing *et al.*, 1998).

Box 7.4 Public engagement: side effects of drug treatments

The side effects of drug treatments for mental disorder were often seen to be as debilitating as the disorder itself. Everyday activities were said to become much more difficult and some described side effects as extreme. Many expressed the view that greater acknowledgement of the severity of adverse effects by consultant psychiatrists would be welcomed. Concern was also expressed about possible long-term impacts on health.

7.3 Schizophrenia

7.3.1 Diagnosis and prevalence

A National Statistics Survey conducted in 2000 indicated that 1 in 200 adults in the UK population had a psychotic disorder such as psychosis or schizophrenia (ONS, 2001). The overt psychosis associated with schizophrenia typically presents in early adulthood or adolescence, although there is evidence that the precursors can begin in childhood (Rutter, 2006). The age of onset of the condition is younger in men than in women and prevalence is higher in migrants and people living in cities (Picchioni & Murray, 2007). Symptoms are associated with severe impairments of social and occupational functioning. There has also consistently shown to be an increased risk for people with psychotic disorders to be violent (for review see Walsh *et al.*, 2002). Patients commonly follow a deteriorating course with progressive development of marked self-neglect, apathy and social withdrawal (Lieberman *et al.*, 2001). Very few patients with schizophrenia are employed. Research examining the possible relationship between schizophrenia and cannabis use is summarised in Box 5.9.

Schizophrenia involves persistent symptoms such as delusions, hallucinations and disorganised speech that are divorced from reality and seemingly outside normal experience. However, surveys reveal surprisingly high rates of symptoms such as delusional thinking and brief hallucination-like experiences in the general population (van Os *et al.*, 2000). Furthermore, such 'schizotypal' symptoms are more common among the relatives of patients with schizophrenia. Severe psychotic symptoms can have a sudden, even overnight, onset with minimal pre-existing symptoms and with no return to normal functioning. Taken together, these factors suggest a continuum of vulnerability to psychotic breakdown, manifest as mild, schizotypal symptoms and social withdrawal,

but with a second process required to trigger major psychotic illness.

There is increasing evidence that schizophrenia is associated with subtle, continuing loss of grey matter in the cerebral cortex (Section 7.7.4); understanding the neurobiology of this process could open the way to developing treatments to halt the progress of the disorder or to abate its onset (Recommendation 18).

7.3.2 Current treatments

Antipsychotic drugs can improve or abolish symptoms of psychosis, hallucinations, delusions and thought disorder in schizophrenia (and bipolar disorder). Recent estimates indicate that over 6 million prescriptions for antipsychotic drugs are made annually (Department of Health, 2007). Indeed, between 2002 and 2003 alone, the number of prescription items for all antipsychotic drugs rose from 6 million to 6.4 million, despite a 19% increase in net ingredient cost. Most of the newer, or atypical, antipsychotics accounted for 58% of all antipsychotic prescription items in 2003.

All current antipsychotic drugs act on the dopamine system. Dopamine nerve terminals and receptors are most concentrated in collections of nerve cells concerned with sensory-motor integration (basal ganglia) and homologous areas concerned with emotion and reward processing (nucleus accumbens). The cortex has a sparse distribution of dopamine synapses except for the medial prefrontal and temporal areas, which are concerned with emotion, social perception and action. Imaging studies using PET show that psychosis is associated with increased dopamine at the synapse (Howes *et al.*, 2007). Antipsychotic drugs therefore appear to reverse a disease-related abnormality of dopamine function by reducing signalling the dopamine D2 receptor. However, blocking the D2 receptor causes a range of serious side-effects, and the older, or 'typical', antipsychotics are frequently associated with Parkinsonian-like stiffness,

abnormal movements (dyskinesia), loss of motivation and pleasure. Newer 'atypical' antipsychotic drugs have reduced side effects of dyskinesia and Parkinsonian rigidity and have been shown to significantly improve patient safety (NICE, 2003). However, the newer drugs have their own characteristic side effects, including obesity, diabetes and increased blood lipid levels.

Antipsychotic drugs have also been shown to have a preventative effect on future episodes. In a MRC-funded study, individuals continuing treatment with antipsychotic drugs had a less than 10% risk of relapse, compared to 65% of individuals who were switched to placebo (Hirsch *et al.*, 1973). This result is typical of many studies (NICE, 2003). Despite these developments, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial reported that, although both older and newer antipsychotic drug treatments are generally effective, many patients change their prescription within 18 months. This probably reflects a combination of partial efficacy and poor tolerability (Lieberman, 2005). Poor adherence to treatment is therefore a major contributory factor to the continuing high rates of relapse and readmission in patients with schizophrenia.

Almost half of schizophrenia patients helped by standard doses of medication nevertheless continue to experience symptoms, which leads to higher doses being prescribed. Individuals with schizophrenia have reportedly been treated with antipsychotic drugs at doses greater than those recommended by the British National Formulary (BNF). For example, a survey of 3,132 patients in the UK demonstrated that 20% were receiving higher than BNF recommended doses, mostly due to prescribing of a combination of two or more types of drug (Harrington *et al.*, 2002a).

The term polypharmacy describes the use of several drugs in combination. Such combinations are often used if one drug is

found to be insufficiently effective (Harrington *et al.*, 2002a; Royal College of Psychiatrists, 2006). Antipsychotics are sometimes prescribed in combination with other medications that have behavioural effects such as mood stabilizers, antidepressants and benzodiazepines. However, polypharmacy can increase the risk of dangerous pharmacokinetic interactions (Stahl & Grady, 2004; Ananth *et al.*, 2004).

As with antidepressants, no new mechanism of treatment for psychosis has emerged in recent years, although there is some promise. Visible on the horizon are drugs that exploit the diversity of glutamate receptor subtypes (Section 7.8.2). The first trial was recently published of a glutamate drug that appeared to have antipsychotic effects, but had no direct action on dopamine receptors (Patil *et al.*, 2007). However, significant challenges to developing new drugs for schizophrenia and other mental disorders remain (Section 7.8.1).

7.4 Personality disorders

7.4.1 Diagnosis and prevalence

The definition of personality disorders is the subject of ongoing debate. In general, personality disorders can be described as persistent traits of personality that are sufficiently severe to impair normal functioning. On the basis of symptoms, the American DSM IV diagnostic system (4th edition) classifies personality disorders into clusters A, B and C: cluster A is characterised by 'odd or eccentric behaviour' and includes the schizotypal traits mentioned in Section 7.3.1; cluster B is characterised by 'dramatic or erratic behaviour' including antisocial behaviour; and cluster C is characterised by 'anxious or inhibited behaviour'. The UK Psychiatric Morbidity Survey found an overall rate for personality disorder of 54 in 1000 for men and 34 in 1000 for women. This compares to mood and anxiety disorders (almost entirely depression and anxiety) of 135 in 1000 for men and 194 in 1000 for women (ONS, 2001).

Whether stable personality traits should be regarded as illnesses has often been questioned. However, an increased understanding of the causes of these disorders is now emerging, involving both early life adversity and hereditary factors (Section 7.7.2). Recent findings indicate that common variants of some genes have an important influence on whether a child will develop antisocial traits in the context of childhood abuse (Caspi & Moffitt, 2006). Similarly, brain imaging studies suggest that circuits concerned with decision-making, behavioural restraint and empathy show abnormalities in personality disorder (Deeley *et al.*, 2006; Völlm *et al.*, 2007). In any case, discussions around categorising personality disorders should not obscure the fact that they can be a source of great suffering, inflicting significant individual and social harms.

7.4.2 Current treatments

Patients suffering from personality disorders tend to be treated symptomatically. For example, borderline personality disorder, which is characterised by rapid changes in mood and transient but recurrent psychotic-like symptoms, can be treated with mood-stabilisers and antidepressants for changes in mood, and with antipsychotic drugs for psychotic symptoms. However, there are very few placebo-controlled clinical trials to guide treatment for this disorder. There are also no current pharmacological treatments for antisocial personality disorder, where impairment in controlling impulses is a major deficit (Herpetz *et al.*, 2007).

In some cases, pharmaceutical drugs may be used to treat clinical conditions not originally foreseen ('off-label' use) (McQuay *et al.*, 1996; Glick *et al.*, 2001; Rowe, 2007). For instance, the antipsychotic drug quetiapine, which is used to treat schizophrenia, is also used to treat other disorders including mood and anxiety disorders, OCD, aggression, hostility, PTSD, borderline personality disorder, delirium and co-morbid substance abuse.

7.5 Mental illness in childhood and adolescence

Studies have indicated that common psychiatric illnesses often have their origins in childhood and adolescence. For example, a cohort study reported by Kim-Cohen *et al.* (2006) followed a population sample from birth until their late 20s, taking assessments at several points over that time to determine rates of mental disorders. A large majority of those who met criteria for mental disorder in adult life were already found by researchers to have symptoms at the age of 15 or earlier. Table 7.1 outlines the most common diagnoses made in childhood.

Few psychiatric drugs are licensed for use in children, with the exception of drugs intended for the treatment of states of inattentiveness and impulsiveness, especially ADHD. Nevertheless, they are frequently used. Adult disorders such as OCD, schizophrenia and major depressive disorder will often require similar medication when they arise in childhood.

Table 7.1 Common mental disorders in childhood and adolescence

<p>Conduct disorder and oppositional-defiant disorder</p>	<ul style="list-style-type: none"> • 'Conduct' problems are characterised as violations of basic rights of others, e.g. repetitive stealing, initiating fights with a weapon and starting fires; 6% of children and young people have a conduct disorder (ONS, 2004). • 'Oppositional' behaviours include aggression to other children and wilful disobedience of legitimate adult authority, often in combination with angry outbursts and irritable mood.
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Attention deficit hyperactivity disorder (ADHD)	<ul style="list-style-type: none"> • Approximately 5% of children meet the broader criteria for ADHD, with 1% of children diagnosed with the more severe hyperkinetic disorder (Harpin, 2008). • Characterised by high and impairing levels of restless over-activity, inattentiveness and impulsive behaviour. These traits show a continuum in the population, and the level required for diagnosis is that which gives rise to impairment (Box 7.5).
Emotional disorders	<ul style="list-style-type: none"> • Comprising disorders similar to those occurring in adults – anxiety, depression, obsessive compulsive disorder – and disorders representing an exaggerated version of ‘normal’ childhood worries, such as separation anxiety and fear of strangers. • Depression can often take a different form in children to adults, being linked to adversity in the environment (such as severe family problems), and tending to be more long term. • Approximately 4% of children and young people (5-16 years) have been found to have anxiety or depression (ONS, 2004).
Attachment disorders	<ul style="list-style-type: none"> • Attachment disorders can result from chronic disruption of the early care-giving relationships from which children derive security.
Autism and autism spectrum disorders	<ul style="list-style-type: none"> • These are chronic neuro-developmental problems characterised by disabling difficulties in social communication, empathy, imagination, and sometimes language; affected children tend to be unsociable or socially idiosyncratic, and to be repetitive in behaviour and resistant to change.
Post-traumatic stress disorders (PTSDs)	<ul style="list-style-type: none"> • PTSDs include mental conditions that can result from a great stress (such as involvement in a major accident) and can affect approximately 30% of children following a traumatic incident (Stallard <i>et al.</i>, 1998; Perry & Azid, 1999; Kar <i>et al.</i>, 2007).

TCAs are ineffective in the treatment of childhood depression and SSRIs are more limited in value in children than in adults, possibly because the neurochemical basis of depression is different in immature brains. There has been concern in recent years about suggestions that treatment with SSRIs is more likely (than placebo) to be associated with suicidal thinking and attempts (e.g. Gunnell *et al.*, 2005). A full review by the Committee on Safety of Medicines suggested that only fluoxetine had a favourable balance of benefit over risk for depression in young people; other SSRIs should be given only cautiously and

on specialist advice (MHRA, 2003). Childhood depression is often more responsive to the non-specific treatments of therapeutic alliance (i.e. the development of a collaborative relationships between the patient and practitioner) and environmental manipulation (Harrington, 2002b). Ultimately, too little is still known about how drug pharmacokinetics differ in children and adults. There is also a lack of long-term safety information on paediatric medicines for mental health. This represents a pressing health concern for which research is urgently needed (Recommendation 22).

7.6 Benefits and limitations of current drugs

The previous sections paint a rather bleak picture of current medical treatments for mental ill health. However, it should be emphasised that drugs, when effective, can transform lives. Historically, until the advent of electro-convulsive therapy (ECT) and effective antidepressants, a significant proportion of long-stay mentally ill patients had chronic depression lasting years. Now it is rare that patients with depression are admitted to hospital; prompt and effective medical and psychological treatment, together with service reorganisation, have made care in the community possible. Much the same applies to the drastic decline since the 1950s in long-stay patients with schizophrenia.

The effectiveness of drugs in psychiatry compares favourably with drugs commonly used in other branches of medicine. Efficacy

is often quoted as 'number needed to treat' (NNT), which is defined as: the number of patients who would need to be treated with the drug to gain one more recovery than would occur with same number treated with placebo. For antidepressants, NNTs of 4 are typical (Anderson *et al.*, 2000) and trial data for antipsychotic drugs typically give NNT values of 2-5 (Citrome & Stroup, 2006). Although some medical treatments can give NNTs of up to 35, NNTs of 4 are comparable to many other treatments, e.g. short-term pain relief using anti-inflammatory drugs in the treatment of arthritis (Osiri *et al.*, 2003).

Although drugs can be effective, the preceding sections have shown that current medicines for mental health share similar limitations, summarised in Table 7.2. The views expressed in the public engagement activities on the topic of drug treatments for mental illness are summarised in Box 7.6.

Box 7.5 Treating ADHD with stimulants

The use of central nervous system stimulants (such as methylphenidate or 'Ritalin') for the treatment of ADHD has raised some public concerns. These drugs do have abuse potential, which raises the question of whether their prescription for therapeutic purposes should be more strictly regulated. As discussed in Section 6.1.4.2, studies show that the risk for substance misuse arises from the disorder of ADHD, not from the medication, and that young people do not abuse the prescribed medication. The use of stimulants in 'healthy' people as a form of cognition enhancement is discussed in Section 8.1.3.

The specificity of effects with these drugs is unclear, and to a certain extent the effects might be seen in anybody, not just people with ADHD. For example, a small study of ordinary children suggested a similar qualitative effect in enhancing focussed attention (Rapoport *et al.*, 2002). The effects are, however, greater in size in people with diagnosed attention problems (Taylor *et al.*, 1987). Ultimately, the decision to prescribe stimulants for children should be made carefully and at specialist level.

Overall, the benefits of stimulants to treat ADHD have been shown by many randomised controlled trials and their use is supported by a NICE health technology assessment. Nevertheless, more research is needed into potential long-term effects (both adverse and beneficial).

Box 7.6 Public engagement: drug treatment for mental illness

Participants with severe mental health problems recognised the value of drugs in stabilising their condition. Patients reported marked changes in behaviour if medication was terminated suddenly and, over the long term, they felt that improvements had been made in the drugs available, mostly through the reduction of side effects. However, there was clear support for research into further improvements.

Participants felt that drugs were often prescribed too easily and for too long. Many also saw the use of drugs as a means of controlling people whose behaviour we do not understand or find difficult to deal with. Some questioned whether drugs are used simply because they are the cheapest option, rather than the most effective. Yet participants also acknowledged that, for many people, a drug that enables them to continue with regular responsibilities is the only viable option.

