ADDICTION NEUROETHICS

The Ethics of Addiction Neuroscience Research and Treatment

Edited by

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Foreword: The Neuroethics of Drug Addiction

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Discussions of neuroethical issues associated with drug addiction, as exemplified in this timely and scholarly volume, are of enormous contemporary social importance. In this discourse we must consider the extent to which such issues are unique to the case of addiction, and which are not. The very status of drug-addicted individuals probably falls under the former, given the special stigma afforded to them. Mental illness often suffers from undue stigmatization which, as we are all only too aware, may dilute opportunities for resource allocation in health care and for research funding in academic medicine. The folk stigma associated with addiction is that of enfeebled willpower in exercising restraint in the absence of dementia or otherwise impaired mental faculties. This enfeebling of inhibitory control contrasts with the stigma often associated with disorders of motivation such as chronic fatigue syndrome, where the latent suspicion is often that of laziness and malingering rather than the exercising of volitional control over such behaviors as craving and drug taking. The stigma around addiction stems from a reluctance of drug abusers to seek treatment that is attributed to apathy or motivational inertia, and their apparent lack of social responsibility that renders them a burden on their own families and society.

The role and perceptions of lost volitional control in drug abuse are hardly weakened by modern neuroimaging studies that reveal significant apparent underfunctioning of regions of the prefrontal cortex traditionally associated with top–down behavioral control and decision making. These regions include the anterior cingulate cortex, the ventrolateral prefrontal cortex and the orbitofrontal cortex. One important scientific issue is how much of this impaired neural function derives from chronic exposure to drugs of abuse and how much is already present prior to drug abuse, and may thus also contribute to the propensity to addiction. Of course, both of these may be true, even in the same individual. Which of these states of affairs holds may also depend on the primary drug of abuse. A critical question, also debated in neuroethical
analyses of studies of illegal behavior, is whether this behavior can be blamed on the individual, or on the individual’s predispositions arising from altered brain structure. In the eyes of some commentators, such a mind–brain dualism may serve to excuse drug abusers from their illegal or socially inappropriate behavior. An alternative view deriving from modern neuroscience, however, would emphasize that it is perhaps more productive to consider an integrated concept of the volitional self in terms of underlying brain mechanisms.

In this foreword to Addiction Neuroethics, I would like to argue further that it is irrelevant to the issue of responsibility whether drugs cause changes in brain function (which further fuel the drive to addiction) or whether there is also a neurobehavioral endophenotype (addictive personality) predisposing to drug abuse (although this is in itself an interesting and relevant scientific question). Notions of responsibility and intentionality, which are central to legal arguments concerning guilt, and which may be suspended in judgments on persons with psychosis or dementia, may still apply to the behavior of drug addicts. The fact that their volitional control may be impaired by permanent brain damage or transient brain dysfunction, or ultimately by genes conferring this impaired brain function, enhances their risky behavior, and may promote compulsive responding, but does not fully determine it. However, it should be realized that exerting volitional control is difficult for these individuals, and that they may need additional help, medical or otherwise, in order to achieve this goal. Both the medical and other models of behavior underlying addictions are discussed in chapters of this compilation. Moreover, the use of structural or functional brain imaging, or ligand-based positron emission tomography (PET) may help to explain the behavior exhibited by addicts and guide forms of treatment, but it cannot be used to excuse it.

Advances in neuroscience and cognate disciplines such as experimental psychology have greatly enhanced the understanding of the neural and psychological mechanisms underlying drug addiction. Thus, we now know the molecular basis of action of virtually all drugs of abuse, as well as their initial sites of action in the brain and how they affect associated neural networks. Addiction can now usefully be conceptualized as a form of aberrant learning, by specific brain regions, with considerable implications for treatment. We know much about the harms to the brain and viscera produced by chronic drug abuse, whether of illegal drugs such as amphetamine, cocaine and alcohol, or legal drugs such as alcohol and nicotine. These advances have made drug addiction an excellent test case for the identification and discussion of ethical issues, as this book clearly illustrates.

