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EMCDDA

MONOGRAPHS

Addiction neurobiology:
Ethical and social implications

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Editorial group

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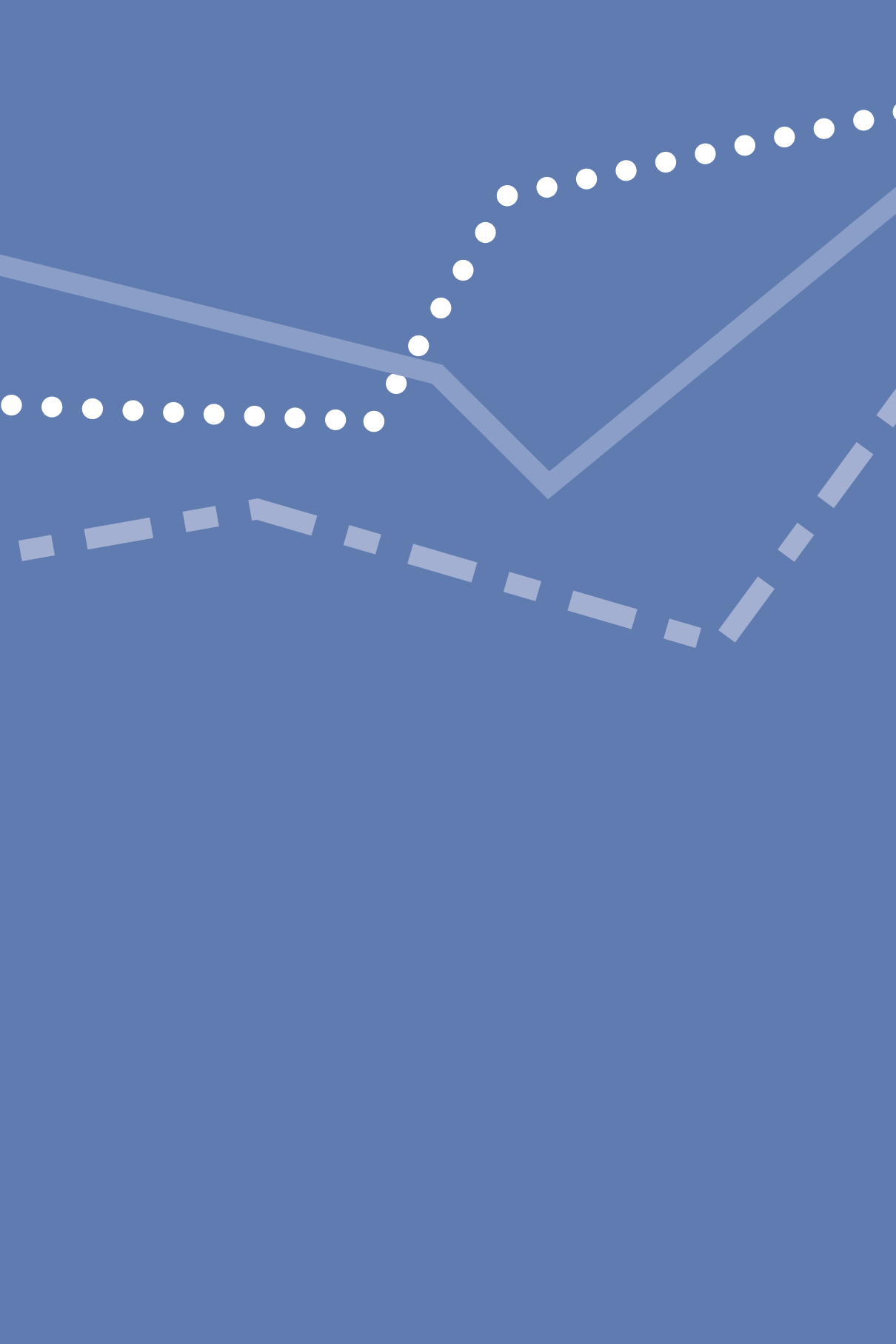


Foreword

In this report we review the developments in the neuroscience of addiction, explore how they might affect the way we view and treat drug problems, and consider the ethical issues that they raise for drug policy in Europe. The reader will find that it is difficult not to be both excited and apprehensive when considering the implications of the developments occurring in this field. Neuroscience provides us with a better understanding of how people become addicted to drugs and why they find it so difficult to stop, even when experiencing severe negative consequences. It also holds out the prospect of providing us with some novel approaches to both the prevention and treatment of drug problems. It may also lead to developments that — if misused — could have serious negative consequences, such as the unrestricted use of sensitive screening techniques or invasive and potentially dangerous surgical interventions.

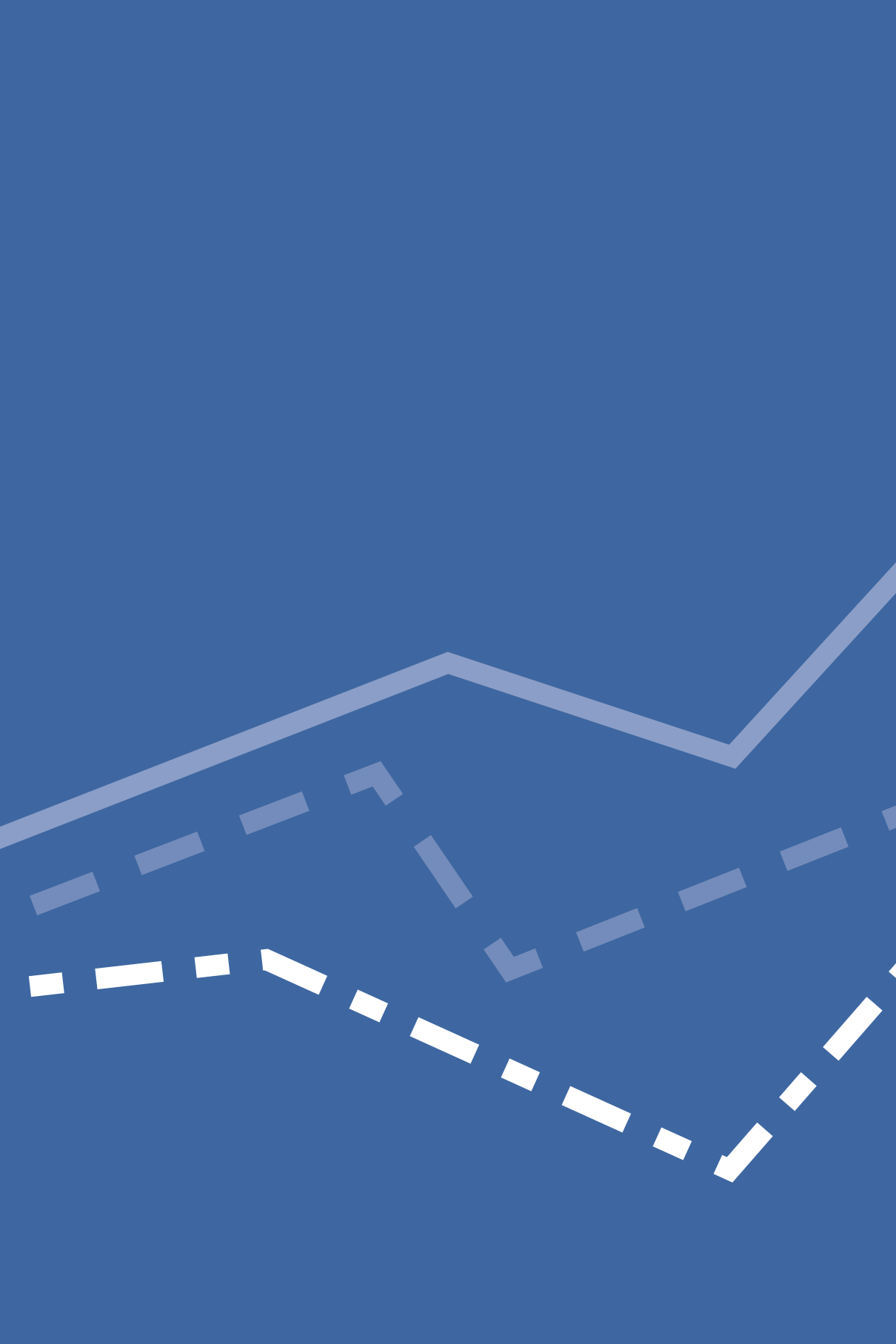
The focus in this report is on illicit drugs, but natural laws are not bound by the same conventions as human ones. The understanding that neuroscience brings is relevant to all drugs that have an abuse potential. Across Europe, a heavy price is paid from the addiction many of our citizens have to illicit drugs, alcohol or tobacco. Despite advances that have resulted in improvements in our ability to treat some drug problems, overall our therapeutic arsenal in this area still remains insufficient. For many, their addiction will constitute a long term and damaging problem where relapse is common and recovery difficult to achieve. Developments in neuroscience raise the exciting hope that a better understanding of the biological mechanisms of dependence will result in much needed new therapeutic opportunities and allow us greater success in reducing the health and social burden that this problem causes.

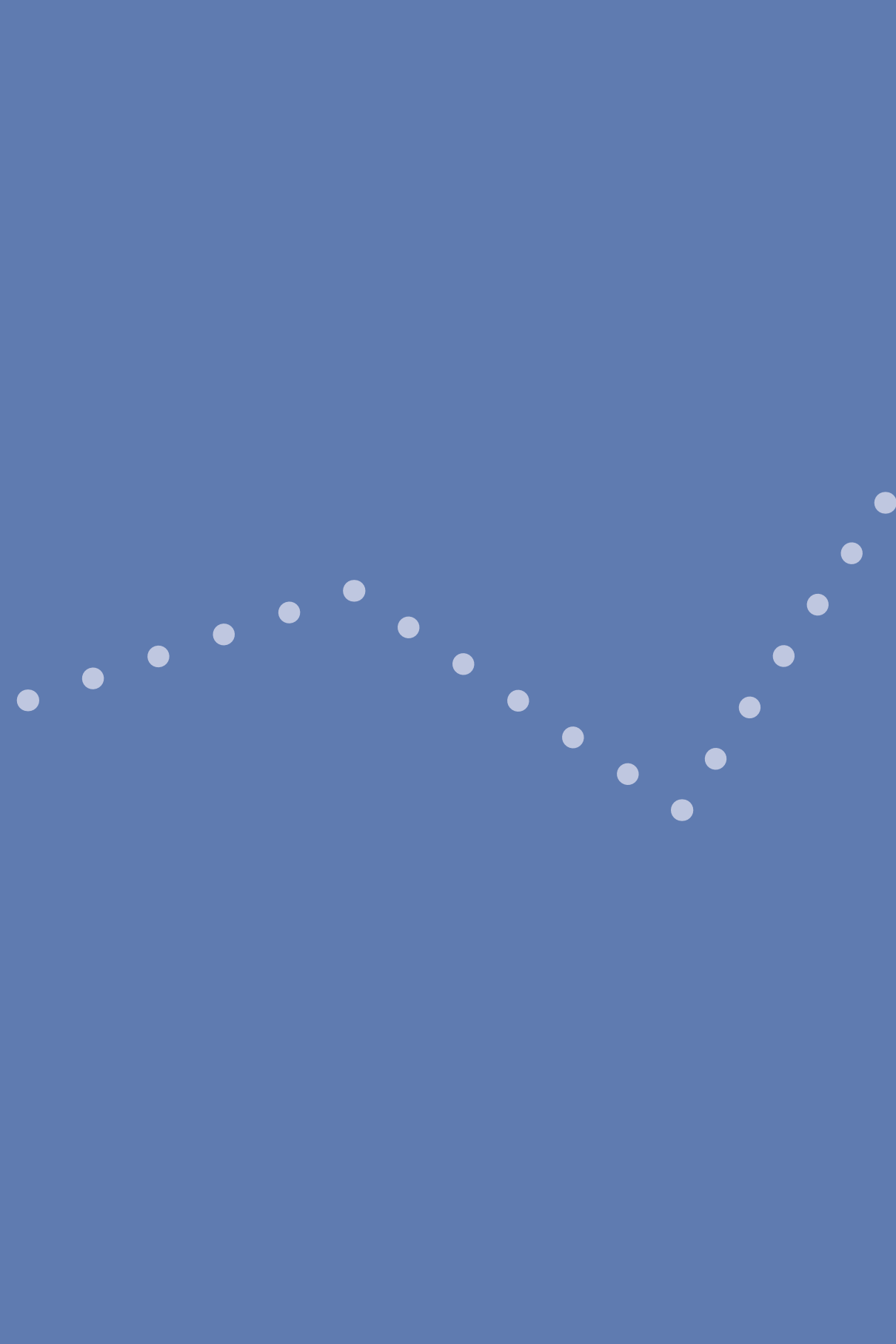
These potential benefits are clearly attractive but can lead to over-optimistic, misleading and even potentially damaging conclusions. The history of medicine provides us with many examples of how a desire to do good can result in harm. Our excitement for new approaches to a historically inextricable problem must therefore be tempered by the knowledge that any new approach requires rigorous testing before being introduced and there is always a need to consider equally the potential costs as well as benefits of any innovation. The rationale behind this report is that it is not only important to understand the basis for a neurobiological perspective on addiction, but equally important to understand the ethical and policy issues that developments in this area raise.

On a conceptual basis, neurobiology presents us with a powerful argument that addiction has a medical basis and addicts are in need of treatment rather than punishment. However, an over-simplistic interpretation of this view could lead to approaches that could undermine the basic principles on which health care is

provided in Europe — the right of patients to make informed choices about the treatment they receive. A major challenge for drugs policy will be to develop approaches that benefit from the advances offered by an understanding of the neurobiological basis of addiction, but that are also sensitive to the complex nature of drug problems. It is important to recognise that drug use and addiction are affected by individual and social choices as well as any underlying biological processes.

Wolfgang Götz
Director, EMCDDA





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The project was managed by Dominique Lopez (project manager) from the European Monitoring Centre for Drugs and Drug Addiction and Paul Griffiths (scientific coordinator). Marie-Christine Ashby ensured the editing and coordination of the final publication. We would also like to acknowledge the helpful comments and input received from other EMCDDA staff members: Cécile Martel, Norbert Frost, Alessandro Pirona and Margareta Nilson.

Executive summary

European burden of addiction and drug abuse

Addiction and drug abuse impose an enormous social and economic burden upon European society. Illicit drug use, whilst at lower prevalence than the use of alcohol or tobacco, has been estimated as accounting for approximately 2% of the total burden of disease in Europe. Estimates for the proportion of the total burden of diseases associated with tobacco and alcohol are around 12 and 10% respectively.

Neuroscience research on addiction

Neuroscience and genetic research of addiction are beginning to make significant progress in understanding the changes in the brain that underlie drug use and addictive behaviours. Neuroscientists now understand how addictive drugs produce neurochemical changes in the brain's reward pathway that make their use so appealing, and that drive some to use them repeatedly despite the harm that they cause. Neurobiological research also suggests that chronic drug use can produce long-term disruptions of neurocognitive circuits involved in motivation and attention, decision-making and the ability to inhibit impulses or urges. These changes focus addicts' attention on drug use, increase their craving for drugs, impair their appreciation of the consequences of their drug use, and make it more difficult for them to resist urges to use drugs.

Neuroimaging of the addicted brain has also identified persistent changes in the areas responsible for learning and memory. Chronic drug use produces neuroadaptation as well as persistent molecular and cellular changes in these neural circuits. These plastic changes can leave addicted persons vulnerable to relapse to drug use after months and even years of abstinence. Addiction research has also provided a deeper appreciation of how social factors, such as socio-economic status, upbringing, and exposure to abuse or violence, particularly while young, can interact with individuals' genetic make-up, leaving them at a higher risk of using drugs, and more vulnerable to developing addiction if they use drugs. Both genes and environment can have a significant impact on the neurobiology and psychology of the individual. Studies have also suggested explanations of why adolescents and young adults appear to be more susceptible to the negative effects of drug abuse, and are at higher risk of engaging in harmful drug use.

New technologies for the treatment of addiction and drug abuse

The emerging understanding of the neurobiological basis of addiction opens up the possibility of powerful new technologies for the treatment and, more controversially, the prevention of addiction or even to develop less harmful substances. Although some

of these developments remain speculative at present and others may prove politically unattractive, nonetheless developments in this area now raise the possibility of:

- novel pharmacotherapies targeted at specific neurotransmitter systems and behaviours;
- new formulations of these drugs, such as drug implants or slow release formulations which may last up to 6 months;
- drug vaccines which block the effects of addictive drugs;
- neurological treatments, such as deep brain stimulation and transcranial magnetic stimulation, that may ameliorate addictive behaviours;
- neuroimaging and genetic technologies to identify individuals who have a vulnerability to develop addiction, or to target appropriate treatments to individuals and possibly;
- the development of less harmful and safer forms of psychoactive drugs.

Ethical implications for the treatment of addiction and drug abuse

Addiction neuroscience also has the potential to change how we think about addiction and consequently the types of policies that may be adopted to deal with it. Neuroscience and genetic research could arguably transform the long running debate between moral and medical models of addiction by providing a detailed causal explanation of addiction in terms of brain processes, often referred to as the 'chronic and relapsing brain disease' model of addiction. It has been assumed by some addiction neurobiologists that this model will lead to public support for less punitive ways of dealing with addiction and increased access to more effective and affordable addiction treatments. However, causal models of addiction, if misinterpreted, could also lead to the neglect of social policies for reducing addiction and drug use and to more coercive policies towards addicted individuals.

Addiction is a highly stigmatised condition which causes significant harm across the EU. Strong moral disapproval of drug use can lead to discrimination against those with an addiction, possibly resulting in violations of their human rights. It could be argued, for example, that the existence of a minority within the European population who are genetically vulnerable to developing an addiction justifies:

- an increased use of legally coerced treatment, including the coercive use of long-acting pharmacotherapies, drug vaccines, and neurosurgical technologies;
- a greater reliance on medical approaches to treating addicted individuals, at the expense of social and population strategies that aim to reduce drug use or drug-related harm;

- preventing such individuals from consenting to participate in further addiction research or clinical trials;
- discrimination against vulnerable populations; and
- the promotion of inappropriate diagnostic tests and unevaluated treatments that may be attractive to desperate and vulnerable persons and their families, suffering from addiction.

Advances in genetic testing and neuroimaging that potentially enable us to identify 'addicts' or to predict future risk of addiction in adolescents also raise ethical concerns that include:

- invasion of privacy;
- the third party use of genetic and neuroimaging data;
- the powers of courts to coerce defendants to undergo tests; and
- consumer protection against the misinterpretation of test results.

In order to fully realise the potential for these new developments in the treatment and prevention of addiction, the EU will need to consider the potential ethical and social consequences of these new technologies and the impact that addiction neuroscience may have on how drug use and addiction are viewed and responded to by society. The ethical and social ramifications of this knowledge need to be considered to ensure that the rights of those with an addiction are upheld, and a balance is found between providing effective medical care and protecting European society from drug-related harm. Failure to do so could lead to unanticipated consequences which could affect the public's perception and acceptance of these technologies. Any inappropriate uses made of newer technologies could even work to the detriment rather than the benefit of those requiring treatment for addiction. Given significant public and media interest in the results of addiction research, a strong case can be made that neuroscientists and geneticists have both a moral obligation and a professional interest in avoiding popular misunderstandings of their work in the media.

An ethical approach to addiction research

There are a number of approaches which may be applied to ethical issues in addiction research. Although it is beyond the scope of this report to necessarily affirm any one of them, a broad conception of human rights has been used to frame the ethical discussions. The framework adopted here is that European policies towards the treatment of addiction and drug abuse, and the use of neuroscience and genetic research, should consider the following ethical values:

1) Autonomy — a person's capacity for self-determination;
2) Liberty — a condition in which an individual has the ability to act according to his or her own will within a coercive — but stabilising — framework of law;

3) Privacy — the ability of an individual or group to keep their lives and personal affairs out of public view, or to control the flow of information about themselves;

4) Consent — intentional mediation of relationships with one another and putting in place new relationships, and signalling their intentions and wishes; and

5) Equality — equal treatment by the law and in medical care.

These ethical values connect human rights to the wider-community interests, and may be used to establish a balance between the individual's rights and the 'public interest' or the 'public good' ([1]).

Policy issues arising for the treatment of addiction and drug abuse

Neuroscience research on addiction has the potential to significantly affect both the way in which we think about addiction and those that suffer from it. In light of recent research on the neurobiology and genetics of addiction, balancing these core ethical values with the broader interests of the European community has the following policy implications for the treatment of addiction and drug abuse:

1) More work is likely to be required to explore the ethical and policy implications of addiction neuroscience research to ensure that these developments are taken forward in ways that adequately safeguard human rights and protect the ethical values of consent, liberty, equality and privacy;

2) Appropriate responses to the drug problem will need to take into account emerging neurobiological 'disease' models of addiction;

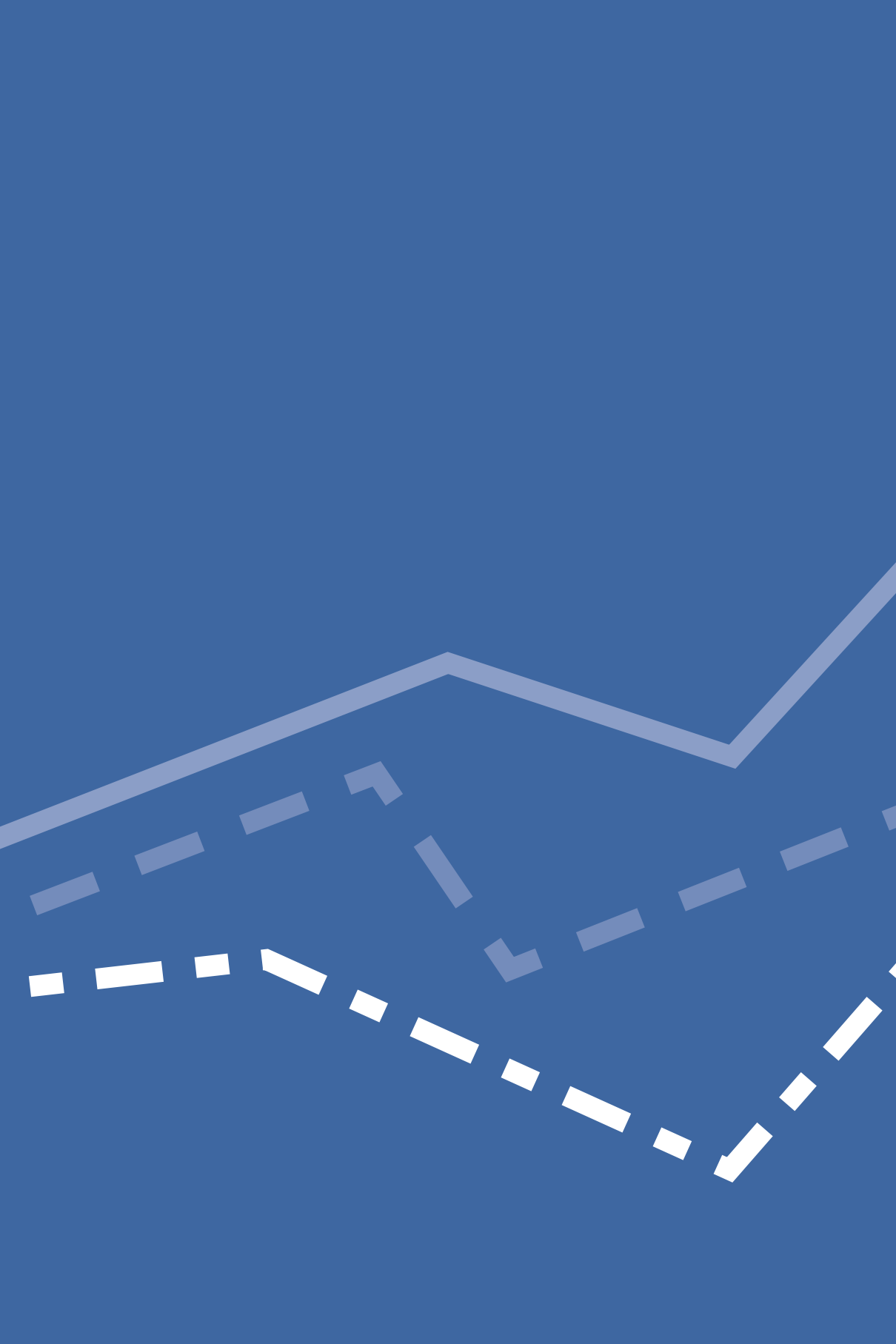
3) As novel neurobiological and genetic technologies are developed for the treatment of addiction, policy responses will need to consider public health issues, as well as criminal justice ones;

4) The autonomy of addicts is variable so care is required in using medical, paternalistic and criminal measures;

5) Measures are required to educate the public about the neurobiological and genetic contribution to addiction while recognising that addiction is nonetheless affected by individual and social choices; and

6) Neuroscientists and geneticists should be encouraged to disseminate their findings responsibly and accurately, and in ways that avoid potential misinterpretations.

([1]) The 'public good' and 'public interest' are sometimes treated as synonymous in the philosophical literature. The latter tends to be predominantly found in legal terminology. For simplicity, we refer to the 'public interest' throughout this report (see Capps, Campbell, ter Meulen, 2008).



General introduction

Over the last 20 years, the development of new techniques for studying the brain has led to a dramatic breakthrough in our understanding of neurobiological processes. The period 1990 to 2000 was designated 'the decade of the brain', and from this time onwards an increase in funding for neuroscience has been accompanied by growing professional and public interest in this subject. One of the issues identified as potentially fruitful for inquiry is: why, in both animals and man, do some substances result in a compulsion to use, even if they are harmful or result in negative consequences?

Historically, the nature of dependence and addiction has been as much an area for philosophical as scientific discourse. Indeed some have, and continue to, argue that the notion itself is a social rather than biological construct. However, this debate has been enriched by our ability to understand better the mechanism of the brain and neuroscience is now providing us with a growing understanding of the neurobiological basis for addiction. This understanding is important as it is likely to have implications for both how we understand, and respond to, the drug problems that modern societies face. There is now increasing evidence that many addictive phenomena have a genetic and neurobiological basis. Research in this area offers the promise of identifying the neural correlates of compulsive behaviour in addiction which could lead to more effective treatments for addiction and as a consequence increased investment in addiction treatment and further research (McLellan et al., 2000; Dackis and O'Brien, 2005; Volkow and Li, 2005). It can also be argued that an increased understanding of the neurobiological basis of addiction or drug dependence ([1]) will lend support for more humane social policies that recognise addiction as a neuropsychiatric condition that should be treated therapeutically (Dackis and O'Brien, 2005; Volkow and Li, 2005). This can be contrasted to the historically more punitive approach to addiction where it is viewed largely as a moral failing best dealt with by the criminal justice system.

Optimism about the benefit that a better understanding of the biological basis for addiction may bring needs to be tempered by more critical considerations, as overly simplistic or reductionistic interpretations of what this kind of approach reveals about addiction could result in less welcome consequences, especially if inappropriate use is made of some of the novel approaches emerging in this field. Indeed, some of the earlier pronouncements made about the implications of the decade of the brain for addiction treatment now appear overly optimistic. Even today, some proponents in this area appear to let their enthusiasm for promoting potentially useful new approaches run ahead of the emerging science and the need for appropriate testing and clinical scrutiny. This report attempts to tread a middle line, alerting the reader to the potential benefits emerging from this exciting area of new research but also arming them with an

([1]) The terms addiction and drug dependence are used interchangeably in this report.

understanding of the issues involved, the uncertainties that still exist, and the potential pitfalls that could result from the inappropriate use of some of the approaches that this research may soon make possible.

To achieve this aim, this report provides the latest understanding of attempts to get to grips with the brain changes that accompany illicit drug use, most notably in those that become addicted. We have tried to make the science understandable to a general audience although by necessity some of the concepts addressed are complex ones. The report investigates here both the possible welcome and unwelcome uses of neurobiological research with the aims of highlighting ways that will maximise the benefits that may arise, while minimising any unanticipated harms. The focus is on illicit drugs, rather than licit psychoactive substances, as this is the remit for the work of the EMCDDA. This distinction, from a neurobiological perspective, is to a large part arbitrary and much of the general argument applies equally to all substances with a potential to cause dependence. However, this approach is not without value as other reports have focused on the implications of neurobiological research on alcohol (Midanik, 2006) and tobacco (Hall, 2007), and the illicit nature of the drugs covered here has important implications for some of the ethical concerns explored.

This report falls naturally into two parts. First, a concise and accessible summary of the key findings of recent research on the genetics and neuroscience of addiction to illicit drugs is provided. Central to this is the delineation of the structures that make up the circuits within the brain that give rise to a system that is fundamental for our survival, reward processing. A number of key chemical neurotransmitters are pivotal in enabling this system to operate with dopamine playing a central role. The understanding that neuroscience provides of the importance of the reward system in addictive behaviour now means it may be possible to develop novel pharmacological treatments that could impact not only on the reward system per se but also on those systems that sub-serve cognitive functions such as learning and memory.

The second part of this report explores some of the key social and ethical issues raised by neurobiological research (a term used as shorthand here to cover both genetic and neuroscience research). This includes a discussion of how this research may influence the way that modern societies think about drug use and addiction and deal with the ethical issues raised by technological applications of this knowledge. The report also considers the more speculative possibility that addiction neurobiology may improve our ability to prevent the development of addiction (e.g. by using genetic screening to identify individuals at high risk of addiction and 'drug vaccines' to prevent these individuals from using drugs). The analysis is limited to the use of medical (e.g. neurological, immunological, and pharmacological) treatments of addiction. However, an important caveat is that psychosocial therapies, although not addressed in detail in this report, play an important part in the treatment of addiction, and are a critical adjunct to the effectiveness of existing medical treatments. This should not be taken as an indication

that psychosocial treatments will not continue to play a significant role in the future of addiction treatment, rather that the major ethical issues raised by developments in the neuroscience of addiction involve the application of medical technologies.

Any report on this topic risks becoming quickly outdated as new scientific findings emerge. Some of the approaches described here have already advanced to the stage of clinical trials and may make an important contribution to the future treatment of addicted individuals. Other approaches may fall by the wayside as further investigation reveal them to have limited potential or practical application. For this reason it is not the aim of this report to make any definitive conclusion on the issues raised. Rather by highlighting recent advances in neurobiology of addiction, and the ethical issues that arise from such knowledge, the aim is to encourage a more informed discourse on the implications of neurobiological research on addiction within the European Union. To this end, the report concludes with some general suggestions about the directions in which this debate is likely to develop and those areas that will clearly require further consideration and investigation. Some observations are also elaborated, within a general context of human rights and good clinical practice that are relevant to any future policy consideration of how new approaches might be applied. Genetic predisposition and the information from genetic treatment, the use of drug vaccines and coercive treatment are just a sample of the issues that both the public and politicians alike will have to contend with in the coming years as our understanding of the neuroscience and genetics advances. It has been an amazing achievement to begin to unravel the complexities of the brain and understand the insights that this knowledge provides for our understanding of drug dependence. But the complex issues in this area are not all biological ones, perhaps an equal challenge will be ensure these findings are applied in ways that maximises benefits and avoids unintended or unwelcome consequences.

Richard Muscat, Adrian Carter, Paul Griffiths, Dominique Lopez and Wayne Hall

Chapter 1

What is addiction?

Adrian Carter, Wayne Hall and Benjamin Capps

Introduction

Addiction and drug abuse exact an enormous toll upon European society, largely as a result of premature death, physical harm and increased health care costs, violence and crime. A significant proportion of the European population will become addicted to licit or illicit drugs during their lifetime. Given the health and social burden of addiction, there is strong public interest in preventing addiction and improving the chances that addicts will stop using drugs. The policies that are often used to pursue these goals depend critically on how drug use and addiction are understood.

Drug addiction is a pattern of behaviour in which an individual uses a drug despite the harm that its use causes, and despite often wanting to stop. Many addicts report they find it difficult to stop using drugs and they are likely to relapse to drug use if they succeed in stopping. There has been significant controversy about the nature of addiction between supporters of two dominant models. Medical models hold that addiction is a psychiatric disorder that requires treatment. In contrast, moral models are sceptical about the existence of an addictive disorder and see drug use as a choice that individuals make and for which they should be punished if the drug use is illegal or if they engage in criminal behaviour to fund their drug use.

Neuroscience research promises to clarify our understanding of drug use and addiction by showing how drugs affect brain function and how chronic drug use changes the brain in ways that make it more difficult for addicts to stop using drugs. The chronic use of addictive drugs produces enduring changes in the motivation, learning and decision-making centres of the brain that focus attention on drug use and impair the ability to choose not to use drugs (see Chapter 2). This research has led to the 'chronic and relapsing brain disease' model of addiction.

This research has the potential to significantly impact upon the way in which we treat addiction. Scientific knowledge about the neurochemical changes underpinning addiction promises to improve our ability to treat, and possibly, prevent addiction. Neuroscience research may also change the way in which society thinks about addiction and the legal and social policies that are appropriate to deal with it. If addiction is a brain disease that impairs behaviour, it may lead to more humane treatment of those with an addiction. Conversely, it may also be used to increase support for more coercive use of medical technology to treat or more controversially 'cure' addiction.

This section outlines the social and economic burden of drug use and addiction in Europe. It also outlines the very different ways in which drug use and addiction have been understood and discusses how this understanding has changed in response to addiction neuroscience research. The sections that follow will explore the impact of neuroscience on addiction in greater detail, and analyse the ethical and social implications of this research for European policy.

The cost of addiction

Addiction, or drug dependence, is a chronic condition which has an enormous adverse impact on society. In most western countries, such as the United Kingdom (UK), United States (US) and Australia, a significant proportion of the population will develop an addiction to illicit drugs during their lifetime (lifetime prevalence range 4–6 %) or alcohol (8–15 %) or both (AIHW, 1999; Kessler et al., 2005; SAMSHA, 2006; McKeganey et al., 2007) ([1]). A wider range of prevalence estimates have been reported in European countries, with point prevalences for illicit drug dependence ranging from 0.1–2 %, and 0.1–7 % for alcohol (Andlin-Sobocki and Rehm, 2005) ([2]).

By definition, addiction is the habitual use of a substance (or engaging in an activity such as compulsive gambling) despite the harms caused and impaired control over use, as indicated by failed attempts to stop. Addiction is commonly understood as a disorder ([3]) in which an individual's control over their drug use is impaired. People with an addiction continue to use drugs in the face of enormous negative consequences, and despite often expressing a wish that they could stop. This definition is codified in the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Illness, 4th edition Text Revised) and ICD-10 (International Classification of Diseases, 10th edition) diagnostic criteria for substance dependence or addiction, which describe it as a 'loss of control' over drug use, where drug taking becomes 'compulsive' and consumes a great deal of an individual's time and resources, to the detriment of other important social roles, such as working or caring for children (World Health Organization, 1993b; American Psychiatric Association, 2000).

Drug abuse and addiction lead to increased deaths from suicide, overdose and drug-impaired driving. There are also increased health costs from the toxic and psychopathological effects of chronic drug use (e.g. liver cirrhosis from alcohol abuse, drug-induced psychoses, cognitive impairments and drug-related injuries),

([1]) These statistics do not include addiction to substances such as nicotine and caffeine.
([2]) Prevalence data varies considerably, and is plagued with methodological inconsistencies. Levels of dependence and substance abuse can differ significantly between countries, and the types of drugs abused may vary across Europe. The EMCDDA website provides more detailed data on drug use prevalence in all EU Member States: http://www.emcdda.europa.eu/
([3]) The term 'disorder' may be seen as implying a disease model of addiction, but in this instance the term is being used in its weakest sense to describe patterns of behaviour that commonly co-occur, are statistically uncommon and are associated with social and personal impairment.

and the complications of injecting drug use that include thromboses, septicaemia and the transmission of human immunodeficiency virus (HIV) and other blood borne diseases. It is estimated that there are between 6 500 and 8 500 acute drug-related deaths (e.g. overdoses) in Europe every year (approximately 3.5 % of all deaths in European adults aged 15–39 years in 2005–06) adding up to about 130 000 deaths since 1990–2005 (EMCDDA, 2008). These figures do not include deaths attributed to drug-related accidents, violence, suicides or chronic illnesses. Within some European cities, approximately 10–23 % of the overall mortality among young adults (15–49 years old) can be attributed either directly or indirectly to opioid use (EMCDDA, 2008).

Addicted illicit drug users also often engage in crime and violence to finance their drug use. This leads to substantial judicial and prison costs. Illicit drug abuse is associated with increased criminality, with 65–80 % of arrestees in the UK having used illicit drugs in the 12 months prior to being arrested (McKeganey et al., 2007). Chronic use of some substances (e.g. cocaine and methamphetamine) can also produce neuropsychological changes associated with impulsive violence. Drug abuse leads to lost employment and increased social welfare, and broader adverse impacts on families and relationships (EMCDDA, 2006; Hall et al., 2006).

The social and economic costs of drug abuse and addiction in European nations are substantial (EMCDDA, 2008). There is limited consistent data on the cost of drug abuse in Europe, as Member States differ significantly in what they report as a drug-related cost (EMCDDA, 2008). While the economic burden of drug abuse and addiction can be difficult to quantify, ([4]) it has been estimated that 10 % of the overall burden of disease in Europe is attributable to substance use disorders and addiction (Rehm et al., 2005). In the UK, where reporting includes a broad range of drug-use associated costs, the estimated current economic burden of illicit drug use is GBP 13 billion/year, largely due to costs associated with crime. Alcohol contributes a further GBP 20 billion/year (Nutt et al., 2007a). Studies suggest that the burden of drug use is rising because of increases in the number of people abusing drugs and in the quantity of drugs that they use (EMCDDA, 2007a; McKeganey et al., 2007).

Despite the enormous costs of addiction and drug use, a minority of those with addiction receive treatment, and often this treatment is only modestly effective (McKeganey et al., 2007). Of those that did receive treatment in 2006, half were treated primarily for opioid use (principally heroin), and increasingly given access to effective treatments, such as methadone and buprenorphine maintenance (EMCDDA, 2008). However, the majority of individuals with a drug addiction do not receive treatment for their condition in the US (Demyttenaere et al., 2004), or the UK (McKeganey et al., 2007).

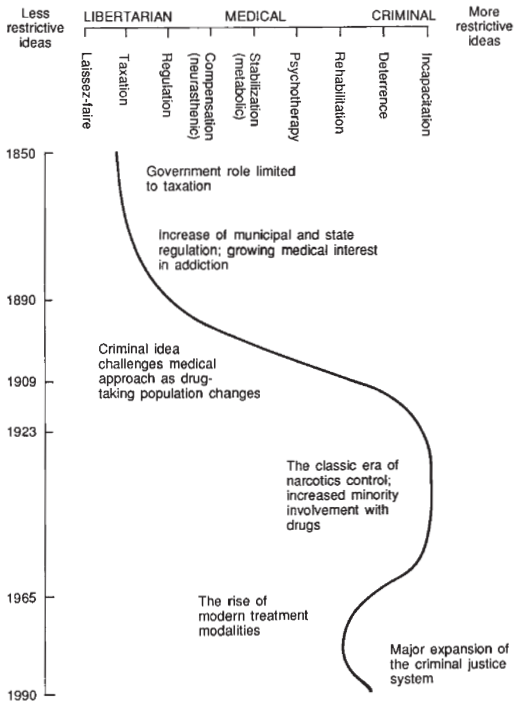
([4]) Not only do countries differ in what they report as a burden on drug use or addiction, but it can be difficult to distinguish between what is a burden of a substance use disorder, and what is a consequence of non-addicted drug use (Andlin-Sobocki and Rehm, 2005).