Participants saw benefits in taking a more informed approach that places the needs of patients at the centre. For instance, time should be invested in diagnosis and prescribing of treatment whereby both doctor and patient are involved in the decision over the type and dose of drug to be used. It was emphasised that alternatives should be available for people terminating medication or for those with less serious conditions, and that GPs could be more informed about mental health problems and the range of support services available in their area.

Table 7.2 Summary of limitations of current drugs

Partial efficacy	Many existing drugs are characterised by only partial efficacy: not everybody responds, residual symptoms are frequent and full benefit takes several weeks to emerge. Crucially, more efficacious drugs are unlikely to be developed until there is a better understanding of the molecular and cognitive mechanisms of disease. Furthermore, very little is known about why some patients respond and others do not. In principle, it should be possible to identify neurobiological and genetic differences between responders and non-responders. However, the necessary studies require information on substantial numbers of treated patients, which will depend on national and international coordination and regulatory frameworks that support the use of personal health data in research.
Side effects and poor treatment adherence	Many psychiatric drugs are poorly tolerated because of side effects, which commonly include weight gain, sexual dysfunction, sedation and nausea. This reduces adherence to treatment and so increases the likelihood of relapse and recurrence. In addition, most people do not want to take psychiatric drugs and their adherence to prescribed treatment is poor. This is due to a complex combination of factors, which may include negative attitude, lack of insight, experience of side effects and lack of rapid improvement.
Sub-optimal diagnosis and drug dosing	Many patients receive inappropriate doses of drugs for an insufficient period. Not only are sub-optimal treatments regimes less cost effective (Andrews <i>et al.</i> , 2004), but incorrect dosing can prevent recovery and can be mistakenly construed as inefficacy or resistance to treatment. These erroneous conclusions might result in unnecessarily changing the treatment, or administering another drug (polypharmacy), and so may be disruptive (or possibly hazardous in the latter case) to the patient.

7.7 Brain sciences and mental health

Drug treatment plays a critical role in reducing the burden of mental ill health but, as the previous sections have shown, there remains a considerable burden of unmet need regarding effectiveness, tolerability and prevention. The promise of the brain sciences is the development of radically new treatments that can induce full remission of symptoms, exert a minimal cost in side effects, prevent relapse and stop deterioration. Ultimately, the goal is to find new treatments that prevent disorders from occurring all together - an objective aspired to by participants in the engagement programme (Box 7.7). These new treatments may need to work in entirely different ways from current therapies.

As highlighted in the Foresight report, these aims can be achieved, but understanding the neuroscientific basis of mental disorders will be key to advances being made. In the following sections we review progress in understanding the nature of vulnerability to mental illness and the transition from vulnerability to disease progression.

7.7.1 Genes and mental illness

It has been known for centuries that psychiatric disorders tend to run in families. In recent years, the role of genetic susceptibility in the development of mental illness has become increasingly well understood. For instance, recent findings indicate that common variants of some genes have an important influence on whether or not a child will develop antisocial

traits in the context of childhood abuse. Genetic influences are also known to operate in autism, ADHD and conduct disorder (Rutter, 2006).

The role of genes in mental disorder can be investigated using linkage studies. These studies investigate patterns of inheritance of DNA markers within families, in order to identify regions of the genome associated with transmission of the disorder (Box 4.4). However, these regions contain hundreds of genes and it appears that no chromosomal region is strongly associated with common psychiatric disorders; while some chromosomal regions have been implicated by more than one study, none has been found that are common to all studies (Züchner *et al.*, 2007). Overall, twin and, for some disorders, adoption studies provide compelling evidence that mental disorders are familial, largely as a result of inherited genes. The size of the effect is considerable: the heritability of disorders such as schizophrenia or autism is in the region of 70-80% (O'Donovan *et al.*, 2003; Freitag, 2007). However, the effects of individual genes are small; as with many medical disorders, the genetic component of common psychiatric illness is due to the action of multiple genes each contributing a small amount of risk (Harrison & Owen, 2003). Compared with linkage studies, genetic association studies can detect genes of much smaller effect. Until recently, association studies have been limited to functional candidate genes; however, in recent years positional candidates within linkage regions have been identified. Genome-wide association (GWA) studies are now well underway and there is considerable

Box 7.7 Public engagement: prevention of mental illness

Participants emphasised the importance of developing a better understanding of the physical and social causes of mental illness and the factors involved. In particular, there was a call for more research into the early stages of depression and how it could be prevented, as well as why particular population groups are more prone to mental illness.

excitement about their potential (see Section 6.1.2 for a discussion of the genetic influences on addiction, including potential findings from GWA studies).

Candidate genes that might plausibly relate to mental illness are present in chromosomal regions linked with psychosis and some variants (alleles) of these genes appear to be associated with an increased risk of schizophrenia and bipolar disorder (Harrison & Owen, 2003). One of the strongest findings implicates a gene called DISC1. Detailed studies of an extended Scottish family have shown that most family members who have psychiatric illness also have a chromosomal re-arrangement in which DISC1 is one of the genes disrupted (Millar *et al.*, 2000). An important aspect of the discovery is that the same genetic variation in DISC1 is associated not only with schizophrenia, but also with bipolar disorder and major depression. This finding and others suggest that genetic influences do not always respect current syndrome-based diagnoses in psychiatry; some genes have general effects in increasing the risk of psychiatric illness, while others determine the form of the illness. There are claims that findings from molecular genetics will have a profound impact on the way the major psychiatric disorders are classified, measured and diagnosed (Craddock *et al.* 2000). While there is considerable optimism that the genetic basis of common mental illnesses is beginning to give way to modern genetics, the lack of consistent findings and frequent discoveries of new ways in which genetic variation can occur argues against premature optimism (see for example Insel & Lehner, 2007).

7.7.2 Gene-environment interactions

There is a growing body of research into how environmental factors interact with genes to influence the risk of mental disorder. Important examples have already received prominent attention in the scientific literature, including:

- The influence of variants (alleles) of the gene encoding the serotonin transporter (5-HTT) in increasing the risk of depression

after adverse life-events. The inheritance of a risk allele from both parents substantially increases the risk of depression after adversity, whereas other alleles are associated with resilience (Caspi, 2003).

- The association of severe abuse early in life with the development of antisocial behaviour in adulthood is mediated by a variant of the gene for the monoamine oxidase (MAO) enzyme. Children who do not possess this allele are resistant to the development of antisocial traits following childhood abuse. Importantly, MAO alleles do not affect the risk of antisocial behaviour in those who are not exposed to childhood abuse (Kim-Cohen *et al.*, 2006).
- The association between smoking cannabis from an early age and the increased risk of later schizophrenia in those who possess risk alleles of the catechol-O-methyl transferase (COMT) gene (Arsenault, 2002; also Box 5.9).

There are three important aspects to these findings. The first is that the genetic variants described above are common, i.e. they are possessed by up to 50% of the population. Their independent contribution to mental illness is therefore very small (otherwise 50% of the population would have the disorder). Their influence becomes important when environmental risk factors are present and, in all probability, when other risk genes are also present (Recommendation 18).

The second point is that several of the dozen or so candidate genes so far implicated encode proteins concerned with the monoamine class of neurotransmitters (serotonin, dopamine and noradrenaline), which have long been known to be the primary site of action of most drugs used in psychiatry. Other gene products are implicated in components of glutamate synapses, the main neurotransmitter system in the grey matter of the cerebral cortex, also suspected of involvement in psychiatric illness. Thus the genetic findings tend to reinforce the hypothesis that monoamines and glutamate are

involved in the causation of common psychiatric disorder (Harrison & Weinberger, 2005).

The third point is that most of the candidate risk genes probably produce vulnerability to illness by altering the development and wiring of the brain, rather than through changes in the gene's products in an otherwise normal brain. This is not surprising because genes may switch on at any time after conception to affect the developing brain. For example, genetically modified animals lacking the gene for the 5-HT1a receptor show anxiety-like behaviour in adulthood (Gross & Hen, 2004). However, in animals where the 5-HT1a receptor gene is inactivated only in adulthood, there is no effect on behaviour despite the total absence of functioning 5-HT1a receptors (*ibid.*) This finding has important implications for drug development: once mis-wiring of the brain has occurred owing to the molecular effects of a risk gene, it is may be too late to be undone. It is also conceivable that a brief period of drug treatment at the critical phase of development could prevent the adverse effects of a risk gene on brain development and thus prevent vulnerability to later environmental risk.

We are beginning to understand how genetic variation influences susceptibility to environmental adversity. However, in a striking revision of the idea that genetic effects are fixed and invariant, it is becoming increasingly understood that environmental factors can cause long-term changes in how actively genes are transcribed. These 'epigenetic' effects involve chemical modification of DNA and of the chromatin scaffolding around which DNA

is wound (Bird, 2007). For example, animal studies have shown that early-life experience of 'good' parenting is associated with reduced hormone responses to stress in adulthood (Diorio & Meaney, 2007; Kaffman & Meaney, 2007). The epigenetic effect is thought to occur through early tactile stimulation by the mother that releases 5-HT in the infant hippocampus. 5-HT activates chemical signalling pathways inside hippocampal neurons that permanently enable gene expression for proteins that in turn regulate stress hormone responses in adulthood (Szyf *et al.*, 2008). An obvious translational target for human studies is to identify whether epigenetic effects have a role in the adverse effects of early parental neglect on later risk of psychiatric disorders.

There are several difficulties in improving our understanding of epigenetic effects in humans. One is that epigenetic effects are likely to occur in neurons within specific brain systems, which can only be studied in the post-mortem brain, guided by findings from experimental studies in animals. Similarly, any therapies to reverse epigenetic changes will need ingenious ways of targeting the relevant neurons in the brain. In this regard, some research groups are checking whether more general effects can be detected in DNA from circulating white blood cells, which could lead to systemic (e.g. oral) treatments. Understanding epigenetic mechanisms creates the remarkable possibility of developing drugs that interact with the regulation of gene expression to undo some of the lifelong effects of early adversity (Recommendation 18).

Box 7.8 Public engagement: causes of mental health problems

Most participants considered that modern life was a primary factor associated with increasing incidence of mental illness. Factors thought to play a role included: the pace of life, increased pressure to achieve in education and work, changes in family and community structures and the lack of time people have to look after themselves and people close to them. Inheritance of disorders and the role of recreational drugs were also considered to be causes of mental health problems. Participants considered work into the social causes of mental illness to be a priority for future research programmes.

7.7.3 Neuroscience and the nature of vulnerability

A combination of brain imaging, cognitive neuroscience and genetics increasingly suggests that gene-environment interactions produce variations in the development of neural systems that process social and emotional information (Rutter & Sillberg, 2002; Caspi & Moffit, 2006). This variation accounts for some of the information processing biases seen in mentally ill patients, in those who are vulnerable to mental illness through past illness or familial risk, or in entirely healthy people who simply possess a risk version of a gene allele. Cognitive biases may also underpin stable personality traits such as neuroticism or schizotypy that are associated with liability to illness.

Studies of face-emotion processing in relation to vulnerability to depression provide good examples of biases in information processing in mentally ill patients (Bhagwagar *et al.*, 2004) (Box 7.9). Further studies have also investigated biases in recall of unhappy experiences (negative memory recall), feelings of low self-esteem and reduced sensitivity to

rewards (Chiu & Deldin, 2007; Ramel *et al.*, 2007; Pizzagalli *et al.*, 2008). These biases in information processing provide biomarkers for disease because they are expressions of underlying disease processes. There is much interest in the use of vulnerability biomarkers to detect the likely effectiveness of new approaches for drug treatment (Section 7.8.4).

The advent of non-invasive techniques, especially functional and structural MRI and high-resolution electro-encephalography (EEG) recording, has greatly enhanced our knowledge of the basis of mental disorders in childhood. For example, structural changes in frontal and striatal brain regions of children with ADHD have been linked to their low ability to suppress inappropriate impulses (Taylor, 1999). Ultimately, there is the prospect of relating changes in brain processes to genetic and environmental influences, as well as to the behavioural presentations of disorder. Such knowledge could result in a level of biological understanding that allows more rational development of new classes of drug and more tailored use of existing drugs to the individual patient (Recommendation 20).

Box 7.9 Vulnerability to depression

Humans can almost instantaneously identify emotions in faces. This ability can be quantified using computer-generated images portraying varying degrees of emotional expression. Patients who have recovered from depression are better able (biased) to detect fear in faces (Fales *et al.*, 2008). Brain imaging studies show that simply viewing fearful faces evokes no subjective emotion, but automatically activates the amygdala, an almond-shaped structure in the temporal lobes of the brain, which is a key component of the fight/flight/fear system (Bhagwagar *et al.*, 2004; Del-Ben *et al.* 2005). This activation is greater in healthy people who carry the 5-HTT allele that is associated with an increased risk of depression (Harriri, 2003; Section 7.1.2).

Evidence from brain imaging studies also suggests that the 5-HTT risk allele affects the development of the amygdala and of the frontal lobe systems that regulate it (Pezawas *et al.* 2005). From this inference it is proposed that vulnerability to depression involves a predisposition to detect negative cues in the environment, which evokes excessive activation of central fear and emotion systems. This provides a neurobiological basis for the finding that life events are more likely to trigger depression in people who have this risk allele (Caspi *et al.*, 2003).

7.7.4 Transition from vulnerability to illness; disease progression

Little is known about the processes that trigger mental illness in those with biological or environmental vulnerability. Adverse life events often precede the first onset of depression with succeeding relapses becoming more autonomous. In contrast, first onset of schizophrenia is typically preceded by deterioration in social functioning and a gradual onset of symptoms, possibly exacerbated by substance misuse; it is the timing of relapses, rather than onset, that is more related to life events (Cannon *et al.*, 2008). Clearly, to prevent illness, it is necessary to identify the factors that trigger onset and to understand how they affect the brain. This requires long-term studies of large samples of people who are at high risk of developing a disorder (Section 7.9 and Recommendations 18 and 20).

The first longitudinal studies of high-risk individuals with a family history of schizophrenia have been done, including an important UK study, funded by the MRC (Johnstone *et al.*, 2000). Using neuroimaging techniques, these studies have shown a loss of grey matter - especially in temporal cortex and hippocampus - in some high-risk individuals as the first episode of psychosis develops. Some of the recently identified genes for risk of psychosis, such as COMT, may be important in determining which high-risk individuals develop schizophrenia. For example, in the MRC study, only individuals with one or both of the COMT risk variants went on to develop psychosis, whereas those without a risk variant of the gene did not progress to disease (McIntosh *et al.*, 2007). Although the numbers of individuals studied are generally too small to be confident about genetic effects, these studies indicate that the onset of schizophrenia is a potentially understandable brain process that could be prevented (Velakoulis *et al.*, 2006). Further understanding of the neurobiology of progression requires a national cohort study of how the brain deviates from normal development as psychosis begins and evolves,

in relation to genotype and other risk factors for psychosis.

At the neurotransmitter level, studies indicate that increased amounts of dopamine are released during periods of active psychosis and that symptomatic recovery is associated with normalisation of dopamine release (Abi-Dargham *et al.*, 2000; Abi-Dargham, 2004). These findings provide good evidence that the ability of antipsychotics to block dopamine receptors is responsible, at least in part, for their therapeutic effect. A current concept under investigation is that the genes and altered brain structure associated with schizophrenia act to sensitise dopamine neurons in development (Borgwardt *et al.*, 2007; Goto & Grace, 2007; Lawrie *et al.*, 2008). According to this concept, when severe life stress occurs, the neurons will release excessive amounts of dopamine leading to psychosis.