We also learn from chapters in this volume that the other main ethical dilemmas posed by addiction derive from its treatment. Modern
neuroscience has revealed a potential panoply of treatments of addiction, of varying degrees of plausibility. Some of these, such as psychosurgery (e.g. lesion of the anterior cingulate or nucleus accumbens) are often motivated by misinterpretations of the published basic scientific evidence, and have the same dubious neuroscientific (and thus neuroethical) status as psychosurgery practiced in the twentieth century for such conditions as schizophrenia and depression. Although cingulotomy turned out perhaps most successfully in cases of obsessive-compulsive disorder (OCD), there is insufficient evidence to believe that it could also work effectively in addiction, and in any case, even the small success found in OCD has not led to its widespread acceptance. The modern neurosurgical approach to the treatment of neurological and neuropsychiatric disorder has been that of deep brain stimulation (DBS), as discussed in Chapter 5. While this has been associated with some outstanding successes, for example in the treatment of Parkinson’s disease, depression and OCD, the application of DBS to addiction is not obvious, partly because we are still identifying the relevant neural circuitry, and partly because we are not entirely certain of its neural and neurochemical effects. Clearly, the same types of general consideration also apply to the use of DBS in addiction as in other mental disorders.

Drugs and various forms of cognitive behavioral therapy have been the mainstays of treatment for addiction, sometimes together. A general practitioner with whom I was being interviewed for BBC Radio asserted that it was blatantly wrong to treat drug addiction with drugs, though I see no logical or ethical problems arising from this. Indeed, this is often necessary, as in the case of treatment of withdrawal from opiate addiction by substitutes such as methadone or buprenorphine. The treatment of heroin addiction by supervised administration of heroin or of amphetamine addiction similarly with amphetamine is perhaps more controversial, to the point of suggestions that it is unethical. Presumably, the dubious moral features of this approach lie in the argument that this form of intended harm reduction is not treating addiction, but rather encouraging it. The cost benefits of such treatment regimens, however, have to be considered in pragmatic terms of the strategies they offer to manage behaviors such as addictions, and reduce crime and thereby the almost certain imprisonment.

In general, there is now a considerable effort to research potential drug treatments for addiction designed to reduce drug intake, craving, relapse and other aspects of addictive behavior. Out of this research initiative has arisen the possibility of employing vaccines against specific drugs of abuse—an innovation prompting previously unrealized neuroethical issues in terms of their use. Foremost among these is the potential coercive use of such treatments for children or fetuses at risk of drug abuse, of prisoners with drug abuse problems, or even of employees at
the workplace. I suspect that the resolution of these dilemmas may hinge on the likely efficacy of such treatments. I would be skeptical that a vaccine against cocaine is likely to reduce drug seeking of other compounds in a determined abuser, but time will tell. At present, despite some excitement around the notion of vaccines, it seems unlikely that society would condone mass inoculation of children with antidrug vaccines. The associated risks are simply not worth taking.

As we accumulate more genomic and epidemiological information about addiction, it seems more likely, however, that our propensities to abuse different drugs may be predicted to some extent, as will the possibility of deleterious consequences of abuse such as the induction of psychosis by cannabis. However, it would seem unlikely that we would expose children to risks associated with PET scanning for dopamine D₂ receptors, for example. Some similar issues arise for drug addiction as for other aspects of genetic counseling in the context of disease. Unless the long-term effects are fully assessed, the most likely outcome of such enhanced knowledge would be to enhance education about risks associated with drug use, rather than resort to prophylactic treatments or major interventions.

Overall, I look forward to seeing how the science–society divide for addiction is bridged as we advance through the next decade. The emerging science of neuroethics has a great deal of responsibility to shoulder as new issues are sure to arise from increasingly sophisticated neuroscientific investigations of drug addiction.
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Introduction: What is Addiction Neuroethics and Why Does it Matter?

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INTRODUCTION

Brain disorders and mental illnesses impose an enormous personal burden upon sufferers and their families, and a substantial economic burden on society. These conditions include psychiatric disorders such as addiction, depression and anxiety, neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases, and acquired neurological trauma or damage such as stroke. The treatment and rehabilitation of those affected by brain and mind disorders command a significant proportion of health-care expenditure (Begg et al., 2007; EMCDDA, 2006; Ezzati, Lopez, Rogers, & Murray, 2004; McKeganey, Neale, Lloyd, & Hay, 2007). In developed countries such as Australia, Canada and the USA, they account for over a quarter of the total burden of disease (Begg et al., 2007; Ezzati et al., 2004; Murray & Lopez, 1996). This figure is expected to grow as populations age and per capita tax bases decrease (Independent Working Group on Brain and Mind Disorders, 2003).

Neuroscience promises to significantly improve treatments and prevention strategies for many disorders of the brain, and even to provide cures where none have previously existed (Insel, 2009). This hope turns on interventions arising from the continuous stream of discoveries about the neurobiological bases of human behavior, and the genetic,
neurochemical and electrophysiological mechanisms of major mental and neurological disorders. Proponents of neuroscience research argue that these advances hold not only technological promise for treating mental illness, but an epistemic promise that will bring forth a radical shift in the understanding of the nature and cause of mental illness and the suffering that accompanies it. The chapters in this volume examine the validity of these promises and discuss challenges that they present in the field of addiction.