The non-therapeutic use of opiates (e.g. heroin or morphine) and psychostimulants (e.g. cocaine or methamphetamine) is prohibited in all European countries. Cannabis is illegal in most European countries although laws on possession and use are often not rigorously enforced. The distribution of these drugs is illegal and many individuals may be charged with an offence, and possibly imprisoned as a result of criminal activities (such as drug selling or property crime) that are engaged in to fund the use of an expensive illegal substance.

Understanding addiction

The way in which society has traditionally understood addiction, and thought of those who are addicted, has changed over many decades (White, 1998). Addiction is a complex behavioural disorder that is influenced by biological, psychological and sociological factors. It is the prototypical biopsychosocial disorder. As our understanding of how each of these elements impacts on addiction changes, so do our social policies to deal with it, as well as the treatments that are used to reduce or prevent it. This section describes two competing models of addiction — the medical and moral, or sceptical models of addiction. These two models represent the extremes of perceptions of addiction and provide a useful construct with which to think about governing views of

Figure 1: Governing ideas about drug use



This is a schematic diagram depicting the development of dominant attitudes towards drug use during the twentieth century. The trajectory of the line was determined from an expert committee's judgements about the 'ideological "centre of gravity"' in the US, based on canonical historic texts (Gerstein and Harwood, 1990). Arguably, since this study was conducted, there has been a considerable shift back towards the medical model of addiction, largely due to advances in the neuroscience research of addiction.

addiction ([5]) (see Figure 1). This section analyses the ability of each model to explain the phenomenology of addiction and highlights some of the potential consequences of each approach for social policies and treatment outcomes.

Sceptical versus medical models of addiction

The dominant 'moral' or 'sceptical' view of addiction holds that 'addicts' are simply drug users who knowingly and willingly choose to use drugs without regard for the adverse consequences that their actions bring upon themselves and others. In this sceptical view, 'addiction' is an 'excuse' for continuing to use drugs while 'avoiding responsibility' for the consequences of doing so (Szasz, 1975; Davies, 1997).

Sceptical views make sense of one of the key features of 'addictive behaviour': drug use is initially a voluntary choice that develops into an addictive pattern in a minority of those who use most drugs, including the most addictive illicit drugs such as heroin, and cocaine (Anthony et al., 1994). Proponents of this view argue that even among the significant minority of drug users who do become addicted, most succeed in stopping their use by themselves (Peele, 2004).

Sceptical views of addiction, however, are inconsistent with a number of reliable empirical observations about drug use and addictive behaviour. First, a significant minority of people who use drugs become addicted and the size of that minority depends on the way that the drug is consumed and its pharmacological actions, e.g. its rapidity of onset and duration of effect (Anthony and Helzer, 1991). Hence, short-acting opioids like heroin that are injected are more likely to result in addiction than drugs like alcohol that people drink. Second, there is also an identifiable subset of individuals who are more likely to develop an addiction. This includes people who have more contact with drugs or peers who use drugs, who use drugs at an earlier age, who are from socially disadvantaged backgrounds or perform poorly in school, who have a family history of addictive behaviour, or suffer from a mental disorder (Hawkins et al., 1992). Third, the use of drugs in the face of often serious negative health and social consequences and in the absence of any pleasure derived from their use, suggests that addiction is more than mere wilful bad behaviour. These observations have led to a 'medical centred' model of addiction, according to which heavy drug use over long periods of time produces physiological and psychological changes in the individual that progressively override the degree of 'choice' they are able to exercise in using the drug.

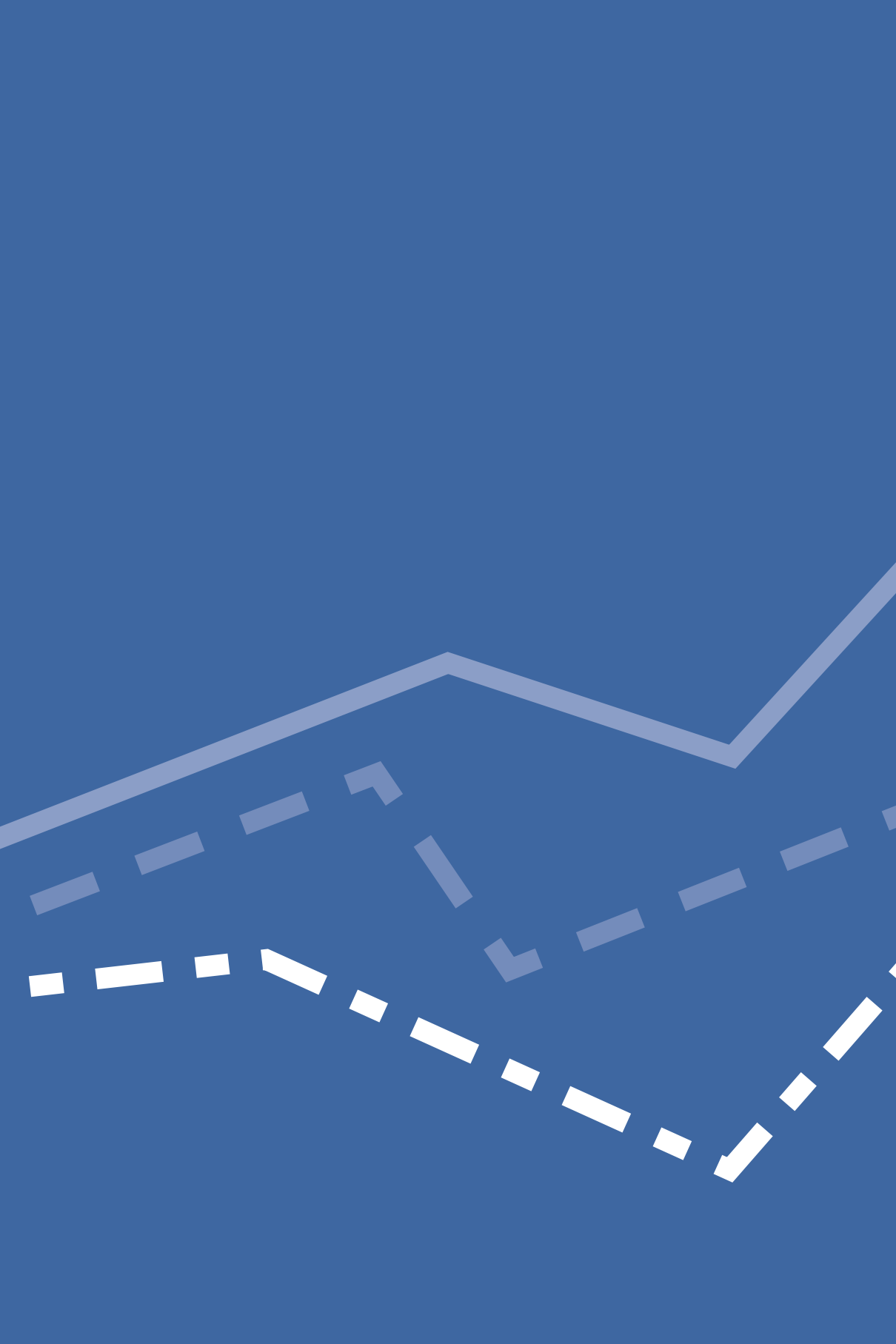
The worldwide prevalence of sceptical views of addiction, and the significant personal and social harm that drug abuse causes, have led to punitive laws to discourage drug use, and a comparative lack of investment in medical research into addiction or the development of interventions to treat it. Despite the broad acceptance of these policies,

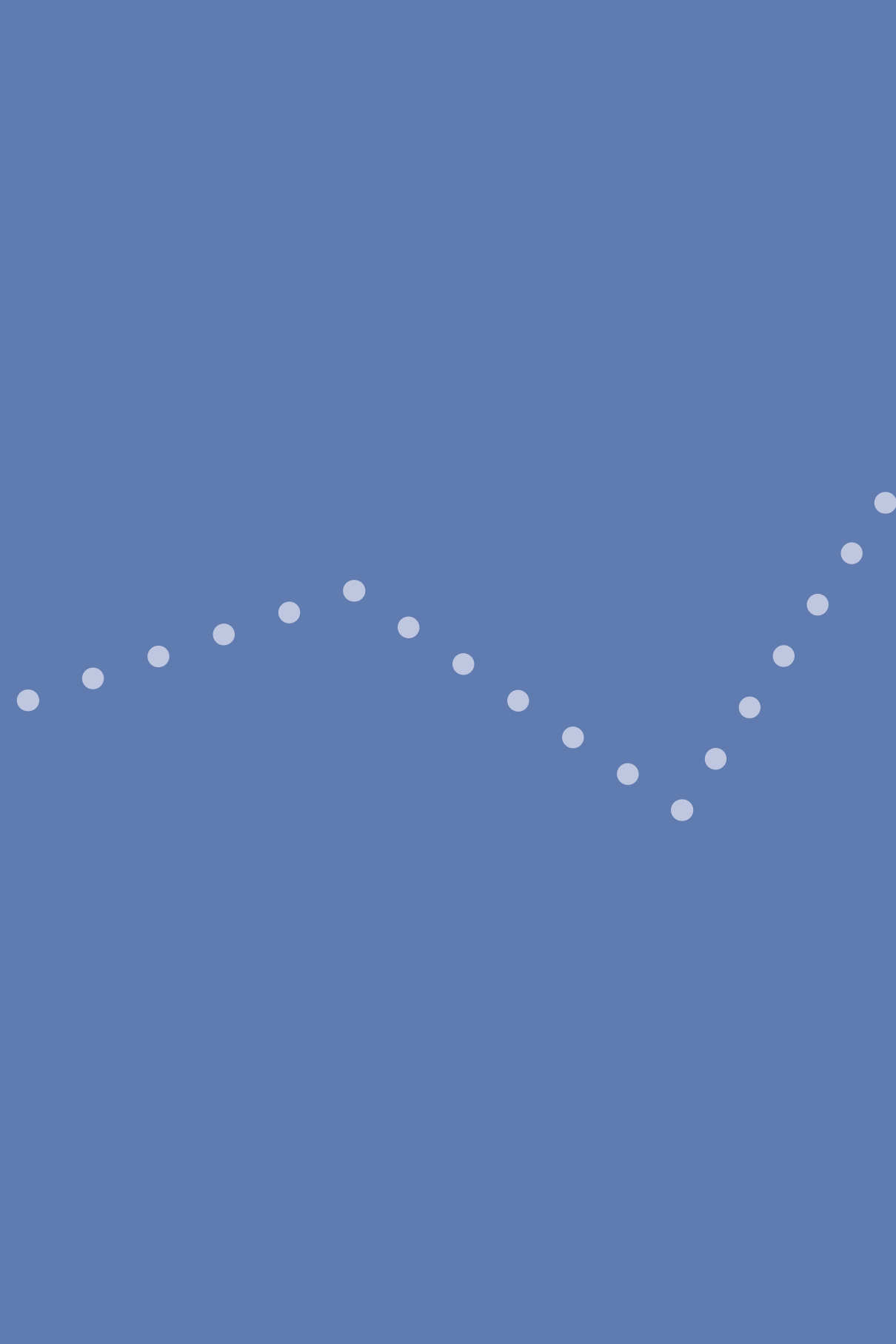
([5]) It is important to note they these two models are generally only theoretical constructs for understanding addiction. Most real-world views on addiction lie somewhere along a continuum between these two views.

efforts have largely proven ineffective in reducing drug use and addiction, and have often contributed to the social cost of addiction by leading to the imprisonment of many drug users who typically return to drug use and re-offend upon release (Gerstein and Harwood, 1990; National Research Council, 2001). These policies have also led to discrimination and inappropriate restriction or derogation of the rights of those who are addicted. The fact that these policies have been largely unsuccessful in reducing drug use or addiction indicates that alternative explanations are required that consider the effect that repeated drug use has on an individual's ability to choose whether or not to take that drug. Such explanations increasingly appeal to neurobiological theories of addiction, which lend support more readily to 'medical centred' policies. Although such policies still advocate predominately punitive measures, medical treatment and social support and action are also encouraged to deal with addicts and problem drug users.

The 'Chronic and Relapsing Brain Disease' model of addiction

Neuroscience research of addiction is challenging traditional notions of addiction as a purely voluntary choice. Studies are beginning to show that chronic drug use can produce long-lasting changes in brain function that make drug use a central preoccupation and undermine the capacity of individuals to refrain from using drugs. A theory that is gaining widespread attention, particularly in the US, is the 'chronic, relapsing brain disease' model first described by the former Director of the National Institute on Drug Addiction (NIDA), Dr. Alan Leshner (1997). According to NIDA, addiction is caused by chronic self-administration of drugs that produce enduring changes in brain neurotransmitter systems, leaving addicts vulnerable to relapse after abstinence has been achieved (Leshner, 1997; Volkow and Li, 2005). In the same way that cardiovascular disease is a result of abnormal heart tissue, the chronic disease model of addiction holds that addiction is the result of abnormal neural tissue (Volkow and Li, 2004).





Chapter 2

The neurobiology of addiction

Adrian Carter, Wayne Hall and David Nutt

Introduction

Neuroscience is beginning to uncover the neurochemical changes that occur within particular functional regions of the brain that are responsible for the behaviour in addiction. In doing so, neuroscience research is beginning to help us see that those who are addicted to drugs suffer from neurocognitive and motivational impairments that require treatment.

Our cognitive abilities enable us to quickly discern which activities are worth pursuing in our environment. We engage in activities that are 'rewarding' and serve survival values such as obtaining food, shelter, or sex. These rewards are generally experienced as pleasurable and motivate behaviour. We quickly learn which activities are rewarding and what environmental cues are associated with receiving these rewards. These cues acquire an incentive or motivating quality that ensures that we pursue the goals that they signal in the future.

Highly motivating goals or events become deeply engrained in our thinking, allowing us to respond to these rewards quickly and effortlessly, habitually and without conscious thought. This learning increases the efficiency and power of thought by focussing our attention and energy on what is relevant in the environment, making it more likely that we will achieve our goals with a minimum of effort.

Not all forms of learned and rewarding activities are desirable. In addiction, drug use becomes over-learned because repeated drug use over-activates the central reward systems in the brain, enabling drug use to take precedence over all other goal-directed activities that are essential to survival. This ability for addictive drugs to strongly activate the reward pathway is commonly referred to as their reinforcing effect. Chronic use of addictive drugs can also dampen the central reward pathway's responsiveness to everyday rewarding activities that motivate us and give life meaning, such as relationships, work and education. These changes are also believed to explain why the pursuit of drugs can come to dominate the lives of many addicts, at the expense of most other interests.

Addiction also impairs a number of other cognitive processes that perpetuate drug use. Many of these are included in the diagnostic criteria for drug dependence or addiction (World Health Organization, 1993b; American Psychiatric Association, 2000). They include:

- a feeling of compulsion to use drugs;
- an impaired ability to avoid using drugs when opportunities arise;
- an impaired understanding of the consequences of continued drug taking; and
- the ability for cues associated with drug use (e.g. location, time of day, or activities) and stress to produce a relapse to drug use in an abstinent individual, even months or years after stopping.

Addiction neurobiology is beginning to uncover how chronic use of addictive drugs can also disrupt other important neural pathways in the brain that lead to these cognitive deficits.

Chronic drug use can produce neurochemical changes in the higher cortical regions of the front of the brain (the frontal cortex), that make drug use so appealing, and can impair the ability to override impulses not to use drugs. This has the effect of focussing the attention of the addicted individual on drug use, and can make decisions not to use drugs more difficult. These changes are also believed to explain the emergence of intense cravings for the drug of addiction, and continued drug use despite enormous negative consequences for the addict. Neuroadaptations within other parts of the frontal cortex are also understood to be involved in the impaired ability to appreciate the consequences of continued drug use.

The discovery of persistent changes within the regions of the brain responsible for learning and memory also helps to explain why relapse to drug use is so common, even despite months and sometimes years of abstinence. Neuroadaptations at the synapses within these regions give memories of drug use a heightened salience. Consequently, events or cues that recall these memories (e.g. an image of injecting equipment or the drug itself; revisiting places where the drug was consumed), have the ability to trigger intense cravings for the drug of addiction, which often results in a relapse to drug use. These neuroadaptations have been seen in addicted individuals who have been abstinent for months (Volkow and Fowler, 2000). Stress is a potent trigger of relapse, and neuroscience is also beginning to explain how chronic drug use can leave addicted individuals vulnerable to relapse when under stress.

Research has also identified neuropsychological and genetic differences in individuals that may influence their chances of developing addiction if they use drugs. By providing a better understanding of how addiction develops, this research highlights the potential for new psychological and pharmacological treatments to treat and, more speculatively, prevent addiction (see Chapter 3).

Neuroscience suggests that addiction is a pathological behaviour in which addictive drugs co-opt normal learning and motivating pathways in the brain so that drug taking comes to dominate all other goal-directed activities. Such a view has the potential to not only unlock a wide array of new and powerful treatments of addiction that target or ameliorate these changes, but also has the potential to change how we think about and treat those with an addiction (see Chapter 1 and this chapter). Given the central importance of the brain and the strong moral attitudes that many people feel towards those who abuse or are addicted to drugs, the nature and impact of these changes needs to be considered. Such an analysis will need to critically examine the emerging neuroscience research on addiction. This research also has implications for the types of social policies we use to reduce addiction and harmful drug use. The social and ethical implications of this research are explored in Chapter 5. This section will review current neuroscience research of addiction, and will explain how the chronic abuse of addictive drugs can alter the neurochemical structure and function of the brain in ways that lead to the psychology of addiction.

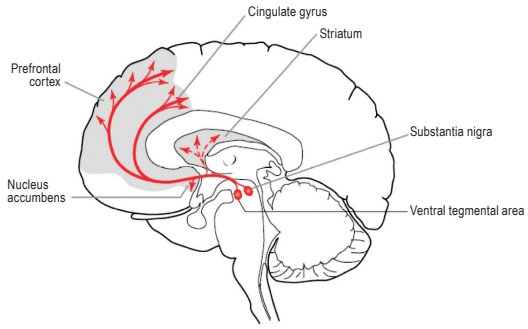
The neuroanatomy of addiction

Addiction is a quintessentially complex behavioural disorder that operates at the biological, psychological and social levels. This complexity is reflected in the number of neurocognitive systems that are affected by drug addiction. These systems have often been studied in isolation, leading to the development of competing partial models that purport to explain all of addiction. A more complete picture of the neuroanatomy of addiction is beginning to emerge from the convergence of these different approaches.

Neuroimaging, using technologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), has provided critical insights into the way in which drug-induced changes in the brain can produce the type of cognitive deficits seen in drug-addicted people. The ability to directly visualise the brain of addicted individuals has identified changes in multiple brain systems that may explain loss of control and compulsive drug taking. These changes may also explain why abstinence is difficult to achieve and why relapse so often occurs after long periods of abstinence.
The neurocognitive systems that are affected by addictive drugs include:

- reward and reinforcement — in the nucleus accumbens (NAcc)
- compulsion, craving and inhibitory control — in the orbitofrontal cortex (OFC) and anterior cingulate gyrus (aCG)
- executive control and cognitive impairment — in the prefrontal cortex (PFC)
- memory, learning and habits — in the amygdala, hippocampus and striatum
- representation of bodily urges — in the insula cortex
- stress — in the hypothalamic-pituitary-adrenal (HPA) axis.

Figure 2: Projections from midbrain and NAcc to forebrain



Dopaminergic neurons from the ventral tegmental area and substantia nigra, project to the central reward area, the nucleus accumbens and to the cortical areas primarily responsible for making decisions, such as whether to use drugs (e.g. the prefrontal cortex and the anterior cingulate gyrus). Projections from the midbrain also make connections with the striatum (e.g. caudate and putamen). Source: (Hyman et al., 2006).

Changes to the dopaminergic reward pathway, with its dense connections to the forebrain and the higher cognitive centres of the frontal cortex, are central to the development of addictive behaviours (see Figure 2). However, this is not the complete picture. This research is still only in its infancy and there is still considerable uncertainty about the degree to which these neural regions are involved in addiction. It is also unclear how the activities in these various brain regions differ between individuals. In particular, there is debate within the field as to whether addiction results from (1) abnormally strong urges, drives or motivation that overcome our normal ability to inhibit behaviour or exercise executive control, or (2) cognitive impairment that reduces the ability to inhibit everyday impulses, or (3) some combination of the two.

This section briefly reviews neuroanatomical and neurochemical changes that underpin these cognitive behaviours and how they develop and maintain the cycle of addiction. It concludes with a brief review of individual differences in genetic and neuropsychological make-up that can leave some vulnerable to drug use, or developing an addiction if they use drugs. The impact that social events can have on how these vulnerabilities are expressed is also briefly discussed.

Reward and reinforcement: the 'Dopamine Hypothesis'

In 2007, neuroscientists celebrated the 50th anniversary of the discovery of the key neurotransmitter, dopamine, by Arvid Carlsson who won the Nobel Prize for Medicine in 2000 (Bjorklund and Dunnett, 2007). It is probably the most widely studied neurochemical, and it has had a greater impact on biological psychiatry and psychopharmacology than any

other neurotransmitter (Iversen and Iversen, 2007). Dopamine is a central neurotransmitter that serves a variety of functions. These include: the fine-tuning of motor control and cognitive function; modulating the salience of events and attention, learning and memory; bonding and attachment in relationships; and the planning and motivation of behaviour. Many of the most widely used medications in psychiatry act on the dopaminergic system. It is now widely accepted that dopamine also plays an important role in addiction to most drugs of abuse (Volkow and Li, 2004), although the nature of this role remains a subject for debate and further study. Research is beginning to show that addiction also involves changes within a number of neurochemicals and neurotransmitter systems such as the endogenous opioids, glutamate and gamma-aminobutyric acid (GABA) (Goodman, 2008), some of which are discussed below. While changes in these systems are indeed important in a variety of addictions, they nearly all appear to exert their influence through the dopaminergic reward system (Goodman, 2008). A complete discussion of all the neurochemicals involved in addiction is beyond the scope of this report. Those interested in the neurochemical activity of other molecules in addiction, in particular the important roles of norepinephrine and serotonin should refer to the comprehensive review by Goodman (2008) ([1]).

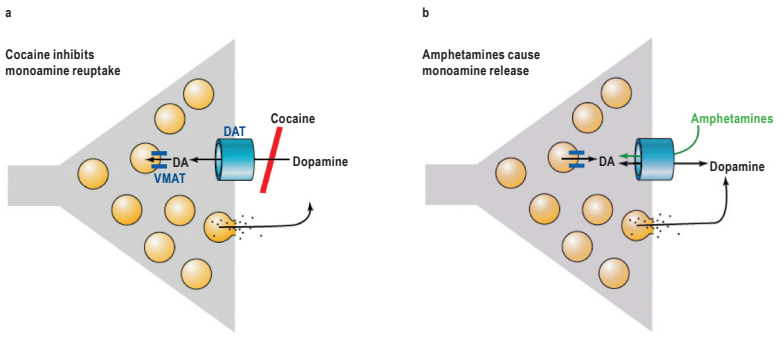
Amphetamines, cocaine, alcohol, nicotine and cannabis, directly or indirectly, act on a forebrain structure known as the nucleus accumbens (NAcc) producing large and rapid releases of dopamine (Robbins et al., 2007). This increase in dopamine is central to the development of addiction. The signal produced by these drugs originates in the neurons of the midbrain ventral tegmental area (VTA), which release dopamine into synapses in the NAcc (Wise and Bozarth, 1987; Koob and Bloom, 1988; Di Chiara, 1998), as shown in Figure 2. Cocaine, amphetamines, and ecstasy directly increase the amount of dopamine available for post-synaptic signalling either by increasing dopamine release or by reducing dopamine reuptake from the synapse (Hutcheson et al., 2001) ([2]). (See Figure 3). Alcohol, cannabis and nicotine ([3]) increase dopamine activity indirectly, by stimulating neurons that influence dopaminergic neurons (Koob and Le Moal, 1997; Nisell et al., 1994). For example, as shown in Figure 4, alcohol binds to GABA receptors that reduce the inhibitory influence of GABAergic neurons on dopamine-firing cells.

([1]) Since 2005, pharmacological and genetic studies have highlighted an important role for norepinephrine and serotonin in the development and maintenance of addictive behaviours (Salomon et al., 2006). It has even been suggested that these changes could occur independently of dopamine (Lanteri et al., 2007). Such research appears to contradict studies that block dopamine during the self-administration of addictive drugs in animals (Koob and Le Moal, 2006). There is considerable debate in this area and more research is required. Interested readers are directed to a recent article in *Biochemical Pharmacology* (Tassin, 2008).

([2]) Dopamine reuptake is reduced by blocking the dopamine agonist transporter (DAT), which increases the amount of dopamine in the synapse, and therefore dopamine signalling.

([3]) It must be noted that nicotine appears to be an atypical addictive drug as the increases in dopamine as a result of nicotine ingestion are not as high as those seen with other addictive substances (e.g. psychostimulants and opiates). There is some evidence to suggest that the addictive capacity of nicotine may depend in part on other chemicals contained in tobacco, such as the monoamine oxidase inhibitors (MAOIs) (see Villegier, 2006).

Figure 3: Psychostimulant increase of dopamine activity at the accumbens



Stimulants such as cocaine and amphetamine increase synaptic dopamine at the nucleus accumbens by: (a) blocking the dopamine agonist transporter (DAT) (i.e. cocaine) which reuptakes dopamine from the synapse, thus increasing the amount of dopamine active in the synapse thereby increasing dopamine signalling; or (b) entering the dopamine neurons via the DAT (i.e. amphetamine) and causing an increase in dopamine released by the neuron (Hyman et al., 2006).

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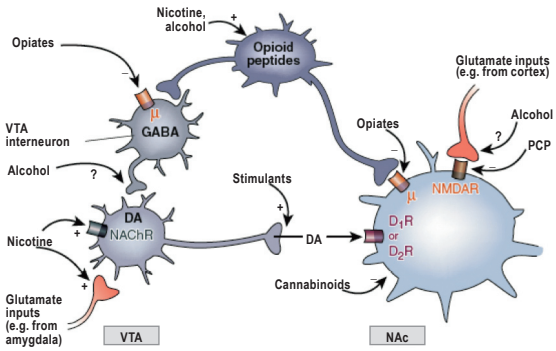
Abbreviations: DA: dopamine; VMAT: vesicular monoamine transporter.

Figure 4: Actions of a variety of drugs on accumbal dopamine activity



Nearly all drugs of addiction act by increasing the release of dopamine in the nucleus accumbens (here indicated as NAc; bottom right). This increase may be direct, such as the case with stimulants, which increases the release of dopamine by neurons of the ventral tegmental area (VTA; bottom left). Other drugs of addiction (e.g. alcohol, cannabis and nicotine) increase dopamine activity indirectly, by influencing neurons which then change the amount of dopamine released into the NAcc. This may be the result of an inhibition of a disinhibiting response, such as occurs with opiates, as well as an excitatory response (e.g. nicotine). Note: '+' refers to an excitatory response, '-' denotes inhibition (Hyman et al., 2006).

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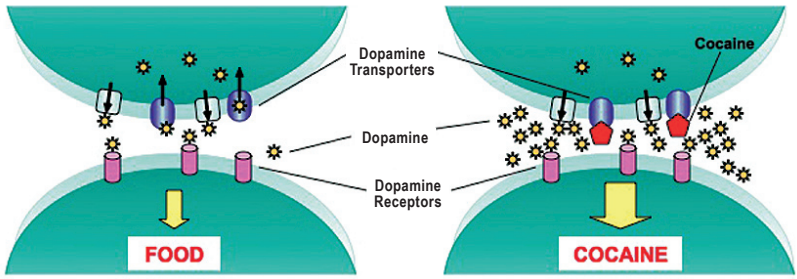
Dopamine, reward and learning

The NAcc is a critical part of the neural system that is involved in learning, reward and motivation. Everyday rewarding activities, or natural reinforcers, such as food, relationships and sex, produce much smaller increases in dopamine in the NAcc than drugs of addiction (Kelley and Berridge, 2002). Some addictive drugs produce over 10 times more dopamine in the NAcc than natural reinforcers, and the increased dopamine response to drugs lasts much longer. It is this excess release of dopamine by addictive drugs that is thought to make drug use so much more appealing than everyday rewarding activities (Hyman, 2005) (see Figure 5).

Figure 5: Rewarding activities increase dopamine signalling



Drugs of addiction act on the brain's reward pathway to cause enormous increases in dopamine activity in the nucleus accumbens. Everyday activities also increase dopamine activity in this reward pathway, but to a much smaller extent. The exaggerated release of dopamine due to drugs such as cocaine produces changes in other parts of the nervous system that focuses attention on drug use.

Redrawn from NIDA 'Drugs, brains and behavior: The science of addiction', Washington DC, 2007.

The increase in dopamine signalling in the NAcc was believed to give drugs their rewarding or euphoric affects. Imaging of brain function during intoxication shows that increases in accumbal dopamine are correlated with subjective reports of euphoria (Volkow et al., 2004a). This is clearest for stimulant drugs where the greater the dopamine release in the NAcc, the greater the euphoria that is reported (Laruelle et al., 1995; Drevets et al., 2001). This is not always the case, however. There are many studies which show a poor correlation between subjective states of pleasure and drug-taking (Robinson and Berridge, 2000). As addiction progresses, the consumption of larger amounts of drugs does not increase the pleasure experienced; in fact in most cases, rewarding or euphoric experiences decrease with increasing use. Moreover, nicotine is a highly addictive drug that increases dopamine release in the NAcc in the absence of

any significant euphoric effects (Nisell et al., 1994; Balfour, 2004; Koob and Le Moal, 2006). Recent research has suggested that dopaminergic release within the NAcc may in fact reflect the salience, or significance, of stimuli, irrespective of their rewarding or euphoria-inducing capacity ([4]). Chronic drug use produces changes in the motivation or reward pathway that sensitise the reward system to addictive drugs and drug-stimuli. These systems do not mediate the pleasurable or euphoric aspect of drug-taking so much as a 'subcomponent of reward' that is called salience (Robinson and Berridge, 2000, p. s94). By associating large increases in dopamine with drug taking and drug stimuli learning drives the motivation to take drugs, independently of any pleasure that their use may bring. Thus, events may be perceived as salient not just because of their rewarding effects, but because they are novel or grab attention. This property may explain why aversive or unpleasant stimuli are also able to motivate behaviour (Robinson and Berridge, 2000), why drug use persists long after its immediate effects cease to be rewarding, and why nicotine increases dopamine release without producing euphoric effects (Robbins et al., 2007).

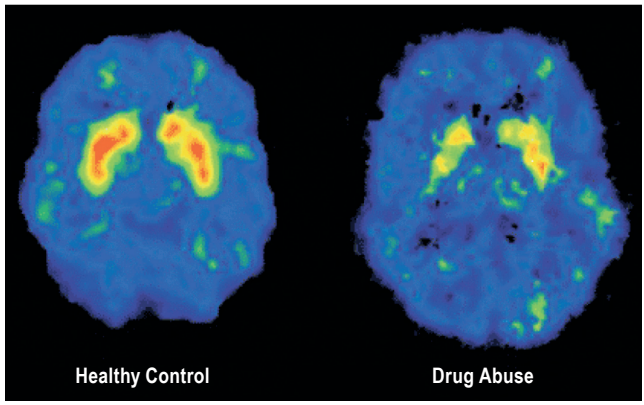
This research suggests that dopamine functions as a signal for learning about experiences. It is released when a rewarding experience is new, better than expected, or unanticipated (Schultz et al., 1997; Schultz, 2006). It is important in identifying and remembering which activities or experiences are worth pursuing and repeating. Dopamine signalling motivates the repetition of behaviour that increases its release (Berridge and Robinson, 1998). Hence, when the dopamine system becomes over-aroused by drug use, pursuit of the repetition of these effects can dominate other important goal-directed activities. Drugs of addiction exploit this natural reward pathway to motivate repeated use of a drug.

The ability for the consumption of an addictive drug to reinforce or motivate repeated drug use by increasing dopamine activity, is the result of acute rewarding events that occur against a background of a normal functioning dopaminergic reward system. While drug use initially increases dopamine release, chronic drug use dramatically decreases dopamine release. The repetitive increase in dopamine release and signalling in the reward pathway leads to a down-regulation of dopamine signalling, and a dampening of activity in the reward pathway. The neurochemistry of the reward pathway appears to adapt to the repeated abnormal elevations in dopamine release by compensatory down-regulation. This is largely the result of a decrease in the number of post-synaptic dopamine receptors in regions such as the striatum (Volkow and Li, 2004) (see Figure 6).

([4]) There is some controversy about the specific role that dopamine plays in these processes of addiction (e.g. reward, incentive salience or motivation, or learning). Nonetheless, it is likely that changes in dopamine activity as a result of drug use are central to the development of addictive behaviours. This review will not attempt to resolve these debates, but will rather focus on areas where there is consensus. For a thorough discussion, see the 2007 review and commentary in *Psychopharmacology* (Berridge, 2007; Robbins and Everitt, 2007), or (Kelley and Berridge, 2002).

These effects significantly reduce activity in the dopaminergic reward system. In these ways, the repeated use of drugs appears to reset the threshold for activating the reward system so that the NAcc becomes less sensitive to the rewarding effects of everyday activities in chronic drug users. However, increased doses of addictive drugs can still produce large dopamine increases that are able to activate the reward centres. As repeated drug use gains enhanced salience over normal or everyday reinforcing activities, the conditioned learning of the association between the drug's effects and associated external cues is strengthened. This reduced activity in the dopamine reward circuit can persist for months after abstinence, and may be one reason why abstinent addicts can relapse months or even years after becoming abstinent (Volkow and Fowler, 2000; Volkow et al., 2004a). The dampening of the dopamine activity within the reward pathway is also understood to lead to the onset of withdrawal symptoms (see below).

Figure 6: Decreased dopamine receptors due to drug abuse



While initial drug use produces large increases in dopamine activity, chronic drug use eventually leads to a significant reduction in dopamine activity. Abuse of the stimulant methamphetamine produces significant decreases in the density of dopamine receptors in the striatum. Such persistent changes in dopamine signalling are thought to explain why individuals with an addiction become so motivated to consume drugs.

Dopamine and withdrawal

The changes in the dopaminergic reward system produced by chronic drug use may also explain the process of drug withdrawal (Hyman, 2005; Hyman et al., 2006). Abrupt cessation of chronic drug use leads to a decrease in dopamine release and elevated thresholds of reward that may lead to drug seeking to relieve the aversive state of withdrawal. In this way, relief of withdrawal symptoms can become a motivational state like thirst or hunger (Hutcheson et al., 2001) that motivates drug seeking (Koob and Le Moal, 1997).

The dopamine theory of addiction is often referred to as an hedonic model of addiction. That is, it assumes that individuals use addictive drugs in order to experience pleasure and avoid withdrawal symptoms. While withdrawal partially explains the desire of addicts to take drugs, it does not explain the compulsion or loss of control over use in addiction (Tiffany, 1990; O'Brien et al., 1998). Nor does it explain why addictive drugs like cocaine and amphetamines that do not produce intense withdrawal symptoms, are nonetheless highly addictive. In seeking to explain these phenomena, recent neurobiological research has focused on the effects that chronic drug use has on the functioning of parts of the brain involved in behavioural control, memory, cognition and decision-making.

The endogenous opioid system

The brain's endogenous opioid system is another system that also plays a role in addiction. This is a peptide neurotransmitter system that comprises a number of different peptides (the endorphins, enkephalins and dynorphin) that interact with one of the three opioid receptors — mu, delta and kappa. Mu receptors mediate the pleasurable effects of both opiate drugs, such as heroin and morphine ([5]) as well as endogenous opioids, such as the endorphins.

The identification of the mu receptor as the site of action for heroin and other opioids led to the use of antagonists (drugs like naloxone and naltrexone that prevent the rewarding effects of heroin by binding to the same receptors) to treat opiate addiction (see p. 60). These antagonists are also clinically useful in alcohol addiction, probably because alcohol also releases endorphins in the brain. Changes in brain opioid receptors may also play a part in addiction to other drugs ([6]), which may explain why opioid antagonists, such as naltrexone, appear to be effective in the treatment of other addictions (see p. 61).

Research has shown that changes in dopamine and opioids in response to drug use appear to be necessary for developing addiction ([7]). But large increases in dopamine activity in the limbic regions are not sufficient for the development of addiction because they can occur in both addicted and non-addicted individuals. Dopamine release explains why drugs of addiction are rewarding or reinforcing, but it does not explain why some users stop while others continue to use these drugs after their rewarding effects have ceased and in the face of negative social and physical consequences of use. Addiction is due to a number of plastic changes or neuroadaptations throughout the brain that are responsible for the cognitive behaviours necessary for maintaining the cycle of addiction. The neurobiological changes that underpin these cognitive deficits is the next topic of this section.

([5]) Mice that do not possess mu receptors do not self-administer opioids (Becker et al., 2000).
([6]) PET studies have shown that opioid receptors are increased in people withdrawing from cocaine (Zubieta et al., 1996), opioids (Williams et al., 2007) and alcohol (Heinz et al., 2005).
([7]) Dopamine antagonists which block the release of dopamine prevent the reinforcing effects of drug use in animals. While rats treated with dopamine antagonists fail to associate the effects of drug use with the context in which the drugs were given (Hyman, 2005).

Molecular and cellular changes in addiction

There is increasing evidence that chronic drug use, and the changes in dopamine signalling outlined above, produce neuroadaptations in the molecular and cellular neurocircuitry that maintain addiction, especially in the mesolimbic dopamine system. Chronic drug use leads to plastic changes at the synapses in key neural circuits that are believed to be responsible for characteristic addictive behaviours discussed below.

There has been significant research since the early 1970s to identify the molecular and cellular processes that can strengthen or weaken the connectivity between neurons; a process first hypothesised to exist as early as 1894 by the pioneering neuroscientist, Ramón y Cajal (Kauer and Malenka, 2007). This process is now referred to as synaptic plasticity. This refers to the molecular and cellular process by which information, experience or learned responses are stored in the brain.