The clinical features of most mental disorders change over time, generally getting worse and less responsive to treatment. This may be due to several factors. For instance, there is evidence of a continuing loss of grey matter during the first years of schizophrenia, mostly in medial prefrontal cortex and temporal cortical regions (Rapoport *et al.*, 2005). Two studies suggest that this loss is reduced with atypical antipsychotic drugs, notably olanzapine and clozapine, but not with older so-called conventional antipsychotics such as haloperidol (Lieberman *et al.*, 2005; van Haren *et al.*, 2007). There is also evidence that repeated episodes of depression and relapse in bipolar disorder result in brain atrophy (Sheline *et al.*, 1996; DelBello *et al.*, 1999). The atrophic changes particularly affect the hippocampus, possibly through the cytotoxic effects of repeatedly raised levels of stress hormones (Sapolsky, 2000).

Remarkably, we still do not know what cellular elements are lost from cortical grey matter in schizophrenia (Harrison, 1999). Similarly, the cellular basis of hippocampal atrophy in

depression is unknown. Without understanding the nature of these progressive changes, there is little prospect of designing drugs to prevent them. It may be that understanding the mechanisms by which clozapine and other atypical antipsychotic drugs exert their protective effects on grey matter might unlock the nature of the cortical loss in schizophrenia. Evidence also suggests that schizophrenic patients lack a specific subpopulation of small, GABA-containing neurons, either because these neurons fail to develop or because they have degenerated (Deakin, 1994). Similarly, neuronal branching and/or the density of synapses onto large cortical neurons may be reduced in schizophrenic individuals (reviewed in Mirnics *et al.*, 2001; Rapoport *et al.*, 2005). All of these findings suggest potential routes to treatment.

7.8 The development of new curative and preventative treatments

7.8.1 The challenges of drug development

Despite the advances in brain science described in the previous sections, mental illness is still treated with drugs that are partially effective and not easy to tolerate, and whose main actions have not changed fundamentally for decades. A major obstacle is the lack of new biological mechanisms (drug targets) on which the pharmaceutical industry can confidently target the development of new compounds. Nor can industry rapidly identify whether a new target is valid until the efficacy of a drug has been established in the clinic; a process that is not conducive to rapid drug development. Many more possible drug compounds and combinations exist than can be tested in clinical trials, but there is no reliable procedure for identifying the likely 'winners' at an early stage.

Compounds are screened for efficacy on the basis of their neurochemical effects (i.e. their effects on particular receptor sub-types or signalling pathways) and on their behavioural effects in animal models of mental illness. However, this approach can generate 'false-

positives' – promising candidates that are later found to lack clinical effectiveness. Indeed, once selected for clinical development, fewer than 10% of compounds that act on the CNS enter clinical use. To add to the problem, most candidate compounds fail in phase III - the large-scale clinical trial of a drug - which is the last and most expensive stage of development. The high failure rate indicates that current methods of target validation for drug development are ineffective.

In some mental disorders, it may be that drugs with multiple actions are required for greater efficacy. The antipsychotic drug clozapine has many actions, and shows broad efficacy (Wahlbeck *et al.*, 1997; Janicak, 2006). However, attempts to reproduce clozapine's efficacy by modelling its biochemical profile in atypicals such as olanzapine have been unsuccessful in increasing efficacy (CATIE, 2008). Identifying the right mix of even a few properties of the drug presents major problems because all possible combinations must be screened for safety and efficacy.

Large-scale clinical trials are needed to identify optimal treatments (or combinations of treatments). As with all trials, there are conflicting demands between rigorous trial design and studying a sample that is representative of the appropriate population, in this case, the mentally ill population. Rigorous trial design means random allocation to active treatments versus placebo, excluding all patients who have common medical conditions or habits that might modify a drug's effect. Examples of the latter would include patients who drink over 21 units of alcohol per week or those with history of head injury.

However, it is possible to conduct large-scale studies that combine rigour with practical realism. For example, the American Star-D study involved over 4,000 depressed patients who were allocated to up to four successive treatments using a process called 'equipose stratified randomisation'. This design enabled

participants - in consultation with their treating physician - to avoid random assignment to an unwanted treatment, yet still remain in the study (Trivedi *et al.*, 2006). In the UK, the BALANCE study (2000-08) (Geddes *et al.*, 2002), funded by the MRC and Department of Health, seeks to identify whether there are differences between two standard treatments, lithium and valproate - both separately and in combination - in the prevention of relapse in 700 bipolar patients; a simple but important pragmatic issue. Patients are entered into the trial by their own physician who reports when relapse occurs, without multiple and time-consuming outcome measures.

It should be emphasised that the pharmaceutical industry requires knowledge about the molecular and cognitive basis of mental illnesses to devise new drug targets; this knowledge can only come from strong university research groups and a national infrastructure capable of accruing large patient samples for the collection of clinical, genetic, imaging and tissue samples. In the following sections we describe the two main approaches to developing new drugs: the molecular approach and the cognitive neuroscience approach. We then discuss how combining these approaches using the methods of experimental medicine is emerging as the most efficient way to detect effective drugs early in development and to eliminate ineffective drug targets.

7.8.2 The molecular approach to drug discovery: neurotransmitters and cell signalling

Historically, biochemical and behavioural studies in animals revealed how early antipsychotics and antidepressant drugs worked by, respectively, blocking dopamine receptors and by increasing synaptic 5-HT content. The development of PET imaging methods to measure neurotransmitter receptors and release has since demonstrated that psychosis and depression are associated with altered dopamine and probably 5-HT function. These studies have been invaluable

in revealing the nature of abnormal dopamine function in psychosis but also in understanding drug action - optimal dosing and how atypical and older antipsychotic drugs differ - and in developing new drugs. This is a continuing story and new and more sensitive methods are likely to result in better ways of directly and indirectly targeting dopamine and 5-HT dysfunction.

Glutamate and GABA, the main neurotransmitters in the circuits of the cerebral cortex, are also strongly implicated in the pathogenesis of depression and schizophrenia (Harrison & Weinberger, 2005; Toro & Deakin, 2005). Both of the neurotransmitter systems have a very elaborate pharmacology with many possibilities for selective targeting of subsystems. The recent development of a novel glutamate-based antipsychotic drug has been mentioned in Section 7.3.2. The compound was developed from the adoption of glutamate as an explicit drug target by the Lilly discovery team and it was found to turn down glutamate release and to oppose some glutamate and dopamine behaviours in animal studies. Studies of safety in humans and then small-scale efficacy studies have followed quickly (Patil *et al.*, 2007). It remains to be seen how clinically useful the drug will be, but it shows that the combination of animal studies and translation into man can produce rapid progress.

PET radio ligands for glutamate are also in development, which will enhance the translation of glutamate drugs for use in humans. The concentration of glutamate and GABA can be non-invasively measured in living humans by magnetic resonance spectroscopy. This has produced evidence for a role of glutamate and GABA in mood disorders. Evidence also suggests that a different type of glutamate drug can reverse intractable depression beginning 24 hours after a single dose (Berman *et al.*, 2000; Zarate *et al.*, 2006). Importantly, translating these experiences back into the laboratory could also lead to improved animal models that can more accurately detect effective compounds for development,

illustrating the importance of the two-way translation process between clinical and animal behaviour studies.

Recent research may hold promise for the development of drugs for conditions such as antisocial behaviour, for which no specific treatments currently exist. A good deal is known about the basic brain circuitry of aggression and how it is modulated by several neurotransmitters. For example, the 5-HT_{1b} receptor seems to have a specific role in modifying aggression (Saudou *et al.*, 1994). The neuropeptides vasopressin and oxytocin are also known to promote affiliative behaviour in animals and possible pro-social effects in humans, i.e. actions that are intended to benefit others. Oxytocin can cause volunteers to rate pictures of eyes as more trustworthy and 5-HT is known to play a role in pro-social effects (Moskowitz *et al.*, 2001; Zak *et al.*, 2004). Thus, there are many approaches to developing drugs that could be of particular benefit in the treatment of personality disorders and other conditions involving impaired social cognition, such as autism or schizophrenia. In short, there is no shortage of plausible neurotransmitter targets for therapeutic drugs. The difficulty of translating these findings into effective treatments lies in successfully identifying the valid targets at an early stage to avoid the time, expense and labour of unnecessary clinical trials.

7.8.3 The cognitive approach

7.8.3.1 Drug modulation of vulnerability and cognitive biases

Much evidence suggests that anxiety and depression, and to some extent psychosis, are disturbances or biases in how the brain processes information (e.g. information about the social environment, memory and plans for future actions). The interconnected neural networks that mediate these cognitive functions can be visualised when they are engaged in cognitive tasks using fMRI or PET imaging. As discussed in Box 7.9, these systems are

influenced by risk alleles present in the general population. Increasing evidence indicates that drugs and neurotransmitters can modulate (i.e. tune up or tune down) specific brain circuits in surprisingly specific ways. For example, 5-HT and antidepressant drugs specifically influence performance in negative face emotion cognitive tasks (described in Box 7.9). Such tasks provide the basis of the cognitive approach to drug development, i.e. using cognitive biomarkers to screen compounds for likely efficacy (Box 7.11).

7.8.3.2 Cognitive neuroscience and new psychological treatments

One of the remits of this report was to explore how advances in the brain sciences can be exploited to develop new pharmacological treatments for mental illness. Accordingly we have not undertaken a detailed analysis of psychological approaches to treating mental ill health. However, participants in the public engagement activities placed a particular emphasis on psychological treatments (Box 7.12), and recent advances in brain imaging methods make it possible to investigate the impact of these treatments on brain processes.

The NICE guidelines summarise the evidence for the effectiveness of Cognitive Behavioural Therapy (CBT) and other psychological therapies in the treatment of depression and schizophrenia (NICE, 2003; 2004). There is good evidence for the efficacy of these treatments, although it should be noted that the evidence is based on only a few studies. In addition, the effective components of these therapies and their mechanism of action remain unclear.

Resolving the unanswered questions about different psychological therapies could be amenable to the experimental medicine approach described in Section 7.8.4. It should be possible to devise experimental tasks that probe the brain processes a psychological treatment is thought to affect by using appropriate biomarkers and fMRI to visualise the effect on neuronal processing.

Box 7.10 Alzheimer's disease: a molecular paradigm for preventing psychosis

It is estimated that 683,597 people suffer from dementia in the UK, 416,967 (62 %) of whom have Alzheimer's disease, making it the most common form of dementia (Knapp *et al.*, 2007). The overall financial cost of dementia in the UK is estimated to be over £17 billion per annum. Dementia can affect people of any age, but is most common in older people; in the UK one in six people over 80 and one in 14 people over 65 suffer from a form of dementia. However the prevalence and associated costs are expected to increase; the total number of people with dementia in the UK is forecast to increase to 940,110 by 2021 and 1,735,087 by 2051 (Knapp *et al.*, 2007). For these reasons there is a pressing need to develop effective treatment and preventative measures for the age-related dementias, and especially for Alzheimer's disease.

Over the past 25 years, much work on the dementias and on other neurodegenerative disorders has concentrated on understanding the molecular composition and relevance of the insoluble deposits that define these diseases. This work has shown that three proteins – amyloid- β , tau and α -synuclein – account for the deposits present in the majority of late-onset neurodegenerative diseases and that, for each protein, a pathological pathway leading from its normal, soluble state to an abnormal, insoluble state is at the heart of the neurodegenerative process (for review see Goedert & Spillantini, 2006). It is widely believed that this work will, in due course, result in the development of effective mechanism-based therapies for these diseases. For instance, major efforts are under way to develop safe and effective protease inhibitors that reduce the production of amyloid- β . Although the prevalence of Alzheimer's disease and Parkinson's disease make them major targets for the drug industry, therapies that target tau and α -synuclein are also likely to be of benefit in other neurodegenerative diseases, including progressive supranuclear palsy and Pick's disease, which are characterized by these inclusions (Goedert & Spillantini, 2006). The Nuffield Council on Bioethics study on dementia, begun in December 2007, will be important in considering the ethical, legal, economic and social issues that arise in the care and treatment of those with chronic, progressive neurodegenerative diseases. In the light of the pressing need to develop new therapies, we recommend that the science of neurodegenerative disease is the subject of a separate, dedicated review. (Recommendation 17).

Schizophrenia has significant affinities with Alzheimer's disease, notably the progressive loss of cortical grey matter that occurs with illness onset and the evidence of cognitive decline. In contrast to Alzheimer's disease, there is no known pathology or clear molecular abnormality. However, new clues to the molecular basis of psychosis are emerging from our understanding of the influence of risk genes on molecular signalling cascades within cells, e.g. in mice genetically modified to carry risk genes. Relating the molecular changes to behavioural changes in genetically modified mice is an important step in working out the molecular basis of disease. There will be many genes each contributing a small risk and finding where in the multiplicity of intracellular molecular cascades the action of risk genes converge will be very important; the points of convergence could become targets for the development of drugs to stop the onset and progression of psychosis. Ultimately, candidate molecular mechanisms can only be validated in human brain tissue obtained at post mortem from people with psychosis. In contrast to the several collections of Alzheimer's disease brains in the UK, there is none for mental illnesses (Recommendation 18).

These biomarkers could be investigated in patients and surrogates both before and after different treatments, to validate their efficacy and mechanism of action. To validate these therapies, it will be important to establish some commonality in the neurobiological process of recovery through either spontaneous remission, psychological therapy or drug treatment. One study reported that recovery from depression with CBT induces changes in regional brain metabolism that are distinct from changes associated with recovery on antidepressant drugs, but with some overlap between the

two (Kennedy *et al.*, 2007). Changes in neural mechanisms of thought processes in patients after therapy have also been demonstrated (Siegle *et al.*, 2006).

There is promising evidence that a combination of psychological therapy and antidepressant drugs is a more cost-effective treatment than either alone (NICE, 2004), and there are now real opportunities to explore how drugs that affect learning and memory could be used in conjunction with cognitive techniques to 'rewire' cognitive biases in depression

Box 7.11 Promising candidates for the cognitive approach

Face emotion processing is a good exemplar of the cognitive approach to drug development. Two different types of antidepressant share the ability to reduce the detection of fear in images of faces viewed by healthy volunteers (Harmer *et al.*, 2004). This effect is accompanied by decreases in the response of the amygdala to face-emotion (Del-Ben *et al.* 2005; Box 7.9). These biomarkers probe cognitive functions that are not dependent on a particular neurotransmitter. Importantly, the drugs have no effect on mood in the volunteers and viewing the faces evokes no subjective emotion. Effective antidepressant drugs with entirely new or even unknown neurochemical actions could be rapidly detected in volunteers by their impact on this 'fear-detection' biomarker, as well impacts on other negative biases characteristic of depression.

The cognitive approach may be particularly useful for the development of anti-impulsivity drugs that could be useful for the treatment of antisocial personality disorder where impairment in controlling impulses is a major deficit. The brain mechanisms of behavioural control are well understood and there are various experimental models in animals in which the effectiveness of anti-impulsivity drugs may be tested. What is required is the translation of these findings from animals to humans - using the cognitive approach - to enable the development of novel drugs.