Overall, this body of work falls within the domain of neuroethics (Illes, 2006), initially defined as “the field of philosophy that discusses the rights and wrongs of the treatment or enhancement of the human brain” (Safire, 2002). Neuroethics has broadened in its now 10-year life to include a wide range of elements of social science, public health, history of science and medicine, and science communication, among others. In this volume we examine the neuroethical challenges raised by neuroscience research of addiction, its potential applications in the treatment and prevention of addiction, and the formulation of social policies toward drug use. We have called this emerging area addiction neuroethics.

WHY ADDICTION NEUROETHICS?

Addiction and the use of addictive drugs raise important ethical questions:

- Are people who use drugs morally responsible for their behavior?
- How should society respond to people who use drugs in ways that harm themselves and others?
- Is it ethically justified to prohibit the use of some drugs in order to prevent addiction or reduce the social and economic burdens that they cause?
- Is it morally justifiable to legally coerce addicted individuals into treatment?
- Should programs be implemented to screen young people vulnerable to developing an addiction? Should systems be implemented to prevent them from becoming addicted?
- Under what circumstances is it justified to test individuals for drug use?
- Should neuroscientists accept research funding from commercial interests whose main aim is to maximize consumption of products that can lead to considerable harm?
- Is it acceptable for health-care professionals to prescribe and keep people on addictive drugs that are otherwise illegal, and if so, under what circumstances?
- And more.
The answers that academics, health-care providers and society overall give to these questions depends critically on how people understand drug use and addictive behavior. These are the sorts of questions that *Addiction Neuroethics* attempts to answer. Compared with other areas in neuroethics, such as neuroimaging for mental health or disordered states of consciousness, addiction neuroethics has received relatively little attention (for exceptions, see Academy of Medical Sciences, 2008; Ashcroft, Campbell, & Capps, 2007; Carter, Capps, & Hall, 2009; WHO, 2004). Yet, there are important reasons why addiction neuroethics is urgently needed.

First, drug use and addiction are major problems facing most societies and one of the largest causes of preventable disease burden worldwide. It is estimated that drug abuse and addiction account for over 10% of the overall burden of disease in Europe and other developed countries such as Australia, Canada and the USA (Begg et al., 2007; Rehm, Room, van den Brink, & Kraus, 2005). In the USA alone, illicit drug abuse and addiction cost society US $180.9 billion per year (ONDCP, 2004); in addition, alcoholism costs US $180 billion (NIAAA, 2000) and tobacco addiction around US $167 billion (Adhikari, Kahende, Malarcher, Pechacek, & Tong, 2008). Given the significant harm caused by drug addiction and abuse, there is a critical need to investigate the associated ethics issues in detail to ensure that advances in the treatment of addiction are translated into clinical practice in ways that minimize harms and maximize benefits. If neuroscience research on addiction is to be translated into effective public health policies, it is critical to understand the ethical, philosophical and social contexts within which neuroscience research is conducted, understood and applied.

Alongside the pressing need to reduce drug-related harm are the salient social factors that make addiction a particularly poignant case study for neuroethical analysis. Neuroscience is believed by some scholars to challenge assumptions about autonomy and willful control over behavior. The impact that addiction has on an individual’s autonomous decision making is a central question in debates about addiction, and is therefore a perfect test bed for examining the impact of neuroscience findings on understandings of agency. It also has important consequences for attribution of responsibility, another area that is often discussed in relation to addiction.

For much of the previous two centuries, addiction has been seen as an excuse for using drugs. This skeptical view is also expressed by some social scientists who argue that addiction is an attribution that enables drug users to avoid responsibility for the social consequences of their drug use (Dalrymple, 2006; Heyman, 2009; Satel & Lilenfeld, 2007). Some scholars, in fact, argue that addiction is not a disease and does not exist (Davies, 1997; Szasz, 1975). This view of addiction is often described as the *moral model* of addiction.
However, neuroscience research is providing growing evidence that the chronic use of addictive drugs produces enduring changes in key neural systems in ways that impair decision making (Goldstein et al., 2009). This research has led to advocacy of a brain disease model of addiction in which the chronic use of addictive drugs hijacks the brains of those who become addicted and drives them to continue to use drugs despite the harm that their use causes, and despite their wishing to stop (Dackis & O’Brien, 2005; Leshner, 1997; Volkow & Li, 2005).

How addiction is understood will have far-reaching social, clinical, philosophical and public policy implications. These two views of addiction, for example, suggest very different approaches for dealing with drug use and addiction: one is often seen to warrant criminal sanctions against those whose drug use harms others, while the other supports a more therapeutic agenda.