The molecular machinery for synaptic plasticity was first observed in the excitatory glutamate synapses of the hippocampus (Bliss and Lomo, 1973). This molecular process is referred to as long-term potentiation (LTP) and describes how observed behaviours or learning can be encoded through molecular and cellular changes in neural connectivity. Synaptic plasticity is an activity-dependent process that allows synapses to be strengthened (LTP), or weakened (long-term depression or LTD). LTP is the signalling process which allows the synaptic connection between two neurons to be strengthened. The most widely studied and best understood form of LTP or synaptic plasticity is N-methyl-D-asparate receptor (NMDAR)-dependent LTP. ([8]) The co-occurrence of NMDAR activation due to presynaptic glutamate release while the post-synaptic membrane is significantly depolarised sets off a signalling cascade that strengthens the synaptic connection. The activation of the NMDAR allows calcium to enter the postsynaptic neuron, triggers the intracellular signalling cascade which results in an increase in the number of α-amino-3-hydroxy-5-methyl-4-isoxazole propinonic acid receptors (AMPARs) in the post-synaptic membrane. This signalling cascade also produces morphological changes of the neuron that appear to be essential for the LTP of the synapse. This change in the synapse allows a form of information, whether it be an experience of an event or a learned response, to be encoded in the brain. The process of LTP is best captured in the phrase: 'neurons that fire together, wire together'. The molecular mechanisms that underpin NMDAR-dependent synaptic plasticity are depicted in Figure 7. These synaptic

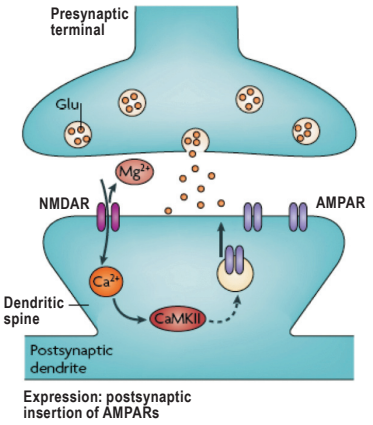
([8]) The signalling processes involved in synaptic plasticity are extremely complex and can vary somewhat in different regions. This research is also in its infancy so there is significant uncertainty about the specific details. Much more research is required. Consequently, only a brief overview of this area of research is provided, with a focus on areas where there is consensus. The NMDAR-dependent LTP is discussed to give readers a greater appreciation of the kinds of molecular and cellular changes that are involved in synaptic plasticity. This section is only intended to give the reader an understanding of how chronic use of addictive drugs interferes with molecular and cellular processes in order to produce the psychological behaviours characteristic of addiction. For a more detailed discussion of synaptic plasticity in addiction, see (Kauer and Malenka, 2007).

changes also involve a number of fundamental cellular processes, such as intracellular signalling, gene regulation and expression, protein synthesis and trafficking, membrane organisation and excitability, and neuronal morphology.

The association between synaptic changes and learning and memory was first described in hippocampal neurons, a region important in remembering the details or facts of events (declarative memory). It has been argued that addiction is a form of pathological learning and memory (Kelley, 2004; Hyman, 2005; Hyman et al., 2006). However, it is becoming apparent that the plasticity of LTP, and the complementary LTD that involves a weakening of synaptic connectivity, are basic molecular processes that occur at most synapses throughout the brain, including the mesolimbic reward pathway, and cortical regions. They are involved in strengthening or weakening synapses that are associated with a wide variety of cognitive functions.

Figure 7: NMDAR-dependent long-term potentiation

Highly simplified schematic diagram of the process of synaptic plasticity observed in the brain's glutamatergic neurons. N-methyl-d-aspartate receptor (NMDAR)-dependent long-term potentiation (LTP) has been observed in many different brain regions. It is dependent upon the co-occurrence of postsynaptic NMDAR activation during significant membrane depolarization, which then initiates internal signalling molecules, such as calcium/calmodulin-dependent protein-kinase II (CaMKII). These signalling molecules result in the insertion of a α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) into the postsynaptic membrane — a major mechanism underlying LTP expression. There are several other types of synaptic plasticity that have been observed. We will not discuss them here, but they all involve a network of complex molecular and synaptic changes, similar to those depicted in the Figure (see Kauer and Malenka, 2007 for a more complete discussion).



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There is now increasing evidence that the processes involved in synaptic plasticity are involved in the development and maintenance of addiction, and provide the molecular mechanisms for the neuroanatomical changes that underpin the psychological behaviours characteristic of addiction, such as craving, impaired impulse inhibition and relapse (Kauer and Malenka, 2007). Many of the molecules implicated in LTP and LTD have been shown to be involved in the synaptic plasticity due to drug abuse (Kelley, 2004). Blocking NMDARs has been shown to prevent the formation of addictive behaviours, and synaptic changes in animal models (Kauer and Malenka, 2007).

Drugs of abuse can co-opt synaptic plasticity mechanisms in the neural circuits involved in reward and reinforcement (Kauer, 2007) in regions of the mesolimbic dopaminergic reward pathway, including the VTA and the NAcc. Other limbic regions, including the prefrontal cortex, also undergo neuroadaptations that result in addiction. Synaptic plasticity within the VTA is responsible for the initial acute responses to drugs of abuse, as well as long-term adaptations in regions innervated by the dopaminergic neurons of the VTA (Kauer, 2007; Volkow et al., 2000).

The development of more deeply ingrained addictive behaviours in response to chronic drug use over longer periods of time are the result of plastic changes in the downstream regions, such as the NAcc and other limbic regions. Synaptic plasticity within these regions result in the formation of strong, long-lasting associations between the reinforcing aspects of drug use and the various cues, both external and internal, connected with drug use (Calabresi et al., 2007). It is these long-lasting changes that appear to underpin the experience of drug craving, the motivation to use drugs, and relapse on re-exposure to experiences associated with drug use or under stress. The study of the synaptic plasticity of addiction is a relatively new endeavour. By identifying the molecular and cellular changes that maintain addiction, it is hoped that it will be possible to develop novel pharmacological drugs by reversing or reducing some of these changes. This will increase our ability to treat and prevent addiction (Calabresi et al., 2007). The psychological characteristics of addiction, and the neuroanatomical changes that underpin it will be discussed below.

Compulsion, craving and inhibitory control

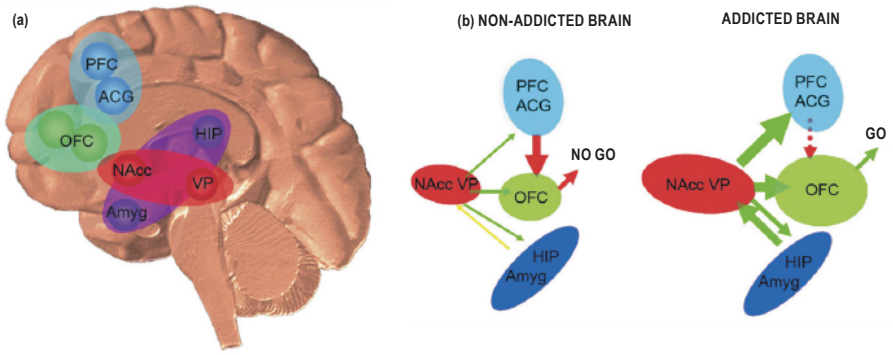
In recent years, neuroimaging research has studied changes in regions of the frontal cortex of addicted individuals. Of particular interest has been the orbitofrontal cortex (OFC) and the anterior cingulate gyrus (aCG), which it is hypothesised are involved in craving and compulsive drug taking, and loss of control over drug use, respectively (Volkow and Fowler, 2000; Volkow et al., 2003). These behaviours are often thought to define addiction. The OFC provides internal representations of the saliency of events and assigns values to them. This allows an individual to compare the likely consequences of pursuing different goals (Schoenbaum et al., 2006). The aCG is involved in the inhibition of impulses to act (Volkow et al., 2004b; Yucel and Lubman, 2007).

Imaging studies have shown that reduced dopamine activity in the NAcc is correlated with changes in activity in the OFC and the aCG (Goldstein and Volkow, 2002; Volkow et al., 2000; Volkow and Li, 2004). Exposure to drugs and drug-related cues dramatically increases dopamine activity in the OFC and aCG of addicted individuals (see Figure 8). The increased metabolic activity in the OFC and aCG of active drug users in response to increased dopamine activity is thought to partly explain craving. Addicts show increased activation in the OFC when presented with drug cues, memories of past drug experiences or their drug of addiction. The degree of activity in the OFC and aCG

is correlated with the subjectively reported drug craving (Volkow and Fowler, 2000; Volkow et al., 2004b; Risinger et al., 2005).

Changes in dopamine activity in the OFC also accompany the process of withdrawal (Volkow et al., 1991). As an addicted drug user undergoes detoxification, metabolic activity within the OFC changes from being extremely high to extremely low. Exposing addicts during withdrawal to either their drug of choice or drug-related cues produces hyperactivity within the OFC that is correlated with self-reported drug craving. OFC-induced craving appears to be responsible for the compulsion to take drugs. These changes within the OFC can persist into abstinence explaining why many abstinent drug users report continued urges to use drugs and relapse in response to drug-related cues.

Figure 8: Plastic changes in the neuroanatomy of addiction



This is a schematic diagram of the neuroanatomy of addiction, which depicts the plastic changes that result from chronic drug abuse and produce addiction. (a) The sagittal view of a brain depicting four circuits that are postulated to have key roles in addiction: (1) the prediction of reward and pleasure (red) involve the nucleus accumbens (NAcc) and ventral pallidum (VP); (2) memory and learning (purple), occur in the amygdala (Amyg) and hippocampus (HIP); (3) motivation, drive and salience evaluation (green) occur in the orbitofrontal cortex (OFC); and (4) cognitive control (blue), in charge of restraining cravings, located in the prefrontal cortex (PFC) and anterior cingulate gyrus (aCG). (b) A hypothetical model of addiction. Chronic drug use increases the salience value of a drug (red) and its associated cues (purple) in addiction (right) when compared to the non-addicted brain (left), whereas the strength of inhibitory control is weakened (blue), setting up the stage for an unrestrained motivation (green). This results in the repeated use of drugs despite the consequences it causes, and attempts to stop.

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Executive control and cognitive impairment

To the lay person, addicts' continued use of drugs despite adverse consequences seems self-evidently to reflect impaired 'executive control', that is, an impaired ability to reason and rationalise decisions and actions. It is only recently, however, that the neural centres of executive control and cognitive decision-making have been implicated in addiction

(Goldstein and Volkow, 2002; Bechara, 2005; Goldstein et al., 2007). The decision to continue to use drugs involves the selection of goals from a range of choices. The ability to represent goals, value and select different sequences of actions is thought to depend on the maintenance of goal representations within the prefrontal cortex (PFC) (Roesch and Olson, 2004; Rolls, 2004).

Hyman (2005, 2006) has suggested that the ability to update information within the PFC, select new goals and avoid the compulsive repetition of a particular behaviour or thought is controlled by dopamine release. It is hypothesised that changes in dopamine signalling can affect our ability to make new goals or choose different behaviours. This appears to be confirmed by computational studies of a type of dopamine firing (called phasic) (Schultz et al., 1997; Schultz, 2006). This suggests that addictive drugs provide a potent signal that disrupts normal dopamine-related learning in the PFC. Natural rewards, with relatively low dopamine signalling, may fail to open the PFC gate, powerfully biasing the behaviour of addicts towards drug use and away from normal everyday activities. This hypothesis is supported by neuroimaging studies. Cues that predict drug availability take on an exaggerated incentive salience because of dopamine release in the nucleus accumbens and prefrontal cortex. As a result, drug-seeking behaviour is strengthened by dopamine effects in the prefrontal cortex (Robbins and Everitt, 1999; Berke and Hyman, 2000; Berke, 2003).

In addition to increased motivation to use drugs, addicted individuals have cognitive impairments that prevent them from recognising the consequences of their drug use and inhibiting impulses to use drugs. Recent imaging research has highlighted changes in the PFC. In particular, changes in the dorsolateral PFC, and the aCG, seem to prevent addicted individuals from considering options other than drug use or for inhibiting drug use (see pp. 40–42), thereby prolonging use and delaying cessation. The results of neuroimaging studies are supported by neurocognitive tests that have found impaired attention and reduced executive control in addicted individuals (Bechara et al., 2001; Goldstein and Volkow, 2002; Fillmore, 2003; Hester and Garavan, 2004; Bechara, 2005; Goldstein et al., 2007; Yucel and Lubman, 2007).

Several commentators have argued that in addition to the more rational cognitive processes of analysing and balancing different action options, decision-making also includes affective and visceral processes (Paulus, 2007). There is an increasing emphasis of the role that introception — the awareness or sensation of the body — plays in driving us towards choosing certain actions (Damasio et al., 2000; Craig, 2002). The insular cortex appears to be central in bodily perceptions or feelings, and in the case of addiction, how it plays a key role in explaining why cravings have the ability to capture or steer our thinking and acting. See 'Representing bodily urges', (p. 44) for further discussion of introception of drug craving in the insular cortex.

In October of 2007, the journal Science ran a special section on the neurobiology of decision-making (Koechlin and Hyafil, 2007; Kording, 2007; Paulus, 2007; Sanfey,

2007; Stern, 2007), that explained how actions that individuals select are the result of interactions between a number of complex and highly integrated hierarchical neural processes that are distributed throughout the brain (from the 'primitive' parts of the mid-brain to the more recently evolved cortical regions) (Paulus, 2007). This includes a number of neurocognitive processes which are discussed throughout Chapter 2 of this report: (1) assessment and planning; (2) motivation and personal preference; and (3) internal bodily state and the response to an event (Paulus, 2007). Chronic abuse of addictive drugs appears to have an impact on many, if not all, of these functions.

Memory, learning and habits

Key areas of the brain involved in learning have also been implicated in addiction (Everitt and Robbins, 2005). Addiction involves learning new habits so it is not surprising that changes in the neural pathways that underpin the learning and memory of habitual behaviours (or conditioned responses) are involved in the development of addiction. The neural system involved in the formation of habits is the mesolimbic pathway, a region of the brain that includes the NAcc, amygdala, hippocampus, and the striatum (caudate and putamen). These memory systems are implicated in: conditioned incentive learning (NAcc and amygdala); habit learning (the caudate and putamen); and declarative memory (the hippocampus).

As noted above, drug-related cues can elicit craving in abstinent drug users and trigger relapse (O'Brien et al., 1998). Animal studies of Pavlovian conditioning consistently show that a single exposure to a conditioned stimulus is enough to reinstate addictive behaviours in animals that have been abstinent for long periods of time (Gold and Koob, 1989). In particular, areas of the limbic system, primarily the hippocampus and the amygdala, have been shown to be critical in the acquisition, consolidation and expression of drug-stimulus learning that drives relapse to drug-seeking behaviours (Weiss et al., 2000; See, 2005). This research suggests that changes in brain functioning can lead to the formation of habits, and give special salience to cues and contexts in which drugs are used. These learned drug associations can then cue internal states of craving that perpetuate addiction and lead to relapse ([9]).

Representing bodily urges

The ability to represent the internal state of the body, or introception, is important for an organism to maintain homeostasis — the process which keeps the body functioning in a stable, generally productive condition (Damasio, 1999). Introception is also critical in shaping or influencing the choices we make (Damasio et al., 2000; Craig, 2002). It is important in helping to decide what an individual requires in a given situation to suit

([9]) More details of the different processes operating in each of these neural regions can be found in White, 1996; Wise, 2004; Robbins, 2002; Everitt and Robbins, 2005.

the body's needs (Paulus, 2007). These states are often referred to as 'affective states', because we are affected by them, and are also considered to be emotional states.

The insula — a region of cortex that lies at the intersection of the frontal, temporal and parietal lobes — has been implicated in this process. The insula receives inputs from the cortex and the thalamus that convey information about the emotional and homeostatic state of the body. The insula also has projections to several cortical regions, including the sensory and association cortices, importantly the OFC and aCG, and the brainstem and limbic system, including the amygdala, hypothalamus, NAcc and striatum. These dense connections enable the insula to link information from the body, emotional centres and conscious feelings from cortical regions. The insula is involved in the conscious perception of the physiological state of the body. It sends this information to prefrontal cortical regions to influence decisions on what to do (Everitt and Robbins, 2005) and it also plays a role in emotions and autonomic responses.

Given the role that these functions play in addiction, it is not surprising that the insula itself also appears to play such a critical role in addiction (Contreras et al., 2007). Animal studies suggest that the insula may represent internal body states, such as craving, withdrawal, or the desire to take drugs, that are triggered by drug-associated cues (Kilts et al., 2001; Bonson et al., 2002). The role of the insular cortex in the experience of drug craving is seen in neuroimaging studies which show that the insula is active during cue-induced craving in addicts and that its activation is correlated with subjective reports of drug craving (Contreras et al., 2007).

The awareness or conscious experience of the body's response to drugs is critical in the maintenance of addictive behaviours. The experience of cravings for drugs is a potent motivator for addicts to use drugs. Inactivation of the insula prevents drug seeking in rats (Contreras et al., 2007). A recent study also showed that individuals who had lesions in the insula cortex were able to quit smoking easily and did not relapse (Naqvi et al., 2007). Damage to the insula did not increase the likelihood of quitting but it increased the success of those who tried and reduced their desire to smoke. The role that introception plays in the choices we make, and the role that the insula plays in this process, particularly in addiction, is receiving increasing attention in addiction neuroscience. Targeting these regions may lead to new medical treatments and may help clinicians to develop psychotherapies that attempt to overcome these changes in cognition.

Stress and drug use

Observational studies of human addicts show that stress is a particularly potent trigger for relapse to drug use (Koob, 1999). Stressful events, particularly when they occur repeatedly, increase negative affect and thereby make an abstinent drug addict more likely to relapse. Chronic drug use also produces neuroadaptive changes in an 'anti-reward' pathway that includes the hypothalamic-pituitary-adrenal (HPA) axis

and the neuropeptide, corticotropin releasing factor (CRF) (Koob and Le Moal, 2005). Individuals in acute drug withdrawal show increased activity of CRF in the HPA and regions of the limbic system, and increased release of noradrenaline and dynorphin, all of which are associated with relapse to drug use. CRF receptor antagonists have been shown to reduce excessive drug taking (Koob and Le Moal, 2005).

Stress and stress hormones can directly affect the natural reward pathways making individuals more vulnerable to developing drug addiction. While both acute and chronic stress affect the dopaminergic reward pathway, the effect they have over time, and their impact on drug use are quite distinct. Acute stress triggers the release of dopamine in the neural reward pathway (Marinelli and Piazza, 2002). The rapid increase of dopamine in the mesolimbic reward pathway can motivate drug seeking in dependent individuals in the short term, which may lead to relapse (Marinelli and Piazza, 2002).

While chronic stress releases hormones that trigger the release of dopamine into the NAcc (Stamford et al., 1991), the repeated increases in stress hormones, and consequently dopamine, sensitises the reward system over a long period of time (Marinelli and Piazza, 2002). Chronic stress results in neuroadaptations within the reward pathway that dampen dopaminergic activity and reduce sensitivity to normal rewards. The neuroadaptations to chronic stress are thought to be due to a reduction in the number of dopamine receptors. These neuroadaptations also lead to the development of anhedonia, or the inability to experience pleasure ([10]). This sensitisation of the reward system makes former addicts who experience stress more responsive to drugs of abuse, and therefore, more vulnerable to the development of addiction if they use drugs (Marinelli and Piazza, 2002). The sensitisation can also persist well after the stress has abated. Genetically based heightened sensitivity to stress or anxiety can make individuals more sensitive to the effects of stress and hence more vulnerable to developing addiction. This is discussed in greater detail below.

Vulnerability to addiction: genetic and neuropsychological factors

This section briefly summarises research on two related topics: studies of twins and genetic association studies which indicate that genetic factors (such as individual differences in drug metabolism and neurotransmitter responses to drug effects) contribute to individual differences in vulnerability to addiction; and neuropsychological and neuroimaging research which suggests that genetic differences in addiction vulnerability may also underlie individual differences in cognitive performance that influence vulnerability to addiction.

([10]) This sensitisation of the reward system due to chronic stress, the down-regulation of the dopamine receptors and the development of anhedonia is thought to be involved in some cases of depression and suggests why dopamine agonists that aim to ameliorate this effect are effective in the treatment of depression. This discussion is beyond the scope of this report. For further information, see Willner, 1997; Willner, 2005.

Genetic susceptibility to addiction

Familial studies have consistently shown that addiction 'runs in families' (Merikangas et al., 1998), suggesting that there is a substantial genetic contribution to addiction vulnerability (Ball and Collier, 2002; Ball et al., 2007). Addiction is among the most heritable of the complex psychiatric disorders (Goldman et al., 2005), despite the facts that an individual must engage in drug use for the genetic predisposition to be expressed, and that the decision to use a drug can be influenced by personal choices and social policies. Evidence from twin and adoption studies suggest that 40–60 % of the risk of developing substance abuse disorders is due to genetic factors, with the percentage depending on the substance (Nestler, 2000; Uhl et al., 2004). Some studies suggest that the genetic contribution to addiction to some substances, such as cocaine, may be over 70 % (Goldman et al., 2005).

An individual's inherited genetic make-up can influence addiction risk in a number of ways. Genes may affect: the way in which individuals respond to particular substances (e.g. drug metabolism, absorption and excretion and activity or sensitivity to drugs); behavioural traits that influence an individual's willingness to try drugs (e.g. risk-taking behaviour, impulsivity, novelty seeking); or the likelihood of developing problem use or dependence if they use drugs (e.g. how rewarding they find the effects of drugs) (Rhee et al., 2003). This suggests two broad types of genetic predispositions to addiction: (1) genetic profiles that make some individuals more likely to find the acute effects of drugs rewarding and (2) genetic profiles that make individuals more or less susceptible to developing addiction if they use drugs.

Significant environmental events, such as adolescent physical or sexual abuse, can interact with genetic susceptibility to increase the risk of developing psychiatric disorders (Nestler et al., 1996; Nestler, 2000; Caspi et al., 2005; Goldman et al., 2005; Ball et al., 2007). These studies provide convincing evidence that both genes and environment play a significant role in the development of addiction (Ball et al., 2007).

Despite the strong evidence of genetic contributions to addiction vulnerability, attempts to reliably identify specific addiction susceptibility genes have been disappointing to date. Large-scale linkage and association studies have identified numerous promising candidate genes that confer vulnerability to addiction (Ball and Collier, 2002; Tyndale, 2003) but few of these alleles have been consistently replicated and many of the associations are modest (Tyndale, 2003). Most of the candidate genes identified so far are associated with the activity of dopamine and the dopaminergic system, dopamine receptors and transporters, ([11]) or proteins which influence the pharmacological activity or metabolism of addictive drugs.

([11]) For example the catechol-*O*-methyl transferase (COMT) and dopamine receptor 2 (DRD2).

Genetically inherited resilience to alcohol addiction

The strongest evidence for vulnerability or resilience to addiction concerns a gene, aldehyde dehydrogenase 2 (ALDH2), which encodes a variant of the enzyme involved in the metabolism of ethanol (Thomasson et al., 1991; Chen et al., 1999). The ALDH2 gene encodes for a less active variant of the metabolic enzyme. Individuals who are homozygous for the ALDH2 allele (i.e. have two copies) are more likely to experience facial flushing, nausea and headaches if they drink alcohol. A high prevalence of these alleles is thought to explain the lower incidence of alcoholism in some East Asian populations (Nestler, 2000).

Addiction is a complex disorder so there are likely to be many genes associated with addiction risk, most of which make a small individual contribution to risk (Khoury et al., 2003; Tyndale, 2003; Hall et al., 2004a; Khoury et al., 2004; Ballet al., 2007). The most plausible hypothesis is that there are a substantial number of genes that are involved in the initiation, adoption, persistence and cessation of drug abuse, each of which carry a small relative risk (Lerman and Berrettini, 2003). The effects of these types of genetic profiles will depend on environmental cues and triggers, such as stress, opportunity to use different drugs, peer and parental drug use and so on.

Improved understandings of genetic contributions to the development of addictive disorders raise the possibility that we can prevent the onset of drug use and addiction in high risk individuals. By identifying those who are genetically vulnerable to addiction, it may be possible to prevent addiction by vaccinating individuals against the rewarding effects of drugs of abuse. Psychopharmacotherapies could also be tailored to an individual's genomic vulnerabilities (pharmacogenomics and pharmacogenetics) to allow more effective and efficient addiction treatments. By identifying genes and genetic products involved in the development of addiction, such as initiation, problem drug use, tolerance, withdrawal, dependence, craving and relapse, it may also be possible to develop treatments aimed at an individual's genetic and neuropsychological vulnerabilities.

Vulnerabilities to addiction: a confluence of the genetic and the social

In addition to the genetic susceptibilities, there are social factors that make some individuals more likely to develop an addiction than others. These include socio-economic background, exposure to parental drug use, peer drug use and early exposure to drugs, physical or sexual abuse, poor performance at school, and mental disorders such as conduct disorder and anxiety and depressive disorders that develop during adolescence (Hawkins et al., 1992).

Both genetic and environmental susceptibilities to developing addiction are mediated by neuropsychological changes in the brains of drug users. Genes implicated in addiction are thought to produce changes in the structure or function of specific neural circuits during development that affect an individual's responsiveness to the effects of drug use. The fact that the addiction liability of different drugs (i.e. their neuropharmacological properties) correlates with the genetic risk of addiction suggests that genetic vulnerabilities to addiction are mediated by neurobiology (Goldstein and Kalant, 1990; Goldman et al., 2005). Environmental stressors and early exposure to drug use, particularly during adolescence and early development, can also have significant neuropsychological effects that leave individuals vulnerable to substance abuse or addiction (Volkow and Li, 2005).

Brain imaging studies suggest that vulnerability may be due to: a decreased sensitivity to natural reinforcers; disrupted activity in control circuits; sensitivity to conditioned drug stimuli; responses of motivation/drive circuits to drugs; and neurobiological factors involved in the modulation of these circuits (Volkow and Li, 2004). These changes are thought to be mediated by changes in dopaminergic signalling.

As already discussed, differences in dopamine circuits are thought to underlie individual differences in responsiveness to drug effects that, in turn, influence vulnerability and resilience (see pp. 32–37). This variation in responsiveness to drugs is largely due to genetic make-up. Dopamine activity is also affected by environmental events since stress can increase dopamine release in the NAcc (Koob, 1999) and levels of the dopamine receptors (Papp et al., 1994). Studies in primates show that dopamine activity is also affected by position in the social hierarchy (Morgan et al., 2002).

Dopamine function also influences predispositions to self-administration of drugs in animals. Genetic manipulation of the dopamine receptor, DRD2, markedly affects drug self-administration. Low DRD2 levels might predispose an individual to use drugs to compensate for decreased activation of the reward circuit, whereas high DRD2 levels might be protective. Genetic upregulation of DRD2 receptors in rats reduces alcohol consumption, suggesting a target for treatment with drugs or environmental manipulations that increase DRD2 expression. The fact that many non-addicted individuals also have low DRD2 levels suggests that low DRD2 only predisposes to addiction.

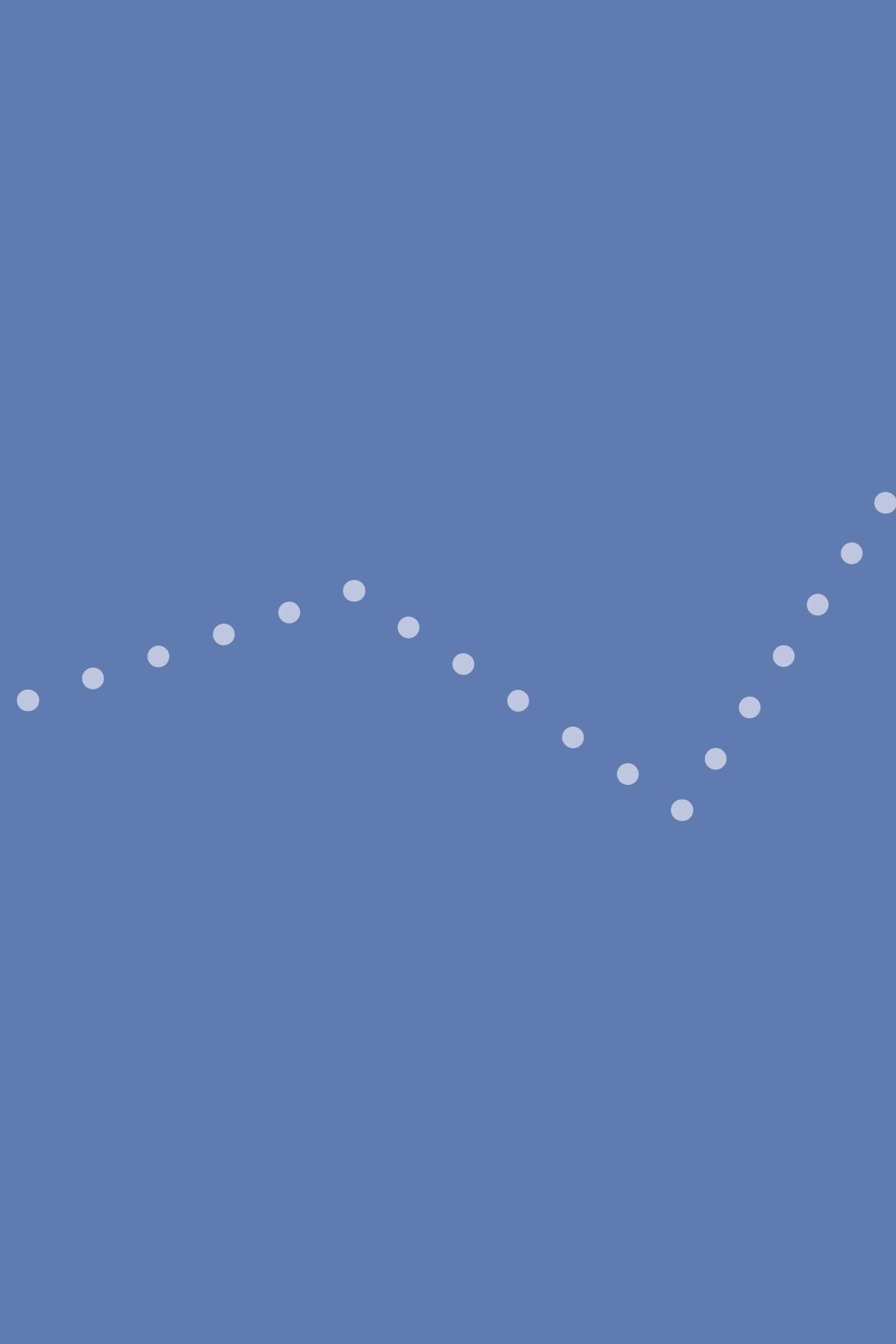
Other behavioural traits or cognitive capacities unrelated to the dopaminergic reward pathway are also thought to influence vulnerability to addiction. Functional MRI imaging of individuals who are impulsive find differences in the corticolimbic behavioural arousal and control circuits that are affected by addiction (Brown et al., 2006). Cognitive control is another relatively stable trait that is an important predictor of life success that plays an important role in the development of addiction (Eigsti et al., 2006). Individuals with disorders of impulsivity such as attention deficit hyperactivity disorder (ADHD) or cognitive impairment are more likely to develop substance abuse disorders

(Lynskey and Hall, 2001). There is also a high incidence of substance abuse among individuals with anxiety or depressive disorders in whom drug use may be a failed attempt to self-medicate dysphoric (unpleasant) symptoms (Khantzian, 1985). Chronic drug use can also produce anxiety and depressive disorders. The causal relationship between addictive and affective disorders can probably occur in both directions, and to varying degrees in different individuals.

Neuropsychological research suggests that the brains of adolescents and young adults may be developmentally more vulnerable to addiction and substance abuse than those of older adults (Volkow and Li, 2005). Mesocortical tracts that are involved in cognitive processing, executive control and motivation are not fully developed in the adolescent brain (Sowell et al., 2004) ([12]). In fact, the PFC does not fully mature until the early 20s (Gogtay et al., 2004). The neuroanatomical connections between the amygdala and PFC — the circuit responsible for cognitive control over emotions — are not fully developed until adult life (Cunningham et al., 2002).

These observations have two major implications. First, as the regions of the brain responsible for impulse inhibition and reasoning about consequences are not fully developed, adolescents are more likely to engage in risky behaviours such as drug use, find it more difficult to inhibit impulses, engage in novelty seeking, and suffer from a temporal myopia that prevents a full appreciation of the future consequences of their behaviour (Volkow and Li, 2005). Secondly, the developmental immaturity of the adolescent brain means that adolescents may be particularly vulnerable to the neurobiological changes that occur as the result of chronic drug use. Neuropsychological changes at such a developmentally sensitive period can reduce the individual's cognitive capacities in overcoming addiction. This could explain why epidemiological studies show that people who engage in substance abuse in early adolescence are more likely to develop addiction and less likely to recover than those who delay drug use until early adulthood.

([12]) Myelination of the mesocortical tracts, a cellular process that enables neurons to signal quickly and efficiently, is not complete in the adolescent brain.



Chapter 3

The treatment of addiction

Adrian Carter, Wayne Hall and David Nutt

Introduction

Neuroscience research is uncovering the neurochemical mechanisms that produce the behavioural and cognitive problems observed in those with an addiction. This includes: the pharmacological sites at which drugs act (e.g. receptors); the neurochemicals involved in the metabolism (e.g. enzymes) and trafficking of drugs (e.g. transporters) that regulate their activity within the brain; and the molecular changes that occur in the brain as a result of continuous use of addictive drugs over long periods of time (see Chapter 2). As our understanding of addiction deepens and becomes more detailed, it opens up the possibility for a wider range of powerful new technologies to treat and, more controversially, to prevent addiction. Because the neurobiological changes underpinning addiction can vary between individuals and over time, neuroscience may allow clinicians to target new treatments to the most appropriate individuals and at the most appropriate times.

Addiction has traditionally been treated by a combination of psychosocial and pharmacological treatments. The most widely used and effective pharmacological treatments remain ones that were developed before the explosion of neuroscience research on addiction. These can be grouped into two types: (1) drugs that either block the addictive drug from working (e.g. naltrexone as relapse prevention for heroin dependence) or make its use unpleasant (e.g. disulfiram for alcohol dependence); or (2) drugs that replace the addictive drug with a less harmful version of the drug (e.g. substitution treatment using methadone and buprenorphine for heroin dependence, or nicotine replacement therapy (NRT) for smoked tobacco). These treatments may be used as a short-term measure to help wean individuals off all drugs (e.g. drug-assisted withdrawal from opiates using clonidine) or they may be used over the long-term as either a replacement or prophylaxis against a return to the use of the (usually illicit) drug of abuse.

Neurobiological research on addiction has provided a stronger rationale for the use of these pharmacological treatments of addiction. It is the impact that neuroscience has on our view of addiction, and those addicted, that may raise as many ethical and social concerns as the actual technologies themselves. As with any new technology, the way in which it is used will affect the benefit and harm that it produces.

Researchers are also developing new pharmacological approaches unlike those currently in use. These include drugs to enhance cognition and memory so addicted individuals can choose not to use drugs, and drugs that manipulate synaptic plasticity. Researchers are also developing novel immunological approaches, such as drug vaccines which bind to the drug and prevent it acting in the brain. Neurological techniques are also emerging as possibilities, such as deep brain stimulation of centres involved in reward and transcranial magnetic stimulation that applies electromagnetic currents to manipulate brain function and cognition. The advantages and disadvantages of each new method of treatment will need to be evaluated to establish their safety, effectiveness, and cost-effectiveness and to identify any potential harms or misuses of these approaches.

In addition to the novel pharmacological and neurological treatments discussed in this section, neuroscientists are currently studying 80 or so neurotransmitter, receptors, transporters and neural hormones from which new approaches to treating addiction may emerge (Hyman, 2005). The therapeutic potential of these large number of new pharmacological targets for addiction treatment is yet to be realised. A great deal of research will be required before the safety and efficacy of these treatments can be evaluated and their potential impact on society assessed.

While the emerging treatments offer the potential to significantly improve the outcome of addiction treatment and reduce the harm it causes, they also have the potential to be used in ways that raise ethical and social concerns that need to be carefully considered. Following on from Chapter 2, this section will describe a number of the most promising technologies emerging from neuroscientific research on addiction, how they are likely to be used, and their potential to be effective and to cause harm. The ethical and social implications of the use of these technologies will then be explored in Chapter 5.

While psychosocial approaches to treatment are a vital aspect of addiction treatment, they will not be discussed at length in this report. The aim of this report is to analyse the potential impact on new technologies from neuroscientific and genetic research of addiction on European society. This omission should not be taken to suggest that psychosocial treatments are not effective or important in the treatment of addiction. They form an essential component of addiction treatment that will continue to be used in combination with new pharmacological approaches (EMCDDA, 2007b). Successful addiction treatment will require combinations of behavioural strategies and drugs that remediate brain circuits damaged by drug abuse. This will require strategies to promote the plasticity of dysfunctional brain circuits, similar to those used to improve reading in children with learning disabilities and to rehabilitate adults after brain injury.

Addiction psychopharmacology and treatment implications

Advances in genomic and molecular biology, such as the ability to clone and sequence receptor subtypes, transporters and endogenous agonists, has significantly increased our ability to develop novel and specific treatments for addiction to a variety of

substances. The pharmacokinetic sites of action for many drugs of abuse have been identified. For most of these drugs, the molecular sites of action are neurotransmitter receptors and transporters that regulate neurotransmitter activity at the synapse (Nutt, 1996; Iverson et al., 2007). Drugs of abuse work by mimicking the effect of endogenous neurochemical signalling. For example, heroin produces its effect by mimicking the action of endogenous opioid neurochemicals (e.g. endorphins and enkephalins) (Nutt, 1996).

These discoveries have enabled scientists to identify and specifically target relevant receptor or transporter sites with drugs that either block (antagonists) or facilitate (agonists) activity at this site. Antagonists are typically those drugs which block the action of the addictive drug (e.g. naltrexone blocks the effect of heroin), while agonists are typically drugs which mimic the effect of the addictive drug. The use of agonists in substitution treatments (e.g. methadone for heroin dependence) and of antagonists in relapse prevention are discussed in greater detail below.

The use of genetic manipulation techniques in animal models has also greatly increased our understanding of the functional role that these molecules play in the development of addiction. Genetic manipulation in a developing animal allows researchers to observe the effect of increasing (e.g. overexpression mutants) or blocking (e.g. transgenic knockouts or dominant-negative mutants) the activity of a specific molecule. These techniques help us to understand the role that these molecules play in the onset and progression to addiction, and in affecting responses to drug use; information that assist researchers in discovering potential new therapeutic agents.

The advent of psychopharmacological neuroimaging techniques have also been invaluable in understanding the impact of functional changes within humans. Neuroimaging of addiction in humans has been critical in linking developments in animal research with our understanding of addiction in humans. By unravelling the various pharmacological processes that underpin the phenomenon of addiction, these discoveries have provided a number of novel and promising sites for intervention. These discoveries also point towards a more rational approach to addiction treatment, and to more encompassing theories of the brain mechanisms underlying addiction (Nutt, 1996; Nutt et al., 2007c).

Pharmacological treatments of addiction can be classified into those that:

- block the target drug from binding to its site of action;
- interfere with acute and chronic central dopaminergic response to addictive drugs;
- interfere with other neurotransmitter systems related to the reward pathway (e.g. opioids, cannabinoids, glutamate/GABA, and the stress response); and
- minimise the harmful effects of drug abuse.

Pharmacological treatments that block drug binding

The traditional approach to the pharmacological treatment of addiction involves using drugs that interfere with or block the site at which the drug of addiction acts (e.g. mu-opioid receptor for heroin). These medications have been most effective in the treatment of addiction to opioids (e.g. methadone, buprenorphine and naltrexone). Nicotine replacement therapy (NRT) is the most common form of substitution treatment, but is not particularly effective (up to 82 % relapse rates). No agonists have proven effective in treating stimulant addiction (Hyman et al., 2006). Opioid antagonists (e.g. naltrexone, nalmefene) have also been shown to have utility in preventing relapse in alcohol dependence (Volpicelli et al., 1995). The use of antagonists to treat addiction has been less effective for addiction to stimulants, such as amphetamines and cocaine, possibly because the wrong antagonists have been used (only dopamine DRD2 antagonists are currently available for clinical use — see below).

Table 1: Molecular targets of drugs of addiction and pharmacological approaches (current and theoretical). Adapted from Lingford-Hughes and Nutt, 2003.