Box 7.12 Public engagement: non-drug treatments for mental health

Participants expressed a feeling that 'non-drug' choices for people with mental health problems are inadequate in type, quality and availability. People in rural areas may find services particularly difficult to access or to get the support they need. Many participants felt that developing non-drug treatments would bring the greatest benefits in the future.

Participants strongly believed that the NHS should provide better and more varied non-drug treatments for mental health problems. Treatment types suggested included: cognitive behaviour therapy, group therapy and psychotherapy, neuro-linguistic programming, relaxation aids such as acupuncture, massage and meditation, counselling, help-lines staffed by a knowledgeable and trained workforce and support for a healthy, less stressful lifestyle.

or in schizophrenia (Ressler *et al.*, 2004). Overall, we urge a greater role for the brain sciences in the development and validation of psychological therapies and for the use of systematic outcome trials in their evaluation (Recommendation 21).

7.8.4 The experimental medicine (EM) approach

The experimental medicine (EM) approach aims to bring the processes of illness and drug effects under laboratory control using biomarkers and surrogates for illness, testing candidate drugs in humans as soon as basic safety is established. The aim is not only to determine whether a particular compound is a promising drug candidate, but also to use compounds with known actions to select and validate which of the many potential targets are the best focus for developing new drugs (Recommendation 20).

7.8.4.1 Molecular and cognitive biomarkers

The identification of biomarkers is key to the EM approach. A biomarker is a measure of a physiological function thought to be disturbed in disease. For example, the fMRI amygdala response to viewing fearful faces is a biomarker for negative attentional bias in depression (Box 7.11). Biomarkers are useful because they offer a more sensitive and direct measure of a disease process than a set of symptoms or subjective experiences. Cognitive biomarkers are not dependent on a particular neurotransmitter but represent the functional outcome of many interacting biochemical processes. Thus they have the potential to detect entirely novel drug classes and drugs with complex pharmacology. They can also be used during the early phases of drug development in development in healthy volunteers.

Molecular biomarkers are biochemical measures relevant to disease processes. A good example in humans involves PET studies of amyloid- β protein deposition as a marker for impending Alzheimer's disease or for the effectiveness of anti-dementia drugs to halt deposition of this protein. Similarly,

PET imaging of abnormal dopamine function in psychosis could be a good molecular biomarker for treatments aimed at preventing psychosis.

The promise of this approach is shown by the collaboration between five UK academic centres and five major pharmaceutical companies, who are currently running large-scale validation studies of biomarkers in healthy volunteers to determine whether they successfully detect standard antipsychotic and antidepressant drugs (<http://www.P1vital.com>). The Wellcome Trust and MRC also have more general initiatives in biomarkers for drug development, but it is too early to say whether these initiatives will have an impact in psychiatry.

7.8.4.2 Surrogates for illness

The ability of functional biomarkers to detect drug actions may be enhanced by measuring them in healthy people who are surrogates for patients. A 'surrogate for illness' is a disturbance in a neural or cognitive function related to the illness that can be observed in healthy volunteers. Surrogates can include healthy people with a previous history of mental disorder, or volunteers who display trait features such as neuroticism or schizotypy, or those who possess risk alleles for disorder.

Another EM approach is to experimentally administer a drug that induces mild symptoms or temporarily disturbs a cognitive or neural process relevant to an illness. For example, small doses of the anaesthetic agent ketamine elicit a mild dissociative mental state that mimics some aspects of the cognitive dysfunctions of schizophrenia, therefore providing a surrogate for the disorder. Indeed, there is evidence that the antipsychotic drug clozapine can attenuate ketamine effects (Malhotra *et al.*, 1997).

7.9 Discussion

This chapter has appraised current provision of, and recent advances in, medicines for mental

health. In summary, several current treatments exist that are effective in ameliorating symptoms of mental disorder and in preventing further episodes. Yet their use is characterised by partial efficacy and poor tolerability, because of the significant side effects associated with each class of drug. Participants in the public engagement programme considered side effects almost as debilitating as the mental disorder itself. They urged the prioritisation of research to reduce or eliminate side effects and more work to tackle long-term adverse influences on health.

In combination with side effects, the response to treatment in schizophrenia patients becomes increasingly poor in each subsequent episode, and each episode that occurs in bipolar disorder increases the likelihood of a subsequent episode occurring. Thus, maintaining long-term, effective treatment is essential to prevent relapse and recurrence, and so decrease the overall burden of these disorders. Improvements must also be made in the detection of illness and prescribing of treatment to improve adherence, quality of life and, ultimately, to reduce the economic and social burdens of mental illness.

There is a clear need to develop new and improved treatments that relieve symptoms and prevent relapse without debilitating side effects. Currently, no new mechanism of antidepressant or antipsychotic treatment has emerged for decades. Optimising current drugs, or developing drugs with novel mechanisms of action, will require a deeper understanding of the neuroscientific basis of mental disorders. This new understanding is likely to come from research, particularly genetics research, into the nature of vulnerability to mental illness, the transition from vulnerability to symptoms and disorder, and the progression of disorder. This echoes the view of the public engagement participants, who wanted an increased focus on improving understanding the physical and social causes of mental illness, including why certain groups are more prone to such illness,

and how progression might be prevented (Recommendations 18 and 20).

There is a need to understand the factors that may induce symptoms or pathology in individuals at risk of a disorder, so that onset and deterioration can be prevented. At the molecular level, preventing onset will require an improved understanding of how gene expression is affected by environmental conditions. The mechanisms by which risk genes affect the expression of other genes in the brain will help to identify downstream consequences that could be corrected by pharmaceutical drugs.

Success in identifying genetic associations with mental illness will require broad and careful phenotypic description, together with measures of cognitive function, longitudinal measures of the evolution of symptoms and of drug response, and measures of early and recent psychosocial environment. This will require collaboration between research funders, researchers and clinical services on a national, and potentially international, scale. We emphasise that this will only be facilitated by improvements in access to patient data, which has formed the basis of a previous Academy report (Academy of Medical Sciences, 2006) (Recommendations 18, 19 and 20).

For psychosis and schizophrenia, a nationwide analysis of 'at-risk' individuals, involving imaging and genetic analysis, will be necessary to identify the factors that trigger onset and how they affect brain function at both molecular and cognitive levels. This effort has to be national in scope and must involve the collection of sufficiently large samples to create normative data against which an individual patient can be compared for diagnosis, prognosis and selection of treatment. In this way, impending psychosis could be identified from a combination of clinical, genetic and imaging data, which would facilitate the evaluation of treatments

aimed at preventing onset and progression to disorder.

It will be crucial to establish a system for collection of post-mortem brains to enable research into the causes, epigenetic effects and neuropathology of disease. For example, epigenetic influences are likely to be specific to brain regions that are inaccessible in humans except through the study of post-mortem tissue. Although genetically modified mice and cell cultures may suggest hypotheses that can be tested in humans, only studies in the human brain can identify patterns of gene and protein expression associated with mental illness. The need for action is particularly urgent since studies of post-mortem brains in psychosis and depression have been stalled in recent years after controversies around cases of organ retention, including at Alder Hey Hospital. With the new Human Tissue Act in place, it is now timely to establish a dedicated programme of collection of post-mortem brains for mental illness research. This could provide decisive answers to many of the long-standing questions referred to in this chapter, and to test and detect molecular and genetic mechanisms thought to be associated with disease. Successful collection schemes of post-mortem brains in the USA have shown that consent can be sought from the relatives of deceased schizophrenia patients without causing offence or distress. The collection schemes rely on notification from the coroner's office that a relevant death has occurred, which they have shown does not present any insurmountable ethical problems (Recommendation 19).

Animal experiments also have an important role to play in this research effort. Such experiments are already beginning to generate hypotheses about which genes may be epigenetically modified by environmental experience and in which brain regions. This research may provide insights into where and when specific genes are switched on or off - knowledge that could revolutionise the

molecular understanding of mental illness and the development of entirely new drugs.

Despite the urgent need for improved treatments and many promising research leads, there are several challenges associated with drug development that must be addressed (Section 7.8.1). It is extremely difficult to predict which drugs will be effective so that only the best candidates are selected for clinical development. We have argued that it would be more effective to test drugs on healthy volunteers and patients as early as possible through the EM approach using molecular and cognitive biomarkers (Section 7.8.4). Overall, there is a need for an increased focus on investigating the effects of drugs on functional processes, as well as continued research into neurotransmitter-based approaches.

Finally, we emphasise that, although much of the original work underlying the neuroscientific advances discussed here was done in the UK, there is a risk that the initiative is slipping away to other countries, particularly the USA. A recent analysis showed that, whereas mental illness accounts for 18% of the UK's burden of disease, it attracts only 5% of the UK research spend (Kingdom, 2006). Experimental medicine in psychiatry barely exists in the UK. A recent initiative by the Wellcome Trust to generate training programmes in experimental medicine across specialities may improve the situation. However, the real possibilities of devising treatments to prevent onset and deterioration of serious mental illness must be seized. Establishing an academic speciality of experimental medicine in psychiatry would be an important step. Constructive engagement between academia and industry will also be an important factor and companies must be encouraged to share promising compounds with academic researchers.

Areas for further research have been identified throughout this chapter. In summary, some of the research priorities include:

- Exploiting the full range of molecular imaging technologies (PET, high field MRS, MRI) in humans to identify neurotransmitter and other molecular changes associated with vulnerability, onset and progression to mental disorder.
- Using sophisticated methods of genetic modelling in mice to identify where and how risk genes converge in molecular signalling cascades to modify behaviour.
- Identifying epigenetic signatures of the long-term effects of early environmental adversity in parallel studies in humans and animal models.
- Identifying cellular and structural changes in the brain associated with mental disorder, including disorders occurring in childhood.
- Using fMRI and PET brain imaging to identify biased cognitive information-processing systems in vulnerable groups and in patients with mental disorder.
- Identifying and validating biomarkers in humans that probe the molecular and cognitive processes of common mental illness; developing surrogates for mental illness that model components of disease processes in healthy volunteers.
- Developing a national strategy for characterising genetic mechanisms of mental illness, including large, longitudinal, case-control studies for different disorders and population studies in young people to detect established and new cases of illness.

Recommendations

17. In the light of the pressing need to develop new therapies, we recommend that the topic of neurodegenerative disease is the subject of a separate, dedicated review.
18. UK research agencies, including MRC and NIHR, should work with OSCHR to enhance research to identify causal genetic, environmental, molecular and cognitive mechanisms of mental illness, including longitudinal cohort studies, multidisciplinary research and other research priorities, such as those referred to in this report.
19. MRC, NIHR and other research agencies should work with the Research Networks to accelerate the establishment of a national post-mortem brain collection for mental illness. It is recommended that the collection is organised on one site and that the collection process is supported by clear legislative and professional guidelines to establish open and ethical communication between coroners, the national brain collection and relatives.
20. To build research capacity and develop new treatments for mental illness, it is recommended that:
 - A greater focus is placed on the experimental medicine approach to developing candidate drugs, where a dynamic combination of brain imaging, functional biomarkers, cognitive neuroscience and genetics is likely to facilitate more rapid clinical application of potential treatments.
 - The NIHR leads a programme of capacity building in translational psychopharmacology and molecular biology in psychiatry. This programme should include new joint academic/industry-funded clinical training posts, located in centres of excellence with appropriate clinical research infrastructure - including fMRI and PET imaging – as well as expert medical and nursing support.
 - UK research agencies should work with OSCHR and industry to foster closer interactions between basic scientists, neuropathologists and clinicians through additional funds and dedicated support.
 - The interactions should involve exploring how industry can be more flexible in releasing compounds for academic experimentation, including the development of active consortia

- that allow pre-competitive collaboration on candidate psychiatric drugs.
21. There must be a greater role for the brain sciences in the development and evaluation of psychological therapies. NIHR should prioritise the evaluation of combined psychological–pharmacological treatments, using brain imaging and neuro-cognitive biomarkers to identify relevant cognitive processes and to evaluate the brain mechanisms associated with improvement.
 22. There is an urgent need for more research into the metabolism and action of psychiatric drugs in children. It is recommended that the Medicines and Healthcare Products Regulatory Agency (MHRA) works with partners to develop a more systematic programme of collecting long-term safety information on prescribing medicines for mental health.

Chapter 8 Cognition enhancers

Introduction

Following the findings of the Foresight project, 'cognition enhancers' have formed one of the key themes of our study. This class of psychoactive substance includes drugs with the potential to enhance cognitive performance, not only in patients with neurological or cognitive disorders, but also in normal, healthy people. By 'cognition' we refer to the internal brain processes that underlie mental activity, such as attention, perception, learning, memory, language, planning and decision-making. Cognitive processes may not always be expressed as overt behaviour, i.e. actions that are visible to the outside world. However, overt behaviour is, to a large extent, under the control of cognitive processes. Cognitive performance depends on several important factors such as arousal (i.e. level of wakefulness) and motivation (see Robbins & Everitt, 1995). Thus, in theory, a cognition 'enhancer' may produce its effects indirectly by acting on arousal or motivation.

The review of cognition enhancers presented in the Foresight report identified 27 major agents

currently available in the UK (Jones *et al.*, 2007). These agents included ten dietary supplements and 17 pharmaceutical drugs that have been tested in human subjects, 14 of which have been subjected to Cochrane reviews (Table 8.1). Research has shown that most of the pharmaceutical drugs act to enhance (or diminish) neurotransmitter function and synaptic efficacy (Box 8.1). For instance, memory enhancers generally work by altering the balance of particular neurotransmitters involved in learning and its subsequent reinforcement.

This chapter focuses on cognition enhancers and does not consider drugs that affect sexual performance or suppress appetite. Also excluded are psychedelic drugs such as LSD and psilocybin, which may affect perceptual function and have been claimed to enhance artistic creativity, although these claims are not supported by objective indications of enhanced cognitive performance. For a recent analysis of the experiential effects of psilocybin, see Griffiths *et al.* (2006).

Box 8.1 Neurotransmitter function and synaptic efficacy

As discussed in previous chapters, neurotransmitters are chemicals that relay, amplify and modulate signals at the synapses (junctions) between neurons. It is the synapses that allow the neurons of the central nervous system to form interconnected neural circuits; they are therefore critical to the biological processes that underlie brain function.

There are many different ways to classify different neurotransmitters. Some of the neurotransmitters referred to in this chapter include:

- Acetylcholine.
- Monoamines, such as noradrenaline, dopamine and serotonin.
- Amino acids, such as glutamate and gamma-aminobutyric acid (GABA).

Synaptic plasticity is the process whereby the strengths of synaptic connections are altered. Such changes in synaptic strength, or efficacy, take place when new memories are formed as a consequence of learning. The change in synaptic efficacy may be brought about by, for example, an increase in the number of postsynaptic neurotransmitter receptors and/or by an increase in the amount of neurotransmitter released.