Drug	Primary target	Primary action	Agonist (substitution)	Partial agonist	Antagonist (relapse prevention)
Opiates	Mu opiate receptors	↑ dopamine	Methadone LAAM	Buprenorphine	Naltrexone Naloxone Nalmfene (3)
Stimulants					
Cocaine	DAT	↑ dopamine	Bupropion (1)	D3 ligands (BP-897) (1)	GR12909 (1)
Amphetamine	DAT	↑ dopamine	Bupropion (1)	D3 ligands (BP-897) (1)	D3 receptor drugs(1)
Nicotine	Nicotinic ACH receptor	↑ dopamine	NRT		Mecamylamine (1)
Sedatives					
Alcohol	GABA/ glutamate	↑ GABA ↓ glutamate	BDZs (2)	BDZ partial agonists (1)	Acamprosate (4) Naltrexone(4)
BDZs	GABA	↑ GABA	Longer half-life BDZs	BDZ partial agonists (1)	Flumazenil
Cannabis	CB1 receptor	? dopamine ? opiates	None	None	Rimonabant
Ecstasy	Serotonin transporter	↑ serotonin	SSRIs (1)	Serotonin drugs (1)	SSRIs (1)

BDZs, benzodiazepines; CB1, cannabinoid 1; DAT, dopamine transporter; ACH, acetylcholine; GABA, gamma-aminobutyric acid; LAAM, Levomethadyl acetate; SSRIs, selective serotonin reuptake inhibitors.
(1) Theoretically effective but no clinical trial data.
(2) Controversial, risk of dependency.
(3) Not available throughout the EU.
(4) Used to maintain abstinence.

Different pharmacological agents have different sites of action and affect different neurotransmitter systems. All treatments which act by blocking the direct binding of the abused drug fall into one of three approaches: (1) agonist; (2) antagonist; and (3) partial agonist. These three approaches are described below. A detailed description of treatments for all drugs of addiction is beyond the scope of this report. However, a brief description of each approach, their potential for effective treatment, as well as their limitations is provided below. A summary of the most common drugs used in the treatment of addiction, and their primary action and application is provided in Table 1 (Lingford-Hughes and Nutt, 2003).

Agonists

Agonists are drugs that act in a similar way on the same receptors as a drug of abuse and produce similar effects. Treatment involves replacing the abused drug with one that is: safer (less likely to produce adverse outcomes); has slower pharmacokinetics (meaning that it will bind for longer); or a stronger affinity for the receptor site (so it will not be readily shifted from the site by the abused drug). The aim of treatment is to block the actions of the drug of addiction, providing some protection against the acute adverse effects of the drug (e.g. overdose in the case of heroin addiction). These drugs should also have slow rates of brain uptake and clearance, thereby providing relatively stable and more enduring concentrations of dopamine in the brain (e.g. oral methadone).

The aim of agonist treatments is to replace the unsupervised use of an illicit drug (e.g. heroin) of unknown strength and purity, with a safer, pharmaceutical grade drug (e.g. methadone) in a regulated manner which offers the potential for support and education. The advantage of agonist treatments is that they reduce the incidence of acute adverse effects of drug use, such as overdose and the spread of BBV. Agonists can also prevent or minimise the symptoms of withdrawal, and reduce craving for the drug of addiction, which leads to greater retention in treatment programmes and increased treatment compliance.

Agonists are often used in substitution treatment programmes where the aim of treatment is long-term maintenance. The most well known is methadone maintenance therapy (MMT). Agonists may also be prescribed for shorter periods to help addicts become abstinent by reducing the symptoms of withdrawal. Agonists have a number of social advantages as well, in that they reduce the incidence of drug-related social harm, such as crime, theft and violence.

The disadvantage of agonists is that they have the potential to cause similar harm as the abused drug, especially if they are used in large doses or diverted to the black market and used by drug naïve individuals who lack the drug tolerance of chronic drug users. Agonist treatments are therefore provided under strict controls and restrictions which can make treatment difficult and unattractive (e.g. daily supervised dosing). Also, because agonists produce a similar reinforcing effect to the target drug, they are also addictive (e.g. methadone and buprenorphine for heroin dependence).

Agonist substitution has not been as successful in the treatment of addiction to stimulants, except for comorbid treatment of ADHD. This is most likely because the agonist has to block nearly all of the dopamine agonist transporter (DAT) in order to interfere with cocaine's effects, or may reflect the importance of changes in other neurotransmitter systems such as norepinephrine. Drugs which increase dopamine can also cause additional health problems, particularly concerning the heart, and they can be abused. Opponents of the prescription of agonists also argue that this leads to increases in illicit drug use by sending a message that recreational drug use is an appropriate behaviour and reducing the deterrent effect of punitive drug policies. There is very little reliable evidence to support either of these claims.

Antagonists

Antagonists are drugs that bind to the pharmacological site of action but do not produce the reinforcing effects of the addictive drug or its agonists. Antagonists work by blocking the receptor sites at which the drug of addiction acts (e.g. naltrexone for heroin addiction), thereby reducing its rewarding effect. Antagonists must also be: safe; have a long half-life (meaning that they remain bound in the brain for long periods, reducing the dose frequency), and; possess a strong affinity for the receptor site so that they cannot be easily shifted by the drug of addiction.

Antagonists are most often employed as a prophylaxis against relapse because they block the reinforcing effect of addictive drugs as long as they are taken (see below). The advantage of antagonists is that they are generally safer than agonists when used as intended; they are not reinforcing or addictive; and they can also reduce acute adverse effects of the abused drug (e.g. overdoses). Their safer profile means that they can be provided with fewer controls and regulations than agonists.

A problem with antagonists is that they can precipitate withdrawal symptoms because they block the activity of the drug of addiction. Thus, initiating their use requires that addicts have not been detoxified and are drug free. Because antagonists do not have any rewarding effect, people often stop taking them and then relapse to drug use, with a higher risk of a drug overdose in the case of opiates because users are no longer tolerant to opiates. New slow-release formulations of these drugs (e.g. naltrexone implants that reportedly last between one and six months) have been developed in order to overcome these compliance issues. These treatments are often promoted for use in some form of coerced treatment (Caplan, 2006), a practice that raises a number of ethical concerns that will be discussed in Chapter 5 (see pp. 93–99).

Partial agonists

Partial agonists are drugs that bind to the site of action and produce less of a reinforcing effect than full agonists (e.g. buprenorphine for opioid dependence, varenicline for nicotine). Like their pharmacological cousins, partial agonists must have a long half-life and a strong affinity for the binding site in order to block the effects of the addicted

drug. Partial agonists also possess many of the advantages of both the full agonists and antagonists and so may provide an effective form of treatment that will benefit both society and the individual. More empirical data is required on their safety and efficacy.

The main advantage of partial agonists is that as they have some reinforcing effects they are therefore more likely to retain people in treatment than antagonists. As their agonistic effects are minor, they are much less likely to cause acute adverse effects. Their safer profile also means that they can be provided under less prohibitive restrictions than full agonists: they can be given in larger doses, and may be provided with less supervision and with takeaway doses. They also provide some protection against the harmful effects of the drug of addiction such as overdose.

Despite these positive features, partial agonists do pose a number of risks. As they produce a small agonist effect, they can still produce overdoses and they are addictive. It is also not clear yet whether partial agonists are as effective in reducing illicit drug use as full agonists (Lingford-Hughes et al., 2004). Partial agonists may not be as effective as full agonists in reducing the urge to use a drug of abuse in some individuals because of their attenuated rewarding effects. It is important that the partial agonists are used with care, and that each is evaluated on its merits.

Treatment aims and philosophy

Agonists and partial agonists may be given for greatly varying lengths of time, depending upon the philosophical aims of the treatment programme. Pharmacological treatments may be used over short periods of time to assist addicted individuals to withdraw from their target drug. This is often referred to as detoxification. The aim of detoxification is to achieve abstinence from all drugs. Agonists or partial agonists may also be used for longer periods to encourage less harmful forms of drug use as substitution treatment (also referred to as replacement or maintenance therapy). Treatments that primarily aim to reduce the harm associated with illicit drug use (also referred to as harm minimisation or harm reduction) involve the use of other rewarding or reinforcing drugs. Substitution treatment for opioid dependence, using either methadone or buprenorphine, is commonly available in Europe and generally considered an important element in the response to this type of drug problem. However, historically this approach has been considered controversial and sometimes viewed as condoning drug use. This view still persists at least to a limited extent in some countries today, although substitution treatment for opioid problems is available in nearly every EU Member State (EMCDDA, 2008).

A longer term form of addiction drug treatment that has not generally been regarded as controversial is the use of antagonists for relapse prevention. The aim of relapse prevention is to prevent the use of any recreational drugs, rather than reducing their harm. It is therefore more acceptable to those who believe that treatment programmes that offer any form of rewarding drug are immoral and send the wrong 'message' to society about drug use.

These different treatment approaches lie along a continuum of treatment philosophy from abstinence to harm minimisation, with drug-free detoxification at one end and agonist maintenance for harm minimisation at the other. Harm reduction strategies also include some of the newer approaches to treating addiction, such as reducing the toxic effects of chronic drug use or finding safer forms of drugs to use (see pp. 117–20). The growing acceptance of the view that addiction is a chronic disease has seen a shift in research towards approaches that aim to treat addicted individuals over a long period. This approach is not always well reflected in social policies towards addiction that sometimes still focus on abstinence in the short term as a primary goal.

Pharmacological treatments targeting the dopaminergic response to drugs

Drugs which target the dopaminergic system have not yet proven effective in treating addiction. This may be because drugs used so far have targeted the wrong dopamine receptor (e.g. DRD2). New treatments may also need to consider changes in other modulatory neurotransmitter systems. The central role that dopamine plays in a range of behaviours and cognition has always meant that it would be difficult to develop an effective dopaminergic drug to treat addiction that did not also produce serious adverse side effects.

The use of agonists to treat addiction to stimulants (by binding to the DAT in order to increase dopamine activity) has been unsuccessful. The DRD2 selective agonists tested have not proven effective. Pharmacological agents targeted at the other dopamine receptors appear more promising. Preliminary studies of the dopamine receptor 1 (DRD1) agonists have been promising (Baler and Volkow, 2006), as has a partial agonist of the dopamine receptor 3 (DRD3) in treating cocaine dependence (Pilla et al., 1999; Lingford-Hughes and Nutt, 2003).

Another approach to treat addiction has been to block the acute dopaminergic response to addictive drugs by blocking dopamine receptors. Neuroleptic drugs (traditionally used in the treatment of schizophrenia) that block the DRD2 receptor reduce the reinforcing effects of drugs in animal models (Hyman, 2005), but this effect has not yet been reproduced in human addicts. Neuroleptics are also not well tolerated by addicts who are particularly sensitive to the extrapyramidal effects of DRD2 blockers, (e.g. disorders of movement and motor control such as those seen in Parkinson's disease) (Hyman, 2005).

Given the role that dopamine plays in everyday motivation, blocking DRD2 receptors is also likely to decrease sensitivity to natural reinforcers. One drug that affects dopamine activity and has proven effective in the treatment of nicotine addiction is bupropion (Zyban) (Jorenby et al., 1999). Its exact mechanism of action is still uncertain although it appears to act by inhibiting the uptake of dopamine and noradrenaline (Ascher et al., 1995). Bupropion is also a nicotine receptor antagonist. Clinical trials are under way to investigate the use of bupropion in the treatment of methamphetamine addiction.

Pharmacological interventions in systems related to the reward pathway

Given the mixed results from directly interfering with dopamine, an alternative approach has been developed to target related neurotransmitter systems that are involved in reward (Lingford-Hughes and Nutt, 2003). These related circuits indirectly affect the reward pathway by: regulating either dopamine cell firing or the release of dopamine in the NAcc (e.g. opioids, and the amino acids, glutamate and GABA); or interfering with the postsynaptic response to dopamine stimulation (e.g. cannabinoids) (Iverson et al., 2007). Interventions in these processes provide some novel and promising treatments to emerge from neuroscience research. More empirical data is required before the safety and efficacy of these potential treatments can be established. Pharmacological interventions in each of these related systems are discussed below.

Opioids

Recent research has suggested that changes in the opioid system play an important role in all forms of addiction, not just opiate addiction. There are three receptor subtypes that mediate the effects of endogenous opiates. Neuroimaging studies suggest that changes in the mu opiate receptor levels may be fundamental in addiction (Zubieta et al., 2000). The kappa receptor may also play a role. Stimulation of kappa receptors reduces dopamine release in the NAcc that may be responsible for feelings of dysphoria. Delta antagonists reduce self-administration of alcohol in rats, and so may play an important role in reinforcement (Lingford-Hughes and Nutt, 2003).

The fact that naltrexone is effective in the treatment of addiction to substances other than opiates highlights the role that the opioid system plays in addiction. As discussed previously, naltrexone is a long-acting opioid receptor antagonist which blocks the effect of opiates like heroin. Naltrexone has been shown to be effective in the treatment of alcohol dependence, probably because it blocks the actions of endogenous endorphins that are released by alcohol (Herz, 1997). Naltrexone has also been shown to be effective in the treatment of obesity (addiction to food) (Volkow and Wise, 2005) and gambling. It is one of a number of anti-craving drugs that have become a focus for research (O'Brien, 2005) and that are being promoted as effective treatments for addiction.

The amino acid neurotransmitters: Glutamate and GABA

Many of the neuroadaptations that occur in addiction involve changes in the prefrontal cortex that have numerous connections with the dopaminergic reward pathway. Activity in these cortical circuits is mediated by the amino acid neurotransmitters, glutamate and GABA. These neurochemicals accordingly represent promising targets for pharmacological intervention. Studies have begun to look at whether drugs that act on these systems reduce drug self-administration in animals (Kalivas and Volkow, 2005). Treatments which affect the glutamate and GABA systems may also prove effective in the treatment of stimulant addiction, which has been largely resistant to existing pharmacological treatment approaches.

The amino acid, glutamate, is the principal excitatory neurotransmitter in the brain. The glutamatergic system is well placed to influence dopamine signalling because its neurons in the prefrontal cortex and amygdala make reciprocal connections with the dopaminergic mesolimbic reward pathway. The glutamate receptor, N-methyl-D-aspartic acid (NMDA), appears to play a particularly important role in addiction to nicotine, cannabis, alcohol and benzodiazepines (Wolf, 1998; Lingford-Hughes and Nutt, 2003). Antagonists of the NMDA receptor inhibit sensitisation to stimulants and the development of opioid dependence (Trujillo and Akil, 1995; Lingford-Hughes and Nutt, 2003). Co-treatment with the NMDA blocker, dizocilpine, also attenuates tolerance to opioids (Trujillo and Akil, 1991). There also appears to be a compensatory increase in the numbers of glutamate receptors in alcohol addiction that may explain the hyper-excitability seen in alcohol withdrawal. Acamprosate, a drug shown to be effective in treating the withdrawal symptoms of alcohol addiction, decreases glutamate release (O'Brien, 2005). Not all NMDA antagonists are clinically useful because some produce hallucinations and psychotic symptoms. N-acetylcystein (NAC), an activator of cystine-glutamate exchange, is currently in Phase 1 clinical trials for cocaine dependence (LaRowe et al., 2006).

GABA-enhancing drugs maintain abstinence by preventing cue- and drug-induced increases in dopamine. Two antiepileptic drugs have shown promise in this area. Topiramate shows promise in treating alcohol, opiate and cocaine addiction (Kampman et al., 2004; Myrick and Anton, 2004; Zullino et al., 2005), while another antiepileptic, gamma vinyl GABA (vigabatrin) might also be effective (Brodie et al., 2005). Baclofen, a muscle relaxant which acts via the GABA-B receptor, has been shown to reduce the reinforcing effects of amphetamines and to reduce cocaine self-administration in rats (Campbell et al., 2002; Brebner et al., 2005).

As discussed above (see pp. 38–40), glutamate, and to a lesser extent GABA, are involved in the molecular processes, such as LTP and LTD, that are responsible for the synaptic changes that maintain addiction. Neuroscientists are also currently investigating the signalling molecules within each neuron that produce the internal cellular processes that lead to synaptic plasticity, such gene expression or gene upregulation, protein synthesis and protein trafficking (Calabresi et al., 2007). The molecules that sustain these processes may yet prove to be significant targets for the treatment of addiction, by helping to reverse or ameliorate the neuroadaptations associated with addiction (Calabresi et al., 2007). A great deal of research is required before this hope may be realised, but it holds significant promise, particularly for addictions that do not yet have an effective pharmacological target.

Cannabinoids

The cannabinoid receptor (CB1) system is believed to be involved in the neural processes underlying reward, learning and memory, suggesting that it might also be a potential pharmacological target in the treatment of addiction. Drugs which act on the cannabinoid system have recently been shown to reduce the reinforcing effects of various drugs

of abuse. The CB1 cannabinoid receptor modulates dopamine cells and postsynaptic responses from dopamine stimulation, and can therefore influence the reinforcing effects of drugs. The CB1 antagonist, Rimonabant, appears to attenuate the reinforcing effects of various drugs of abuse. Rimonabant was originally developed as a treatment against schizophrenia, as cannabis can lead to psychosis, and later obesity and the metabolic syndrome (Van Gaal et al., 2005). Preclinical studies suggest that it may also be effective for the treatment of nicotine addiction (Le Foll and Goldberg, 2005).

Pharmacological treatments for chronic changes in dopamine activity

Chronic drug use also produces neuroadaptations in other neural systems that can significantly affect an individual's ability to refrain from using drugs (Baler and Volkow, 2006). There has consequently been an increased effort in recent years to develop pharmacological treatments that ameliorate these neuroadaptive changes. Given that these changes affect cognitive processes such as executive control, memory and conditioned response, and responses to stress, these drugs may be more effective when combined with cognitive behavioural therapy.

Corticotropin releasing factor stress response

Since stress is a potent trigger for relapse, dampening the stress response may be a way of reducing relapse to drug use (Bruijnzeel and Gold, 2005). The stress response is mediated by CRF in the HPA axis and amygdala. Drugs, such as CRF antagonists, which can interfere with the stress response may prevent relapse. Drugs which block CRF activity have been shown in animals to block the initiation of drug use and stress-induced reinstatement of drug seeking behaviour for a variety of drugs (Koob, 1999; Koob and Le Moal, 2005; Baler and Volkow, 2006). Dynorphin is another molecule in the stress pathway that is being targeted.

Oxytocin is a neuropeptide hormone that is involved in the formation of relationships (Pitman et al., 1993; Insel, 2003; Heinrichs and Gaab, 2007) and the development of trust (Kosfeld et al., 2005; Domes et al., 2007a; Domes et al., 2007b). Recent research has suggested that it may be a possible target in the treatment of addiction (Kovacs et al., 1984; Sarnyai and Kovacs, 1994; Kovacs et al., 1998; Sarnyai, 1998). Oxytocin is released by the posterior pituitary and has been shown to reduce stress, dampen HPA activity (Kovacs and Telegdy, 1988; Devries et al., 2007), and reduce dopamine transmission. Oxytocin also inhibits the development of tolerance to addictive drugs and reduces the symptoms of withdrawal from morphine in rats (Kovacs et al., 1984; Kovacs et al., 1998).

Memory manipulators and cognitive enhancers

Pharmacological treatments which either enhance or dampen memories associated with drug use have also been investigated as addiction treatments. The use of the adrenergic beta blocker, propranolol, interferes with the formation and recall of emotionally salient

memories, and may be effective in the treatment of Post-traumatic Stress Disorder (PTSD) (Pitman et al., 2002). Propranolol may also prove to be effective in reducing conditioned responses to drugs such as cocaine (Kampman et al., 2001; Milekic et al., 2006). Memory enhancers have been suggested as an adjunct to psychotherapy because of the effectiveness of a similar approach in the treatment of phobias.

Drugs which improve alertness and attention, such as modafinil, a drug used to treat narcolepsy, have been suggested as treatments for stimulant addiction. Modafinil appears promising in the treatment of cocaine addiction (Dackis et al., 2005) ([1]). The development of effective treatments for Parkinson's and Alzheimer's diseases which increase memory and attention, may also provide novel approaches to the treatment of stimulant addiction (e.g. ampakines).

Pharmacological approaches to minimise the harmful effects of drug use

Research is under way to develop new forms of drugs which reduce the toxic or harmful effects of drug use (e.g. toxicity of alcohol for liver and neural tissue). Nutt (2006), for example, has suggested that neuroscientists should develop a less toxic, water soluble GABA-agonist that would produce the euphoric effects of alcohol without its neurotoxic and hepatotoxic side-effects (Nutt, 2006b). An analogous approach has been suggested with tobacco harm reduction in which cigarette smokers would be encouraged to switch from smoking to much less hazardous oral tobacco products, such as snus (Gartner et al., 2007). Snus has been treated to remove the primary carcinogens and because it is orally consumed, has a substantially reduced incidence of adverse health effects (e.g. lung cancer). To date, these approaches remain controversial and it is likely that there would be considerable opposition to any attempt to market a safer alternative to illicit drugs like heroin or cocaine.

An alternative approach to harm reduction is using other drugs to mitigate the acute negative effects of particular drugs of abuse. One suggestion is to use drugs to prevent memory loss associated with alcohol intoxication (Nutt, 2006b). A similar strategy is used in the prescription of combined pharmacological treatments of addiction with the aim of reducing the abuse potential of the treatment. One example is the combination of a small dose of an opioid antagonist, naloxone, with buprenorphine (marketed as Suboxone) to reduce injecting use of the diverted drug. Because of its low oral biodisponibility (3 to 10 %) naloxone does not affect the reinforcing properties of buprenorphine when taken orally but precipitates withdrawal if the product is injected. It remains to be seen if this will prove effective. A summary of all the main treatments for drug addiction in use or development are listed in Table 2.

([1]) Modafinil, while not addictive, has an abuse liability. It is already reportedly being abused by long-distance drivers to drive for longer and by athletes in competition.

Table 2: A summary of current or developing treatments of addiction

Proposed targets	Medication	Clinical effectiveness for
Interfere with the reinforcing effects of a drug		
Substitution treatments	Methadone Buprenorphine LAAM Nicotine replacement	Heroin Heroin Heroin Nicotine
Trigger aversion	Disulfiram	Alcohol (cocaine)[a]
↓ dopamine release	Topiramate	Alcohol (cocaine)
(antiepileptics)	(Gabapentin) (Gamma-vinyl-GABA)	(Cocaine) (Cocaine)
Non-dopamine targets mu-opiate receptors cannabinoid receptors	 Naltrexone Rimonabant	 Alcohol and heroin (being tested for weight loss, nicotine and others)
GABA receptors	(Baclofen)	(Alcohol and cocaine)
Interfere with drug delivery to the brain	Vaccines	Nicotine and cocaine (heroin in development)
Interfere with drug metabolism	Methoxsalen	Nicotine
Compensate for long-term effects of drugs		
Interfere with conditioned responses	Antiepileptics (above) Glutamate Acamprosate[b] (Modafinil)[b]	Alcohol (cocaine) Alcohol (cocaine)
Strengthen saliency of natural reinforcers	Enhance DA function Bupropion (deprenyl + nicotine)	 Nicotine (Nicotine)
Interfere with stress responses	(CRF antagonist)	Not tested
Interfere with withdrawal	Clonidine Benzodiazepines Antiepileptics Propanolol	Heroin Heroin Alcohol

Medications for which there is only preliminary clinical data are identified in brackets to differentiate them from those for which there is proven efficacy.
(a) The effects in cocaine addiction are not understood but do not seem to be mediated by triggering aversive responses.
(b) Mechanisms of action are not properly understood.

Source: Elsevier; Academic Press: *Trends in Molecular Medicine*
http://www.us.elsevierhealth.com/article.jsp?pageid=388.

Novel approaches to drug treatment

Immunotherapies

Immunotherapies represent a new strategy in the development of addiction treatment. These are in the form of vaccines against the effects of nicotine, cocaine and heroin that act by binding to the target drug in the bloodstream and preventing it from reaching the brain. Drug vaccines are primarily intended to be used in relapse prevention but the term 'vaccine' also raises expectations about their potential use to prevent drug addiction when used as a prophylactic treatment (e.g. in combination with genetic screening of adolescents for addiction susceptibility). The effectiveness of such an approach is uncertain and even if successful, it would raise a number of ethical concerns that will be addressed in Chapter 5 (see pp. 111–14).

Depot or slow release formulations

Researchers are developing implantable slow release or long-acting formulations of naltrexone and buprenorphine. This will make it possible to reduce dosing from a daily event to a monthly or even half-yearly implantation, overcoming the problems of poor compliance with antagonists and diversion of agonists and partial agonists if take-away doses are given. Implantable antagonists are a particularly attractive option for proponents of legally coerced treatment of addiction.

Neurosurgery and deep brain stimulation

A novel, so far rarely used, treatment for addiction is neurosurgical ablation of brain structures implicated in addiction. Neuroscientists in Russia and China have used neuroscience research of the effects of chronic drug use on the nucleus accumbens and the cingulate gyrus to justify the stereotactic ablation of these regions (Gao et al., 2003; Medvedev et al., 2003). Neurosurgery is the most invasive and permanent form of treatment used and is often only considered appropriate in a few severe conditions where there are few options which have been tried unsuccessfully. It is generally considered a treatment of last resort, requiring careful consideration (Valenstein, 1973; Valenstein, 1986; Hall, 2006). The ethical implications of the social and political context in which these treatments have been used will be discussed in subsequent sections.

Deep brain stimulation (DBS) is another form of neurosurgery that has been suggested as a treatment of addiction (BBC News, 2007). It involves the insertion of electrical stimulating electrodes deep into the brain regions involved in addiction, such as the insula. When the electrodes are stimulated, activity in these areas can be manipulated. The use of DBS in these areas has so far only been trialled in obsessive compulsive disorder (Gabriels et al., 2003), although DBS has been used in the treatment of Parkinson's Disease and is currently being trialled in the treatment of depression. While this treatment is not as damaging as ablative neurosurgery, it does present considerable

risks and can result in permanent damage. The side effects of this novel treatment are also unknown. Some patients with Parkinson's Disease who have been treated with DBS have developed impulsive behaviours that appear similar to impulse disorders (Frank et al., 2007). A patent has also been placed on the use of intracranial (vagal) nerve stimulation as a treatment for addiction.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a far less invasive treatment that involves placing a small magnetic coil against an individual's skull in order to block or enhance neural activity in a particular cortical region (Machii et al., 2006). The coil produces a strong magnetic field that can change neuronal electrical activity (Pascual-Leone et al., 2002). By manipulating cortical activity, it is hoped that TMS might prove to be a useful treatment for a range of psychiatric disorders, including addiction (Ridding and Rothwell, 2007). TMS raises fewer health and safety concerns than neurosurgery or DBS because it does not involve physical penetration of neural tissue (Anand and Hotson, 2002). However, it has been shown to cause psychotic and epileptic symptoms in a minority of patients (Wassermann, 1998; Machii et al., 2006).

TMS is capable of producing significant behavioural changes. Studies have shown that a session of TMS can have a significant impact on the decisions individuals make (Fecteau et al., 2007), and may enhance cognition and memory (Illes et al., 2006a). A recent pilot study has shown that a session of high frequency repetitive stimulation of the right prefrontal cortex can reduce craving in cocaine-addicted subjects (Camprodon et al., 2007). This technique appears promising but requires more research to evaluate its safety and efficacy.

Neuroimaging for prevention and treatment of addiction

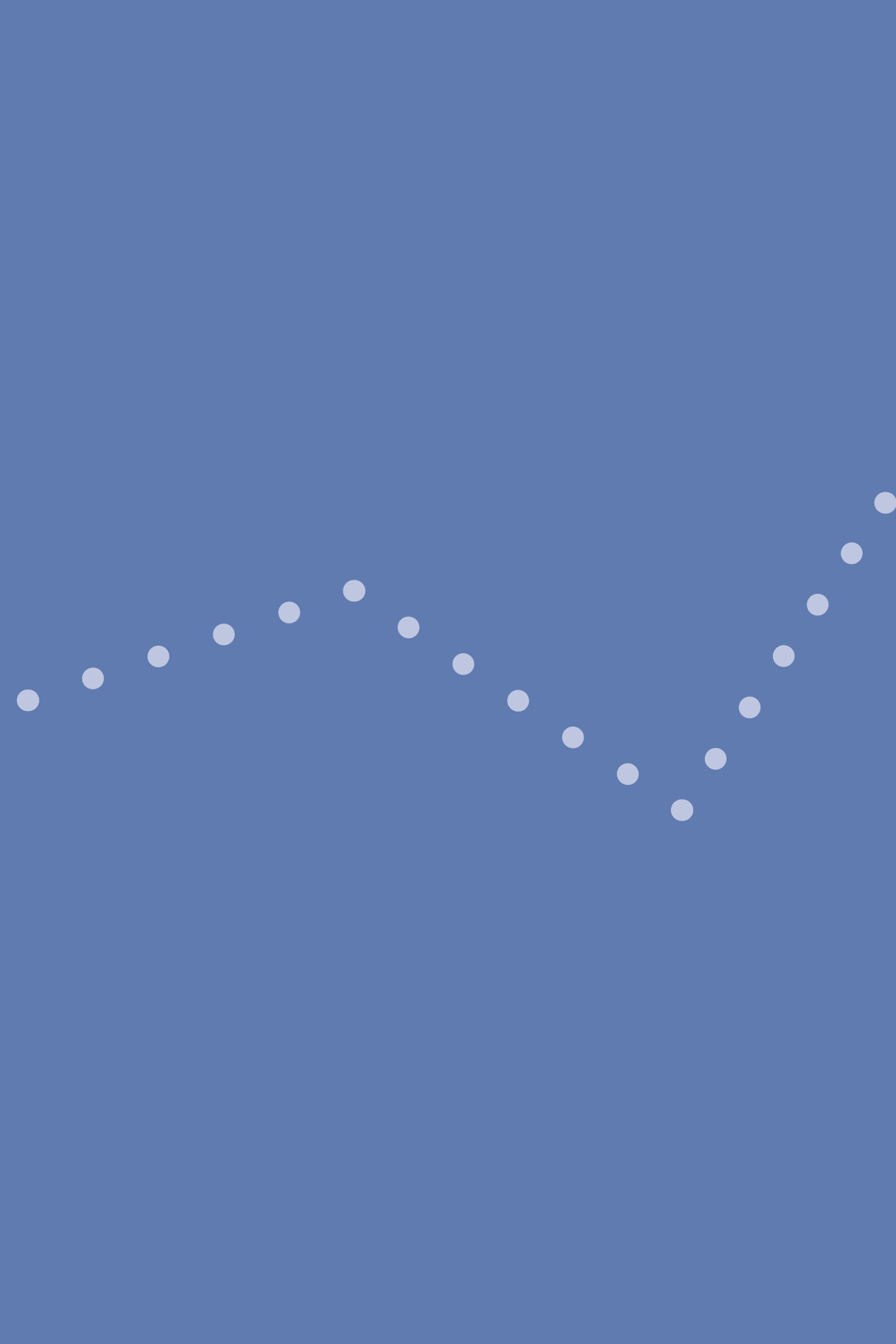
Neuroimaging using fMRI, PET, single photon emission computed tomography (SPECT), magnetoencephalograph (MEG), and electroencephalograph (EEG) are non-invasive techniques that enable researchers to identify functional and structural abnormalities in the brains of addicted individuals. Neuroimaging has played a critical role in increasing understanding of the neurobiology of addiction. It has been suggested that these techniques might also be used in preventing addiction and developing more effective treatments (Volkow and Li, 2005).

As with genetic screening, neuroimaging might be used to identify neuropsychological vulnerabilities that predispose some individuals to developing addiction if they abuse drugs (e.g. poorly functioning inhibitory control circuits). Neuroimaging may also help to identify neuropsychological deficits that are the primary source of an individual's inability to stop using drugs (e.g. enhanced salience, poor executive control). This would allow clinicians to target specific pharmacological treatments to individuals that would hopefully have a better chance of success.

Psychosocial treatment of addiction

Psychosocial interventions such as cognitive behavioural therapy, motivational interviewing, drug counselling, and 12-step support groups provide an important adjunct to pharmacological and medical treatments in achieving a long-term successful outcome. While psychosocial treatments are outside the scope of this report, it is important to acknowledge the need for greater attention and investment in psychosocial treatment and research. Advances in neuroscience and cognitive psychology showing cognitive deficits in impulse inhibition and a pathological focus on drug use in addiction highlight the importance of psychosocial therapies that aim to ameliorate these cognitive deficits (Volkow and Li, 2005).

Neuroscience may also help in designing therapies which are more effective for addicted individuals with particular kinds of cognitive deficits. The neuroscience of addiction vulnerability during adolescence may assist in driving social policies for dealing with addiction, such as prohibitions on alcohol and tobacco use in minors, and the importance of early education on the dangers of drug use. One particular ethical concern in relation to psychosocial treatments of addiction is that simplistic brain disease models may lead to the neglect of psychosocial approaches in favour of more biological approaches to treatment, sometimes referred to as 'medicalisation'. This concern will be discussed in Chapter 5 (see pp. 106–09).



Chapter 4

Human rights, ethical values and the implications of current addiction research

Benjamin Capps and Richard Ashcroft

Introduction

Ethics is the domain of inquiry whose task it is to formulate and interpret the most appropriate principles to guide human conduct. These philosophical and applied enquiries, when related to neuroscience, have been termed 'neuroethics', although the methods of analysis and theoretical frameworks used in these inquiries are not unique to this field.

There is a bewildering diversity of approaches to this task, resulting in a wide variety of ethical theories which purport to provide rationales for common moral rules (Rachels, 1999; Beauchamp and Childress, 2001). Policy rarely appeals directly to any single moral position; and for this reason, it is possibly unwise to rely only on any one doctrine (and all its many manifestations) to shape ethical analyses of the implications of research on addiction neurobiology. The basis of European bioethics has been characterised by at least three ethical approaches which have presided over the debates: human rights, dignity and utilitarianism. In this report, it is suggested that the first of these — human rights — has a particular prominence in EU policy. Such an approach is not without controversy, and there are two principal debates in this regard: the moral basis of human rights and the role of government in applying such principles. Such debates are beyond the scope of this report, which intends to present the ethical arguments in respect to neuroethics.

From a human rights perspective, the following principles could be taken to be requirements for treatment to be regarded as ethical:

1) There should be rigorous evidence of the safety and effectiveness of the treatment that is provided;

2) Effective treatment should be provided safely in well-structured, well-resourced and well-managed treatment programmes;

3) Human rights law should be clearly understood and prioritised over the competing claims of the public interest. A balance must be found between these competing claims and this should be expressed in the ethical values of autonomy, liberty, privacy and consent;

4) Restricting individual rights in the public interest must only be done for compelling reasons based on empirical, clinical and scientific evidence;

5) Policies should observe the ethical values of respecting patients' autonomy by defining the constraints of their liberty and by ensuring that they give free and informed consent to participate in treatment, protecting their privacy of information;

6) Treatment programmes should ensure that dependent persons have equitable access to treatment which maximises its effectiveness for each individual (by matching patients to the treatment that meets their individual needs and situation), and ensures that they do not bear a disproportionate social burden in accepting treatment;

7) It is important that pharmacological treatment should not be used to compensate for poor social policies that lead some to drug abuse and addiction, contribute to a general erosion of human rights, or inappropriate 'public interest' drug policies that may be over-focused on the negative and criminal impact of drug addiction.

Ethics and addiction

The promise of neuroscience and genetic research raises major ethical and social issues (Safire, 2002; Hall et al., 2004b; Farah, 2005; Illes, 2006; Ashcroft et al., 2007). These can be considered under two broad headings: (1) ethical issues that arise from neuroscience and genetic research on addiction; and (2) the broader social and ethical implications of the potential technological applications of neuroscience (e.g. for therapeutic, preventive, and enhancement purposes). This part of the report is concerned with (1). In Chapter 5, questions arising under (2) are discussed in respect to the novel developments in addiction neuroscience and genetics that may impact upon the treatment and prevention of addiction, and policies to reduce drug use.

Various ethical approaches have been applied to locate and reflect on the ethical issues in neuroscience research, and to frame and justify policy responses. A number of ethical values have emerged as being fundamental in balancing individual and public interests; and of particular importance have been issues of autonomy, liberty, privacy, consent and equality. These ethical values may be framed within a broad conception of human rights, and by balancing such rights with the public interests, a framework may be developed which can inform our responses to addiction and the emerging findings from current research. A possible framework is suggested in the box on p. 74. The sections that follow explore how these highlighted ethical values are affected by the key role of choice in drug use, and the possible ways in which the environment and genes affect an addict's neuropsychological capacity for decision-making, as understood by addiction neuroscience.

In modern liberal democracies there tends to be an emphasis on the public good; this involves a proportional response to addicts' behaviour. For example, policies

entirely based on the 'moral' or 'sceptical' model may not take into account the social circumstances of drug use, the lack of effectiveness of punitive measures, and the benefits of treatment and reintegration. On the other hand, the 'medical' model may be used to downplay the criminal behaviour of some drug users. Therefore, while autonomy is a guiding premise in respecting the rights of individuals, individuals do not have rights to do as they please; their actions must be guided by responsibility towards others. Thus, in some situations, where individuals are incapable of controlling their actions, or acting in a way which may harm themselves or others, punitive measures may be justified. However, given the complexity of drug addiction, the scientific evidence would strongly point to the need for a balanced use of the medical model with other perspectives when considering which policy options are appropriate. This would ensure that both human rights and the public good are both adequately protected (see box below).

Developing a balanced drug policy

Developments in neuroscience suggest that a balanced approach is required in addiction policies. The justification for such an approach is grounded in the medical model of addiction and the requirement for punitive measures. Currently, policies tend to be often weighted towards the deployment of criminal responses to addiction. On the one hand, most states have laws that prohibit adults from using cannabis, cocaine, and heroin. These laws are justified on paternalistic grounds that they prevent adults from harming themselves or others. On the other hand, if one accepts that paternalism is sometimes ethically acceptable (e.g. if one supports compulsory seatbelt laws or the regulation of pharmaceutical drugs), a major ethical problem remains in explaining why adults are permitted to use other substances, like alcohol and nicotine, which also cause a great deal of harm to users (Husak, 2004).

There is no obvious neurobiological justification for the fact that some psychoactive substances are legal while others are not (Ashcroft et al., 2007). Nor does the legal status of these drugs necessarily directly correspond to the relative harms caused by their current levels of use (Room, 2007).

Some neuroscientists (e.g. Blakemore, 2002; Iversen, 2002; Nutt, 2006a; Iverson et al., 2007; Nutt et al., 2007b) are hopeful that their research will facilitate the development of policies towards drugs that reflect their prevalence of use and their capacity to harm users and others. The extent to which developments in this direction are likely, however, is questionable in the current context of strong policy support for the international drug control conventions and considerable opposition in most developed societies to any liberalisation of policies towards illicit drugs. Indeed, arguably it can be more easily imagined that advances in addiction neuroscience could be selectively used to justify more coercive policies towards illicit drug use in the name of preventing adolescents from acquiring a 'chronic brain disease'.

Taking all of the possible developments in neuroscience together, it is evident that an increasing influence of a 'global' economy on the development, manufacture and supply of drugs by 'online' and small-scale 'garage' agents make simple ethical choices difficult. These developments are likely to pose an important challenge for both European and inter-regional regulatory policies. This shift of focus from traditional sources of drug research and development, such as 'visible' biotech companies, to manufacturers and suppliers of illicit drugs, such as international cartels and 'garage' industries within the expansion of global markets, such as the Internet, is likely to challenge traditional approaches to regulation (Reidenberg, 1996). Long-established approaches which focus on drug trafficking control are likely to be increasingly challenged by these novel and more 'invisible' supply networks. Furthermore, attitudes based on the harm caused by drugs could potentially also be challenged by the development of 'safer' or non-addictive substances (Prinz, 1997). Drug-control policies may therefore be required to confront the need of putting into place a regulatory framework for the development, evaluation and use of novel drugs. This would involve questions of whether regulation is effective, legitimate and if its design is optimal (Brownsword, 2004). To some extent this problem is already developing as regulators are increasingly faced with the problem of distinguishing between products sold often over the Internet as food supplements, alternative medicines, cognitive enhancers and even legal and supposedly 'safer' alternatives to illicit drugs (EMCDDA, 2008).

Human rights framework for addiction policy

Human Rights

1) Protection and provision of necessary goods required for human life (e.g. health, housing)

2) Procedural rights to allow fair representation under law and to lead one's life free from arbitrary constraints: e.g. (from the ECHR) Right to a Fair Trial, Right to Equal Treatment.

Ethical Values

1) Autonomy
Refers to a person's capacity for self-determination.

2) Liberty
Condition in which an individual has the ability to act according to his or her own will within a coercive — but stabilising — framework of law.

3) Privacy
Ability of an individual or group to keep their lives and personal affairs out of public view, or to control the flow of information about themselves.

4) Consent
Intentional mediation of relationships with one another or to put in place new relationships, and to signal their intentions and wishes.

5) Equality
Equal treatment by the law and in medical care.

The Public Interest

Referring to the 'general welfare', contrasts with individual interest (protected as human rights), under the assumption that what is good for society may not be directly good for a given individual and vice versa.

Autonomy in addiction

By definition, addiction is a disorder in which an individual's control over their drug use is impaired. People with an addiction continue to use drugs in the face of enormous negative consequences and despite often expressing a wish that they could stop. This perspective is codified in the diagnostic criteria for substance dependence or addiction, in which a loss of control over drug use is central, and drug use is compulsive and at the expense of all other goal-directed activities, such as working or caring for children (World Health Organization, 1993b; American Psychiatric Association, 2000). This definition of addiction is contested by some commentators who are sceptical about the existence of addiction and see drug use as a decision that users make (see Chapter 1: 'Sceptical versus medical models of addiction', p. 25) (Szasz, 1975; Dalrymple, 2006; Satel and Lilenfeld, 2007). The effect of drug use and addiction on autonomy is of fundamental importance to this debate which, as discussed in Chapter 4, is also central to the expression of one's rights.

Autonomy is becoming increasingly more important in research on addiction (Levy, 2006). For much of the 20th century, drug-dependent persons were seen as autonomous, self-governing individuals who wilfully, knowingly, and voluntarily engaged in criminal and immoral behaviour (Gerstein and Harwood, 1990; Peele, 1998; White, 1998). As discussed in Chapters 1 and 2, the presumed autonomy and responsibility of such individuals has been called into question by recent genetic and neuroscientific research on addiction (Leshner, 1997; Volkow and Li, 2004). It is increasingly argued, most notably by the directors of the National Institute on Drug Abuse (NIDA) and the National Institute on Alcoholism and Alcohol Abuse (NIAAA), who fund a significant proportion of all current research on addiction, that addiction is a 'chronic, relapsing brain disease' (Leshner, 1997, p. 45).

The brain disease model of addiction challenges the traditional belief that drug use is always a voluntary choice by arguing that prolonged drug use results in long-lasting

changes in brain structure and function that undermine voluntary control (Leshner, 1997; Volkow and Li, 2004). These neuroadaptations can persist for months — possibly years — after abstinence and may explain why many abstinent drug addicts relapse (Volkow and Li, 2004). Neurocognitive studies have also shown that addicted individuals display cognitive deficits in decision-making tasks (Jentsch and Taylor, 1999; Grant et al., 2000; Bechara, 2001; Rogers and Robbins, 2001; Fillmore, 2003; Hester and Garavan, 2004; Bechara, 2005; Yucel and Lubman, 2007). A more detailed discussion of this research can be found in Chapter 2 of this report.

These results are used to support a neurobiological account of how addictive drugs subvert endogenous reward circuits that are essential to survival, thereby giving drug use an overriding motivational salience that works to the detriment of all other goal-directed activities (Dackis and O'Brien, 2005). According to proponents of the medical model, these brain changes also explain why addicts continue to use drugs despite tolerance to their pleasurable effects and in the face of serious adverse consequences. The 'chronic and relapsing brain disease model of addiction' therefore suggests that addicts have difficulty in understanding or considering the long-term consequences of drug use and have a diminished ability to control their drug use as a result of neuropharmacological changes in their brains.

Although extreme, if taken literally, the 'chronic and relapsing brain disease model' could be used to argue that those with an addiction lack the autonomy to make informed choices about drug use (informed consent). As some researchers have suggested (see box p. 77), the choice to enter treatment or to participate in research (Cohen, 2002; Charland, 2002) can be referred to as informed consent. This model could also be used to justify the inappropriate use of coerced treatment (see pp. 93–99), the use of treatments whose proponents are overly optimistic about their ability to 'cure' addiction, or the use of highly invasive treatments, such as neurosurgery (see box p. 108). It may also encourage a reliance on medical or biological approaches to treatment, referred to as 'medicalisation' (see pp. 106–109) at the expense of possibly more effective psychological or social policies to tackle drug use. The impact that addiction neuroscience is having on our understanding about these issues is discussed below.

Neurobiological research on addiction has significant contributions to make in understanding whether addicts are autonomous or not, and therefore responsible for their actions (see box p. 77 for an example of this). The debatable status of addicts before the law has thrown open a complex response to their criminal activities: both in consuming (and continuing to do so) an illicit drug and in engaging in criminal behaviour while intoxicated or in order to fund drug use. Criminal responses to drug use differ between the Member States ([1]). A large part of the debate concerns the addict's capacities, such as capacity to consent, or to take responsibility for their actions. Responses have varied

([1]) See the EMCDDA website for up-to-date information on current drug policies of the Member States: http://eldd.emcdda.europa.eu/

between the treatment of addiction as a medical condition and criminal justice approaches which assume that drug users should take responsibility (and pay) for their 'choices'.

At the start of this report it was emphasised that the 'medical' and 'moral' models have a large part to play in the development of appropriate responses to addiction. It is clear from the neuroscience of addiction that decision-making is impaired by addiction. However, it is generally not so impaired that those addicted lack autonomy, or forfeit their ability to express their liberty by virtue of the fact that they are addicted. Policy responses to addiction need to find a balance between restricting the liberty of those who cause harm to others as a consequence of drug use and taking measures, such as treatment, which aim to maximise an addict's autonomy. This issue is discussed in greater detail in the next section.

Do opioid-dependent individuals possess autonomy?

The 'chronic and relapsing brain disease model' of addiction has prompted some ethicists to question the capacity of opioid-dependent individuals to consent to some forms of treatment for their dependence (Charland, 2002; Cohen, 2002; Elliott, 2002; Roberts, 2002; Caplan, 2006). It is argued that heroin addicts are unable to make rational decisions about whether to accept an offer of heroin either in the setting of a research study (Cohen, 2002), or in a clinical trial of heroin maintenance treatment (Charland, 2002). Charland argues that heroin addicts are incapable of saying 'no' to heroin: 'their decision is not truly theirs' (Charland, 2002, p. 43). Based on their reading of the neuroscience literature, these ethicists argue that heroin addicts are 'neurochemically driven' to take heroin; they are 'hijacked' by the drug. These arguments, if accepted and directly applied, would raise ethical objections to addicts participating in research or clinical trials that involved consumption of their drug of addiction (e.g. trials of injectable heroin), or its agonists (e.g. methadone). It would raise similar doubts about the capacity of opioid addicts to freely consent to substitution treatments (e.g. MMT) (Carter and Hall, 2008).

The arguments of Charland and Cohen interpret the DSM-IV criteria that describe 'loss of control' and 'compulsive' behaviour in absolute terms. However, the DSM-IV criteria that they rely on do not constitute evidence. Charland's argument is based on the testimony of a single reformed heroin addict who claimed that heroin users are unable to say 'no' to an offer of heroin. In fact, overwhelmingly this view is not supported by empirical evidence, as illustrated by:

- Swiss heroin trials (a clinical trial of prescribed injectable heroin to severe heroin addicts) were not inundated with untreated heroin addicts seeking 'free heroin'. This was clearest in a randomised controlled trial of immediate versus delayed entry to heroin maintenance (with the delayed entry group given access to usual treatment, methadone maintenance or abstinence) (Perneger et al., 1998). The researchers

intended to recruit 40 patients in each group but only recruited 24 and 27 patients, respectively. Moreover, when those who were allocated to delayed entry to heroin treatment were offered the choice at the end of six months, two thirds of the group decided against receiving heroin (Perneger et al., 1998). Severely dependent treatment refractory Swiss heroin addicts were thus capable of saying 'no' to an offer of prescribed heroin.

- Many addicts are able to control their drug use in certain circumstances, without assistance and for varying periods in order to reduce their tolerance; to take time out from the rigours of their lifestyle; or respond to changes in life situation (e.g. birth of a child, input from friends, family and employers).

- Returning Vietnam veterans were able to quit opioid use without treatment once back in the U.S. (Gerstein and Harwood, 1990).

In order for 'addiction' to plausibly deny the autonomy of opioid-dependent individuals, this internal 'neurochemical drive' must be irresistible and absolute. The neuroscience evidence that Charland and Cohen rely on is not as clear as they suggest:

- evidence for 'compulsive' drug use emerged from highly controlled laboratory animal studies that arguably have a limited application to human compulsive behaviour or the contexts in which humans typically use drugs.

- human neuroimaging and neurocognitive research shows that addicts as a group show changes in brain function that are associated with a reduced ability to control drug use and they perform more poorly in neurocognitive tests of decision-making than non-addicts. These studies demonstrate a tendency for addiction to diminish neurocognitive capacity and function in some but not all addicts. Significantly, not all those who are addicted display these cognitive deficits while some non-addicted people do (Bechara et al., 2001; Bechara, 2005).

In summary, neuroscience research on addiction does not prove that addicts lack autonomy: while their autonomy is clearly impaired in some situations, particularly during withdrawal or intoxication, addicts retain some degree of control over their drug use and hence, some degree of autonomy. The aim of treatment should be to increase patient decision-making capacity and autonomy (Spriggs, 2005) rather than prevent addicts from participating in research and treatment that may be of benefit to them.

Informed consent and addiction

Consent refers to the capacity of agents to act according to their will, or to understand the consequences of an outcome, usually in relation to a decision to agree to enter treatment or participate in research. The question as to whether an addict possesses autonomy is central to whether they have the capacity to give consent. To give consent is to exercise one's autonomy.

When drug-dependent individuals seek treatment, they are often in a desperate state psychologically, socially, financially and physically. Addicts may also be neurocognitively impaired when they are intoxicated or in withdrawal. Given that many people who are addicted do not wish to be treated, they are often under some degree of social duress or external coercion to enter treatment. There can also be conflict between the interests of the person seeking treatment and the community who regularly funds the treatment programmes and decides how they are run. This can influence what people are required to consent to when they enter treatment and how their consent is obtained.

Informed consent is the formal process by which individuals agree to enter treatment in the full knowledge of its possible risks and benefits and in the absence of duress or coercion (Faden et al., 1986; Roberts, 2002; Walker et al., 2005). Individuals must be fully informed about the options open to them in order to be able to make autonomous decisions and therefore express their human rights. The process of informed consent is generally understood to require that an individual:

1) has the capacity to understand treatment and communicate their wishes;

2) is fully informed of the risks and benefits of treatment, as well as those of other treatment options;

3) is free of internal or external coercion in making their decision (Faden et al., 1986; Roberts, 2002; Walker et al., 2005); and

4) has equal access to all effective forms of treatment that are appropriately provided (Carter and Hall, 2008) ([2]).

The minimum requirements for obtaining informed consent to the treatment of addiction are provided in the box on p. 80. Surprisingly, there has been very little research into: how informed consent is obtained in the treatment of addiction; participants' perspectives on the consent process; the impact that particular consent procedures have on treatment outcomes; or how these procedures might be improved (Sugarman et al., 1999; Walker et al., 2005). There has been some limited research on the capacity of individuals with an addiction to give internally uncoerced consent and to understand the consequences of agreeing to research (Harrison et al., 1995; Fureman et al., 1997). More research is urgently required. Promising research that attempts to develop neurocognitive tools that may help both researchers and clinicians to assess an individual's ability to provide free and informed consent is under way (Hazelton et al., 2003; Cairns et al., 2005; Hotopf, 2005; Smith et al., 2006).

([2]) This last provision, which is not included in traditional formulations of consent, is particularly relevant in the provision of drug dependence treatment where there are competing social and political forces that determine what treatment options are available, and the manner in which these treatments are provided.

Minimum requirements for ethical consent to addiction treatment

Addicts can differ markedly both in the severity and length of their addiction, as well as in their social, financial and psychological circumstances (Roberts, 2002). They will also differ in their willingness to overcome their addiction (Walker et al., 2005). An informed consent process that is too narrow and rigid, epitomised by signing a medico-legal consent form, can therefore gloss over the complex nature of consenting to enter addiction treatment, making it difficult to ascertain whether consent is free and informed. This is especially true when an individual's capacity to consent may change dramatically over time. Adopting too narrow a view of the consent process may also lead to poorer treatment outcomes.

The autonomy of addicts in making choices about their drug use is undoubtedly impaired when they are acutely intoxicated or experiencing severe withdrawal symptoms. A strong argument therefore exists that addicts who enter treatment while intoxicated or in withdrawal should not be asked to sign detailed treatment contracts on admission to treatment. The worst of drug withdrawal symptoms should be reduced by medication (or have abated as a result of completing withdrawal). Patients should also be given time to consider their treatment options before they are required to make long-term or far-reaching decisions that are often implied by signing a treatment contract.

Once patients have stabilised, they should be provided with enough information to make a decision that is in their own interests. Given that there are a number of external social factors which influence what and how treatment is offered, the type of information provided during consent is likely to be critical, both to the outcome for the individual, and to ensure that the process of consent conforms with appropriate ethical requirements.

From an ethical perspective, it is important that the treatment chosen reflects the aims of the individual rather than those of the staff or the wider community. The issues around the justification for compulsory treatment are addressed later in this report. To allow the patient to make an informed choice about what sort of treatment they are entering, information is required about (Carter and Hall, 2008):

- the treatment programme (e.g. its aims, risks and benefits, and costs);
- programme rules and regulations (e.g. information on drug testing regimes, responses to positive urine samples, the intended length of treatment, costs, where and how often drugs are to be dispensed and the involvement of the criminal justice system and rights to privacy and confidentiality);
- the effectiveness of the programme and the likelihood of competing alternative treatment options;
- their freedom to refuse treatment or seek treatment elsewhere.

Liberty and addiction

Liberty is the condition in which an individual has the ability to act according to his or her own will within a coercive — but stabilising — framework of law. Liberty is premised on the notion that each individual can have a different conception about what is good for them, and therefore they should have the freedom of choice. Their choices are, however, restrained by the state which upholds individual rights and equality of opportunity. Such coercion is justified, or so it is maintained, because different conceptions of the good will inevitably come into conflict, and therefore social stability calls for rules to govern each others' private lives in the public sphere (Capps, 2007). Liberties can thereby be justly removed on the grounds that they are not human rights (Kramer, 2002, pp. 10–20). Liberty therefore refers to the freedom to engage in some activity without hindrance from others, so long as the expression of one's liberty is not to the detriment of others' human rights.

A commitment to liberty demands that individuals accept certain sacrifices — especially to exercise self-restraint — in their day-to-day lives. This means that each individual is responsible for their actions, and they are expected to observe rules pertaining to their actions. Liberty calls for a legal system which enforces rules according to the public interest, which in turn reflects on, and provides for, a stable existence for all citizens. Thus, in systems of rights, individual 'choices' are often qualified by the public interest, which include the justification of interference. This relationship is expressed in various human rights instruments. For example, the UK's Human Rights Act 1998 states that rights may be justifiably suspended:

> 'in accordance with the law and as is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' (Article 8, Right to respect for private and family life; similar statements accompany the other Articles of the Act).

When one breaks legally enforceable rules, they should expect that they will be dealt with fairly before the law, through a system of adjudication that may deprive them of some of their liberties. Thus, human rights frameworks recognise the value to individuals of their personal liberty and their ability to exercise their autonomy, and hence they recognise the need for an appropriate justification for any interference in the enjoyment of these.

Equality and addiction

Equality expresses a social benchmark which prescribes that in pluralistic cultures, where there are competing conceptions, each individual will be treated equally in morally relevant ways. This will extend to treatment under the law. Given that there are no established criteria of what moral aspects count as relevant, proactive measures normally

aim to reduce inequality. This has significant implications for the operation of the law (e.g. a right to a fair trial, and rights against some degrading or tortuous punishments) and for individual autonomy (such as equality of resources, welfare and freedom). This amounts to a requirement that policies not discriminate between individuals on the grounds of sex, race or social status, and contribute to and affirm social and economic equality. This latter condition is particularly relevant to how individuals are given fair access to medical interventions. Questions of distributive justice are important, and are subject to detailed analysis below.

With regard to addiction, the moral and medical models have very different implications for how addicted individuals and drug users are dealt with by the law. On the one hand, the 'moral' or 'sceptical' model is likely to place an emphasis on the criminal aspects of drug use, and thereby consider addicts and illicit drug users to have forfeited claims to equality and opportunity during the course of social 'punishment'. Importantly, such a position may have more to do with an idea of equity, in the narrow sense of the term, which has its basis in the principle 'to give each his due'. Such measures may not take account of prior failings in equality and opportunity, or the role of luck in maintaining a 'moral life'.

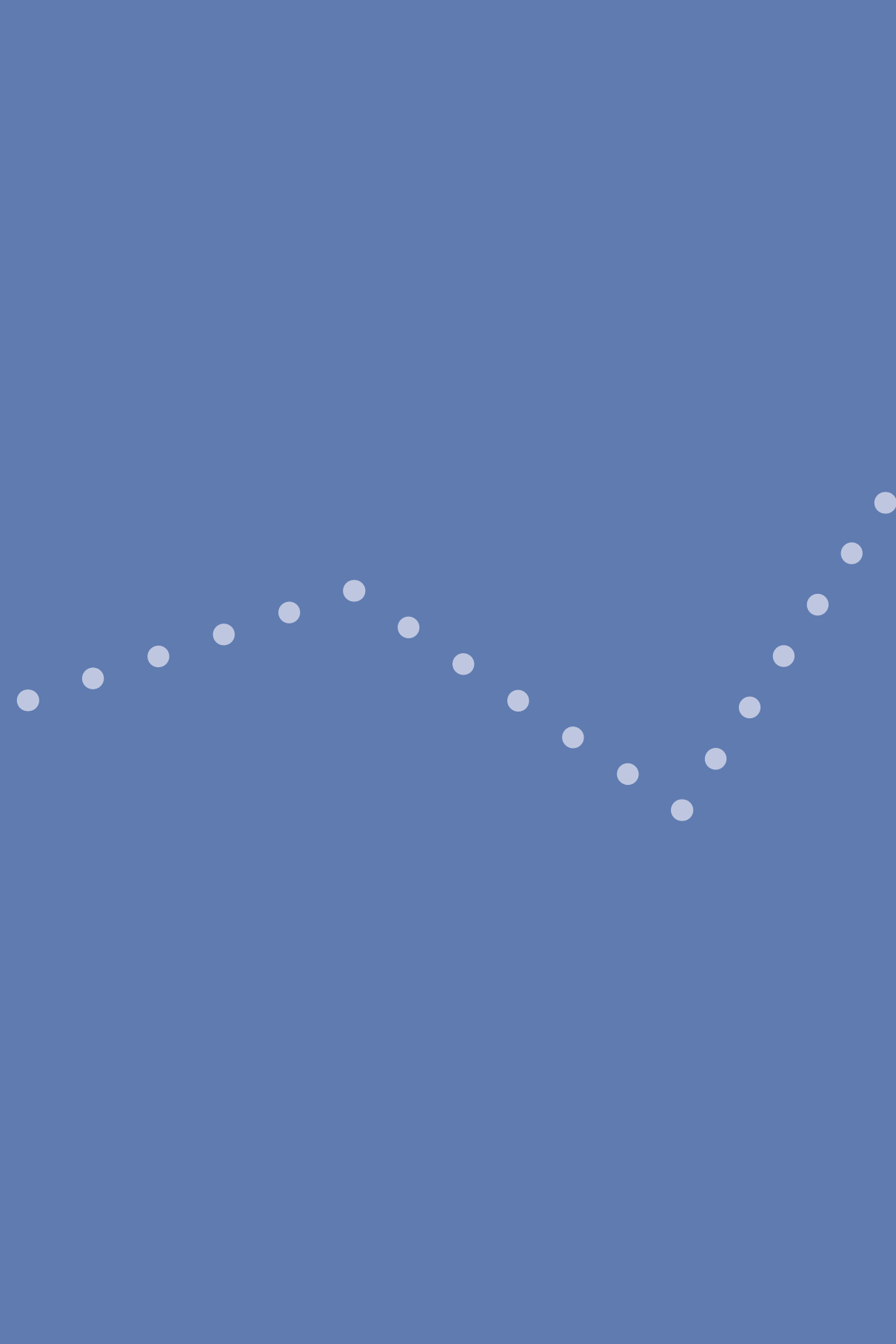
On the other hand, the medical model takes account of the observations that addicted individuals, by virtue of their condition, require 'additional' state assistance — such as medical care, social support to enable employability, and guidance in their responsibilities — above what a non-addicted person might receive. Equality, in this case, may lead to measures which attempt to raise the status of addicts to a more equitable level.

Privacy and addiction

Privacy is perhaps best understood as a bundle of rights that an individual or group have to keep their lives and personal affairs out of public view, or to control the flow of information about themselves (e.g. protect confidentiality). Protection of privacy is not an absolute moral principle, and therefore, a balance has to be found between privacy and other ethical considerations (Nuffield Council on Bioethics, 2007, p. 28). Thus, strengthening privacy rules should not indicate that drug users' privacy or confidentiality should not be over-ridden by justified legal measures. As already stated, privacy stems from rights which entail certain duties, and therefore responsibility in living one's life includes obligations to the community — not a right to do as one wants.

With a better understanding of neurobiology comes a greater capacity and power to pry into the innermost secrets of the brain, mind and selfhood. For some, this is an alarming development, that has been described as the use of pharmacotherapy to expand the '… drug war battlefield … to a new terrain directly inside the bodies and brains of drug users' (Centre for Cognitive Liberty and Ethics, 2004, p. 6). Some commentators have even argued that the ability to directly monitor brain activity is a

'threat to cognitive liberty' (Centre for Cognitive Liberty and Ethics, 2004, p. 4). Similar claims have been made about genetic screening. These bold claims need to be justified by an objective evaluation of what technologies such as neuroimaging are actually able to find reliably. The ethical implications of being able to monitor brain activity through functional neuroimaging is discussed in greater detail later in this report (see 'Neuroscience, prediction and privacy', p. 117).



Chapter 5

New developments in the treatment of addiction

Adrian Carter, Wayne Hall, Benjamin Capps and Ruud ter Meulen

Introduction

Neuroscience research of addiction holds the promise of providing a number of novel treatment technologies that may significantly reduce the impact and prevalence of addiction and drug abuse. However, along with the considerable potential for good comes a potential for significant harm. As with any new technology, the impact that these novel developments have upon the individual being treated, and the rest of European society, will depend on how they are used.

As discussed in Chapters 1 and 2, addiction is a complex neurobiological, mental and social disorder. The use of new technologies is complicated, not simply by the complexity of the disorder, but by the tension between a goal of treating a neuropsychiatric condition and the goal of protecting society from the harmful behaviour of drug users. This balance is further complicated by the social and moral attitudes held by many towards those who are addicted to drugs. It is accordingly important to carefully consider the ethical motivation for intervention and the social context in which these technologies are used.

Establishing a human rights framework requires balancing individual and public interests. In the previous chapter, it was suggested that this could be achieved by committing to ethical values which strike a balance between these two competing interests. In the context of this report, the ethical values of autonomy (empowering individuals to make worthwhile choices about their lives), liberty (the freedom to act according to one's choices but within the constraints of a fair socio-legal system), privacy (the power to protect the flow of information about oneself), and consent (the power to modify inter-agent relationships), are central to the ethical use of new technologies arising from neurobiological research on addiction.

Of central importance to this task is a consideration of how neuroscience research on addiction influences our understanding of addiction and in particular, our understanding of the autonomous decision-making capacity of the addicted individual. This has important implications for how society attempts to engage or encourage addicted individuals into treatment, particularly those who may not want to be treated. A review of the literature on the neuroscience of addiction reveals that chronic drug use does impact upon the neurocognitive systems involved in making decisions and controlling behaviour. However, this impact does not prevent absolutely the ability for addicted

individuals to choose not to use drugs. While neuroscience does provide a strong justification for the need for medical treatment and intervention, it does not suggest that this intervention should override the autonomous decision-making capacity of the individual, based solely on their being addicted.

Individuals with an addiction should be treated in the same manner as other members of society within the dictates of law and fundamental rights and with respect to access to appropriate medical and social supports. The choice of treatment available to the addicted should be dictated by a need to treat their condition and not as a form of extrajudicial punishment. This is particularly relevant to policy decisions regarding the use of substitution or replacement therapies where their use may be limited, or provided in ways that are not motivated by the desire to treat. A corollary of this argument is that treatments should be provided in a way that does not further harm society. Treatments often involve the use of drugs which can cause harm to society if misused.

This section uses the ethical framework developed in Chapter 4 to analyse how the neuroscience research and technologies outlined in Chapters 2 and 3 could be used in a way that allows for the greatest benefit, while protecting society and individuals from unanticipated consequences or misuses. This section provides a detailed analysis of the competing issues that impact on how technologies are used. The analysis has led to the following observations on the use of emerging technologies for the treatment of addiction in a number of circumstances, which are summarised below:

Coerced treatment

1. The use of some form of coercion or persuasion is a legitimate part of ethical treatment of addiction, and necessary in order for a state to fulfil its human rights obligations of offering the highest possible attainable standard of healthcare, ensuring equity, and enabling addicted individuals to express the full state of their autonomy and liberty. It is also important in recognising that some crimes committed by some addicted individuals arise from their addiction.

2. However, any use of legal coercion should not override whatever autonomous decision-making capacity addicts have. It should also be motivated by a desire to treat the individual, and not used as a form of cost-cutting (treatment being generally cheaper than imprisonment) or as a form of extrajudicial punishment.

3. Consequently, individuals who are legally coerced into treatment should be offered a dual-constrained choice: first, a choice of whether to enter treatment or not, with refusal leaving them to face criminal proceedings for their crime like any other individual charged with the same offence; and secondly, a choice of treatment from a range of effective options that are available to the wider community, which could include for those addicted to opioid drugs substitution or maintenance therapy.

4. While new prophylactic technologies which aim to block drug use are an important treatment option, they should only constitute one type of treatment among a choice of many. In making a choice about treatment, addicted persons should be given accurate information about the advantages and disadvantages of each, including their likelihood of success.

Medicalisation of addiction

1. Neuroscience research has made significant advances in our understanding of the nature of addiction, and the cognitive and behavioural changes that underpin it. This will potentially lead to more effective treatments, and more appropriate social policies, although it should be noted that success has been limited to date.

2. Enthusiasm generated by developments in this area needs to be tempered by an acknowledgement of the role that social and psychological factors play in initiation of drug use, the development and expression of addictive behaviours, the way that society responds to addiction, and the proven effectiveness of some existing responses.

3. Addiction neuroscience may help us to understand the biological and cognitive aspects of addiction, but does not reduce the importance of the social and psychological in the way in which society responds to it. Acknowledging this is important in preventing neuroscience research from being used to promote unproven or dubious 'cures' for addiction (e.g. neurosurgery, ultra-rapid opioid detoxification) which may be marketed to vulnerable and desperate addicts, and where evidence of their safety or efficacy may be limited or absent.

Pharmacological relapse prevention

1. Relapse to drug use is the norm in persons treated for addiction. Pharmacological treatments that help to reduce relapse, such as naltrexone implants, may prove to be an important innovation but they need to be properly evaluated in controlled clinical trials before being used clinically.

2. Clients need also to be made aware of any potential side effects (e.g. detection, dysphoria), the likelihood of success, and in the case of opiate addiction, the potential for overdose should they cease treatment and revert to heroin use, or try to override the implant.

3. The offer of these implants under legal coercion should include the choice of other treatment options.

Preventive vaccination

1. Vaccines which provide an immunological block against drug activity are another novel development which may prove to provide prophylaxis against relapse.

2. More speculatively, vaccines may protect those who are identified as vulnerable to addiction (e.g. genetic or psychological screening), particularly during adolescence when many forms of addiction begin.

3. Preventive use of genetics and vaccines is limited to the predictive power of the screening technology. Wide-scale genetic screening for the entire population is not feasible on the basis of present data.

4. Some parents may wish to vaccinate their children, particularly if there is a family history of drug addiction but enthusiasm for these preventive technologies must be tempered by an acknowledgement of the limited protection that these vaccines may provide. Unlike normal vaccines, they are likely to be short-lived, requiring boosters, and can be overridden by using larger doses of the addictive drug or by using another drug. Preventive vaccination could also prove to be counter-productive and the cost versus benefits of any developments in this area require considerable scrutiny.

Drug testing

1. Drug testing can be an important part of managing an effective treatment, or monitoring the effectiveness of a particular treatment programme. But drug testing is only as good as the responses to the test results. A strong argument can be made that drug tests should be used to provide better treatment, and not used as a form of extrajudicial punishment, within the constraints of protecting society from further harm.

2. All information gathered as a result of drug testing should remain private, and treated with the same regard for confidentiality as other medical records.

Neuroscience and privacy

1. Neuroimaging has enabled researchers to gain insight into the neurobiological contributions to behaviour, cognition and personality. It is important that the claims made reflect what neuroimaging is able to show. Reports should acknowledge the important technological limitations and experimental caveats associated with this technology. Often neuroimages only show trends of difference between groups of people.

2. All neuroimaging results should remain private as for all other medical information.

Psychopharmacological harm reduction

1. Neuroscience holds out the possibility of developing safer forms of currently addictive drugs. Should this happen, a number of controversial and difficult issues are likely to arise for policy making and regulation. It will be necessary to consider any new drug on its merits, based on a cost/benefit analysis of the harms that any new substance is likely to cause, or alleviate.

Personal health and the public interest in addiction treatment

Addiction affects an agent's autonomy and ability to consent. The treatment of drug dependence is complicated by two additional issues. First, many of those addicted who seek treatment are involved in the criminal justice system because they have been arrested for offences committed to fund their drug use. As a result, they may be coerced into treatment (thus directly losing their autonomy and liberty through the actions of a third party) to reduce the adverse effects that their behaviour has on society. Second, many drug-dependent persons are not able to pay the costs of their treatment. In many developed countries, this usually means that drug treatment is provided either by charitable non-government organisations (NGOs) or by governments, with a small private sector catering to wealthy addicts. This is particularly true of opioid addiction ([1]). The NGO sector has traditionally provided drug-free forms of treatment such as residential rehabilitation programmes, self-help groups and outpatient counselling. Government programmes have more often provided pharmacologically-based treatments such as agonist maintenance treatment. These programmes have often been funded because they provide a cost-effective form of treatment, with the largest cost savings arising from the fact that these programmes have been shown to substantially reduce crime among opioid-dependent persons. Importantly, these treatment programmes have also been shown to be effective in reducing the physical and social harms associated with drug abuse, such as overdose, crime and violence. These treatment programmes can therefore be referred to as 'harm reduction' programmes (Ward et al., 1998; Hall et al., 2006) (see pp. 94–95).

The fact that pharmacological treatment of addiction serves mixed personal, public health and public order goals complicates its provision. As noted above, it often involves interactions between the health and criminal justice systems, in which conflicts can arise between different professions and their distinctive priorities (e.g. law enforcement, clinical staff, and public health). The same can be true for conflicts between public health and personal medical care professionals who observe different aims, methods of acting, and guides according to their professions. The use of pharmacological treatments means that maintenance treatment falls under the umbrella of medicine as these drugs are prescribed by physicians. Yet, as noted, the justification for public funding of maintenance treatment for drug dependence often depends at least in part upon the public health and public order benefits (via reduced criminal activity) that they produce (Hall et al., 2006).

Clinical medicine 'focuses on the treatment and cure of individual patients', while public health medicine 'aims to understand and ameliorate the causes of disease and disability

([1]) The following analysis is based largely on the experience of opioid-dependence treatment. This is because there has been considerable effort in the last century to develop treatment programmes for opioid addiction and because opioids are the only drugs for which a variety of different pharmacological treatments are available (e.g. agonist, antagonist, partial agonist).

in a population' (Childress et al., 2002, p. 170). While 'the physician-patient relationship is at the centre of medicine', public health involves 'interactions and relationships among many professionals and members of the community as well as agencies of government' (Childress et al., 2002, p. 170). The latter involves many government institutions, and a likely consequence of their involvement in drug policies is use of the criminal justice system to coerce patients into treatment, amplifying opportunities for conflict between the competing goals of addiction treatment. The tensions between these competing goals calls for management structures which can appropriately balance the medical needs of addicted individuals, their rights and the public interest (the public health and criminal justice responses).

Public ambivalence about maintaining addicts on agonist drugs and a desire to limit any potential negative impact on the wider community of substitution treatment often results in the development of standards, rules and regulations for this form of treatment that:

- are intended to minimise the risk of non-addicted persons entering treatment (e.g. by demanding evidence of an extensive history of dependence and documented failure at abstinence treatment);
- aim to prevent the diversion of addictive drugs intended for substitution treatment to the black market where they may be used inappropriately and result in physical or psychological harm, overdose deaths or further addiction;
- result in programmes which specify the frequency of urine testing and may require patients to be excluded from programmes if they provide 'dirty' urine samples;
- or that may place time limits on treatment or insist upon a goal of abstinence from all drugs being achieved within some arbitrary period (e.g. one or two years).

These regulatory frameworks may have unintended medical effects that may have a negative impact on the health of some addicts. For example, these types of regulations may: discourage dependent persons from seeking treatment until their condition is chronic, reduce programme retention because of the onerous requirements made of patients, or force stable patients to withdraw from treatment and return to illicit drug use (Ward et al., 1992).

Ethically acceptable and effective agonist maintenance treatment of dependence requires programme rules and regulations that balance patient and community safety while permitting patients to remain in and benefit from treatment. The goal should be to provide effective treatment which is based on a multifaceted strategy that addresses all of the needs of the individual. It is important that treatment choices made by those seeking help are not limited by the ideological viewpoints of the staff that operate individual treatment programmes, even if some treatment services work within a particular model of care. Individuals who receive support and counselling must have

access to appropriate pharmacological drugs if required, while those in maintenance and relapse prevention programmes should not be limited to just pharmacological strategies. Treatment services should also recognise that the circumstances and needs of their patients may change as their treatment progresses, and this will require a flexible response.

Distributive justice: balancing the burden of disease and treatment

The justification of the public funding for addiction treatment programmes in terms of the public benefits is important in obtaining support. However, there is a danger that public policies that are beneficial to the majority may impose unfair burdens on a vulnerable minority. An important aspect of ethical analysis of drug dependence treatment is ensuring that public policies do not unfairly burden or discriminate against a vulnerable minority in order to serve the public good ([2]).

Distributive justice is a difficult and emotively charged issue in the case of addiction because drug use and drug policy have negative impacts on both society and the dependent individual. This raises important questions about the distribution of responsibility between society and the addicted individual. For treatment to be ethical, it should demonstrate that it is effective in reducing negative outcomes for both society and the individual. However, it would be arguably unethical to use pharmacological treatment of dependence as a form of compensation for inappropriate social policies or the neglect of vulnerable populations, no matter how effective the treatment was in improving the status quo.

Those who receive treatment, particularly when it is publicly funded and subsidised, also arguably have a responsibility to engage in a reasonable treatment programme, to meet its aims and to avoid behaviour that adversely affects society. The remainder of this section is focused on analysing: (1) the impact that society and social policy has on drug use, the responsibility of society to reduce this impact and the ethics of providing pharmacological treatment to a vulnerable population, and (2) the responsibility of addicts to engage and comply with treatment, and what measures society may reasonably take to ensure compliance with this obligation.

The ethics of pharmacological treatment of vulnerable populations

Few public issues have produced a global consensus in the way that prohibition of the recreational use of illicit drugs has, particularly for what are regarded as the 'harder' drugs such as heroin and cocaine. While there is disagreement around the margins, such as exactly which drugs should be illegal, and how to treat those that use and become

([2]) Such a public policy would be justified on a purely utilitarian analysis as already outlined, however this report takes the more generally held perspective that that there are other important ethical principles that need to be respected and balanced against the greater good.

dependent on illicit drugs, most nation states have enacted laws that prohibit or restrict their use. These restrictive policies are designed to protect the majority of society who do not use illicit drugs for recreational purposes and discourage their recreational use. These policies are effective in reducing rates of recreational illicit drug use but arguably they also can result in aggravating or causing problems for the small minority of those who continue to use illicit drugs. Discussion on the fairness of pharmacological treatment of drug dependence therefore needs to consider the impact that the illegality of these drugs has on those who use them.

An analysis of the arguments for and against the prohibition of illicit drugs is beyond the scope and not the intention of this report. While acknowledging the debate in this area which raises important and interesting ethical and policy issues, the remainder of the report accepts the current legal status of illicit drugs in the majority of EU Member States. This acknowledges the reality that the global policy of prohibiting recreational illicit drug use is not likely to change and it ensures that our arguments have the potential to affect the ethical provision of treatment for drug dependence under current legal regimes.

Policies that govern the treatment of dependence need to acknowledge the social, biological and psychological factors that can lead to addiction. While it is important that drug treatment programmes are available, it is also important to ensure that pharmacological treatment does not become a surrogate for social policies that neglect certain populations. This is particularly pertinent given the strong association between social disadvantage, family history of violence and drug use and the presence of comorbid psychiatric disorders, and emerging evidence of genetic and neuropsychological vulnerabilities to addiction (Hall et al., 2006). While social differentials in addiction risk do not free from blame those who use drugs, they do create an onus on social policymakers to be mindful of these social differentials and to work to reduce them, in the interests of ethical drug policy, and in order to reduce addiction. Social policies that are based on solidarity and social responsibility should provide more humane and less punitive treatment for those who become dependent and use interventions that aim to reduce the social disadvantage and adversity that increases the likelihood of addiction. This may include ensuring equal opportunities exist for those disadvantaged through public investments in education, family education and support, and social welfare (Spooner and Hall, 2002).

Reciprocal obligations for individuals receiving treatment

As argued above, a solidarity-based approach puts emphasis not only on the responsibility of society, but also on the responsibility of the addicted individuals. Those with an addiction still have some capacity to make choices, as was discussed earlier. They therefore arguably have some obligations to comply with the reasonable demands of treatment. Society is justified in expecting that drug-dependent individuals who engage in treatment adhere to treatment demands and do not act in ways that

adversely affect society. For example, while methadone maintenance treatment (MMT) has been shown to be relatively safe and effective in reducing opioid use, it can lead to overdose if methadone is diverted to opioid-naïve users. In the UK during the 1990s, poorly regulated methadone programmes lead to the diversion of methadone onto the black market resulting in fatal methadone overdoses involving persons not in treatment (Hall, 1998). The same may occur with the new pharmacological agents that are likely to be used to treat addiction to stimulants and other illicit drugs. This risk highlights the importance of delivering treatments in ways that protect the person receiving them and the broader society. It indicates the need for regulations, procedures and treatment requirements in the provision of treatment that protect both patients and the wider community.