Table 8.1 UK pharmaceutical drugs that act on cognition: summary of Cochrane reviews

Name	Proposed mechanism	Cochrane review	Conclusion	Comments
Donepezil	Acetyl-cholinesterase inhibitor.	Update published in 2003 in Alzheimer's disease (AD). Update published in 2003 in vascular cognitive impairment.	Efficacy in all stages of disease, for up to a year's treatment. Benefits for possible mild to moderate disease for 6 months.	Cost-effectiveness data awaited for AD treatment. Extension of studies and better diagnostic criteria are desirable.
Galantamine	Acetyl-cholinesterase inhibitor; also possible cholinergic agonist.	Update published in 2004 in AD.	Consistent positive benefits in mild to moderate disease with 3–6 months' treatment.	Daily dose of 16mg titrated over 4 weeks offered best tolerability.
Rivastigmine	Acetyl-cholinesterase and butyryl-cholinesterase inhibitor.	Update published in 2000 in AD. Update published in 2003 in Lewy body dementia.	Benefits on various markers in mild to moderate AD after 26 weeks of 6–12mg. Benefits in some markers only if observed cases analysed.	Further study needed on optimum dosage to minimise side-effects. Evidence for efficacy is weak.
Nicotine	Acetylcholine agonist and releaser.	Update published in 2002 in AD.	Unable to find evidence for or against benefit.	One trial found, but did not present results suitable for inclusion.

D-cycloserine	Partial NMDA Agonist; enhances glutamate signaling.	Update published in 2002 in AD.	No place for this agent in treatment of AD.	Lack of positive effects in well-powered, controlled trials.
Memantine	Moderate NMDA antagonist – may protect from excitatory cell death.	Update published in 2004 in dementia.	Clinically noticeable reduction in deterioration at 28 weeks.	Benefit discernible in moderate to severe disease only, but early benefits seen, and well tolerated.
Nimodipine	Calcium-channel blocker – might reduce neuronal death due to excess calcium influx.	Update published in 2002 in various dementias.	Some short-term benefits in dementia due to unclassified or mixed disease, Alzheimer's, or vascular dementia.	Further evaluation of unavailable trial data is desirable, and new research must focus on longer-term outcomes.
Propentofylline	Adenosine uptake and phosphodiesterase inhibitor; also anti-inflammatory effects.	Update published in 2002 in dementia.	Limited evidence of benefits in AD, vascular dementia, or mixed disease.	Review limited by unavailable data on 1,200 patients not released.
Selegiline	Monoamine oxidase-B inhibitor; promotes dopamine signaling.	Update published in 2002 in AD.	No evidence of clinically meaningful benefit.	Further trials in AD are not justified.
Piracetam	Metabolic enhancement, antithrombotic, and neuro-protectant.	Update published in 2001 in dementia or cognitive impairment.	Does not support use.	Further evaluation warranted both on available data and as new studies emerge.
Hydergine	Increased cerebral blood flow, effects on neurotransmitters.	Update published in 2000 in dementia.	Significant treatment effects on generic scales.	Selection criteria for trials is outdated so benefit remains uncertain.

Nicergoline	As above, plus antioxidant and neuroprotectant properties.	Update published in 2002 in dementia and other age-related cognitive impairment.	Some positive benefits on cognition and behaviour in older patients with mild to moderate impairment.	Studies have differing outcomes; also, newer diagnostic criteria not used so not clear who might benefit.
Vinpocetine	Metabolic and blood-flow enhancement, antithrombotic, neuroprotectant, phosphodiesterase inhibitor.	Update published in 2002 in cognitive impairment and dementia.	Evidence does not support clinical use.	Large trials in well defined populations are needed to evaluate efficacy.
CDP-choline	Precursor of phosphatidylcholine.	Update published in 2003 for chronic cerebral disorders in the elderly.	Some evidence of positive benefits on memory and behavioural disturbances (up to 3 months).	Longer trials warranted with current diagnostic criteria.

(From Jones *et al.*, 2007)

Much of the recent attention directed towards cognition enhancers is due to the pharmaceutical industry's interest in treatments for dementia (including Alzheimer's disease, Pick's disease and Lewy body dementia, as well as the dementia associated with Parkinson's disease) and, more recently, stroke, schizophrenia and Attention Deficit Hyperactivity Disorder (ADHD). The economic arguments underpinning this interest are compelling, given the prevalence of these disorders and the potential market for effective therapies (see Jones *et al.*, 2007). However, it is important to recognise that the nature of brain pathology and cognitive dysfunction varies enormously between these disorders, and each will require a different type of treatment.

Although some drugs for the treatment of cognitive disorders are potentially suitable for use in healthy older people, many of the drugs in development are targeted to arrest or remediate a specific neuropathology (i.e. a

disease-associated change in brain structure or function) that is not present to any significant extent in the healthy or 'normal' ageing brain; for instance, potential monoclonal antibody therapies for use in Alzheimer's disease (Geylis & Steintz, 2006) and neural stem cell treatments for Parkinson's (Snyder & Olanow, 2005) and Huntington's disease (Dunnett & Resnes, 2007). Similarly, many of the future therapies for stroke are likely to have the primary purpose of preventing cognitive deficit, rather than promoting cognitive enhancement.

The Foresight review 'Perspective of the Pharmaceutical Industry' emphasised that there are no current programmes to develop cognition enhancers for the healthy population (Ragan, 2007). The report cited regulatory and legal issues as major factors contributing to this lack of commercial interest. However, it is likely that some cognition enhancing drugs, including those developed to treat specific clinical conditions, may be suitable for healthy subjects. It would be wise to expect that, in

such instances, word of mouth, the media and the internet may lead to considerable 'off-label' use. Although awareness of cognition enhancers was low among participants in the public engagement programme (Box 8.2), the expectation that 'off-label' use will increase is borne out by existing advertising of cognition enhancers and 'smart drugs' on the internet and current trends in the use of modafinil (Section 8.1.4).

8.1 Existing cognition enhancers

The following sections describe the effects and actions of several groups of existing cognition enhancers. Dietary supplements, or nutraceuticals, are considered first, followed by pharmaceutical agents broadly categorised as:

- Cholinergic drugs.
- Psychomotor stimulant drugs.
- Atypical stimulants such as modafinil.
- Cerebral vasodilators and nootropics.
- Neuroprotective and neural growth factors.
- Treatments for cognitive symptoms in schizophrenia.

Other (non-pharmaceutical) agents and interventions that can affect central neurotransmitter systems and thus potentially affect cognition are explored in Box 8.3.

8.1.1 Nutraceuticals: dietary supplements and vitamins

Claims of cognition enhancement are made for many current dietary supplements. Such supplements are usually well tolerated with no known abuse potential, and are regulated in the UK under the Food Safety Act 1990. They include vitamins E, B6, B12, folate, thiamine, lecithin, neurosteroids such as dehydroepiandrosterone (DHEA), α -lipoic acid, acetyl-L-carnitine and Gingko biloba.

The Foresight review concluded that, for most of these supplements, there is insufficient evidence to assess efficacy, either because the trials were too small or too few in number, or included only poor measures of effectiveness (Jones *et al.*, 2007). In most cases, trials have focused on specific clinical indications, such as the use of thiamine in cases of alcoholic Wernicke-Korsakoff syndrome (*ibid*). Studies of healthy individuals have produced some suggestive effects, for example associations between vitamin B6 and memory (*ibid*), but these findings remain inconclusive. Overall, it is clear that more and better designed/controlled trials will be needed to assess the true efficacy of nutraceutical agents, both for specified clinical disorders and for use in healthy individuals. Interestingly, participants in the public engagement programme often

Box 8.2 Public engagement: distinguishing treatment and enhancement

The results of the public engagement activity in this area emphasise that current awareness of cognition enhancers is extremely low. To most participants, the idea of healthy people using a drug to improve their cognitive capability was new. The overwhelming view was that a lot more research should be undertaken before this class of drug should be licensed or made more widely available.

Importantly, discussions at the workshops and responses to the online survey showed that participants made a clear distinction between treatment and enhancement; there was greater support for the use of cognition enhancers by, for example, patients with Alzheimer's disease or young people with ADHD, than for potential pharmacological enhancement in healthy, 'normal' people.

made a clear distinction between 'natural' enhancements in food and drink and 'unnatural' enhancements in the form of pills (Box 8.4).

8.1.2 Cholinergic drugs

Several existing cognition enhancers are based on the concept of enhancing neural transmission through the cholinergic system - the system that uses acetylcholine as its neurotransmitter. This system is impaired in disorders such as Alzheimer's disease, Parkinson's disease and Lewy Body dementia. The major classes of drugs involved are:

- Cholinesterase inhibitors, which retard the breakdown of acetylcholine and thereby increase its concentration at neural synapses.
- Nicotine and related agents, which stimulate nerve cell receptors that are sensitive to acetylcholine.

8.1.2.1 Cholinesterase inhibitors

These are among the few drugs approved for the treatment of cognitive impairment in Alzheimer's disease. One early trial of a cholinesterase inhibitor in Alzheimer's disease showed that its efficacy was restricted to cognitive 'domains' such as general alertness

and attentional performance, but it was not shown to affect memory function *per se* (Eagger *et al.*, 1991). Subsequent reviews of clinical trial of these drugs, e.g. Donepezil, rivastigmine and galantamine, have indicated significant, but relatively limited, efficacy in ameliorating cognitive symptoms of Alzheimer's disease (Giacobini, 2004). More recently, the use of cholinesterase inhibitors for Lewy Body dementia has been proposed. Preliminary indications are promising, especially given the profound loss of cortical acetylcholine known to occur in these disorders (Perry *et al.*, 1999). Some cholinesterase inhibitors, such as phenserine, have been claimed to have additional actions to reduce the toxic levels of β -amyloid associated with some forms of dementia, which may make them particularly effective compounds for clinical use (e.g. Shaw *et al.*, 2001).

Cholinesterase inhibitors have been found to induce cognitive improvements in laboratory tests in healthy volunteers (reviewed in Sahakian, 1988), although effects on different types of cognition can vary between individuals. Studies of the drug Donepezil, which has been used to treat Alzheimer's disease (Clegg

Box 8.3 Non-pharmaceutical based cognition enhancement

Several interventions, including environmental enrichment, behavioural training, and electrical brain stimulation, have been associated with cognitive enhancement. Studies in rodents have shown that environmental enrichment and exercise can induce neurogenesis (growth of new nerve cells and neural circuits) in some brain regions (Kemperman *et al.*, 2004). Evidence from functional neuroimaging in humans shows that increasing the blood flow to specific brain areas through particular kinds of cognitive problem-solving may be beneficial for overall cognition. Although there is a considerable media interest in the applications of such strategies, there is currently a dearth of detailed objective evidence for their efficacy (see Orrell & Sahakian, 1995). 'Deep brain stimulation' - electrical stimulation of structures that lie deep in the brain - has been used as an experimental treatment for conditions such as Parkinson's disease (Kleiner-Fisman *et al.*, 2006) and depression (Mayberg *et al.*, 2005). Evidence from patients with Parkinson's disease shows that deep brain stimulation improves not only motor function, but also cognitive performance, both of which may be impaired by the disease. These findings raise the possibility that deep brain stimulation, and a related development called 'Transcranial Magnetic Stimulation' (TMS), may be used more generally to enhance cognition (Kleiner-Fisman *et al.*, 2006; Steven & Pascuale-Leone, 2006).

et al., 2001), showed that it enhanced the performance of healthy middle-aged pilots after flight simulator training (Yesavage *et al.*, 2002).

8.1.2.2 Nicotine and related compounds

Nicotine has long been known to be effective in promoting attention, but it also appears to have beneficial effects on learning and memory (Levin, 2006). Nicotine has been shown to improve performance in laboratory tests of sustained attention in young adults, elderly volunteers and in patients with Alzheimer's-associated dementia (Sahakian *et al.*, 1989; Jones *et al.*, 1992). More recently, pharmaceutical companies have been actively trying to develop novel nicotine agonists, for example as potential therapeutic agents for schizophrenia, where deficiencies in nicotine receptor mechanisms have been identified (see Levin, 2006). Some of these novel agonists, such as ABT098, exert their actions through novel configurations of nicotine receptor subunits (Martin *et al.*, 2004).

8.1.3 Psychomotor stimulant drugs

Psychomotor stimulant drugs such as a d-amphetamine ('Adderall') and methylphenidate

('Ritalin') are most widely known for their use in treating ADHD, where there is now considerable evidence of their effectiveness and no convincing evidence of any major problems of abuse (Greenhill, 2001; Kutcher *et al.*, 2004). Concerns about the potential for abuse and unwanted effects from using cognition enhancers were raised throughout the public engagement activities (Box 8.5 and Section 8.4).

'Psychomotor' refers to a motor action or movement directly proceeding from mental activity. Psychomotor stimulant drugs are known to exert some mild beneficial effects on cognition in normal adults, especially under conditions of fatigue (Weiss & Laties, 1962). For instance, methylphenidate ('Ritalin') can enhance aspects of cognitive performance in young, healthy volunteers (although not in elderly volunteers), including spatial working memory, cognitive flexibility and stop-signal reaction time (Elliott *et al.*, 1997; Rogers *et al.*, 1999; Turner *et al.*, 2003a). Effects on vigilance, verbal learning and long-term memory are often relatively small and are restricted to certain laboratory test conditions.

Box 8.4 Public engagement: 'enhanced' food and drink

Participants in the public engagement activities often made a distinction between 'natural' and 'unnatural' enhancements. The former tended to include vitamin supplements, herbal preparations and doing brain-teaser puzzles. These 'natural' enhancers tended to elicit a more positive response than 'unnatural' enhancers in the form of 'pills' or 'drugs'.

Interestingly, the way in which a substance is delivered into the body impacted significantly on participants' views. For instance, it was seen as much more desirable to add cognition enhancers to foods such as broccoli; the idea of feeding 'enhanced broccoli' to one's family was viewed far more favourably than dosing a child with a pill before they leave for school.

Most participants reported using caffeine regularly: tea, coffee, cola or 'Red Bull'. However, despite evidence that caffeine has a significant effect on cognition, most participants argued that the long history of using these drinks and their social context put them in a different category to other forms of cognition enhancers.

However, small percentage increments in performance can lead to significant improvements in functional outcome; it is conceivable that a 10% improvement in memory score could lead to an improvement in an A-level grade or degree class.

Importantly, the effects of these drugs cannot simply be ascribed to their prevention of drowsiness. Functional neuroimaging evidence suggests that some of these effects are accompanied by reductions in cerebral blood flow in brain regions engaged by particular tasks (e.g. the prefrontal and parietal cortex during a spatial working memory task; Mehta *et al.*, 2000). A common explanation of this apparent paradox is that stimulant drugs enhance the efficiency of cortical processes, which is consistent with the hypothesis that such drugs improve neural processing by enhancing the 'signal to noise' ratio. This enhancement may be brought about through actions on the dopaminergic and noradrenergic systems that innervate the cerebral cortex. However, the relative involvement of these systems is still unclear and is the subject of current research.

Recent evidence confirms that related drugs such as L-Dopa (an intermediate in dopamine synthesis) can effect improvements in healthy subjects in forms of learning that are guided by rewarding feedback. It appears that the

neural mechanism for these effects may involve the dopamine system (Pessiglione *et al.*, 2006). There is also evidence for beneficial effects of drugs affecting noradrenergic systems in aspects of response inhibition and emotional memory (Chamberlain *et al.*, 2006a; 2006b). This field of research originally received a significant boost from animal studies demonstrating that both dopaminergic and noradrenergic systems are implicated in mediating functions such as working memory in 'higher' brain regions including the prefrontal cortex (e.g. Williams & Goldman-Rakic, 1995; Arnsten, 1998; Robbins, 2000; Schultz & Dickinson, 2000). Such actions appear to be at least partly distinct from those that act on the sub-cortical brain regions implicated in mediating the 'rewarding' or 'reinforcing' effects of stimulant drugs such as methamphetamine and cocaine.