A broad set of ethical principles are relevant to treatment regulations that impose obligations on those who enter treatment. These include: (1) not unduly violating the privacy and autonomy of individuals; (2) ensuring that the responses made to individual lapses in meeting objectives are proportional in relation to the overall treatment goals sought; (3) being mindful and consistent with the ability of individuals to meet their obligations (including actively helping individuals to do so); and (4) being sensitive to the situation of the individual, with regard to both internal (neurophysiology and neuropsychology) and external (social) circumstances.

Coerced treatment of drug abuse and addiction

There is reasonable evidence that those who enter pharmacological treatment for drug abuse will benefit from the treatment and the longer they remain in treatment, the better off they will be (Gerstein and Harwood, 1990; Ward et al., 1998). The fact that many drug-dependent persons do not wish to enter treatment has led to the use of various forms of coercion to encourage them to enter and remain in treatment. This raises the questions: to what extent can legal coercion be used ethically and effectively in the treatment of drug addiction and if so, under what conditions is it ethical to do so?

There are different forms of coerced treatment for drug addiction that vary in the amount of force used, and therefore in the degree to which they contravene an individual's liberty, freedom and autonomy. Mild informal coercion includes social pressure from friends and family to enter treatment (Maddux, 1988). More formal coercion (not involving criminal proceedings) may come from employers and government agencies who make it a condition of continued employment that an addicted person undergoes treatment (Weisner, 1990). Legally enforced forms of coercion involve the use of the criminal justice system to enforce entry to treatment on pain of imprisonment (Klag et al., 2005).

Social coercion is an effective motivation for addicts to enter and complete treatment (Room et al., 1991; Hasin, 1994; Wild et al., 1998). Addiction puts an enormous emotional and financial burden on families so it is not surprising that pressure from loved ones (e.g. highlighting the destructive impact of a person's drug use or threatening to end a

relationship if they continue to use drugs), can motivate those who still have strong social ties to seek treatment. Many addicts do not appreciate the impact that their drug use has on themselves or their friends and families; pressure from friends and family to cease their drug use often provides an external indication that their drug use is problematic.

Unfortunately, for some long-term drug abusers, such important social ties have lost either influence or significance in their lives so more coercive forms of intervention may be required. When this is the case, they require formal non-criminal coercion and negotiation between agencies or employers and the individual and the ethical guidelines for how these programmes should operate need to be codified in the appropriate laws (e.g. industrial relations).

While informal social coercion and formal non-criminal coercion represent very important motives for entering treatment, they arguably raise fewer ethical issues in the treatment of dependence than legally coerced treatment. In both these cases, the dependent person is relatively free to agree to treatment or suffer the threatened consequence (such as loss of employment or relationship). The coercive pressure in these situations arguably does not deprive them of their liberty or deny their autonomy. The form of coercion that raises more ethical concerns is court sanctioned coercion in which the threat of imprisonment is used to motivate entry into, or compliance with, addiction treatment.

The case for legally coerced treatment

One of the major justifications for the use of legally coerced treatment is that treating offenders' drug dependence will reduce the likelihood of their re-offending (Gerstein and Harwood, 1990; Inciardi and McBride, 1991). Studies have shown quite convincingly that treatment for heroin dependence significantly reduces criminal and violent behaviour while addicts remain in treatment (Hubbard, 1989; Gerstein and Harwood, 1990; Bell et al., 1992; Ward et al., 1992). The use of drug treatment programmes as an alternative to incarceration has also been motivated by the failure of prison terms to reduce drug use and drug-related crime and the over-representation of drug dependent people in prisons (Pedic, 1990; Stathis, 1991; Stathis et al., 1991; Hall, 1997).

Medical models of addiction highlight the causal role that addiction plays in leading to imprisonment and the high rates of relapse to use after release (Gerstein and Harwood, 1990). The advent of HIV/AIDS has provided an additional argument for treating drug abuse (Dolan et al., 1996). By keeping injecting users out of prison, there is likely to be a reduction in the transmission of infectious diseases such as HIV and hepatitis C virus (HCV). Those injecting drugs in prison may be at a significantly increased risk of contracting blood-borne viruses because of a lack of access to sterile injecting equipment in most prisons (Dolan et al., 1996; Small et al., 2005;

Wood et al., 2005). The incidence of HIV and HCV is also generally significantly higher in prison populations than the wider public (Dolan, 1999; Dolan et al., 2006). The ethical, correctional and public health arguments for drug treatment under coercion are reinforced by the economic argument that it is less costly to treat offenders who are drug dependent in the community than it is to imprison them (Gerstein and Harwood, 1990).

Legal coercion covers a wide range of strategies for getting individuals into treatment programmes. The most coercive is compulsory treatment programmes, such as civil commitment programmes in the US and Sweden where individuals are sentenced by the court to enforced addiction treatment in a secure facility for an extended period of time (Weisner, 1990; Farabee and Leukefeld, 2001). While such treatment strategies were used frequently in the past in the US, these civil commitment programmes now appear to have fallen out of favour arguably in part because of the difficulty in ethically justifying such deprivation of liberty, and because of evidence suggesting that newer legal options for coerced treatment are more effective (Wild, 1999) ([1]).

The form of legal coercion that has become increasingly popular within the criminal justice system is the use of diversionary programmes that offer drug-dependent persons treatment as an alternative to imprisonment at various stages in the criminal justice process. In the first instance, treatment may be offered as an alternative to being prosecuted with an offence prior to being charged by police. This is not an ideal method of coercion as it falls outside judicial oversight. It is possible that relying on the discretion of the police may open the way for individuals being coerced into treatment for reasons other than criminal behaviour, such as odd or unconventional behaviour or being a member of an ethnic minority (Hall, 1997).

Legally coerced treatment is most often advocated for persons charged with or convicted of an offence to which their drug dependence has contributed. It is generally offered as an alternative to imprisonment in order to have legal sanctions deferred, reduced or lifted, or as a condition of parole (Rotgers, 1992; Klag et al., 2005). Suspension of legal sanctions is usually made conditional upon successful completion of a treatment programme, with the threat of imprisonment if the person fails to comply (Hall, 1997; Spooner et al., 2001). Each of these forms of legally coerced treatment have different legal and social consequences for the offenders subjected to them, requiring varying degrees of deprivation of liberty, restraint and hardship. The ethical validity of the use of these forms of coercion will be outlined below.

([1]) While civil commitment statutes were created throughout the 1960s in the US, no state is currently committing significant numbers for drug treatment (Gostin, 1993).

When is coerced treatment ethical?

Careful consideration of ethical issues is critical when the state uses the threat of imprisonment to encourage drug-dependent persons to seek treatment. Coerced treatment of addiction should operate within a constitutional and legal framework which protects the civil liberties of the people being coerced (Klag et al., 2005). It is important that treatment does not override an individual's basic human rights in order to achieve broader social goals (Anderer, 1992; Bersoff, 1992; Wexler, 1993; Kleinig, 2004).

Coerced treatment for addiction may be justified by appealing to either of two ethical principles: paternalism or the public interest. Addiction is a harmful behaviour in which to engage; it impacts negatively on an individual's health and social welfare, with a significantly increased mortality and morbidity. Coerced treatment of addiction could therefore be justified for paternalistic reasons: that is, on the grounds that it is in the best interests of the individual. This would involve coerced treatment for the addict's 'own good'.

Two forms of paternalism can be distinguished on the basis of the degree of coercion involved. Treatment that is provided against an individual's wishes, where the individual is deemed competent to make this decision is referred to as hard paternalism. When an individual is deemed incapable of making a competent decision, treatment is imposed because it is argued that their condition prevents them from making informed decisions on their own behalf. This form of coerced treatment is referred to as soft paternalism. It is soft paternalism that is most likely to be used to justify coerced treatment in the case of addiction.

In many countries, people with serious mental illnesses can be compelled to accept treatment under certain circumstances, usually after some form of judicial or quasi-judicial review. Society does not, however, generally treat people suffering from other medical conditions against their will, unless the individual lacks the capacity to give free and informed consent to treatment, as in minimally conscious patients. While there is a strong beneficent justification for providing treatment, respect for an individual's liberty to make their own decisions about treatment generally overrides the beneficent drive to intervene (Dworkin, 1972; Childress et al., 2002). This would prevent the use of coerced treatment using a hard paternalistic justification.

The use of paternalistically coerced treatment could be justified if addicted individuals were seen to suffer from a brain disease that robbed them of their autonomy and impaired their capacity to consent to treatment, as has been argued by some bioethicists (Charland, 2002; Cohen, 2002; Elliott, 2002; Dackis and O'Brien, 2005). This justification would be similar to the forced treatment of minimally conscious patients or children, or mentally ill adults where consent to treat is obtained from a surrogate, usually the next of kin. However, as argued above, this soft paternalist rationale for coerced addiction treatment would be based on a misrepresentation of the neurobiology of addiction. While addicts' decision-making is impaired, they retain some degree of

control over their drug use which undermines the soft paternalistic justification of coerced treatment.

The second principle that can be used to justify coerced treatment of drug abuse and addiction is to protect the social welfare or the public good. The public good claim for the use of coerced treatment depends upon the negative impact of drug dependent users on society (e.g. via drug dealing and other criminal activity to finance their drug use). The ethical justification of coerced treatment in order to protect the public good therefore becomes a distributive justice issue: that is, providing a fair distribution of the costs and benefits of drug use and drug treatment. This analysis arguably creates an obligation on society to provide treatment, and an analogous obligation on drug abusers to accept treatment under certain circumstances. This has been the most commonly used justification for coerced treatment of addiction (Hall 1997). The question is: when or under what circumstances is coerced treatment justified in order to protect the public good?

Some authors reject any form of treatment under coercion for drug dependence. Radical libertarians such as Thomas Szasz and Theodore Dalrymple deny that drug dependence exists, arguing that all drug use is always voluntary (Szasz, 1975; Dalrymple, 2006). According to Szasz, the law should not prohibit adults from using any drug, and any drug user who commits a criminal offence should be punished. The punitive policy consequences of Szasz's libertarianism often enjoys more public support in developed countries than the proposal to legalise the use of all currently illegal drugs.

Others, such as Newman, accept that drug dependence exists but oppose compulsory drug treatment on the grounds that it does not work (Newman, 1974). If treatment under coercion were ineffective (as Newman claims), then there would be no ethical justification for providing it. Of course, even if treatment under coercion is effective, it does not follow that it should be provided. For example, the community might place a higher value on punishing than rehabilitating offenders (Hall, 1997).

A consensus view on drug treatment under coercion prepared for the World Health Organization (Porter et al., 1986) concluded that coerced treatment was legally and ethically justified if and only if: (1) the rights of the individuals were protected by 'due process' (in accordance with human rights principles); and (2) if effective and humane treatment was provided. Due process would require some form of judicial oversight of the coerced treatment process. In the absence of such due process, coerced treatment could become de facto imprisonment without judicial oversight. In the absence of humane care and effectiveness, coerced 'drug treatment' would not meet the World Health Organization (WHO) ethico-legal standard.

The uncertain benefits of coerced treatment have led some proponents to argue that offenders should be allowed two 'constrained choices' (Fox, 1992). The first constrained choice would be whether they participate in drug treatment or not. If they declined to be treated, they would be dealt with by the criminal justice system in the same way

as anyone charged with the same offence. The second constrained choice would be given to those who agreed to participate in drug treatment: this would be a choice of the type of treatment that they received. There is some empirical support for these recommendations in that there is better evidence for the effectiveness of coerced treatment that requires some degree of 'voluntary interest' by the offender (Gerstein and Harwood, 1990).

The constrained choice condition has three implications. First, as they are regarded as effective and generally available to those outside of the prison or judicial setting, a strong argument exists that pharmacological treatment options, including agonist maintenance, should be included in the range of options that are offered to coerced addicts. There has been a tendency for coerced treatment programmes to only offer 'drug-free' abstinence-oriented treatments which could prevent coerced addicts from accessing the forms of treatment that may be most likely to benefit them (Hall, 1997). Second, pharmacological treatment options should not be the only options available; there should be a range of drug-free treatment options available for those who do not wish to use pharmacological treatments. Third, the safety, effectiveness and cost-effectiveness of whatever forms of treatment offered should be rigorously evaluated (National Research Council, 2001).

Ethical issues in coerced addiction treatment also arise from the interaction between the correctional and drug treatment systems (Sheldon, 1987; Skene, 1987; Platt et al., 1988; Reynolds, 1992; Rotgers, 1992). A major problem is the conflict between the expectations of correctional and treatment personnel about the effectiveness of drug treatment and their understanding of each other's roles and responsibilities.

Treatment staff usually regard the drug offender as a client, that is, as someone who should be involved in treatment decisions and the confidence of whose personal information should be respected. Treatment staff expect that their clients will have relapses to drug use which should be dealt with therapeutically rather than punitively. Correctional and judicial personnel, by contrast, often expect treatment to produce enduring abstinence. They see treatment as something directed by the court, and hence regard drug use in treatment as an offence that treatment staff are legally obliged to report. When these expectations of treatment effectiveness are not met and there is little communication between courts and treatment services, judges and magistrates may become sceptical about the value of coerced treatment and reduce their use of it (Baldwin, 1979; Skene, 1987).

The effective and ethical use of coerced drug treatment accordingly requires a shared understanding of the likely benefits of treatment and a clear statement of the roles of correctional and treatment staff. The latter should include agreement upon their respective responsibilities for monitoring and reporting upon an offender's progress in drug treatment. These issues need to be addressed in written protocols that govern interactions between courts and treatment personnel.

Is compulsory addiction treatment ethically acceptable?

Compulsory treatment — unconditional, enforced entry to addiction treatment — does not offer a drug-dependent individual any choice. This type of coerced treatment involves an extreme violation of an individual's autonomy and liberty. Mandatory treatment has generally involved the confinement of individuals in specialised drug-treatment facilities, or prison hospitals, usually with the goal of attaining abstinence from their drug of addiction (Weisner, 1990; Gostin, 1993; Farabee and Leukefeld, 2001; Klag et al., 2005) ([1]). Upon successful completion of an abstinence programme, individuals may be released from the facility into some sort of intensely supervised outpatient facility. Failure to comply with any condition of the programme usually results in being readmitted to a secure inpatient facility (Gostin, 1993).

Because compulsory treatment involves a maximal deprivation of liberty, it requires a correspondingly greater ethical and legal justification than other forms of coerced treatment. Arguably, this includes stronger evidence that this form of treatment is effective and that the consequences of not treating the person are serious and very likely to occur (Aronowitz, 1967; Childress et al., 2002). Given the evidence presented above, it is hard to justify the use of compulsory treatment regimes, for either paternalistic or public good reasons (Leukefeld and Tims, 1988). Importantly, compulsory treatment programmes completely abolish the autonomy of the individual, and arguably constitute a violation of civil liberties in a manner that contravenes the UN Bill of Human Rights. Coercive diversion strategies, by contrast, are less restrictive because they involve constrained choices. They are accordingly less ethically objectionable than compulsory treatment. A choice not to enter treatment would leave the person to face the judicial system, but with their civil and human rights intact.

Another concern with the use of compulsory treatment is the effect that this has on the ability for those seeking treatment to find it. It makes little sense if providing treatment places for compulsory treatment reduces the availability of places for those voluntarily seeking them (National Institute on Drug Abuse, 1983; Hall, 1997). Also, compulsory treatment programmes can increase the burden on programmes that are effective, well-funded and well resourced. It can also affect staff morale and have a negative impact on what might otherwise be successful treatment centres (Hall, 1997).

([1]) Antagonist treatments such as naltrexone detoxification or maintenance are the favoured pharmacological treatment methods in such situations. The advent of sustained release formulations of naltrexone or opioid vaccines may be particularly attractive to proponents of compulsory treatment regimes (Caplan, 2006). The ethics of these forms of treatment will be discussed below.

Treating vulnerable populations

The negative impact that addiction and drug abuse has on others in society can complicate treatment. This is particularly true of two groups within society where the harms caused to others raise strong emotions: pregnant women and prisoners. These two populations are particularly vulnerable to unjustified discrimination that can lead to neglect of their basic human rights and poor treatment outcomes.

Addiction treatment during pregnancy

The treatment of substance abuse or addiction during pregnancy presents difficult challenges. Substance abuse during pregnancy is a significant problem. In the USA, almost 5 % of pregnant women under the age of 44 have abused illicit drugs in the last month, 10 % have abused alcohol; and up to 18 % of pregnant women are smokers (SAMSHA, 2004). The use of licit and illicit drugs during pregnancy can have adverse effects on the mother and the developing foetus (Nordstrom-Klee et al., 2002; Day and Richardson, 2004).

Substance abuse during pregnancy can increase the risk of medical complications during birth (Huestis and Choo, 2002) and produce neurocognitive deficits in children that may persist for the life of the individual. Individuals born to substance using mothers may suffer from significant structural brain abnormalities (e.g. significant neuronal loss and smaller brains). Alcohol use in pregnancy may produce a foetal alcohol syndrome (FAS) that is associated with behavioural and cognitive impairment (Ikonomidou et al., 2000; Olney, 2004). Persistent attentional and cognitive deficits may appear in early adolescence as a result of prenatal cocaine exposure (Singer et al., 2004a). Memory and attention may be impaired as a result of structural changes in subcortical regions in the children of methamphetamine abusing mothers (Chang et al., 2004). Also, children born to a substance using mother may experience withdrawal symptoms after birth (Godding, 2004).

Most jurisdictions will impose limits on the autonomy of individuals when their behaviour results in a significant and likely harm to others. An extreme example is the overriding of a competent patient's refusal of treatment as the only way of preventing the spread of an infectious disease. Although such measures involve a serious interference with autonomy, authorisation is normally justified through compelling counter-concerns of the public interest. The case of pregnant mothers is different, however, because the counter-claim is not for the interests of the public, but those of the foetus. With regard to the mother's use of drugs, two issues come to the fore: the foetal interests and the maternal lifestyle. Both signal a duty on the part of the mother towards the unborn child, and a state-mandated limit to the freedom of the personal behaviour of the mother.

In the case of the former, in many jurisdictions the criminal liability of the mother has been lacking — the foetus does not have a legal status in the eyes of the law and therefore there is no statutory basis for any criminal charge (Mason et al., 2005). Likewise, there have

been few courts willing to protect the interests of the foetus to the extent necessary to limit the freedom of the mother. The problem, as the courts have seen it, is that protecting the 'vulnerable' foetus — even when it may be seriously harmed by the mother's use of drugs during pregnancy — would restrict the mother's autonomy to the extent that it would involve conflicts of fundamental rights (Mason et al., 2005). Thus, in England and Canada, it has been held that the courts have no jurisdiction to place controls on the autonomy of pregnant woman or deprive them of their liberty, right to self-determination, and bodily integrity ([3]). Furthermore, forcing mothers to undergo treatment without their consent, involving forced restraint and confinement, could possibly be seen as torture or degrading treatment, and thus may directly evoke human rights doctrine.

However, it could be argued that because society has to deal with the health and social consequences of babies affected by maternal drug and alcohol use, then the state has the right to intervene to prevent harm to the unborn. Society already intervenes in a variety of ways to promote the health of the foetus, e.g. by encouraging mothers to take folic acid supplements during pregnancy and offering antenatal classes and antenatal screening for major birth defects. Coercion is used to overcome the difficulty in getting pregnant women into treatment, or refraining from drug use while pregnant. In the USA, there has been significant public support for state intervention, including criminal prosecution, incarceration and forced treatment of pregnant women who abuse drugs (Campbell and Fleischman, 1992). Likewise, the foetus has been protected from the actions of the mother in New Zealand, where the foetus has been made a ward of the court ([4]).

Societies have tended to reject approaches that would penalise mothers for actions during pregnancy which might harm their unborn child; the notable exceptions are where apparently immoral behaviour has influenced opinion. For example, most countries allow abortion under strict controls, and have rejected so-called 'wrongful life' suits. There is a clear indication that the unborn life has different interests than those of born individuals: for example, the Council of Europe has stated that an unborn foetus does not have the same rights as a born individual, including a right to life ([5]). The spectre of eugenics and the prospect of children suing their parents for negligence are considered by many to be stern warnings against taking such a coercive or punitive approach to maternal behaviour during pregnancy.

([3]) England: Re. F (in utero) [1988] 2 WLR 1288; [1988] 2 All ER 193; [1988] Fam 122 (CA). Canada: Winnipeg Child & Family Services (Northwest Area) v G (1996) 138 DLR (4th) 238.

([4]) In 'Nikki's Case', the foetus was given personhood to the extent that, although the mother could not be ordered to do something against her wishes by the court, it could make orders forbidding her to do things that would harm the child (see Skegg et al., 2006). In 2006, a District Court confined a pregnant woman to hospital to undergo methadone treatment and was then held in a residential placement until the birth of her baby. The order was justified against her wishes by the judge on the grounds of the 'health and safety of this young woman and her unborn child'.

([5]) Case of Vo v. France (2004). Application No 53924/00. European Court of Human Rights.

At the very least, in order to justify compulsory treatment of pregnant substance abusers, intervention must be shown to be effective and not present any additional harm. There are two major utilitarian objections to compulsory treatment of pregnant women: (1) the stress and anxiety associated with forced detention or medical intervention (Ridgely et al., 2004), or the experience of intense withdrawal symptoms (Fiscella et al., 2005) can have serious adverse effects on the mother and foetus; and (2) the threat of compulsory treatment programmes may deter women from presenting themselves early for prenatal care and pre-term health checks in order to avoid compulsory detention or intervention (Harwood and Myers, 2004). Both of these outcomes could adversely affect the health and welfare of the child and mother in ways that may offset any benefits of coerced treatment. Further issues concern the stripping away of the rights of the mother and the state's supposed role in protecting the interests of the unborn foetus.

Emerging treatments, such as drug vaccines and implantable antagonists like naltrexone can be provided in ways that do not require detention. But these treatments may still be administered forcibly and without consent, leading to maternal stress and anxiety that could adversely affect the pregnancy. In this report, it has already been suggested that addicts do not necessarily lack autonomy at all times. Therefore, there would be no case of forced treatment in their best interests except in emergency situations (i.e. when they are intoxicated). Forced 'treatment' may also be considered as 'torture' or 'cruel and inhumane treatment' under European and Member States' human rights law. Even if this treatment were to be used without the consent of the mother, these technologies would require a rigorous evaluation of the potential side effects — both medical and psychological — before being used in pregnant women. There is also the possibility of adverse effects on the developing foetus, such as on the activity of endogenous neurochemicals (e.g. endorphins and dynorphins), which are unknown, and could have effects that last a lifetime. An analysis of efficacy would also need to consider the effects of any attempts to circumvent these forms of prophylaxis, such as physically removing the implants (e.g. extracting subcutaneous drug implants) or attempting to overcome the immunological blockade of a vaccine (e.g. by consuming greater quantities of their preferred drug or choosing to use other illicit drugs whose effects were not blocked by the vaccine or antagonist). Either outcome could potentially lead to greater drug use, and therefore increased harm to the mother and foetus.

The use of an addiction treatment option in consenting mothers is to be welcomed; it reflects the moral responsibilities towards the foetus that the mother has taken on and she should be supported in this endeavour. Given the potential harms from forced treatment of pregnant women, a strong argument exists that treatment programmes should rely on less restrictive and coercive forms of treatment that do not override the autonomous decision-making of the mother. This may involve improving engagement with clinicians and education, reinforcing abstinence using vouchers, offers of free prophylactic support to prevent relapse, less punitive responses to positive drug tests and offers of effective and safe substitution treatments (Ward et al., 1999).

Addiction treatment in prisons

A number of commentators have argued that the treatment of addiction and injecting drug use within prison is an area of public policy requiring reform (Jurgens and Betteridge, 2005). In many countries, current approaches appear often to be inadequate, and are largely dominated by punitive responses to prisoners who are addicted to or use illicit drugs. In general, and despite some innovative programmes and increasing policy concern, very few prisons provide effective treatment for addiction and few have introduced measures to reduce the incidence of HIV/AIDS and HCV. This is despite a general over-representation of addiction and drug abuse by those incarcerated and high rates of HIV and HCV infection within prisons (Hammett, 1988).

In one study of European prisons, up to 34 % of those incarcerated reported injecting drugs during their detention and up to 21 % of these began injecting while in prison (EMCDDA, 2002) although considerable differences exist between prisons in respect to reported levels of drug use and injecting in European prisons. High rates of injecting drug use in prisons are seen in other countries as well (Jurgens and Betteridge, 2005). HIV rates in prisons are also often much higher than in the general population although the number infected can vary markedly between countries and prisons (Jurgens and Betteridge, 2005). HCV infection rates are even higher among those reporting drug injection (Dolan, 1999; Macalino, 2004) and in some prisons a significantly high proportion of inmates report sharing injection equipment during incarceration (EMCDDA, 2002).

Human rights declarations and legally binding instruments, such as the International Covenant on Civil and Political Rights (ICCPR), state that restrictions on the rights of prisoners should only include those necessary for their incarceration. People incarcerated should only have the right to liberty restricted as per their sentence. They should not be subjected to violations of other rights, such as the right to health, life and the right to be free from cruel and inhumane treatment. Their punishment should not include the arbitrary restriction of these rights, and they should not be subject to the double jeopardy of 'punishment' for drug addiction. Prisoners should not be discriminated against by virtue of their status as prisoners; they are entitled to 'equivalence' in treatment. Therefore, as the WHO and United Nations Commission on Human Rights (UNCHR) guidelines state: prisoners should have access to the same medical health care that is available to the broader public (World Health Organization, 1993a; UNAIDS, 2006).

An increasing number of commentators have argued that these extrajudicial punishments not only violate the human rights of those imprisoned, but also lead to further harm for prison staff and the general public (World Health Organization, 1993a; Canadian HIV/AIDS Legal Network, 2004; Jurgens and Betteridge, 2005; UNAIDS, 2006; UNODC, 2006). Despite unambiguous directions from bodies such as the UNCHR, the United Nations Office on Drugs and Crime (UNODC), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the WHO, the rate of

change in this area has been slow. These guidelines animate a number of human rights instruments that would appear to be relatively explicit about the types of treatment and health programmes that should be offered to prisoners to treat addiction and reduce the harm of drug use (United Nations General Assembly, 1955; United Nations General Assembly, 1988; United Nations General Assembly, 1990). The ICCPR is also clear on this matter: prisoners have the legal right not to be subjected to cruel, inhumane, or degrading treatment or punishment and the right to the highest attainable standard of mental health.

Often, addicted prisoners receive little or no treatment for their condition. Many undergo forced, unsupervised detoxification, or 'cold turkey', which can produce intense withdrawal symptoms, including nausea and extreme diarrhoea, convulsion, anxiety and dysphoria, may cause serious medical consequences for pregnant women and their foetuses, immuno-compromised individuals, and those with other comorbid medical disorders (Fiscella et al., 2005). The stress of prison life, compounded by the onset of severe opioid withdrawal can also increase the risk of suicide, particularly those with comorbid mental illnesses, which are commonly found among prison inmates (United States Department of Health and Human Services (HHS), 2005). As opiate substitution programmes are often not available in prison, prisoners who are stabilised on methadone or buprenorphine maintenance treatment prior to entering prison can be forced to go through detoxification and withdrawal. The failure to provide effective pharmacological treatment to ameliorate the symptoms of withdrawal can even be viewed as a violation of the right not to be subjected to cruel and inhumane treatment or punishment as forced detoxification would generally be regarded as unacceptable in the wider community. Given that the freedom and liberty of prisoners are restricted by the state, they are unable to take action themselves to prevent symptoms of withdrawal (Lines, 2006). This can be seen as placing a further ethical obligation on the state to ensure that these symptoms are treated (Jurgens and Betteridge, 2005).

The lack of adequate treatment may also create conditions in which there is the risk of increased use of drugs within prison, increasing the associated risks of drug overdose and HIV and HCV infection. The human rights claims for this failure are particularly significant for someone on a legitimate and widely accepted treatment programme prior to incarceration, such as methadone maintenance, who contracts HIV after returning to injecting drug use in prison (Gore and Bird, 1995). As stated by the Joint United Nations Programme on HIV/AIDS, 'By entering prisons, prisoners are condemned to imprisonment for their crimes; they should not be condemned to HIV and AIDS.' (United Nations Commission on Human Rights, 1996). Forced detoxification can also lead to overdose if individuals with no opioid tolerance relapse to opioid use upon release, as many do. Such an outcome could also be viewed as a violation of a prisoner's right to health.

Attempts to reduce the risk of HIV and HCV infection due to intravenous drug use is also inadequate in most prisons. Few prisons currently provide access to sterile injecting equipment. Consequently, prisoners who inject in prison often share needles, or improvised injection equipment. These individuals are at high risk of contracting HIV or HCV. Failure to provide prisoners with methods to avoid these diseases not only denies them access to health measures available to the rest of society, but may violate the right to health and, arguably, even the right to life, given that HIV can result in premature death.

In addition to violating prisoners' rights, current approaches to the treatment of addiction and drug use in prisons may be counterproductive from a public health point of view. Most prisoners are only detained for short periods of time, whereupon they are released back into the community, increasing the incidence of HIV and HCV. Prisons have consequently become an incubator of HIV and HCV in society. The present situation existing in many prisons can therefore be viewed as problematic on both ethical/human rights grounds, as well as from a utilitarian, public health perspective.

Therefore, as suggested in the ICCPR and the Universal Declaration on Human Rights (UDHR) and explicitly articulated in human rights guidelines (United Nations General Assembly, 1988; United Nations General Assembly, 1990; World Health Organization, 1993a), the treatment of addiction and drug abuse in prisons should consider the following:

1. People in prison should have access to all effective types of treatment of addiction, as substitution programmes, such as methadone and buprenorphine maintenance, are generally available in the community. Evidence from prisons which have introduced substitution programmes shows that they can be effective in reducing HIV and HCV risk behaviour and harms associated with injecting drug use (e.g. overdose) (Dolan et al., 1996; Dolan et al., 2006).

2. As with community-based treatment, it is also important that adequate doses of methadone or buprenorphine are administered. If a punitive approach to treatment is adopted that results in the prescription of doses insufficient to stabilise patients, this will result in withdrawal and craving that may lead to use of supplemental injection of opioids, and therefore be counterproductive.

3. As studies have shown that injecting drugs can occur in prison, consideration is required as to how some harm minimisation measures for IDU, such as bleach or needle exchange programmes, can be provided. Overwhelming evidence shows that these programmes are effective in reducing HIV infections. The human rights principle of equivalence provides a strong argument that inmates should have access to needle exchange programmes, which are widely available to the general public in most countries.

4. Providing prisoners with access to drug-related education and counselling is also likely to be important especially given that: many are poorly educated, socially disadvantaged or may suffer from neurocognitive deficits, resulting from criminal and violent behaviour, non-fatal overdoses or their drug use.

5. A strong argument also exists that prisoners should have access to HIV testing and counselling, where testing is voluntary and information remains private and confidential. Education has been shown to lead to decreases in harmful drug-related behaviour and reduced transmission of HIV.

Medicalisation of addictive behaviour

Medicalisation is the process whereby behavioural or social problems are understood as medical disorders that should be treated medically, often at the expense of social approaches. Some commentators believe that a focus on the genetic and neurobiological basis of behaviour will lead to a 'medicalisation' of stigmatised forms of behaviour including behavioural disorders such as addiction (Conrad, 1992; Verweij, 1999; Press, 2006; Ashcroft et al., 2007) ([6]). These commentators argue that medicalisation will lead to an overemphasis of the biological origins of behaviour at the expense of social and psychological explanations. Critics of the medicalisation of behaviour believe that this will adversely affect people who engage in stigmatised forms of behaviour like smoking or other drug abuse (Caron et al., 2005). If addictions are seen as medical disorders that reflect neurobiological predispositions, these critics argue society will come to rely on medical interventions and neglect social policies that can reduce drug use and addiction (e.g. high taxes, restrictions on sale and access to drugs) (Merikangas and Risch, 2003; Caron et al., 2005; Carlsten and Burke, 2006). The legal status of drugs affects their price and availability in ways that affect patterns of use and the effects that drug use have on health and public safety and order, including criminal activities that addicts engage in to fund their drug use or that is associated with the production, supply and trafficking of these substances.

The medicalisation of addiction may also undermine addicts' preparedness to stop if they come to believe that they are unable to stop because of their neurobiological and genetic traits or *fatalism*. More evidence is needed to evaluate such claims. It may be that addiction neuroscience encourages individuals to seek treatment, or empowers them to make choices not to use drugs because there is an authoritative scientific explanation of their experiences (Hall et al., 2008). In the interim, information about 'addiction genes' should be carefully communicated to avoid undermining addicts' belief in their capacity to stop using drugs.

([6]) Medicalisation of addiction does not require that scientific research finds that addiction is solely a brain disease that is largely the result of our genetic makeup. Rather, it requires that it be seen as such. There are those observers who have already made such claims. Attitudes towards stigmatised conditions such as addiction can often precede scientific evidence. Society and the scientific community need to anticipate these misinterpretations and misrepresentations to prevent ineffective and unethical policy responses.

The medicalisation of addiction also raises the question: should drug policies treat differently those who come from different socio-economic backgrounds or have different genetic vulnerabilities to addiction? While the moral model often subjects addicts to double jeopardy, an inappropriate emphasis on genetic predispositions and social triggers risks could also undermine health and social responsibility. Social policies need to appropriately acknowledge the social, genetic and environmental causes of addiction. Drug using and addictive lifestyles often (but not always) go hand in hand with poverty and low social status. Both the medical and moral models raise the possibility of targeting at-risk individuals or communities, rather than addressing the criminal and social environments that may increase the risk of addiction.

Critics of medicalisation also argue that it could restrict the types of treatments that are provided for addiction. Pharmacological treatments and genetic tests could be marketed to drug addicts for commercial rather than health gains, as some argue has happened with NicoTest — an online genetic test that purports to identify vulnerability to nicotine addiction (GeneWatch UK, 2004; De Francesco, 2006). Alternatively, addiction neurobiology could be used to market invasive and doubtfully effective 'treatments' that are misleadingly advertised as 'cures' of addiction, and provided at high cost to addicts and their families (e.g. neurosurgery (see box pp. 108–109) or ultra-rapid opioid detoxification (UROD)). The promotion of these technologies is often given credibility by an uncritical use of neuroscientific research of addiction, particularly NIDA's 'chronic and relapsing brain disease model' (see box p. 26). The Internet increases the ability of proponents to promote these treatments. This is particularly relevant for the treatment of addiction, where the consumer is often desperate to quit and vulnerable to exploitation.

Critics also argue that the medicalisation of addiction could change the ways in which society thinks about drug use and dependence, and therefore the appropriate means available to treat those with an addiction (Backlar, 1996; Caron et al., 2005). Such a view could lead to the further stigmatisation of those who are vulnerable to addiction, such as those that possess particular genetic alleles or mutations, or are positive for genetic markers associated with drug abuse (Caron et al., 2005). On this view, neuroscience and behaviour genetics could lead to both institutionalised discrimination, particularly by courts, educators and employers, and health and life insurers, as well as intensifying more informal modes of stigmatisation (Billings et al., 1992; Rothenberg et al., 1997; Hall and Rich, 2000; Anderlik and Rothstein, 2001; Greely, 2001; Geppert and Roberts, 2005). It is not clear how realistic these fears may prove to be, but given their potential negative implications they merit further investigation and ongoing vigilance (Caron et al., 2005; Condit et al., 2006; Bennett and Smith, 2007).

Neurosurgical treatments for addiction

Up until 2002–03, Russian and Chinese surgeons used neurosurgical procedures to treat heroin addiction, when international concern forced both countries to abandon the controversial treatment. Three hundred and five patients were reportedly operated on in Russia (Walsh, 2002) and over 500 in China (Xinhua News Agency, 2005). In China, stereotactic surgery has been used to destroy the nucleus accumbens (Gao et al., 2003), the brain region where the rewarding effects of opioids and other drugs appear to be mediated (Robbins et al., 2007), while Russian neurosurgeons lesioned an area called the cingulate gyrus; a brain region that has previously been removed to treat obsessional disorders (Orellana, 2002). The aim of the surgery is to interrupt obsessional thoughts about drug use (Orellana, 2002). A recent report suggests that clinicians in China have recommenced neurosurgical treatment of opioid addiction as part of a clinical trial (Goff, 2005).

These reports raise a number of important ethical concerns (Hall, 2006):

1. There is no compelling reason to use neurosurgery to treat heroin addiction. There are effective forms of treatment that substantially reduce illicit opioid use and stabilise the lives of heroin addicts (e.g. substitution or maintenance treatment on methadone or buprenorphine (Ward et al., 1998; Mattick et al., 2003; Amato et al., 2005). Patients and practitioners who find opioid agonist maintenance morally objectionable, or who work in settings that prohibit its use, can use the antagonist naltrexone in oral or implantable form (e.g. (Krupitsky et al., 2004)).

2. There are major concerns about the safety and efficacy of these neurosurgical procedures. Stereotactic neurosurgery is an invasive procedure that involves drilling holes in the patient's skull and inserting electrodes deep into the brain to destroy the target region. Advocates of these procedures argue that they are less invasive and destructive than older forms of psychosurgery, and report low rates of complications. However, these conclusions are based on uncontrolled studies that do not properly evaluate the cognitive and behavioural effects of destroying such important neurological regions as the NAcc and aCG (Gao et al., 2003; Medvedev et al., 2003).

3. There are major concerns about the effects of producing irreversible lesions in neural centres that are not only implicated in drug-mediated reward but in the control of food intake, sexual behaviour and the formation of social bonds, among other pleasures. What effect will these procedures have on the person's responsiveness to reward, their motivation, mood state, risks of depression and suicide and capacity for planned action? What will happen if heroin addicts

attempt to compensate for the attenuated reward from heroin by increasing their heroin dose to levels that may be lethal in overdose? No attempt has been made to answer these important questions.

4. The published evaluations of the procedures were only compared to patients' experiences after detoxification (Gao et al., 2003; Medvedev et al., 2003). Since relapse to opioid use is common after detoxification, a more informative comparison would have been with a more effective treatment of opioid addiction, such as methadone or buprenorphine maintenance. However, MMT is not readily available in China (Cohen, 2004) and prohibited by law in Russia (Krupitsky et al., 2004). There has not even been any attempt to compare its efficacy with oral naltrexone, which has been used in Russia, reportedly with better results than in western countries (Krupitsky et al., 2004).

5. There are also doubts about whether patients have given free and informed consent to participate in this surgery (Kleinig, 1985). Chinese policies towards opioid dependence are often punitive, with imprisonment and compulsory detoxification as first line responses. It could be argued that it is difficult to obtain free and informed consent within such a context.

Prevention of addiction

Predictive testing of genetic liability in addiction

In 1999, Francis Collins, Director of the US Human Genome Institute, outlined an optimistic vision of 'genomic medicine': the use of genetic information to improve human health (Collins, 1999; Collins, 2003). Collins foresaw genomic screening being used preventively to: (1) identify healthy individuals who carry susceptibility alleles for diseases, such as cancers and heart disease and (2) to intervene with those at higher genetic risk to either change their behaviour (e.g. increasing exercise or eating a healthier diet) or to use drugs (e.g. antihypertensives) that reduced their risk of developing these diseases. Collins imagined, for example, screening smokers for genetic susceptibility to lung cancer and counselling those at high risk to stop smoking. Similarly, optimistic projections have been expressed by some addiction genetics researchers (Uhl and Grow, 2004).

If susceptibility genes are identified for addiction risk, then children and adolescents could be genetically tested and those at higher risk given preventive behavioural and pharmacological interventions to reduce their likelihood of using drugs (Collins, 1999). There is an obvious objection to this proposal in that it is not good public health policy to encourage people to use drugs, regardless of their genetic risk of dependence (Hall et al., 2002). Chronic drug use can have severe physical or psychological health

effects without resulting in addiction. An alternative rationale is that such screening would allow individuals who were at highest genetic risk of addiction to make informed decisions about whether to avoid drug use. Even if society places a high value on individual autonomy, there are a number of good reasons why on current information genetic screening for addiction is unlikely to be regarded as a good policy choice (Holtzman and Marteau, 2000).

First, when multiple genes predispose to a common disease, individual susceptibility alleles only predict a very modestly increased risk of dependence (Hall et al., 2004a). Testing multiple genetic variants that were individually weak predictors would improve prediction if the results of multiple genetic tests were combined (Khoury et al., 2004). However, the larger the number of genes that are involved in disease susceptibility, the less useful most individuals will find information about their genotype (Hall et al., 2004a; Khoury et al., 2004). It also means that a very large number of individuals need to be screened to identify the few at highest risk (Vineis et al., 2001).

Second, predictive genetic testing may have unintended adverse effects. This would be the case, for example, if testing adolescents for susceptibility to addiction increased their preparedness to try drugs, as could happen, for example, if they were prompted to test the accuracy of the genetic predictions (Hall et al., 2002).

Third, screening is only ethically justifiable if there is an effective intervention to prevent the disorder in those who are identified as being at increased risk (Khoury et al., 2003). No such interventions currently exist but the prospect of preventive vaccination against cocaine and nicotine may raise this possibility in the future (Hall and Carter, 2004).

Third-party uses of genetic information

Genetic information on addiction risk may potentially be used by third parties such as insurance companies, employers and educators, and the courts. Given the nature of genetic transmission, the implications of this information not only affect the individual being tested, but also their close relatives. This raises a number of ethical issues about who should be able to access this information. What measures should be taken to protect privacy? Under what circumstances should this information be shared and with whom (Anderer, 1992; Rothstein, 1998; Rothstein and Anderlik, 2001)?

Bioethicists' concerns about the ethical and policy implications of genetic testing have been strongly influenced by experiences with genetic testing for Mendelian disorders, the paradigm case being Huntington's disease (Marteau and Richards, 1996). Because the mutations that cause this serious neurological disorder are strongly predictive of disease risk, genetic testing creates serious ethical dilemmas for affected individuals and family members (Marteau and Richards, 1996). Such testing

also raises real concerns about the discriminatory use of genetic risk information by health and life insurers and employers (Billings et al., 1992; Taylor, 1998).

But Huntington's disease is a poor model of the situation that arises with addiction. They are most likely to be polygenic disorders, involving multiple alleles of weak effect and environmental interactions. The predictive validity of genetic testing may only modestly improve upon the crude prognostic tool of family history. Discussion of the ethical implications of the predictive genomics of addiction has to take account of the most likely ways in which genomics information will be used.

If the pessimists are right, the ethical and policy issues identified by bioethicists will not arise because research will not identify predictively useful alleles for addiction. Even in the most optimistic scenario, the predictive genomics of addition is unlikely to lead to genetic screening of whole populations for the reasons outlined above. Rather, predictive genetic testing is more likely to be offered to the minority of persons with a family history of early onset addictive disorders, perhaps 10 % of the population. Fear of genetic discrimination may nonetheless deter people with such family histories from having genetic tests that may benefit them. Similar fears may also deter individuals from participating in genetic research on addictive disorders, thereby impairing the acquisition of scientific knowledge about the prevention and treatment of these disorders. It remains to be seen whether community concerns about third-party use of genetic information prove to be a major impediment to addiction genomic research and future medical applications.

Of course, it is possible to eliminate the risks of third-party use of genetic information by banning all genetic tests, but this policy could prevent us from realising any benefits that genetic testing may bring; it would also be an overly paternalistic and arguably unethical policy. A better approach would be to look for safeguards to prevent individuals' privacy and confidentiality being unfairly compromised so that they need not fear breaches of confidentiality and privacy. The challenge will be to develop policies that allow for the use of genetic information to reduce the incidence of disease and improve the health and welfare of individuals and society, while minimising any negative consequences of stigmatisation and discrimination.

Vaccines and slow release drug treatments

If it is possible to predict genetic liability to drug dependence, society will need to decide if it is ethical to use more coercive means to prevent adolescents from using drugs (Hall et al., 2002). For example, vaccines being developed against nicotine, primarily for smoking cessation (Ashcroft and Franey, 2004; Harwood and Myers, 2004; Hall, 2005;

Kosten and Owens, 2005), could potentially be used to prevent 'high risk' children and adolescents from smoking (Hall et al., 2002; Ashcroft and Franey, 2004).

In order to be ethical, use of preventive nicotine vaccination would need to demonstrate: (1) the long-term benefits of the vaccine (Hall et al., 2002; Ashcroft and Franey, 2004; Harwood and Myers, 2004) and (2) that genetic tests accurately predict the risk of nicotine addiction. Given the limited predictive power of genes studied to date, and doubts about the long-term efficacy of preventive vaccination (Hall, 2007), it is unlikely that preventive vaccination would be an effective or an ethical intervention (Hall, 2005).

Immunotherapies, such as a 'nicotine vaccine' block the psychoactive effects of a drug by either stimulating the immune system to produce antibodies (active immunisation) or through the introduction of synthetic monoclonal antibodies into the bloodstream (passive immunisation) (Harwood and Myers, 2004). These antibodies bind to the target drug, preventing it from acting on receptors in the brain (Nutt and Lingford-Hughes, 2004; Kosten and Owens, 2005). Animal studies have shown that anti-drug vaccines reduce the rush and euphoria associated with the target drug, the amount of drug that reaches the brain, dopamine release in the nucleus accumbens, the rate of clearance across the blood-brain barrier, and the volume of drug distribution, and self-administration of the target drug (Hall, 2002a; Kosten and Owens, 2005). Vaccines have a very clear advantage over traditional small molecule agonists and antagonists in that they are long-lasting, highly specific, and as they remain primarily in the bloodstream, have no apparent central nervous system side effects. These advantages suggest that immunotherapies may be effective in reducing relapse to drug use, a major hurdle in overcoming addiction.

Active vaccination against nicotine could reduce relapse to smoking in abstinent smokers during the first few months after quitting when most smokers relapse (Vocci and Chiang, 2001). A nicotine vaccine could be circumvented by increasing the dose of nicotine but attenuating the rewarding effects of nicotine may be enough to reduce rates of return to daily smoking (Vocci and Chiang, 2001; Hall, 2002a). Similar vaccines are also being developed for cocaine and heroin.

The term 'vaccine' inevitably prompts discussion about its possible preventive use. Misconceptions that a vaccine will produce lifelong immunity against nicotine may prompt parents to vaccinate their children (Cohen, 1997). As minors, children would not be legally able to consent to vaccination but since parents already make choices for their children about other vaccines and other interventions that affect their lives (e.g. their diet and education), some have argued that vaccination against nicotine and other drugs is simply another decision that parents should be able to make on behalf of their children (Cohen, 1997). Given that there is a fundamental difference in vaccinations to prevent infection and vaccines to control behaviour, this argument is likely to be contested by civil libertarians and others who place a high value on personal autonomy (Hasman and Holm, 2004), as well as adolescents who disagree with their parents' wishes.

Even if one sets aside the ethical issues, there are major practical obstacles to the preventive use of a nicotine vaccine in children. First, the limited period of protection provided by existing vaccines would require booster injections, perhaps every two or three months throughout adolescence (Kosten et al., 2002). Second, the fact that the vaccine could be circumvented by using higher doses of nicotine means that vaccination could be counterproductive if adolescents were prompted to test its efficacy. Third, it would be costly to universally vaccinate children against nicotine with a vaccine of modest preventive efficacy (Hall, 2002a).

Vaccination of 'high risk' adolescents seems a more plausible and less expensive option. The feasibility of even this approach is doubtful, however, given the low predictive validity of genetic screening for smoking risk (outlined above), the doubtful preventive efficacy of a nicotine vaccine, and the possible adverse effects of vaccination, such as stigmatisation of those who screened positive and discrimination against them by third parties, such as life or health insurance companies.

The 'off label' use of a drug vaccine by a physician acting at the request of a parent is the most likely way in which a vaccine will be used preventively. It is difficult to see how this could be prevented if a nicotine vaccine is approved for therapeutic use, other than by education of physicians and parents about the likely limitations and possible disadvantages of this approach (Hall, 2002b).

In addition to these practical issues, the use of immunotherapies also raises several ethical concerns. Firstly, individuals would have to give fully informed consent. It is likely that immunotherapies would be most often used in situations that are inherently coercive, as treatment will often be the result of encounters with the justice system, such as a condition of release from prison or to avoid incarceration, in pregnant women, or parents involved in the child welfare system. The benefits will need to be balanced against rights of the individual to privacy and liberty (Ashcroft and Franey, 2004).

Secondly, vaccines may also prove counterproductive if an individual attempts to overcome the antagonistic action of the vaccine by increasing drug dose. Those who ambivalently agree to vaccination may later switch to using other possibly more dangerous drugs, different routes of administration (e.g. intravenous injection), or much higher than usual doses (Murray, 2004). Vaccines may also paradoxically make experimentation with drugs seem less risky, and therefore unwittingly increase drug use. The likelihood of this occurring should not be underestimated given the compulsion and motivation to use drugs displayed by some individuals, even in the face of certain negative consequences. The use of vaccines under any form of coercion will therefore require careful monitoring by the treating physician.

Thirdly, vaccines will produce long-lasting (possibly life-long) markers that will be detectable in the blood and urine, and may lead to false positive drug tests (Murray, 2004). This raises the issue of confidentiality and discrimination which could discourage some from seeking immunotreatment.

Fourthly, vaccines do not ameliorate underlying problems that may be associated with compulsive drug use and addiction. Vaccines may be problematic if viewed as 'magic bullets'. They do not deal with the underlying addictive condition (such as craving, loss of control or withdrawal), events that may lead to relapse, or comorbid mental conditions (Ashcroft and Franey, 2004). Addiction is a chronic condition and vaccines, like traditional addiction medications, will presumably need to be used in conjunction with behavioural treatments if life-long abstinence is to be achieved (Nutt and Lingford-Hughes, 2004). Many will be wary of a treatment that prevents them from using drugs to either relieve withdrawal symptoms or to attenuate the symptoms of an undiagnosed mental illness (McGregor and Gallate, 2004), other sub-clinical conditions involving distress, or the effects of a stressful or abusive social situation. This is not to uncritically accept self-medication as an explanation of addiction (Mueser et al., 1998), but to acknowledge that psychological and social factors may sustain drug use in ways that vaccination alone will not address. Finally, the use of a vaccine may also block the action of agonists or partial agonists (e.g. methadone and buprenorphine for opioid dependence) eliminating the use of maintenance therapies while vaccination remained effective. Vaccines may also block the action of medications used in the treatment of other physiological conditions (e.g. opioid analgesics for pain relief) (Ashcroft and Franey, 2004).

Relapse prevention and maintenance with depot medications

Depot medications are sustained-release formulations of current medications for treating addiction, most often antagonists that block the brain receptors for the target drugs. They involve a slow, timed release of the medication to counteract the rewarding effects of drugs. Depot medications have an advantage over traditional treatment medications as they are only required to be taken once a month, as compared to three to four times a week for conventional orally administered drugs. This has made depot medications an attractive option in preventing relapse. Sustained-release preparations of the antagonists naltrexone for alcohol and opioid dependence (Kranzler et al., 1998; Comer et al., 2002) and lofexidine for nicotine dependence (Rawson et al., 2000) have been developed.

If these treatments are used with patients who give free and informed consent, their use arguably presents no special ethical issues. Ethical issues do arise if sustained release antagonists are used to prevent relapse in situations where capacity to give free consent is compromised. Depot medications raise similar ethical questions as vaccines (see pp. 111–13) if used under coercion, as has recently been advocated (Caplan, 2006). Depot antagonists also present similar safety concerns if addicts change to using other illicit drugs or attempts to overcome their antagonist effects by increasing the dose of their preferred drug (Murray, 2004).

Currently, in virtually all EU Member States substitution treatment is available for opiate dependence (Hedrich et al, 2008). However, the availability of treatment varies between countries and among the general public and some policymakers remain opposed to the use of agonist drugs in addiction treatment. This raises a potential concern that the treatment choice could be limited to depot medications, such as the antagonist naltrexone, or that addicts will be coerced into using implantable naltrexone and not offered other forms of treatment, even where a good evidence base exists that they can be effective. In Australia, depot medications have been implanted in thousands of patients without clinical trials being conducted to demonstrate that they are safe or effective. This raises important concerns, as clearly the safety and efficacy of these and all other treatments, should be evaluated rigorously, as is the case for all other pharmacological treatments, prior to their use clinically.

Challenges for public education

Popular understandings of the role of genetics, at least as expressed in the media, are often deterministic, suggesting that if you have 'the gene for X' you are very likely to develop that disorder and conversely that you will be at low risk of doing so if you do not have the 'gene' for that disorder (Khoury et al., 2000). For example, popular media reporting of a commercially available pharmacogenetic test for choosing either NRT or bupropion for smoking cessation, the NicoTest (www.nicotest.com), describes it as a test for 'the smoker's gene' or the 'addiction gene' (BBC News, 2004; Doyle, 2004).

These views probably reflect the media focus on Mendelian disorders like Huntington's disease, cystic fibrosis and Tay-Sachs disease, where modes of genetic transmission are easier to understand (Khoury et al., 2000). If these views are indeed widely held, the challenge for public education will be explaining the personal and public health implications of polygenic disorders in which individual alleles weakly predict risk, and interact with each other and with the person's environment. If done well, this type of public education may allay anxieties about the third-party uses of genetic information.

Public education will also need to avoid any unintended message that public health drug control strategies can be replaced by high risk genomic medicine strategies (Willett, 2002; Merikangas and Risch, 2003; Carlsten and Burke, 2006). The surest way for many individuals in developed societies to reduce their disease risks remains to stop drug use, reduce caloric intake and increase exercise (Rose, 1992; Peto, 2001; Vineis et al., 2001; Merikangas and Risch, 2003). If society is to avoid blaming individuals for their risk status we also need to modify our physical and social environments in ways that facilitate desirable changes in risk behaviour.

Drug screening and testing

Drug testing involves biochemical testing of blood, urine, hair and saliva for drugs, or their metabolites. It can tell if an individual has used a drug within a particular time period and, in some cases, whether they are intoxicated. Many would maintain that drug testing does not raise any major ethical issues if a person's drug use puts others at risk (e.g. when they are driving a motor vehicle, flying a plane, or operating machinery). In these cases, drug testing is ethically justified if there is evidence that: (1) drug use impairs performance in ways that endanger others; (2) the drug testing provides valid assessment of impairment; and (3) drug testing deters people from using drugs in ways that put others at risk. These conditions are satisfied, for example, when blood alcohol concentration is used to test for impairment in automobile, train and truck drivers, and pilots.

Testing in the workplace and other settings for drug use rather than intoxication, raises additional ethical issues (Allsop, 1997). Workplace testing may have primary goals of reducing employer costs (health and sick leave) and increasing productivity, as opposed to ensuring the safety of employees or the public. There is very little evidence that this kind of drug testing achieves these goals (Allsop, 1997). Moreover, in the USA, workplace drug testing is often confined to testing for metabolites of illegal drugs (particularly cannabis which is easiest to detect) (DeCew, 1994) rather than alcohol, which is much more commonly used and much more likely to impair work performance. In this type of testing impairment has not been demonstrated (Allsop, 1997), and concerns are raised about the right to privacy and confidentiality, workers' freedom to consent to testing, and discrimination and stigmatisation of workers who screen positive for drug use rather than impairment (Allsop, 1997).

There are many other populations which may be targets for screening and testing. The acceptance of screening requires a balance between the public good (protecting individuals from the irresponsible actions of others, public health goals, detecting illegal activities), and individual liberty and privacy. Where the balance lies often depends on the type of drug being tested or screened for, the context of use, and the aims of testing. There are substantial ethical differences between testing, for example, in schools and workplaces; likewise there are also different ethical considerations between testing in elite sports, the military service or commercial pilots.

For example, a recent study of drug testing in schools concluded that:

> 'The use of such tests in school may undermine the confidence necessary for a good pedagogic and educational relationship between teachers, parents and pupils.
>
> Testing in schools may conflict with ethical principles such as individual autonomy and respect for privacy, to the extent that they are unjustified intrusions by the state or other authorities into young citizens' private lives that expose them to humiliating or ambiguous situations.

> Such tests may also infringe the beneficence — or doing good — principle, since it is doubtful whether the benefit of carrying out tests in schools for preventive purposes outweighs the disbenefits for the young persons concerned, and the non-maleficence — or not doing harm — principle, since the young persons would always suffer unnecessary inconvenience from being subjected to such tests' ([7]).

In sports, the question of justified testing comes down to satisfying a number of issues surrounding drug use, as it is: (a) contrary to the spirit of sport, (b) unfair, and (c) dangerous for the athlete's health (according to the World Anti-Doping Agency's Code, 2003) ([8]). Opponents of anti-doping policies question all of these criteria for existing drugs. They emphasise the use of coercion, the encroachments on privacy and the autonomy of professional competitors, and reject claims that drug use undermines the primacy of 'authenticity' and the 'sports ethos' (e.g. by achieving success through using drugs rather than via 'natural' means, such as training, practice and hard work) ([9]).

In these examples, screening and drug testing raise different ethical issues in different settings and when carried out with different purposes and goals. This makes it difficult to provide authoritative opinions on possible future developments in drug monitoring. Each new development will need to be considered as it arises.

Neuroscience, prediction and privacy

Neuroimaging may prove a useful clinical tool in the diagnosis and treatment of addiction by identifying individuals with subtypes of addiction and comorbid mental disorders who may require different combinations of treatment. These uses do not present special ethical issues but the ability to identify the neural correlates of addiction may have other uses outside the clinic that do. For example, neuroimaging studies are able to detect dramatic changes in limbic responses to drug-related cues that would identify an individual as drug dependent (Childress et al., 1999). This opens up the possibility of discrimination and violations of privacy (Canli and Amin, 2002; Farah and Wolpe, 2004; Illes and Racine, 2005). It may also raise issues of consent, given that these neuroimaging tests could use drug cues that are presented without the subject's awareness (Whalen et al., 1998) ([10]). Given the enormous costs associated with addiction, this use of the technology may be attractive to employers, insurance companies and courts. Because the changes in the limbic regions that respond to

([7]) Taken from Pompidou Group Expert Committee on Ethics, 2005.
([8]) Available at: http://www.wada-ama.org/rtecontent/document/code_v3.pdf
([9]) Tamburrini, C. 2007, 'Enhanced Bodies', Paper presented at Enhance Final Conference, Bristol, 27 September. To be published as part of the Enhance Project 2005–07 (Enhancing Human Capacities: Ethics, Regulation and European Policy). Sixth Framework Programme: Priority 4.3.2.3 — Deepening Understanding of Ethical Issues. Grant No SAS-CT-2005-017455.
([10]) It is possible to mask images by presenting them for intervals that are too short to be perceived consciously so that the viewer is not aware of having viewed the image while producing changes in neural activity that can be detected by neuroimaging.

drug-related cues persist well into abstinence, there is the possibility that an individual will be discriminated against even when they are drug-free. The fairness of such a discriminatory policy would need to be established.

Advances in neuroimaging technologies raise the possibility of 'reading people's minds' by using these methods to ascertain the truthfulness of what defendants or suspects tell the police (Farah, 2002; Foster et al., 2003; Ross, 2003). This is more of an aspiration than reality at present, although some entrepreneurs claim that electrophysiological methods can be used to tell if a person is telling the truth (Foster et al., 2003). Future improvements in neuroimaging may, even if imperfectly, disclose facts about a person that they may prefer to keep private (Ross, 2003). Advances in neuroimaging technology are making it possible to obtain personal information about an individual that may predict behaviour or identify aspects of personality (Fischer et al., 1997; Fischer et al., 2001; Canli and Amin, 2002; Farah and Wolpe, 2004; Singer et al., 2004b; Abler et al., 2005). The claims of entrepreneurs promoting these technologies to the public (e.g. truth-telling, personality matching and as tests of marital fidelity) raise the issue of the need for appropriate consumer protection against the over or misinterpretation of equivocal test results and bogus claims (Caplan, 2002; Farah, 2002; Farah, 2005).

Important ethical issues would be raised if persons are compelled to undergo these tests by courts, insurance companies or employers. During the course of neuroimaging studies, up to 40 % of brain scans of research participants show 'suspicious' brain anomalies, with between 0.5 to 8 % of research brain scans uncovering clinically significant neuropathologies (Illes et al., 2004b; Illes et al., 2006b). The emergence of incidental findings from neuroimaging research can lead to discrimination, which complicates consent to participate in these studies (Illes et al., 2004a; Anon, 2005; Illes et al., 2006b). This issue is amplified if imaging is conducted under coercion.

Neuroscience investigations may also provide information that proves to be predictive of disease risk in the same way as genes for Mendelian disorders like Huntington's disease (Greely, 2002; Foster et al., 2003). Characteristic patterns of brain activity in childhood and adolescence, for example, may predict increased risks of addiction later in adult life (Volkow et al., 2003). This possibility raises the same ethical issues (e.g. privacy and discrimination) that are raised by testing for alleles that predict an increased risk of serious neurological disease (Greely, 2002). There are also subtler questions of human rights to consider. The increased use of these methods lead to the development of the belief that a refusal of a 'suspect' to undertake these fMRI on civil liberties grounds is indicative of 'guilt'.

Psychopharmacological harm reduction

Neuroscience research on addiction could potentially be used to engineer safer recreational drugs. It may be possible, for example, to use pharmacology and neuroscience to engineer a recreational drug that was a safer alternative to alcohol

(Nutt, 2006). Nutt persuasively argues that it is technically possible to develop a gamma-aminobutyric acid (GABA) partial agonist that possesses most of the socially desirable properties of alcohol with few of its disadvantages, including its biological toxicity. The major obstacles to any such product being introduced are social, ideological and regulatory. This is true for any of the ways in which such a drug may be introduced into developed societies; namely, by being approved for use as a therapeutic drug, or being manufactured and distributed by freelance psychopharmacologists.

There are major doubts about whether the pharmaceutical industry will invest the substantial funds needed to: (1) undertake preclinical and clinical R&D on such a drug and (2) to sponsor the drug's passage through the pharmaceutical regulatory systems, such as the US Food and Drug Administration or its British and European equivalents. Attempts have been made to introduce alcohol-like drugs in the recent past. The recent Foresight Brain Science, Addiction and Drugs project's survey of pharmaceutical executives (Ragan, 2007) suggests that the industry is now more risk averse. This has been partly in response to critics who have accused the pharmaceutical industry of 'selling sickness' to promote drugs such as hormone replacement therapy (HRT), Viagra and the serotonin selective reuptake inhibitor (SSRIs) antidepressants (e.g. (Healy, 2004; Moynihan and Cassels, 2005)).

The regulatory system is also likely to discourage any attempt to introduce such a drug as a harm reduction intervention in alcohol-dependent patients. Experience with substitute prescribing for nicotine dependence reveals a regulatory double standard that insists upon much tighter regulations for less harmful nicotine products than are imposed on the far more dangerous smoked tobacco products (Stratton et al., 2001). These regulations provide major disincentives to pharmaceutical harm reduction approaches. It could be argued that the prevailing regulatory philosophy sometimes seems to be that a patient's health is less important than being drug dependent, even if this means being dependent on a less hazardous drug or a less harmful way of using it. Safer recreational drugs may emerge as a by-product of basic pharmacological research or they may be approved for therapeutic use for an unrelated indication in which case their desirable properties may be discovered by amateur psychopharmacologists. If these drugs prove relatively easy to produce using widely available precursors, then recipes disseminated via the Internet may be used for home production, as has happened with GHB (Gahlinger, 2004) and other substances (EMCDDA (in press) Risk assessment 8: 'Report on the risk assessment of BZP in the framework of the Council Decision on new psychoactive substances').

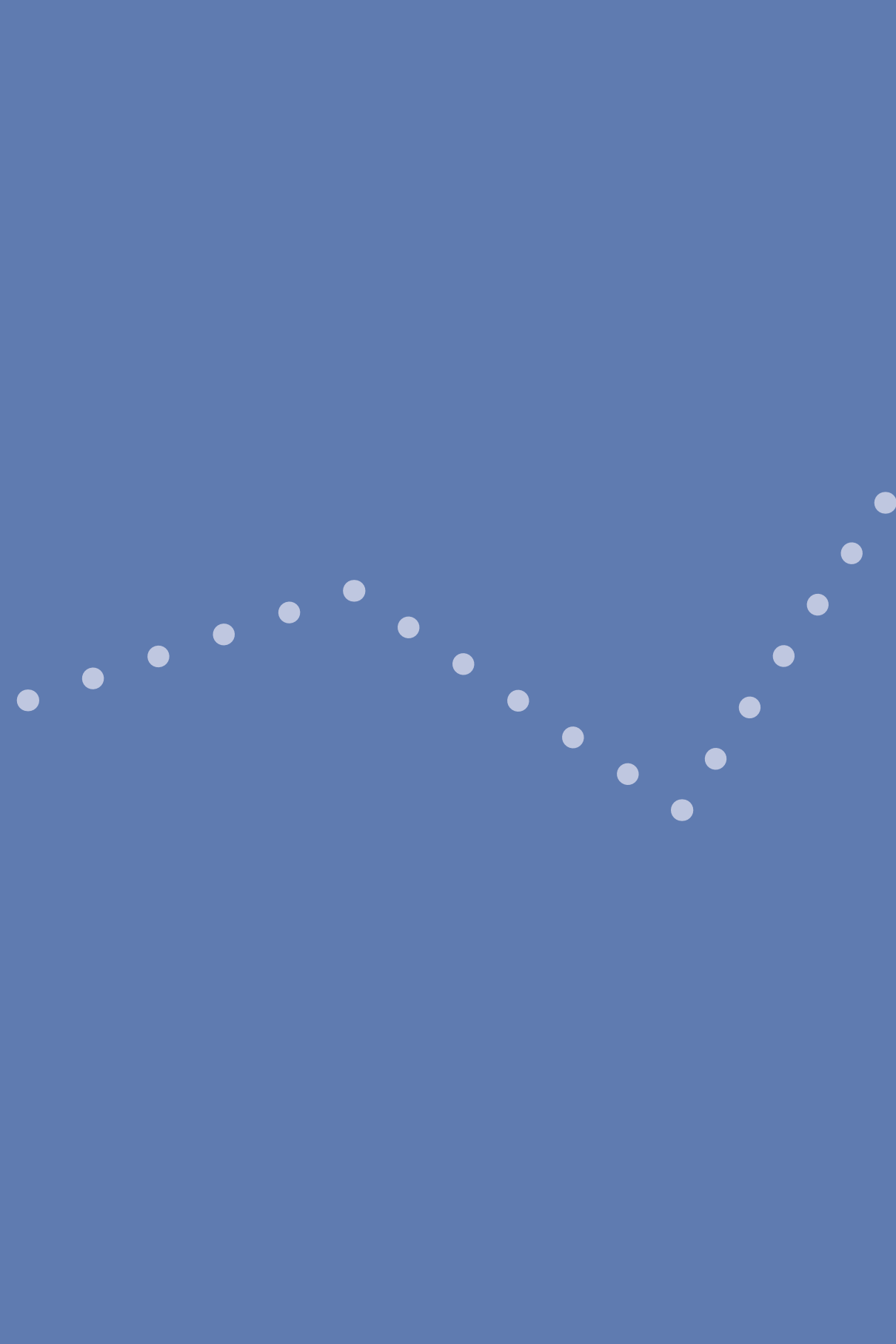
The experience with GHB suggests that if this were to happen, a likely regulatory response would be to explore options to restrict the availability of the substances commonly through making it an offence to produce, sell or use it. In Europe, Council Decision 2005/387/JHA of 10 May 2005 provides the basis for an early warning system where new psychoactive substances with no medicinal use may be subject to risk

assessment and subsequent control ([11]). During the 20th century, the recreational use of drugs with psychoactive effects that resemble alcohol to at least some extent, (cannabis, ecstasy, benzodiazepines and GHB) has prompted their prohibition by classifying them as controlled substances under international drug control treaties (McAllister, 2000).

Clearly, the potential development and marketing of new psychoactive substances for recreational purposes, or as substitutes to existing commonly used illicit or licit existing substances, is likely to raise difficult questions on future policy in this area. Currently major social and regulatory barriers and challenges exist that inhibit the development and marketing of new psychoactive substances for recreational use. However these are already being challenged on a number of fronts and this is likely to continue with the Internet now creating a global marketplace in which regulatory frameworks in many areas are either complicated or under challenge.

Moreover, there may be good public health and scientific arguments for continuing to explore the possibility of the development of a ´safer tipple´ or less damaging substitutes for tobacco or even illicit drugs. A wider public discussion of the possibility is also well worthwhile for its educational value in reminding citizens in developed countries that: their favourite recreational drug alcohol affects brain chemistry in the same way as many prohibited drugs; it is an extremely toxic substance when used to excess, as it so often is; and is a major cause of violence, injury and social disorder, especially among young adults.

([11]) Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances (OJ L 127, 20.5.2005, p. 32).



Chapter 6

Conclusions and possible implications of advances in addiction neurobiology for future drug policies

Benjamin Capps, Adrian Carter, Wayne Hall, David Nutt, Richard Ashcroft and Ruud ter Meulen

There is a consensus within European Union policy that the approach to drug control should be balanced, comprehensive and focus simultaneously on the need for demand reduction, supply reduction, the fight against trafficking and international cooperation. It combines action at a number of levels:

- within the framework of European Community competence (public health, precursor control, money laundering, development aid);
- close cooperation between Member States (foreign policy, justice and home affairs);
- partnerships with Member States, other states and international organisations.

The potential developments mentioned in this report raise issues that are likely to become important for policymakers within Member States and will require careful consideration at European level in regard to the EU's role. They raise important questions for both drug policy and human rights and may have implications for the future regional role of the EU in developing policies, monitoring the activities of Member States and taking appropriate action with regard to Member States' policies. The EU itself may use monitoring and prevention technologies in controlling the criminal aspects of drug use (such as trafficking) and their effects on public health. The EU has already taken affirmative action with regard to tobacco and alcohol in respect to public health.

It is not the purpose of this report to comment upon the fact that some drugs (e.g. amphetamines, cannabis, cocaine and heroin) are illicit while others with similar effects (alcohol and tobacco) are not. The psychoactive substances discussed in Chapter 3 will be classified according to existing policies. For example, the drugs described in this chapter may similarly represent the 'particular dangers inherent' in existing illicit drugs; ([1]) a leading cautious presumption is that: 'New psychoactive substances can be harmful to health' ([2]).

([1]) Official Journal L 127, 20.5.2005, pp. 32–37, paragraph (1).
([2]) Ibid. paragraph (4).

There are positive uses of currently illicit drugs and some argue that the harms from illicit drugs have been overplayed, while those of currently licit ones have been underplayed (Nutt et al., 2007b). Drug policies have always been controversial, especially with regard to the legal status of currently illicit drugs. Much of this stems from the criminal behaviour that is linked to some forms of illicit drug use.

The act of using a drug and the risk of addiction have been used to justify paternalistic government policies that prohibit the use of some drugs (Hunt, 2003; Kleinig, 2004). Policies, therefore, reflect some of the harms of some types of drug use but it is the 'recreational' use of illicit drugs that has largely shaped our 'medical' policies. There is compelling evidence that widespread use of many licit and illicit drugs has massive economic and social costs but their links to crime and social problems are not always straightforward. The distinction between use for therapeutic and recreational reasons has significant socio-political consequences.

An approach grounded in neurobiology will affect policies in ways that are difficult to anticipate. It may reduce the reliance on policies that aim to avoid harm and increase support for a disease model of addiction. It may lead to a more rational approach to the harms caused by drug use rather than policies based on cultural and historical agendas. In the best of all possible worlds, addiction neurobiology may allow us to reconsider our social responses to the minority of drug users who become addicted by reducing their stigmatisation and increasing their access to more effective psychological and biological treatments; but an improved understanding of the neurobiology of addiction will not relieve us of the obligation to prevent problem drug use in some youth populations. Policies will, therefore, still need to aim to reduce the number of troubled young and otherwise vulnerable people who are susceptible to the appeal of all forms of drug use by reducing the social conditions that contribute to their vulnerability.

The implications of new developments, or potential new developments in addiction neuroscience are likely to have implications for future drugs policy in a number of important areas.

1) Neurobiological research on addiction is revealing complex interactions between drugs of addiction, biological responses to them, and the social circumstances of drug users. As this work develops over the next decade, more work will be required to build upon the current research by more systematically exploring the social and ethical implications of addiction neurobiology and its application to the treatment and prevention of addiction.

2) Appropriate societal responses to drug use and addiction will need to give due consideration to 'disease' models of addiction while still acknowledging the social conditions that lead to drug use and the choices that individuals make to use drugs.

3) Policies towards drug use and addiction will continue to need to address both their public health and criminal justice consequences.

4) The autonomy of addicts is variable so care is required in using medical, paternalistic and criminal measures to control and treat addiction. If an addict is conceptualised as being wholly without autonomy, which is not the case in lucid periods, then human rights and appropriate ethical values are likely to take a back seat to the public interest. When autonomy is seriously impaired, it may be appropriate to take paternalistic measures to protect addicts from harming themselves or others. Responses to addiction need to include both punitive measures (i.e. in response to the autonomy and responsibilities of drug users) and improved access to addiction treatment.

5) The autonomy of addicts is impaired by their addiction but not usually sufficiently so to warrant strong paternalistic interventions that override their wishes. Treatment of addiction should aim to build on and support addicts' autonomy and ensure that their consent to treatment is as informed and given as freely as possible.

6) A major challenge for addiction policy and ethics will be finding ways to educate the public about the neurobiological basis of addiction in ways that recognise that drug use and addiction are nonetheless affected by individual and social choices.

7) Strong public interest in neuroscientific research on addiction and the potential for misunderstandings mean that addiction neuroscientists should disseminate their findings responsibly and accurately, anticipate potential misinterpretations and proactively engage with the media and politicians.

8) While many of the prospective developments in neuroscience will support measures of addiction treatment, prevention and monitoring, the potential limitations of a neuroscientific approach also need to be considered. Although this report has not dealt in detail with the social responses to addiction, future policies should continue with those current methods that are successfully tackling aspects of drug addiction, while integrating potentially new methods that emerge from addiction neuroscience.

9) All new treatments and preventive interventions for addiction should be rigorously evaluated for safety and efficacy before being introduced into routine practice.

10) Equitable access to treatment should not disproportionately deny human rights, privacy, consent or liberty to satisfy criminal-focused public opinion. Addicts are already vulnerable, and often live in disadvantaged situations. This should not be compounded by discrimination and stigmatisation.

11) The EU's current Drugs Strategy (2005–12) provides a balanced approach to drug control with a focus on both reducing illicit drug trafficking and dealing with problem

users. Future developments in addiction neuroscience may assist in reducing the prevalence of illegal drug use and levels of drug dependence while promoting public health and improving social conditions that are associated with drug use. To ensure that the benefits from any developments in this area deliver maximum benefit and that potential problems are anticipated and avoided, an ongoing debate is required that considers how novel developments in neuroscience may affect current and future policies at both Member State and European level.

Specific policy implications

Although developments in neuroscience offer the possibility of allowing individuals to be more autonomous with regard to their future decisions, care should be taken to minimise any adverse effects on human rights. Therefore, further research will be required to ensure that these developments are taken forward with adequate ethical safeguards for human rights and with the aim of achieving an appropriate balance between the ethical values of autonomy, consent, liberty, equality and privacy.

Areas that require specific consideration include:

Genetic data

While gene chips containing personal data on susceptibilities may provide important medical benefits, access to such data could potentially lead to stigmatisation and discrimination if inappropriately used. This is currently highly speculative technology and it is important that it not be rolled out without sufficient empirical evidence demonstrating its efficacy and appropriate attention given to data protection issues.

Vaccinations

Vaccines and slow release formulations of antagonist drugs are potentially useful treatments that may assist addicts to remain abstinent. The long-term potential of vaccines in particular is currently unclear. However, even if this technology is successfully developed it will not represent a magic bullet solution to drug problems nor is it likely that they will be appropriate for all people with drug problems. Should developments in this area progress successfully, controlled evaluations will be required to establish their safety and efficacy and individuals who receive these treatments should give free and informed consent to their use.

A strong ethical argument exists that the safety and efficacy of these treatments should be well studied before the treatments are used under legal coercion. And that any such use should be separately evaluated before it is widely introduced.

The same is true for the more speculative use of vaccines in children and adolescents to prevent drug use and hence addiction. It would appear wise to discourage the use of

vaccines for this purpose until considerable clinical experience has been obtained with the use of vaccines in the treatment of addiction.

Depot or sustained release pharmacological treatments

Similar ethical requirements for drug vaccines are also raised by the potential use of drug implants. This leads to the same conclusion that the efficacy of these treatments should be evaluated in registered clinical trials before being used widely.

If these prostheses were to be used under legal coercion, then sound arguments exist that they should be offered as a range of treatment choices, which includes other options of proven effectiveness.

Neurosurgery and deep brain stimulation

Neurosurgery treatment of addiction is an invasive, irreversible and risky form of treatment. It is hard to draw any other conclusion than this. Its use should be discouraged in preference to using less invasive and reversible forms of psychosocial and pharmacological treatments. While it is less invasive, similar recommendations would apply to deep brain stimulation.

Transcranial magnetic stimulation

Transcranial magnetic stimulation is a non-invasive neurological treatment that appears to have limited adverse effects. Preliminary studies suggest that it may be effective in treating addiction (e.g. reducing impulsive or compulsive behaviours). More research should be conducted into the safety and efficacy of transcranial magnetic stimulation in the treatment of addiction.

Neuroimaging

Neuroimaging methods are promising investigatory tools that have and will continue to illuminate the neurobiological mechanisms underlying drug use and addiction. Their use as screening methods for forensic, employment or other purposes is premature until the strengths and limitations of these methods are better understood.

Drug testing

Drug testing, when it is used, should be for the purposes of monitoring and improving treatment of the addicted individual or safeguarding the wider community. It is ethically unacceptable to use it as a form of extrajudicial punishment.

The results of drug tests should remain private and confidential. Access to this information should be protected from third parties, including law enforcement, unless access has been granted by a formal legal process (e.g. court order, subpoena or other appropriate legal framework), or the individual gives fully informed and uncoerced consent.

Treatment in prisons

The principle of equivalence of care means that addicted prisoners should have access to drug treatment and harm minimisation measures that can help protect their health. The options available should generally mirror those available to the wider community. For opioid-dependant individuals, this would in the EU generally include some form of substitution treatment. Prisoners should also have access to voluntary HIV and HCV testing and counselling.

Both ethical and medical objections exist to forced unsupervised opioid detoxification. These are particularly strong for those who were stabilised on a maintenance treatment, prior to their incarceration.