8.1.4 Atypical stimulants: the striking case of modafinil (Provigil)

Modafinil (Provigil) is licensed in the UK for treating the excessive daytime sleepiness associated with narcolepsy and disorders of breathing during sleep (sleep apnoea). The drug is also used in the treatment of sleep disorders resulting from shift-work. Recent studies have shown that non-sleep deprived volunteers may also benefit in certain domains of cognitive function. For instance, tests in young adults have shown improvements in verbal

Box 8.5 Public engagement: concerns about addiction and unwanted effects

It is notable that, in the 1950s, the cognitive 'enhancing' effects of psychomotor stimulant drugs led to their use by military personnel and others (e.g. long-distance lorry driving), as well as their use (and abuse) for recreational purposes. Participants at the public engagement workshops expressed concerns about the potential side effects of cognition enhancers (of all kinds) and their possible addictive qualities.

Questions were raised about what would happen when users stopped taking the drugs: would they retain any gained abilities/knowledge or return to the same or even a lower level of ability/intelligence? Participants also emphasised that addiction can be psychological, as well as physical, and that success achieved as a consequence of using enhancers might lead a person to think they were not able to get by without them.

working memory, visual recognition, planning performance and executive inhibitory control (stop-signal reaction time) (Randall *et al.*, 2003; Turner *et al.*, 2003b; Muller *et al.*, 2004). However, improvements were not seen in other tests of learning and memory, suggesting that the beneficial effects of modafinil may be limited to particular brain systems. Clinical trials and laboratory studies of modafinil have shown improvements in cognitive function in cases of ADHD (Turner *et al.*, 2004a) and schizophrenia (Turner *et al.*, 2004b). However, in the USA, the licensing for the use of modafinil to treat ADHD has been delayed by reports of rare dermatological side effects. The beneficial effects of modafinil, and its lack of obvious toxic effects or apparent abuse liability (Myrick *et al.*, 2004), appear to have led to considerable 'off-label' use of this compound, in addition to its recent use by the USA military (Box 8.6)

A major question about modafinil relates to its mechanism of action, which is still unclear. Early suggestions that it acts on the noradrenergic and dopaminergic systems were later replaced by claims of actions on the orexin system - a neurotransmitter system implicated in sleep-waking cycles and appetite. Other hypotheses have postulated effects on the GABA-ergic or histaminergic systems. Understanding the mode of action of modafinil may prove important in the future development of further cognitive enhancing drugs.

8.1.5 Cerebral vasodilators and nootropics

Cerebral vasodilators are agents that act to widen blood vessels in the brain, increasing blood flow. Vasodilators such as naftidrofuryl have been proposed to enhance cognition in disorders such as vascular or multi-infarct dementia, but have not yet been subject to detailed review and evaluation. Several other agents, including phosphodiesterase inhibitors and calcium channel blockers, may also affect cerebral metabolism and blood flow. These agents may too have a role as cognition enhancers. A Cochrane review of the calcium channel blocker nimodipine suggested associated benefits for cognition in dementia, but not in overall functioning (Lopez-Arrieta & Birks 2002). Inhibition of phosphodiesterase by such agents as rolipram and papaverine can lead to increases in cellular signalling by molecules such as cyclic AMP, which has been implicated in cellular processes underlying memory. However, there are currently few data to indicate any therapeutic potential of these drugs.

The racetam group of agents, including the pyrrolidinones derivatives piracetam, oxiracetam, aniracetam, nefiracetam and levetiracetam, have long been designated as cognitive enhancers or 'nootropics'. They have been used for several cognitive disorders, including dementia, post-concussion syndrome and dyslexia. However, many of the clinical trials of piracetam for

Box 8.6 Public engagement: 'professional' use of cognition enhancers

Only a few participants felt that employees should be at liberty to use these drugs if they so wished, and only then if safeguards were in place. Views were divided on whether employees and schools should be allowed to test for their use.

There was some debate about the use of cognition enhancers by people in professions demanding high levels of concentration and this should be explored further in any future research. The idea of the military using such drugs during operations shocked many participants, perhaps because of the association of drugs with a loss of control. Participants found it difficult to accept that some cognition enhancers can decrease impulsive behaviour, increase reflection, focus and problem-solving skills, all of which might be of benefit to soldiers. Concerns over individual soldiers' rights to refuse to take such drugs were also raised.

dementia have been methodologically flawed, and its efficacy is still under debate (see Flicker & Grimley Evans, 2005).

Finally, natural ergot derivatives such as hydergine have been approved in the UK as an adjunct in elderly patients with mild-to-moderate dementia. A Cochrane meta-analysis of 12 trials showed significant benefit of hydergine for dementia (Olin *et al.*, 1998).

8.1.6 Neuroprotective and neural growth factors

Jones *et al.* (2007) reviewed several compounds that may potentially act as cognition enhancers by preventing damage to the brain due to oxidation and free radical neurotoxicity. These agents include idebenone, a synthetic analogue of the respiratory co-enzyme Q, cerebrolysin, a putative neurotrophic compound, and neuropeptides such as vasopressin. The effectiveness of these compounds as cognition enhancers has yet to be determined.

8.1.7 Treatment of cognitive symptoms in schizophrenia

Recently, it has become clear that there are substantial cognitive deficits associated with schizophrenia (Section 7.3.1). These deficits are major obstacles to rehabilitation, even in patients whose psychotic symptoms have been controlled effectively by anti-psychotic agents (Green, 1996). The need to treat these cognitive deficits has been recognised by the USA National Institutes of Health in such initiatives as the MATRICS project, which aims to identify effective new pharmacological therapies (Bromley, 2005).

The commonly held view is that these cognitive deficits arise from impaired functioning of cortical neural circuits. However, it is possible that some of this impairment occurs as a side effect of chronic anti-psychotic medication. Studies with non-human primates have found that chronic treatment with haloperidol, a typical anti-psychotic agent, leads to cognitive difficulties that are associated with impaired function of the frontal lobes; these

difficulties were alleviated by treatment with an experimental drug that boosted frontal dopamine function (Castner *et al.*, 2000).

8.2 Cognition enhancing drugs of the future: theoretical pointers from basic research

There is considerable evidence that many of the neurotransmitter systems that innervate the cerebral cortex modulate the activity of its neural networks (Robbins, 2000). These networks mediate cognitive functions. An important inference from this evidence is that the relationship between cognitive performance and neurotransmitter function follows an inverted 'U' curve. That is, there is an optimal level of neurotransmitter function, and deviations from this optimal level - in either direction - will lead to inferior performance.

Although levels of cognitive performance will vary in all individuals according to a range of factors, there are good reasons to suppose that the underlying baseline level of cognitive performance in patients with cognitive disorders is far from optimal (Arnsten, 1998). This performance can theoretically be enhanced by appropriate drug treatment to restore the balance of neuromodulatory activity (*ibid*).

There are several other implications of this inverted-U shaped concept for understanding the potential of cognition enhancing drugs. The first implication, based on empirical evidence from both human and animal studies (Robbins, 2000) is that there are different optimal neurotransmitter levels for different types of cognitive task. This finding implies that cognitive enhancement is likely to be sharply dose-dependent, but also that it may not be possible to achieve enhancement across all aspects of cognition. Indeed, benefits in certain forms of cognition may be at the cost of impairments in others. Cognition enhancement will then be context-dependent: enhancement

that is effective in one context may be ineffective, or deleterious, in another context.

The second major implication concerns normal human cognition. How is it possible to boost cognitive function in healthy individuals, if they already perform at or near the optimum? The reason is that normal cognition often strays from optimum, for example as a function of fatigue, sleep deprivation or stress.

It is becoming increasingly clear that genetic mutations are linked to considerable variation in aspects of cognition in normal humans. For example, polymorphisms (i.e. different variants or versions) of the gene regulating the enzyme catechol-o-methyl transferase (COMT) are associated with different levels of working memory performance, hypothetically linked to variations in prefrontal dopamine function (Mattay *et al.*, 2003). Moreover, it has been shown that improvements in cognitive function produced by amphetamine depends on which variant of the COMT gene is present in the individual; some individuals show benefits while others show mild deficits with the same dose of the drug (Mattay *et al.*, 2003). This finding has enormous implications for the possible future utility of cognitive enhancers in both patients and healthy normal subjects.

8.3 Cognition enhancing drugs of the future: current strategies and indications

For most of the pharmacological classes considered in Section 8.1, there are on-going attempts to improve on existing medications by varying their chemical structure to enhance efficacy and/or reduce side effects. The following sections discuss more novel strategies for discovering cognitive enhancing drugs, particularly those that affect the glutamatergic, GABA-ergic and cannabinoid neurotransmitter systems.

Contemporary discoveries about the molecular basis of learning and memory in experimental animals have also identified a variety of agents, such as CREB compounds, that work inside nerve cells as 'secondary' or 'tertiary' messengers in the hierarchy of signalling that begins with the neurotransmitter binding to the receptors of the nerve cell (Section 8.3.4). One example of a secondary signalling molecule is cyclic adenosine monophosphate (c-AMP). Influencing these molecules may provide viable targets for future memory enhancing drugs (Lynch & Gall, 2006).

8.3.1 Glutamatergic agents

Glutamate and GABA are the two principal amino-acid neurotransmitters of the cerebral cortex. The mechanisms governing glutamate transmission are complex and involve three main types of receptor, including the NMDA (N-methyl d-aspartate) and AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors.

One experimental model of learning at the level of nerve cell networks is called long-term potentiation (LTP) and is based on the premise that nerve cells that 'fire together, wire together' (Hebb, 1949). Importantly, drugs that act as antagonists at the NMDA receptor also block LTP (Collingridge & Bliss, 1995).

Ultimately, changes in NMDA receptor activity lead to increased neural transmission at AMPA receptors. The glutamate system is subject to very precise regulation by various molecular mechanisms, and several drugs have been identified that can both increase and reduce glutamate function (Kew & Kemp, 2005). Many drug companies are actively trying to develop such glutamatergic drugs. These drugs are likely to be leading candidates for new therapeutic approaches in treating cognitive disorders, including those associated with schizophrenia.

The AMPA-kines (or AMPA-potentiators) have been shown to enhance glutamate transmission and LTP (see Lynch & Gall, 2006). Positive effects of an AMPA-kine have been reported

on verbal recall in elderly normal volunteers, although these effects were found in only a subset of the sample, specifically those subjects with inferior memory on baseline (*ibid*). It is still unclear how efficacious this drug would be in a clinical setting. Another AMPA-kine has been tested in non-human primates and shown to significantly enhance recognition memory. This drug also counteracted the disruptive effects of sleep deprivation (Porrino *et al.*, 2005). D-cycloserine, a glutamatergic agent that enhances NMDA receptor function, selectively enhances a special form of learning called extinction. In this form of learning effects of conditioned associations are actively suppressed. Conditioned associations between a stimulus and a behavioural outcome are often involved in cases of anxiety, addiction and phobia, and their suppression can be an effective form of treatment: a recent study reported that D-cycloserine led to significant improvements in phobic symptoms in patients who were also undergoing desensitisation therapy (Ressler *et al.*, 2004).

8.3.2 GABA-ergic agents

In contrast to glutamate, which is excitatory in its effects on nerve cells, GABA is the major inhibitory neurotransmitter in the brain. There is at least one strategy for cognition enhancement based on GABA-receptor antagonism. Benzodiazepines such as librium and valium work by affecting an ion channel associated with the GABA-A receptor. Such drugs produce a profound (though transient) amnesia in normal volunteers, as well as several other actions including sedation, muscle relaxation and anti-convulsant action. The different actions of benzodiazepines depend on different sub-types of GABA receptor (which is composed of different configurations of protein sub-units).

A GABA-receptor subunit associated with cognition has been found to be selectively present in the hippocampus, which is implicated in memory. This discovery has led to the development of a strategy to design a drug

with opposite effects at this GABA-receptor to those of benzodiazepines (a so-called inverse agonist). Tests of this new drug in patients with Alzheimer's disease have not apparently been successful, although a recent study in normal volunteers has shown that it can antagonise the amnesic effects of alcohol (an effect that also probably depends on actions on GABA receptors) (Wilson *et al.*, 2005).

8.3.3 Cannabinoids

The effects of cannabis and its active constituent, Δ -9tetrahydrocannabinol, are mediated by two cannabinoid receptors, CB1 and CB2 (see Breivogel & Childers, 1998). CB1 receptors are present in the mammalian brain at high levels, with the highest levels occurring in the hippocampus and several areas involved in motor control. Cannabinoid effects on CNS activities correlate with the regional distribution of cannabinoid receptors. These effects impact on movement, memory, endocrine regulation, thermoregulation, sensory perception, cognitive functions and mood. With a similar logic to the strategy described above (Section 8.3.2), there has been a search for compounds that would have the opposite effects to the sedative, often cognitively-disruptive effects of cannabinoids. Thus, several pharmaceutical companies are developing drugs that act as cannabinoid receptor antagonists. Such drugs may have cognitive enhancing potential, but it is too early to assess their likely impact.

8.3.4 CREB agents

CREB is a protein that responds to increasing levels of c-AMP in the nerve cell and is considered to mediate a transition from short to long-term memory (Tully *et al.*, 2003). Phosphodiesterase inhibitors increase the level of c-AMP and thus indirectly enhance the action of CREB. Two such drugs, MEM 1414 and HT0712, are currently in development. Other targets, involving the suppression of the CREB repressor protein, are also being pursued by relatively small USA biotechnology companies (Tully *et al.*, 2003). In the long-term, it seems likely that agents that

can affect the formation of memories will eventually become available.

Recent discoveries also suggest that memories are relatively labile (changeable), even after being laid down (or 'consolidated'), and may be susceptible during 'reconsolidation' to pharmacological interventions (Nader, 2003). Evidence from studies in rats indicates that memories can be deleted by suitable treatments, e.g. with protein synthesis inhibitors or manipulations of specific genes in brain structures such as the amygdala or hippocampus (e.g. Lee *et al.*, 2004).

These findings have important implications for the potential removal of the pathological memories that occur in cases of post-traumatic stress disorder (PTSD) or drug addiction. The specificity and therapeutic potential of such 'amnesic' treatments requires much further basic research, and we are at least 20 years from any clear application in humans. However, the durability and specificity of the effects seen in animal models are promising (Lee *et al.*, 2004). Moreover, the theoretical possibility remains that labile memory trace could be enhanced, rather than deleted, which could also prove to be of therapeutic and social significance.

8.4 Ethical and regulatory issues

Any potential human enhancement challenges traditional ideas about medicine, i.e. that the role of medicine is to overcome some sort of impediment to normal physical or mental functioning, and thereby restore an individual to 'normal' health. An intervention that may enhance an individual beyond normal health therefore cannot always be easily accommodated within existing perceptions.

It may be that some of the concern expressed in the public engagement activities (Box 8.7), comes from a sense that enhancement is a misuse or corruption of medical techniques.

However, physical enhancement, through cosmetic surgery and other means, is gaining increasing acceptance. Widespread use of enhancers would raise interesting societal questions. Currently, individuals with higher than average cognitive abilities are valued and rewarded, but making such attributes available to all individuals could reduce the diversity of cognitive abilities in the population, and change ideas of what is 'normal'. As some participants in the public engagement activities noted, use of cognition enhancers may have an economic impact with more people able to work and fewer mistakes/losses due to negligence.