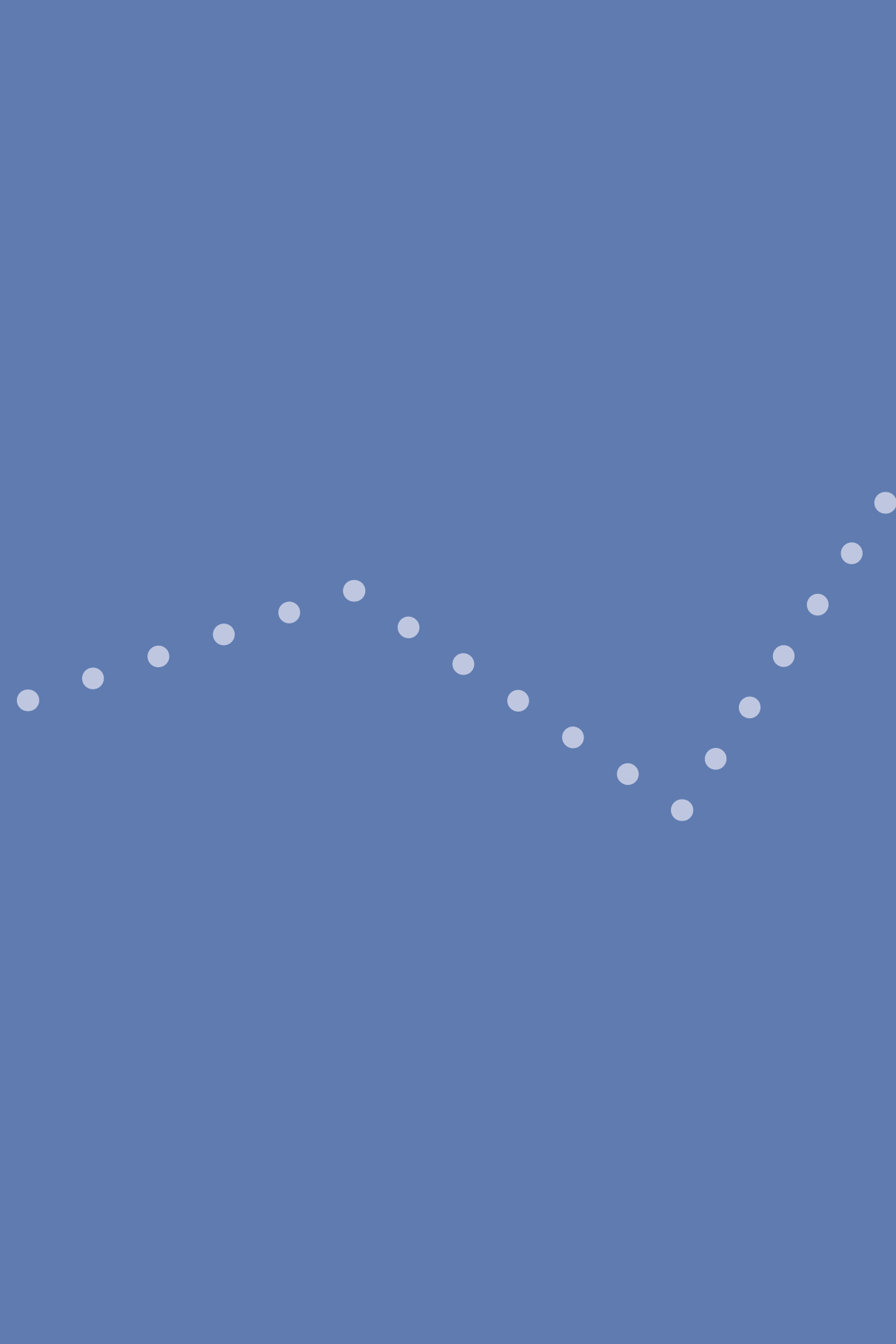
A general principle, again with both ethical and medical justification, is that similar privacy protections should apply for prisoners as to the rest of the population.

Treatment during pregnancy

Pregnant women should be engaged and positively encouraged to enter treatment and receive early antenatal care.

Ethical objections exist to the forcible treatment for addiction of pregnant women and measures in this area can be counterproductive, may cause greater harm to the mother and child and may discourage pregnant women with drug problems from seeking help.

There is, in many countries, a need for more investment in treatment programmes tailored towards the needs of drug-dependent women.



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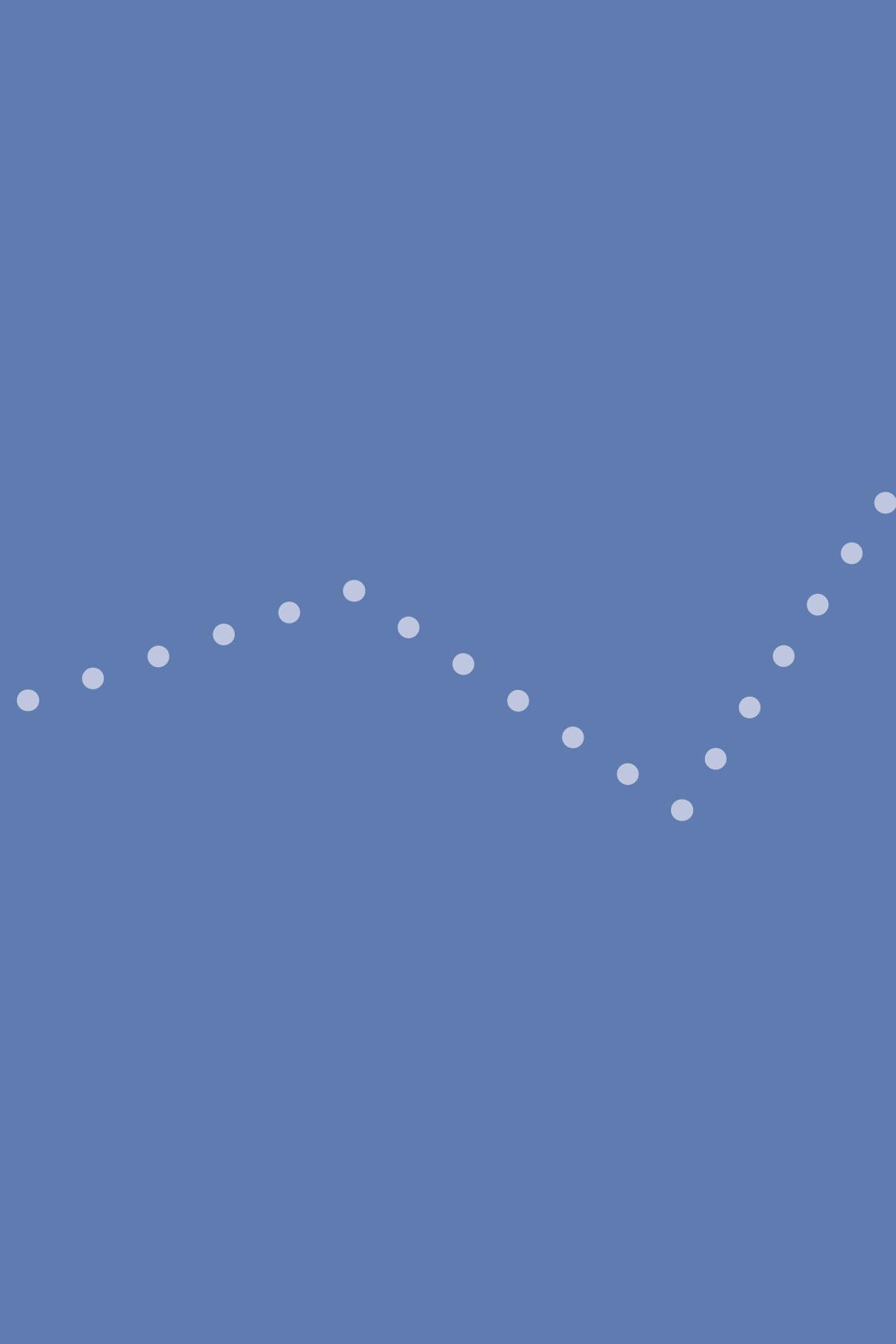
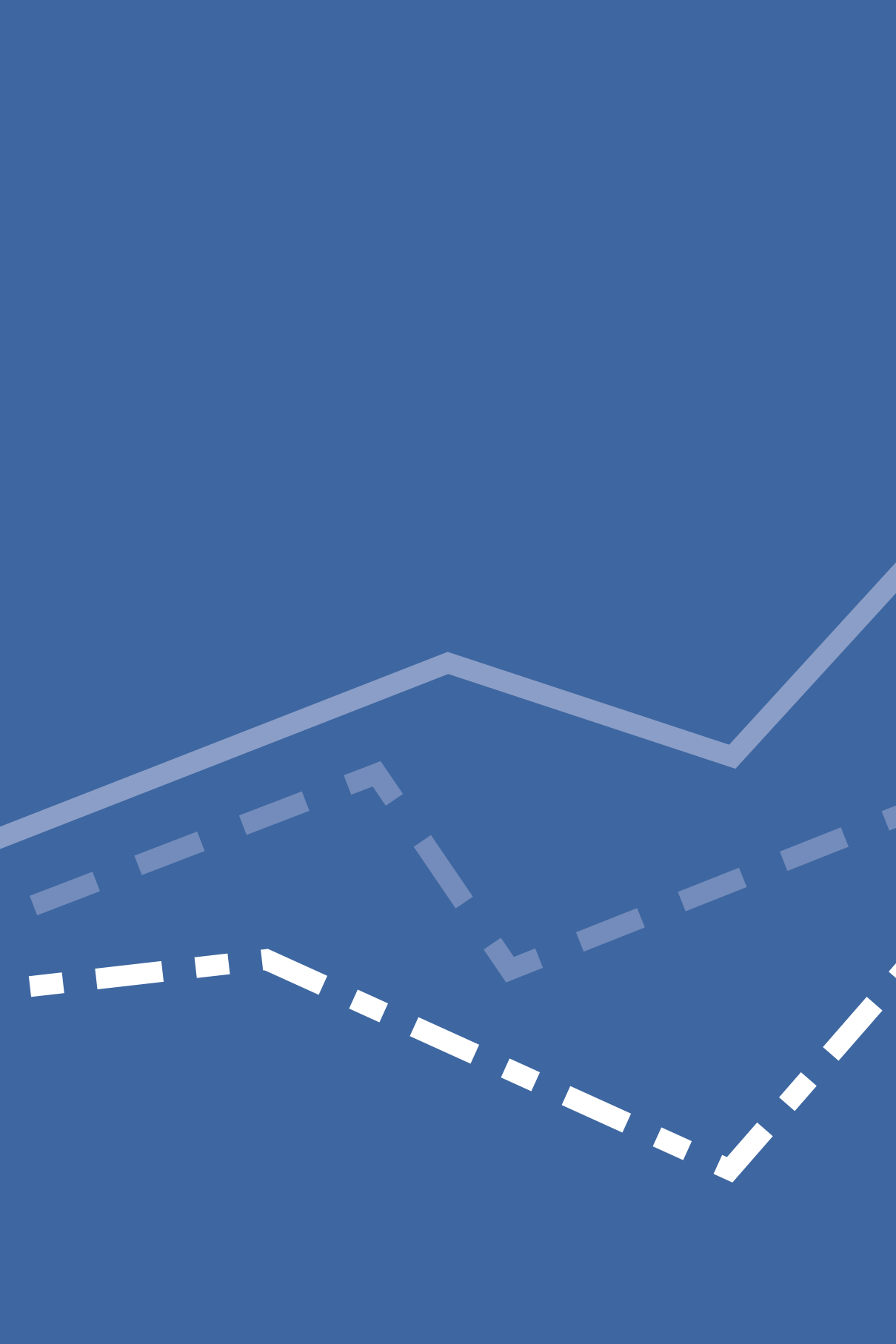
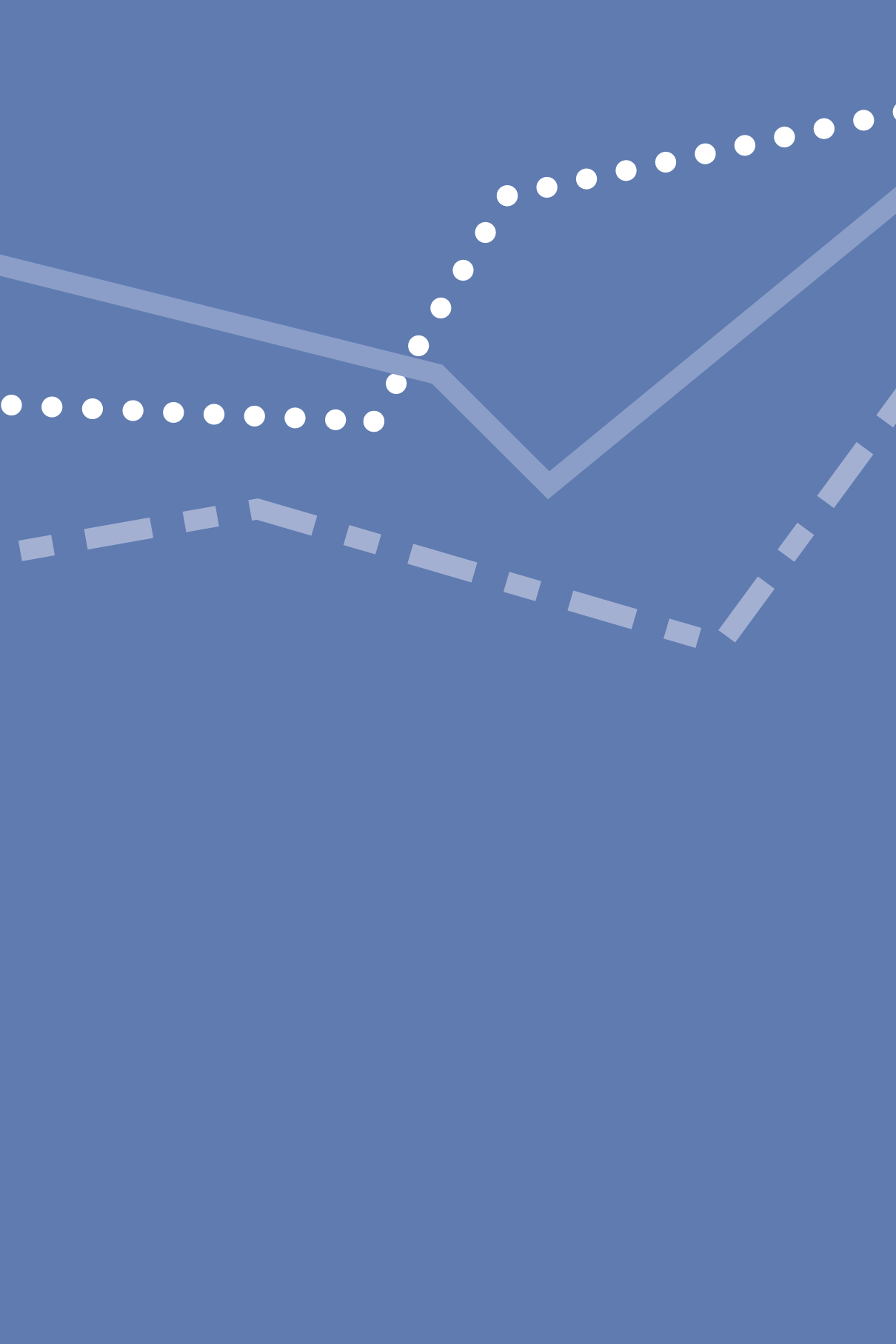


Abbreviations

aCG	Anterior Cingulate Gyrus
AIDS	Acquired Immune Deficiency Syndrome
ADHD	Attention Deficit Hyperactivity Disorder
ALDH	Aldehyde Dehydrogenase 2
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazole propinonic acid receptor
BBV	Blood Borne Virus
CB1	Cannabinoid receptor 1
COMT	Catechol-*O*-methyl Transferase
CRF	Corticotropin Releasing Factor
DA	Dopamine
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DRD2	Dopamine Receptor 2
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Illness, 4th Edition, Text Revised
ECHR	European Convention on Human Rights and Fundamental Freedoms
ECJ	European Court of Justice
EEG	Electroencephalograph
EU	European Union
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-aminobutyric Acid
GHB	Gamma-hydroxybutyric Acid
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C Virus
HPA axis	Hypothalamic Pituitary Adrenal axis
HRT	Hormone Replacement Therapy
ICD-10	International Classification of Disease
ICCPR	International Covenant of Civil and Political Rights
IDU	Injecting Drug User
LSD	Lysergic Acid Diethylamide

LTD	Long Term Depression
LTP	Long Term Potentiation
MEG	Magnetoencephalograph
MMT	Methadone Maintenance Treatment
NAC	N-acetylcystein
NAcc/NAc	Nucleus Accumbens
NGO	Non-Government Organisations
NIDA	National Institute on Drug Abuse
NIAAA	National Institute on Alcoholism and Alcohol Abuse
NMDA	N-methyl-D-aspartic Acid
NRT	Nicotine Replacement Therapy
OFC	Orbitofrontal Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PTSD	Post-traumatic Stress Disorder
SPECT	Single Photon Emission Computed Tomography
SSRI	Serotonin Selective Reuptake Inhibitors
TMS	Transcranial Magnetic Stimulation
UDHR	Universal Declaration on Human Rights
UK	United Kingdom
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNESCO	United Nations Educational, Scientific and Cultural Organization
UNODC	United Nations Office on Drugs and Crime
UROD	Ultra-rapid Opioid Detoxification
US	United States
VMAT	Vesicular Monoamine Transporter
VTA	Ventral Tegmental Area
WHO	World Health Organization





Glossary

Abstinence	The cessation of drug use after an extended period of use of an addictive drug. Abstinence in a dependent drug user may lead to the experience of withdrawal symptoms.
Addiction	The repetitive engagement in an activity, such as drug use, gambling or eating, despite the negative consequences that it causes. Addiction usually involves intense craving for the addictive activity and an impaired ability to control use. These aspects of addiction are sometimes referred to as psychological dependence. Addiction also often involves the development of tolerance towards the drug of abuse, and symptoms of withdrawal upon cessation of use. This is often referred to as physical dependence.
Agent	A person who is the subject where there is action. The person who performs an action. Ethical conduct is usually taken to presuppose the possibility that individual human agents are capable of acting responsibly.
Agonist	A substance which binds to the same receptor as the target drug (in this case the drug of addiction) producing the same or similar pharmacological effects.
Amygdala	A small group of neurons in the limbic system of the brain that is involved in the processing of emotional information, learning and memory.
Anterior cingulate gyrus	The front part of the cingulate cortex, a region along the medial surface between the two cerebral hemispheres, that is involved in decision-making and particularly the regulation of emotional impulses to act.
Antagonist	A substance which binds to the same receptor as the target drug (in this case the drug of addiction) preventing it from having its usual effects.
Autonomy	(Greek 'self' and 'law') The capacity for self-government. Agents are autonomous if their actions are truly their own.

Beneficence	The ethical principle that one should aim to be good to others.
Buprenorphine	A drug that is a partial agonist of opioid receptors. It is often used in the treatment of opioid dependence, either as a form of maintenance, or as an aid to withdrawal. It can also lead to dependence.
Cerebrum	The two uppermost lobes of the brain that consists of a left and right hemisphere. An evolutionary recent part of the brain that sits above the more primitive parts of the brain, such as the mid and hindbrain. Also often referred to as the forebrain.
Coercion	The use of force to encourage someone to enter treatment. The type of force used may vary depending on the amount of choice that an individual has. Mild forms include pressure from friends and family; the strongest forms involve detaining individuals in treatment against their wishes.
Confidentiality	Ensuring that information is accessible only to those authorised to have access. It restricts the use of personal information about an individual so that it cannot be communicated without their consent. In some professions, access and use to information is often 'privileged', and therefore may not under normal circumstances be discussed or divulged to third parties.
Cortex	The outer mantle of the brain, specifically the cerebrum, which is involved in the highest cognitive functions, such as conscious sensation and movement, language, and decision-making.
Craving	An intense and seemingly irresistible desire to experience the effects of drugs.
Compulsion	In addiction, compulsion refers to an experience of a strong, usually irresistible drive or desire to consume drugs that is often contrary to one's will.
CNS depressants	A class of drugs that slow central nervous system function, and can lead to fatal overdose in large doses from respiratory and cardiac failure.

Cues, or drug cues	Events which have the ability to bring up memories that can often trigger emotional responses. Drug cues are those which recall memories associated with drug use that often trigger intense cravings for the drug.
Detoxification	Supervised withdrawal from a drug of addiction that allows the drug to disappear from the brain and body. It is nearly always accompanied by withdrawal symptoms that may be managed using other drugs (medicated) or psychological support (unmedicated).
Dignity	Associated to a number of definitions. The most popular are that it relates to respect, esteem or worthiness of action; the innate value of all human beings; or the empowerment of agents to make decisions and choices about their own lives.
Distributive justice	The ethical principle according to which all individuals should be treated fairly and there is a fair distribution of the risks and benefits of certain actions.
Dopamine	A chemical in the brain, or neurotransmitter, that is central to the development of addiction. It is found in the regions of the brain that are involved in the regulation of movement, motivation, emotion and reward.
Dysphoria	A feeling of being unwell, anxious, depressed and restless.
Endogenous	A chemical or substance produced within the body.
Endorphins and enkephalins	Forms of endogenous opioids: naturally occurring substances in the human brain that bind to the same receptors as morphine.
Equality	The principle of equal treatment by the law and in medical care.
Ethics	The study of the concepts involved in practical reasoning: good, right, duty, obligation, virtue, freedom, rationality, choice etc. (sometimes referred to as the study or formalisation of morality).
Euphoria	A feeling of exuberance, elation and maximum well-being.

Fatalism	The belief that a set of pre-existing circumstances or events predetermined a particular outcome. It is often used in genetics and biology to suggest a belief that an agent could not avoid a particular outcome, and should not attempt to do otherwise.
fMRI	Functional magnetic resonance imaging (or fMRI) is a brain imaging technique that measures changes in blood flow in order to visualise brain activity during particular tasks.
Forebrain	The largest and most evolutionary recent division of the brain, including the cortex, limbic system and basal ganglia. It is the region of the brain involved in our most advanced cognitive functions.
Freedom	The belief that everyone is entitled to make choices. The corollary of this is that persons are to be held responsible for the consequences of their actions. Freedom is closely related to the notion of autonomy.
Frontal cortex	A region of the cerebrum that is involved in our most higher order cognitive functions, such as decision-making and social or moral judgement.
Harm minimisation (or reduction)	An approach to the treatment of addiction and drug abuse whose principle aim is to reduce the harm caused by drug use to both the individual and society without necessarily eliminating drug use. Harm reduction is an evidence-based approach towards drug policy. Needle exchange programmes and methadone maintenance treatment are two types of programme that have harm reduction objectives.
Heroin	A synthetic opiate that is the most commonly abused and one of the most addictive illicit drugs.
Hippocampus	An area of the brain involved in learning and memory, specifically memory for the facts or details of events, referred to as declarative memory.
Homozygous	A term used to describe when an individual carries two identical copies of a gene (one from each parent) at a particular locus on each of the two chromosomes. An individual who carries two different copies of a gene is said to be heterozygous for this gene.

Hypothalamus	A small, but important part of the brain that maintains many of the body's internal functions, such as eating, drinking and the regulation of hormones, such as the stress hormones.
Human Rights	Protections of human (moral) interests (see Rights).
Informed consent	A process whereby individuals are fully informed about a particular treatment that they are to receive, and where individuals are free to participate or not.
Insula cortex	A region of cortex that lies at the intersection of the frontal, temporal and parietal lobes that is involved in the process of introception, or the conscious experience of the body.
Introception	The conscious experience, awareness or sensation of the body.
Liberty	A condition in which an individual has the ability to act according to his or her own will.
Limbic system	A diverse array of densely connected brain regions that are involved in the regulation and generation of our emotions and desires. These regions are also involved in learning and memory.
Long-term depression	A molecular adaptation that occurs at the synapse between two neurons that leads to a weakening of the connection between these neurons.
Long-term potentiation	A molecular adaptation that occurs at the synapse between two neurons that leads to a strengthening of the connection between these neurons.
Maintenance therapy	The long-term replacement of an abused drug with its agonist in a regulated way to prevent relapse to more dangerous and illicit drug use. The most well known type is methadone maintenance.
Medicalisation	The process whereby behavioural or social problems are understood as medical disorders that should be treated medically, often at the expense of social approaches.
Mesolimbic pathway	See Reward pathway.

Mu receptor	The primary opioid receptor that mediates the pleasurable effects of both opiate drugs, such as heroin and morphine, as well as endogenous opioids, such as the endorphins.
Naloxone	A potent opioid antagonist that is used to treat opioid overdose, and is included in the drug, Suboxone, to discourage its injection.
Naltrexone	A potent opioid antagonist that binds to the target opioid receptors preventing heroin and other opioid agonists from having an effect. Naltrexone is often used as a form of relapse prevention. Naltrexone is also used to treat alcohol dependence and eating disorders.
Natural reinforcers	Everyday activities which are reinforcing or rewarding, such as food, sex and relationships. Natural reinforcers also activate the brain's reward pathway, but to a far lesser extent than addictive drugs.
Neurotransmitter	A chemical produced within the neurons in the brain that carries signals to other neurons, usually by binding to receptors on adjacent neurons at the synapse. They are a type of signalling molecule that also includes other substances such as neural hormones.
Nonmaleficence	The ethical principle that we should cause no harm to others.
Nucleus accumbens	A central part of the mesolimbic reward pathway that encodes information related to the rewarding or reinforcing properties of an event, or drug, and signals its salience. Nearly all drugs of abuse act upon the nucleus accumbens, thereby reinforcing their use.
Opioid naiveté	The term given to a condition in which a former opioid addict who has withdrawn from opioid use, loses their tolerance to opioids. Opioid-naive users who return to opioid use are at a higher risk of overdose if they inject their usual dose of opioid.
Orbitofrontal cortex	A region of the prefrontal cortex involved in the attribution of salience to events, craving and the motivation to use drugs.

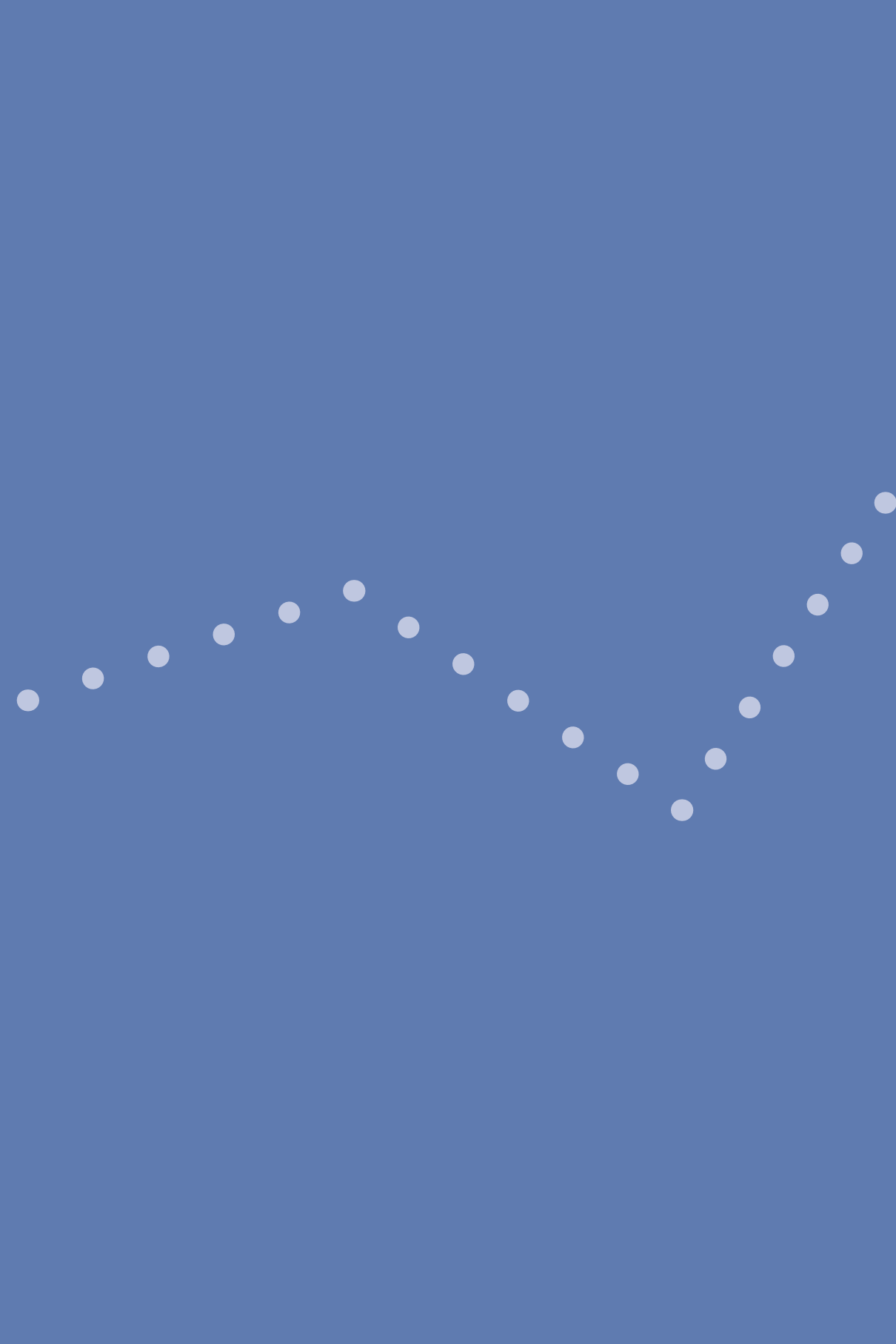
Overdose	An acute condition that results from taking too much of a drug. It can cause unconsciousness, brain damage and death (drug-induced death). It is more commonly used in reference to the CNS depressants, such as alcohol and heroin.
Partial agonist	Drugs that bind to the target receptor of a drug of addiction, partially blocking and partially activating the receptor. They can be used to treat drug dependence (e.g. buprenorphine for the treatment of opioid dependence).
Paternalism	The name given to the position that persons have a right to act in the interests of others without the consent of, or even against the will of, these others. (Sometimes substituted by parentalism).
PET	Positron emission tomography (or PET) is a brain imaging technique that uses radioactively labelled molecules to visualise brain structure and function.
Pharmacogenomics/genetics	The use of genetic or genomic information about an individual to select the pharmacological or psychosocial treatments that will maximise the chance of successful treatment for that person.
Physical dependence	A physiological state that is indicated by the occurrence of withdrawal symptoms when regular drug users abruptly stop taking the drug and accompanied by the development of tolerance, requiring higher doses to achieve the same drug effect.
Prefrontal cortex	The very anterior of the frontal cortex of the brain, that includes the orbitofrontal cortex and the anterior cingulate cortex. It is considered the highest cortical area in the brain and underlies our most complex behaviours, including personality, social and moral behaviour, executive control and planning.
Privacy	An individual's right to keep their personal information and affairs confidential, and out of public view, or to control who has access to this information and what they can do with it.

(The) Public interest	Refers to competing claims made by a public concerned with such values as equality, happiness, security, or safety. There is a view that public interest, also sometimes held to be equivalent to the 'public good', is roughly synonymous with a definition of 'general welfare', and juxtaposed with autonomy and individual interests.
Receptor	A large molecule on a cell's surface that is a specific target for particular chemicals. In the brain, this is most often neurotransmitters, but it can also include hormones and other endogenous chemicals, that bind to it and signal what is going on outside the cell (signal transduction).
Reinforcement	A neural process within the reward pathway that ensures that an activity or event is seen as salient and motivating. A stimulus that produces this effect within the reward pathway is said to be a reinforcer. Addictive drugs are potent reinforcers.
Relapse	The resumption of regular drug use after a period of abstinence, often in response to drug-related cues or stress. Relapse is common after addicts have achieved abstinence.
Relapse prevention	The use of a prophylaxis, usually pharmacological (e.g. naltrexone) or psychological support, to reduce the likelihood of returning to regular drug use. Most drugs used in relapse prevention work by preventing the drug of addiction from binding to its receptor. Drug vaccines have also been developed to reduce relapse to the use of some drugs of addiction (e.g. nicotine, cocaine).
Reuptake	The chemical process whereby signalling molecules or neurotransmitters are removed from the synapse by transporters on the cell surface. Reuptake is an important process that regulates the activity of signalling molecules.
Reward	The neural process that reinforces behaviour and signals that some experience, such as using drugs, is positive. It is usually associated with pleasure or euphoria. It is partly mediated by the release of dopamine into the nucleus accumbens.

Reward pathway	A central circuit in the brain that reinforces behaviour when activated. Most drugs which activate this reward pathway are addictive, and their effects are usually experienced as rewarding and pleasurable. The circuit includes neurons of the ventral tegmental area, nucleus accumbens and part of the prefrontal cortex, referred to as the mesolimbic pathway, and the amygdala and hippocampus.
(Moral) Rights	Justified (strong) claims to the protection of individuals' important interests. When these rights are effective, this protection is provided as something that is owed to persons for their own sakes. Not to be confused with contractual (weak) rights created by agreement, law and convention (called liberties, powers and immunities).
Salience	The motivating quality of an event or experience. In contrast to reward, salient events need not be pleasurable. They are things that grab our attention and motivate us to pursue them. Salient events are also reinforcing.
Snus	An oral form of tobacco that has been treated to remove the major carcinogens from traditional chewed tobacco.
Stimuli	Events or experiences that trigger a neurochemical response in the brain.
Striatum	A region deep within the brain that is involved in the planning and regulation of movement and executive control pathways.
Substitution treatment	See Maintenance therapy.
Suboxone	A combination of drugs used in the treatment of opioid dependence. Its principal ingredient is buprenorphine but it also contains the opioid antagonist, naloxone, to discourage patients from dissolving and injecting the drug as injecting naloxone produces opioid withdrawal symptoms.

Swiss heroin trials	A series of clinical trials of the prescription of injectable pharmaceutical heroin to long-term, treatment refractory heroin addicts.
Synaptic plasticity	Molecular and cellular changes between two cells that either strengthen or weaken their connection. Also see Long-term potentiation and Long-term depression.
Synapse	The specialised junction between two neurons across which neurotransmitter release allows signalling from one neuron (the presynaptic neuron) to the next (the postsynaptic neuron). Molecular and cellular specialisations at the synapse allow for quick and highly regulated communication between the two neurons.
Thalamus	The thalamus is the key relay station for all incoming sensory information. It is located deep within the brain, and is responsible for isolating important messages from the mass of sensory information entering the brain.
Tolerance	A physiological state in which an individual is less responsive to the effect of a drug, leading to the use of higher doses. Tolerance is the result of neurochemical changes within the brain as a result of regular drug use. It often leads to physical dependence.
Transporter	A large molecule in the cell membrane that pumps signalling molecules such as neurotransmitters out of the synapse, thereby regulating their activity.
Ultra-rapid opioid detoxification	A form of opioid detoxification that reduces the withdrawal process to 24 hours by administering high doses of the antagonist, naltrexone, while the patient is under general anaesthesia.
Utilitarianism	A set of moral theories that decide what is ethically right by evaluating the consequences of an action or a rule. The simplest form is that of Jeremy Bentham (1748–1832) according to whom right actions were those that produce the greatest happiness for the greatest number of people.

Ventral tegmental area	A group of dopaminergic neurons that make up a key part of the brain's reward pathway. Neurons in the VTA synapse on to neurons in the nucleus accumbens and the prefrontal cortex.
Withdrawal	Symptoms that develop when an individual abruptly stops or abstains from chronic drug use. The symptoms of withdrawal can include nausea, headaches and seizures, depending on the drug of addiction. Some drugs have very mild or no withdrawal symptoms (e.g. cocaine), while others cause intense discomfort (e.g. alcohol, heroin).



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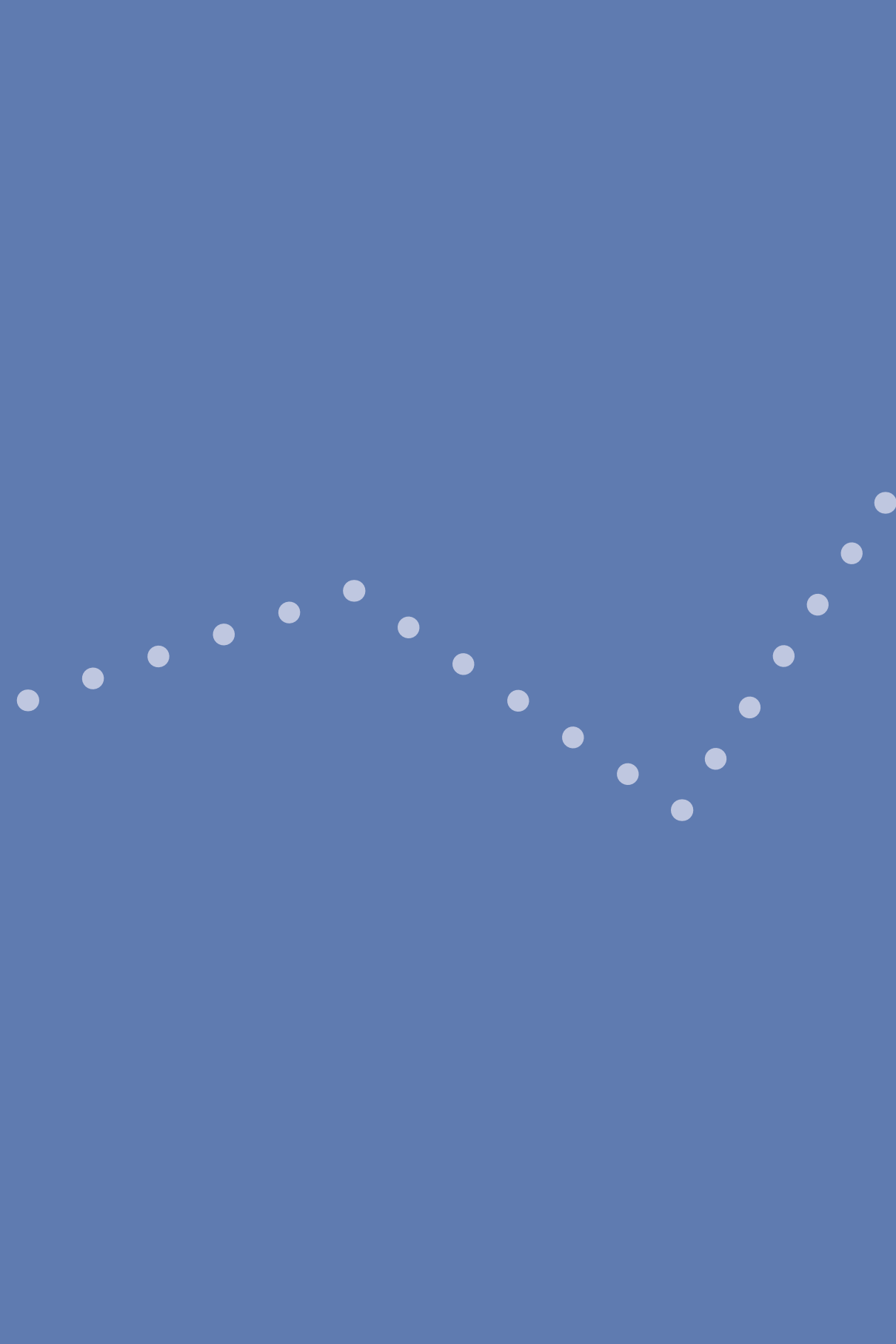

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