Many of the ethical issues involved would depend on the culture that develops around the use of cognition enhancers. It is unclear whether this would more closely resemble, for example, the consumption of coffee, or whether it would have parallels with illegal recreational drug use. A detailed discussion of the ethical aspects of cognitive enhancement, including pharmaceuticals and nutraceuticals, has recently been published by the British Medical Association (BMA, 2007). This publication provides a useful contribution to the ongoing debate on how society should respond to developments in the enhancement of cognition. From the public engagement work completed for our report, it is evident that participants were concerned about the potential implications of the widespread use of cognition enhancers. Pressure to use enhancers to succeed in a competitive society and inequality in access to enhancers were just two of these concerns (Box 8.7).

8.4.1 Approaches to regulation – risks and circumstances of use

One of the main issues raised by cognition enhancers is the question of how they should be regulated and which regulatory agencies should be responsible. The Medicines and Healthcare Products Regulatory Agency (MHRA) regulates medicinal products – generally defined as any substance presented as having properties for treating, preventing or curing

disease. A licence will only be granted with evidence that a drug is efficacious and safe - based on robust clinical trials - and that its intended benefits outweigh any risks. The Food Standards Agency (FSA) regulates the safety of food and nutritional supplements on sale in the UK. Recent European legislation has applied stricter controls to the health claims that can be made about foods and nutritional supplements.

Regulatory issues around the use of cognition enhancers are similar to those around recreational psychoactive substances (Sections 5.1 and 5.2). Considerations of regulatory legitimacy and effectiveness will be particularly relevant (Section 5.2.2). Like recreational drugs, regulation of cognition enhancers must operate on an evidence-based approach accounting for the associated benefits and harms.

Like all drugs, there is variation in the risk associated with different cognition enhancers, as well as in the circumstances in which they are taken. Although no drug is ever completely safe, it may be possible to make a rough gradation between those drugs for which there is good evidence that they are relatively safe (e.g. they have few side effects), and

those where there is evidence of greater risk (Recommendations 23 and 24).

For circumstances of use, it may be possible to distinguish between 'competitive' and 'non-competitive' circumstances, which will fall along a continuum. An example towards the 'pure competitive' end of the spectrum would be a drug that could boost performance on a specific cognitive test (such as a school or university exam), but has no further advantageous effects. At the other end of the spectrum would be a drug that generally makes people less forgetful, e.g. they are better able to remember where they left the car keys. There may be some competitive advantage to this too, but it is likely that its main advantage will be non-competitive: it simply enhances individual life.

Competitive use of cognition enhancers raises many of the same issues as the use of performance-enhancing drugs in sport, something that was picked up by the participants in the public engagement activities. For instance, use of cognition enhancers could lead to problems of coercion, where there is pressure on individuals to take the drugs, even if they do not wish to. Similarly, if such drugs were available to only a proportion of competitors, they could be seen as giving an

Box 8.7 Public engagement: concerns

It is clear from the results of the public engagement programme that most of the hopes for cognition enhancers focus on their potential use in helping people who are ill, rather than enhancing the 'well'. Participants cited several concerns related to the possibility of cognition enhancers becoming widely available for use by healthy adults. These can be broadly categorised as follows:

1. Unwanted or unknown side effects, related to a general fear of addiction and the absence of information about their long term effects.
2. Devaluation of 'normal' achievements and the potential reduction in the intrinsic value of the effort and motivation involved in learning.
3. Inequality, particularly if such drugs were expensive.
4. Pressure to use and exacerbation of an already over-competitive culture.
5. Control of people's behaviour.
6. Personality change, perhaps resulting from long-term use.

unfair advantage, or to be a form of cheating. Alternatively, if the drugs were available to all competitors, it may be that virtually all competitors would take them, such that all competitors would subject themselves to potential health risks without gaining any relative advantage over each other (steroid use in sport provides an analogy here). Where cognition enhancers are used in competitive situations, and where there may be serious risks, there are strong arguments against their use. There is, of course, a wide range of cases in between the 'competitive' and 'non-competitive' situations outlined above. In some cases, a drug may have both competitive and non-competitive advantages, such as a drug that could raise confidence.

School and the workplace are the most likely arenas in which cognition enhancers would be used and it is perhaps these environments that should be a focus for regulation. Indeed, legislation has already been introduced in the USA to prevent school personnel promoting the use of cognitive enhancers (see Legislative Commissioner's Office, 2005). It may be unrealistic for the Government to regulate cognition enhancers on grounds other than safety; except in special circumstances, it is not the Government's place to ensure that 'private' competitions are fair. Instead, schools and employers, like professional sports associations, may seek to regulate the use of cognition and performance enhancing drugs at the organisational or 'professional' level. This regulation may include banning the use of certain substances in particular contexts and applying sanctions for misuse. However, it is likely that concerns would be raised about the potential for coercive usage of such drugs at the 'organisational' level, e.g. to ensure good behaviour in juveniles with ADHD in certain schools in the USA (Farah, 2005) and conceivably in the workplace (Recommendation 25).

In practice, it may be difficult to restrict access to cognition enhancers; drugs such as

modafinil are already offered for sale. It may be desirable to enforce some sort of gate-keeping, perhaps through a GP or pharmacist. In this way, cognition enhancers could be treated in the same way as *viagra*, allowing access in a controlled and regulated environment that allows assessment of long-term effects and discourages the use of drugs bought from illegal sources. It may also be desirable to introduce a minimum age for the legal use of enhancers, in the same way as for alcohol or tobacco (Recommendation 25).

8.5 Discussion

This chapter has surveyed several pharmacological and other strategies for producing cognition enhancement. Several drugs already exist that produce modest enhancement in certain forms of cognition in patients with, for example, Alzheimer's disease or ADHD. Considerable efforts are currently being devoted to improving the efficacy and safety of these agents. In laboratory situations using psychological tests, it is clear that normal individuals can show significant improvements in certain forms of cognition with drugs such as methylphenidate and modafinil. These effects seem to be supported by the growing use of these drugs by normal individuals in specific contexts, e.g. during fatigue or shift-work, although the functional outcomes of such use require urgent objective evaluation.

It would appear that, from recent improvements in our molecular and cellular understanding of learning and memory, there has been sufficient scientific advance to take claims of future cognition enhancement seriously. There is a growing realisation that it may be feasible to reverse cognitive impairments in a range of disorders and there are several advanced programs of drug development, although the difficult and protracted nature of this process should not be underestimated. Taking a future perspective spanning the next 20 years or so, it does not

appear inappropriate to begin to consider the wider implications of cognition enhancers.

As discussed in Section 8.4, more widespread use of cognition enhancers raises significant ethical, social and regulatory questions (Sahakian & Morein-Zamir, 2007; and subsequent correspondence in *Nature* (2008) 451, 520-521). These drugs form one of the main themes of the burgeoning new subject of 'neuroethics' (see especially Farah *et al.*, 2004; Farah, 2005; Illes, 2006). As with all physiological, psychological or lifestyle interventions, each cognition enhancing 'agent' will need to be considered on a case-by-case basis, within a broader regulatory framework accounting for the risks involved and the circumstances of use.

It is important to emphasise that cognition may be impaired over a wide range, from very mild to severe. While drugs are usually developed to treat patients at the severe end of the spectrum, once they are available on the market, there may be a tendency to seek extensions to the licence that would allow them to be prescribed to people with less severe impairment. Pressure for such extensions may come from both consumers and drug manufacturers. As discussed elsewhere in this report, this pressure could result in a shift in the boundary between what is considered a 'normal' and what is considered to be a medical condition. It has been suggested that that this shift is already occurring, for example the rising diagnoses of ADHD, where there is conflicting information as to whether the disorder is under-diagnosed or whether more people receive drugs than necessary (e.g. Coghill, 2004). Currently, there is no UK or EU agency with the task of monitoring 'non-medical' uses of cognition enhancers, because they are generally not regulated substances. At a broad level, current oversight systems that focus on the clinical efficacy and safety of new drugs, will need to adapt to consider the non-medical use of cognitive enhancers by healthy individuals. As with other drugs, Government

and regulators will need to consider efficacy and safety and regulate accordingly. Regulation may involve limitations on availability by age and outlets, as well as constraints on advertising. Both the monitoring and regulation of cognition enhancers would be facilitated by imposing the requirement that such substances are obtained only by prescription (Recommendations 23 and 24).

In line with the findings of the public engagement work, further research will be needed into the health and social effects of using cognition enhancers, including their addictive potential. It is possible that many of these compounds would not lead to addictive behaviour in the usual sense of the word, but may induce novel forms of drug dependence (which may not necessarily be dangerous or undesirable: many of us are dependent on caffeine for example) (Recommendation 23).

Beyond national regulation on the basis of safety and efficacy, there may be a need for more localised regulation around the use of cognition enhancers in schools, colleges or the workplace, particularly to guard against any danger of pressure or coercion to use. According to this approach, the following overall framework emerges:

- Government – through regulators such as MHRA and NICE - regulates the medical and non-medical use of cognition enhancers on the basis of safety and efficacy.
- If non-medical use is allowed on this basis, local and/or professional regulation may be introduced around the use of a particular cognition enhancer in specific circumstances.

The Foresight project concluded that pharmaceutical companies have not pursued cognition enhancing drugs for use in the healthy population because of perceived regulation and litigation issues that enhance commercial risk. Further debate is needed about whether it is, in fact, desirable for pharmaceutical companies to have explicit programmes for developing cognitive enhancing drugs to be used by

'healthy' individuals in non-medical contexts. If such programmes are found to be desirable, incentives for their development should also be considered (Recommendation 23).

Researchers will need to explore novel approaches to evaluating the effects of cognition enhancers in healthy individuals, particularly in relating laboratory evaluations to everyday functional outcomes. For instance, how does the laboratory observation that modafinil enables human volunteers to hold an average of seven digits in short term memory, rather than six, relate to everyday performance, say in planning a shopping trip or in enhancing performance in the workplace? To validate laboratory measures as predictors of real life effects, researchers will have to be able to measure such everyday performance in significantly better ways than at present. The need for more scientific and social research to assess the effects on 'healthy people' of short- and long-term use of enhancers was just one of the research priorities identified by the participants in the public engagement programme (Box 8.8).

The outcomes from the public engagement work emphasise that an ongoing dialogue around the potential benefits and risks of cognition enhancer use will be needed, involving patients, the public, the media and health and social care professionals, among others. This field of science is still at an early stage, with relatively few examples around which to base discussions. As with regulation,

a case-by-case approach to future dialogue will be needed, as attitudes are likely to vary between different cognition enhancing agents and the particular circumstances of use (Recommendation 25).

Overall, there is a need to monitor current and future use of cognition enhancers, to determine whether they do in fact have significant effects on everyday functioning, in a variety of contexts, and to evaluate possible harms (including addiction), both to detect them in society and to predict them in the laboratory. These assessments will be needed for each new compound as it becomes available.

Recommendations

23. The Government, with research funders, the National Institute for Health and Clinical Excellence (NICE) and industry, should support research on current and future cognition enhancers to:
- Assess the effects of long- and short-term use in healthy people, including the effects of cessation, effects in children and younger people and addictive potential.
 - Understand individual differences in responsiveness to cognition enhancers; this research should form part of the growing field of pharmacogenomics.
 - Improve laboratory evaluations to predict everyday functional outcomes of using cognition enhancers; such evaluations

Box 8.8 Public engagement: research priorities

Participants felt that much more scientific and social research should be done before policy is developed on the use of cognition enhancers by 'healthy' people. This included research into:

- The benefits of cognition enhancers for people with mental health problems or neurological disorders, including dementia and ADHD.
- Their effects on 'healthy' people of short- and long-term use, and cessation.
- The possibility of addiction.
- Their effects on the developing brain.
- The social and financial impact of widespread use.

may require the development of entirely new methodologies, including computerised tests and virtual reality.

- Objectively evaluate the non-medical use of cognition enhancers in specific contexts where use might be considered to be beneficial, e.g. during shift-work and military service.
- Assess the social and economic impacts of widespread cognitive enhancer use.

24. There is a need to consider the future regulation of the non-medical use of cognition enhancers. It is recommended that the Government, NICE, the Medicines and Healthcare Regulatory Authority and, in the cases of food stuffs and nutrients, the Food Standards Agency, should work together to:

- Further consider how the use of cognition enhancers in non-medical contexts can be regulated on the basis of safety and efficacy.

- Establish mechanisms to revise regulation as necessary in the light of increased knowledge of the harms and benefits of specific cognition enhancers; if a cognition enhancer is found to induce psychological dependence or addiction, it should be referred to the ACMD.
- Monitor the potential diversion of cognition enhancers developed for a specific clinical condition, such as Alzheimer's disease, for non-medical uses.
- Monitor the quality (i.e. purity) of cognition enhancers.

25. In cases where a cognition enhancer is deemed to be safe and effective for 'non-medical' use, the Government should work with stakeholders, including industrial and professional associations, trade unions and educational authorities, to consider 'localised' regulation around use in schools, universities and the workplace. The coercive use of cognition enhancers should

Recommendations

Part I: Recreational drugs

Chapter 3 Magnitude of the problem

1. The Government should appoint a single body, such as the Office of National Statistics (ONS), to work in partnership with academic institutions to:	Refer to section:
<ul style="list-style-type: none"> Review and improve the accuracy and reliability of existing population surveys that seek to measure the prevalence, duration and type of drug use. When assessing the variation in drug use attributable to factors such as gender, age, geographical regional, ethnicity and socio-economic class, account should be taken of potential inequalities in treatment access and involvement with the criminal justice system. 	3.4.1 3.1
<ul style="list-style-type: none"> Develop 'evidence synthesis methods' that combine information from police, health, social and other services to provide more accurate estimates of the scale of substance misuse, the amount of drug-related harm, and the relationship between harm and misuse. 	3.5

Chapter 4 Neuroscience, addiction, pharmacology and treatment

2. UK research agencies, including the Medical Research Council (MRC) and National Institute for Health Research (NIHR), should work with the Office for the Strategic Coordination of Health Research (OSCHR) to:	
<ul style="list-style-type: none"> Enhance basic, translational and multidisciplinary research into the neuroscience of addiction; create additional academic and clinical posts, including new training fellowships, and invest in state-of-the-art brain imaging and other technological facilities. 	4.1.6 4.4
<ul style="list-style-type: none"> Expand translational studies in humans, including proof-of-concept studies, to test and screen possible pharmacological and psychological treatments for addiction, making full use of the resources of the NHS. 	4.2.3 4.3.2 4.3.3
<ul style="list-style-type: none"> Facilitate collaborations with industry to identify novel approaches to developing new pharmacological treatments for addiction and to bring successful compounds into clinical use. 	4.4
3. The Government could encourage research and innovation, and incentivise the pharmaceutical development of new addiction medicines, by adopting a flexible approach to the Pharmaceutical Price Regulation Scheme, taking account of the overall societal value of such medicines.	4.2.3 4.4
4. Advances in the neuroscience of addiction and in the development of new treatments will be facilitated by improved co-ordination of research, training and translational studies across Europe. UK research funders and institutes should be encouraged to work with European partners. Improved co-ordination and the creation of a European Institute for Addiction Research would create a critical mass of research, enable the pooling of expensive technological facilities and facilitate activities such as large-scale genetic and epidemiological studies.	4.4

Chapter 5 Harm and regulation

5. The Advisory Council on the Misuse of Drugs (ACMD), together with the Home Office, the Department of Health, Office for National Statistics and other relevant bodies, should develop new, quantitative indices of all harms attributable to individual illegal and legal psychoactive drugs.	5.3.5 5.3.6 5.4 Table 5.4
6. In developing effective measures to regulate the use of illegal psychoactive substances, it is recommended that: <ul style="list-style-type: none"> • The framework of classification, and the place of each drug in that framework, should be based on evidence of harm and should be reviewed in the light of new evidence, including information provided by the proposed new indices of harm (Recommendation 5). • A balance is struck between individual freedom and the harms of substance misuse to individuals, families and society; that account is taken of the long-term harms of criminalising individuals for infringing current legislation for possessing drugs for personal consumption; and that regulatory measures are related to the harmfulness of individual drugs. • Dependent users given custodial sentences should be offered treatment both while in detention and on release. • All regulatory measures are reviewed five years after implementation for effectiveness in reducing harm. 	5.1, 5.2 5.3, 5.4
7. On the basis of the proposed new indices, the ACMD should continue to provide advice on the classification of drugs and on the category into which individual substances are placed. As part of its remit, the ACMD should: <ul style="list-style-type: none"> • So far as possible, be responsible to both the Home Office and the Department of Health. • Report annually to an inter-departmental Government committee including representatives from the Department of Health, Home Office, and Departments for Children, Schools and Families; Innovation, Universities and Skills; and Communities and Local Government. • Take the lead in maintaining a continued, informed dialogue between policy makers and the public to maintain trust and ensure credible regulation. 	5.4
8. To mitigate the serious consequences of injecting drug use, and subject to positive outcomes from current pilot studies, supervised injecting facilities for treatment-resistant addicts who use this method of drug delivery should be introduced on a wider scale.	5.3 4.2.1
9. The Government and the NHS should continue to communicate to the public the dangers of legal psychoactive substances, for example tobacco and alcohol. The recommendations in the Academy of Medical Sciences' report 'Calling time' (2003) should be taken forward.	Box 5.7
10. The Government should continue to monitor, and where necessary improve, the enforcement of restrictions on selling or giving tobacco and alcohol to minors. Minors' access to tobacco and alcohol should be restricted by more effective use of existing laws forbidding sale and gift, and by the use of child protection laws and practice. The health effects of children using small amounts of alcohol should be investigated.	3.2.1 3.2.2

Chapter 6 Risk factors and prevention

<p>11. Longitudinal and cohort studies are needed to clarify the routes of entry into substance misuse and dependence, and to determine more accurately the relationship between drug use/misuse and a range of genetic, individual, family, social and environmental variables. It is recommended that:</p> <ul style="list-style-type: none"> • Information collection begins at an early age, before drug use and misuse occurs. • Information about drug misuse is incorporated into appropriate existing longitudinal studies. 	<p>3.1.3, 3.4.2, Box 5.9 6.1.4.1 6.4.1 6.6</p>
<p>All interventions described in Recommendations 12-16 should be evaluated according to best practice, using randomised controlled trials and long-term follow-up whenever possible.</p> <p>12. The Department of Health and NHS should emphasise the hazards to both mother and fetus of taking legal or illegal drugs before and during pregnancy and breast-feeding. Established support systems for pregnant women known or thought to be at risk of drug misuse should be expanded and systems developed to enhance the identification of substance use during pregnancy. Support given to women using legal and/or illegal drugs should be non-judgemental and provided by skilled professionals.</p>	<p>6.1.1 and 6.6 6.1.1.3</p>
<p>13. The Government, led by the Department for Children, Schools and Families (DCSF), should increase investment in evidence-based family support programmes targeted at children identified as at increased risk of substance misuse. Programmes should be introduced before substance misuse has developed and should involve a broad-based support package.</p>	<p>6.2.2, 6.3 and 6.6</p>
<p>14. Children and young people with mental health problems are a high-risk group for developing substance misuse, partly because they share risk factors with those who may become substance misusers. Interventions should target common risk factors (e.g. in family life and school failure) as well as the relief of their mental health problems. It is recommended that:</p> <ul style="list-style-type: none"> • Health and social care services should work with schools to provide a comprehensive service for young people with mental health disorders, as well as for their families. • Interventions should include the early identification and treatment of children with conduct disorder and attention deficit hyperactivity disorder (ADHD), including measures to discourage harmful drug use. • Young people who are misusing drugs should be assessed for mental health problems so that they can be treated for these conditions in conjunction with treatments for substance misuse. 	<p>6.1.4 and 6.6 6.1.4.2 6.1.4.4</p>
<p>15. Trials of skills-based school education, delivered by peers and ex-users, should be extended in both primary and secondary schools. The outcomes of promising schemes, including 'Communities That Care' and the 'Blueprint' drugs education programme, should be evaluated by Government for their effectiveness in reducing risks of substance misuse.</p>	<p>6.3.1.1 6.3.2 6.6</p>

<p>16. The media and creative industries should be encouraged to see themselves as having responsibilities in public health and in discouraging substance misuse. The Government should engage with the media and creative industries to minimise positive references to, and images of, illegal psychoactive substances in advertising, music, film, interactive games or other media targeted at young people.</p>	6.3.3
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Part II: Medicines for mental health

<p>17. In the light of the pressing need to develop new therapies, we recommend that the topic of neurodegenerative disease is the subject of a separate, dedicated review.</p>	Chapter 7 Introduction Box 7.10
<p>18. UK research agencies, including MRC and NIHR, should work with OSCHR to enhance research to identify causal genetic, environmental, molecular and cognitive mechanisms of mental illness, including longitudinal cohort studies, multidisciplinary research and other research priorities, such as those referred to in this report.</p>	7.8 7.9
<p>19. MRC, NIHR and other research agencies should work with the Research Networks to accelerate the establishment of a national post-mortem brain collection for mental illness. It is recommended that the collection is organised on one site and that the collection process is supported by clear legislative and professional guidelines to establish open and ethical communication between coroners, the national brain collection and relatives.</p>	7.7.4, 7.8.2 and 7.9
<p>20. To build research capacity and develop new treatments for mental illness, it is recommended that:</p> <ul style="list-style-type: none"> • A greater focus is placed on the experimental medicine approach to developing candidate drugs, where a dynamic combination of brain imaging, functional biomarkers, cognitive neuroscience and genetics is likely to facilitate more rapid clinical application of potential treatments. • The NIHR leads a programme of capacity building in translational psychopharmacology and molecular biology in psychiatry. This programme should include new joint academic/industry-funded clinical training posts, located in centres of excellence with appropriate clinical research infrastructure - including fMRI and PET imaging – as well as expert medical and nursing support. • UK research agencies should work with OSCHR and industry to foster closer interactions between basic scientists, neuropathologists and clinicians through additional funds and dedicated support. The interactions should involve exploring how industry can be more flexible in releasing compounds for academic experimentation, including the development of active consortia that allow pre-competitive collaboration on candidate psychiatric drugs. 	7.8 7.8.3 7.9 7.8.1 7.9

25. In cases where a cognition enhancer is deemed to be safe and effective for 'non-medical' use, the Government should work with stakeholders, including industrial and professional associations, trade unions and educational authorities, to consider 'localised' regulation around use in schools, universities and the workplace. The coercive use of cognition enhancers should normally be prohibited, with any exceptions to this rule considered extremely carefully.	8.4 and 8.5
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Public engagement

26. The Government and Advisory Council on the Misuse of Drugs should undertake further and continuing dialogue with the public on issues relating to brain science, addiction and drugs, including those topics identified in this report.	Chapter 2 and shaded boxes throughout the report.
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Appendix I Report preparation

Working group

This report was prepared by an Academy of Medical Sciences working group. Members participated in a personal capacity and not on behalf of their affiliated organisations. A summary of working group members' interests is given below.

Chair

Professor Sir Gabriel Horn FRS, Sub-Department of Behaviour, University of Cambridge

Sir Gabriel has a long-standing interest in neuroscience, seeking to relate brain function with behaviour. He has worked on the neural mechanisms of attention and on the neural bases of learning and memory, inquiring how information acquired through learning is stored in the brain. In 2001 he chaired an independent Committee to review the origin of bovine spongiform encephalopathy, reporting to the Secretary of State for the Environment, Food and Rural Affairs and the Secretary for State for Health. More generally, he has actively sought to keep members of the Government informed about advances in science, medicine and technology, and their economic, ethical and legal implications for society.

Members

Professor Jacqueline Barnes, Professor of Psychology, Birkbeck, University of London

Professor Barnes has been involved for a number of years in the USA and UK in evaluating intervention programmes designed to improve outcomes for young children and their families living in disadvantaged circumstances. Most recently she co-directed the National Evaluation of Sure Start, a UK Government programme for children under four years old and their families. She has a long-standing academic interest in the relevance of neighbourhood characteristics for child development, and ways that neighbourhood or community level interventions may lead to fewer parenting problems and enhanced child socio-emotional development.

Professor Roger Brownsword, Professor of Law and Director of The Centre for Technology, Ethics and Law in Society, King's College London

Professor Brownsword is interested in researching the interfaces between law, ethics, and technology, focusing in particular on what it takes to get the regulatory environment right for emerging technologies, and on the limits to the legitimate and effective use of technology as a regulatory tool. His latest book, 'Rights, Regulation and the Technological Revolution', was published in March 2008. Professor Brownsword is a member of the Nuffield Council on Bioethics and served on the working party that produced the report 'Public health: ethical issues'.

Professor JF William Deakin FMedSci, Professor of Psychiatry and Director of the Neuroscience and Psychiatry Unit, University of Manchester

Professor Deakin heads neuroscience research in the Department of Psychiatry. An important focus of his research is to use modern imaging techniques to observe how the brain responds to drugs chosen to probe serotonin or glutamate functioning. His research group also investigates how these neurotransmitters modify how the brain processes information in patients with anxiety, depression and antisocial behavior. Most recently, his research has focused on comparing brain responses in individuals with different genetic variants.

Professor Ian Gilmore, Consultant Physician and Gastroenterologist, Royal Liverpool University Hospitals; Honorary Professor at the Department of Medicine, University of Liverpool; and President, Royal College of Physicians

Professor Gilmore's interests lie in liver disease and the wider implications of alcohol misuse. He chaired the Royal College of Physicians working party that produced the report 'Alcohol - can the NHS afford it?' and was Secretary to the Academy of Medical Sciences working party report 'Calling Time: The Nations Drinking as a Major Health Issue'. He continues to work with the Royal College of Physicians to influence policy on public health issues including smoking, alcohol, obesity and climate change.

Dr Matthew Hickman, Senior Lecturer in Public Health, University of Bristol

Dr Hickman is based in the Department of Social Medicine at the University of Bristol and holds a national public health career scientist Fellowship. His research covers drug misuse and addiction and in 2005 he published a series of articles examining the prevalence of problematic drug use. He is a current member of the Advisory Council on the Misuse of Drugs. Prior to moving to Bristol, Dr Hickman was the Deputy Director of the Centre for Research on Drugs and Health Behaviour at Imperial College, and the Acting Director of Public Health at Hammersmith and Fulham PCT. He has also served as the Assistant Editor of both the 'International Journal of Drug Policy' and 'Addiction'.

Professor Les Iversen FRS, Visiting Professor, Department of Pharmacology, University of Oxford

Professor Iversen's principal areas of research include neurotransmitter and neuropeptide mechanisms in the mammalian central nervous system and the discovery and development of novel neuropharmacological agents. Professor Iversen is a Fellow of the Royal Society and a Foreign Associate of the National Academy of Sciences, USA. He is a current member of the Advisory Council on the Misuse of Drugs and acted as the specialist adviser to the House of Lords Science & Technology Committee's enquiry into Cannabis (1998). He was previously the Director of the Wolfson Centre for Research on Age-Related Diseases at Kings College London and Director of the Neuroscience Research Centre of Merck Research Laboratories.

Professor Trevor Robbins FRS FMedSci, Professor of Cognitive Neuroscience, University of Cambridge

Professor Robbins led the Medical Research Council (MRC) Field Review on Drug Addiction (1994) and was Chairman of the MRC Neuroscience and Mental Health Board from 1995-1999. He was a co-Project leader on the Technology Foresight Project 'Drugs Futures 2025' and co-edited the resultant publication 'Drugs and the Future', for Elsevier in 2007. He is Head of the Department of Experimental Psychology and Director of the University of Cambridge Behavioural and Clinical Neuroscience Institute, which features neurobiological basis of drug addiction as one of its most prominent themes. He combines cognitive and behavioural neuroscience approaches, including human brain imaging, with psychopharmacology and has Programme Grant funding from the Wellcome Trust and the MRC on drug addiction (the latter as co-applicant with Professor Barry Everitt FRS). He also researches in the area of cognitive enhancement for the dementias, schizophrenia and other neuropsychiatric disorders.

Professor Eric Taylor FMedSci, Professor of Child and Adolescent Psychiatry and Department Head, King's College London

Professor Taylor is a child and adolescent psychiatrist in clinical practice in the NHS. He also heads a university department in Child and Adolescent Psychiatry, an interdisciplinary research group

and a theme within a National Institute of Health Research biomedical research centre. He holds (or has recently held) research grants from the Medical Research Council, Wellcome Trust, UK Health Technology Assessment Programme, various charities and the food industry. He publishes books and articles on child neuropsychiatry and edits journals on child psychiatry and brain-behaviour relationships. Professor Taylor chairs a guidelines development group on Attention Deficit Hyperactivity Disorder for the National Institute of Clinical Excellence, is a member of the Psychiatry Expert Advisory Group for the Medicines and Healthcare Regulatory Agency, and is a trustee of the National Academy of Parenting Practitioners and of the South London and Maudsley NHS Foundation Trust.

Professor Jonathan Wolff, Professor of Philosophy and Head of Department of Philosophy, University College London.

Professor Wolff's research interests are primarily within social and political philosophy. His current interests concern how to bring abstract political philosophy into contact with pressing problems of social and public policy, such as the regulation of public safety. He was previously a member of the Gambling Review Body (2000-2001) and is a trustee of the Responsibility in Gambling Trust. He is a member of the Nuffield Council on Bioethics and served on the Council's Working Party on the ethics of animal research. He has also worked as a consultant to the Rail Safety and Standards Board.

Secretariat

Dr Robert Frost (Lead Secretariat)
Senior Policy Officer, Academy of Medical Sciences

Dr Helen Munn
Director, Medical Science Policy, Academy of Medical Sciences

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Review Group

This report was reviewed by an external panel appointed by the Council of the Academy of Medical Sciences. Reviewers were asked to consider whether the report met the terms of reference and whether the evidence and arguments presented in the report were sound and supported the conclusions. Reviewers were not asked to endorse the report or its findings.

Professor Lewis Wolpert CBE FRS FMedSci (Chair)
Emeritus Professor of Biology as Applied to Medicine, University College London

Professor David Fergusson
Executive Director, Christchurch Health and Development Study, Christchurch School of Medicine and Health Sciences, New Zealand

Professor Alan North FRS FMedSci
Vice President and Dean of Faculty of Life Sciences, University of Manchester

Professor Gunter Schumann
Professor of Addiction Biology, Institute of Psychiatry, King's College London

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Academy of Medical Sciences
10 Carlton House Terrace
London, SW1Y 5AH

Tel: +44(0)20 7969 5288
Fax: +44(0)20 7969 5298

Email: info@acmedsci.ac.uk
Web: www.acmedsci.ac.uk