There is no doubt that, like many psychiatric disorders, the causes of addiction are multifactorial. These causes include social determinants as well as genetic and neurobiological antecedents. However, addiction is arguably a psychiatric condition where the impact of social factors is the most salient: individuals have to use a socially available drug before they can develop the condition. Drug availability and ease of use are the strongest predictors of drug addiction (Room, 2007). Addiction is also strongly associated with education, socio-economic status and proximity to areas of dense drug use. Policies to reduce drug-related harm need to consider population-level or environmental approaches as well as medical and psychotherapeutic treatments. While these are not mutually exclusive, they are often portrayed as such in policy debates.

Understanding and applying addiction neuroscience is further complicated by a number of competing interests. The punitive criminal justice approach often conflicts with clinical therapeutic approaches to addiction. Commercial interests, with the goal of protecting and increasing profit margins, compete with the public good that seeks to minimize social harm, often by regulating or reducing use of drugs, and therefore drug producers’ profits (see also Miller et al., Chapter 15 in this volume). Finally, psychiatric disorders, such as addiction, provoke strong moral responses that can influence how neuroscience is understood and applied (Pescosolido et al., 2010; Read & Law, 1999; Rose, 2003; Sartorius, 2010).

Nowhere else are these conflicting views and tensions more evident than in addiction. Moreso than many other psychiatric disorders, addiction occupies the complex intersection of medical, social and legal responses to abnormal and socially disapproved behavior. Addiction arguably represents a prototypical case for understanding many of the neuroethical challenges that neuroscience research presents. This volume seeks to understand how these various elements can influence the
response to addiction in light of significant developments in neuroscience research into addiction. *Addiction Neuroethics* is therefore relevant not only to those involved or interested in addiction treatment and policy, but also to those fascinated by the ethical, social and public policy issues raised by neuroscience research more generally.

**OVERVIEW OF THE BOOK**

Understanding the social, ethical and legal impact of neuroscience requires an integrative multidisciplinary approach. In this five-part volume of *Addiction Neuroethics*, we have brought together scholars from the full range of disciplines implicated by the challenges of addiction neuroscience to consider its neuroethical impacts.

The first two sections of the volume cover the technological promise of neuroscience for addiction. In *Section I: State of the Science*, contributors introduce readers to the molecular, genetic, cognitive and behavioral aspects of addiction. David Nutt and colleagues describe the gross neuroanatomical changes that are believed to be responsible for the behavioral and cognitive changes in addiction. Professor Nutt, a highly regarded addiction neuroscientists, critically reviews the latest brain imaging and neurocognitive studies of addiction in human addicted individuals. Jhodie Duncan and Andrew Lawrence follow with a critical review of the molecular and cellular effects of acute and chronic drug use, including the major neurochemicals involved in common forms of addiction, and the molecular processes that underpin drug-induced changes in the brain. Many of the current treatments for addiction interfere with these neurochemical changes. Duncan and Lawrence also review the genetic differences that can leave some individuals more likely to try drugs, or more vulnerable to developing an addiction should they do so.

In *Section II: Treatment*, authors examine the technological promise of addiction neuroscience, unraveling the many neuroethical issues raised in the treatment of addiction. James Bell and colleagues review the history of opioid substitution treatments, and discuss the ethical and social issues that this type of treatment raise. Coral Gartner and Brad Partridge review the neurobiological basis of tobacco addiction and discuss its possible implications for tobacco control policies. Co-editors Adrian Carter and Wayne Hall, together with Benjamin Capps, write about the potential use of the emerging neurotechnologies to treat addiction. These include new psychopharmacological approaches such as those designed to mitigate craving, long-acting drug implants, drug vaccines and deep brain stimulation. In this chapter they identify a number of ethical and
social imperatives that will need to be considered when using emerging neurotechnologies therapeutically, in addition to scientific questions of safety and efficacy. Hall and colleagues conclude this section with a review of research on the use of genetic screening and neuroimaging to predict addiction liability and to select addiction treatments for alcohol and nicotine dependence. They also discuss the ethical and public policy issues that may arise from the use of such technologies, including the potential use of genetic information by third parties to discriminate against individuals, medicalization of drug use, subversive use by producers of addictive commodities to undermine effective public health strategies to reduce population-level harms from alcohol and cigarette consumption, and premature commercialization of genetic tests marketed directly to consumers.

The remaining three sections in the volume consider the neuroethical implications of the epistemic promise of neuroscience. In Section III: Philosophical Reflections, authors examine philosophical questions raised by neuroscience research of addiction, such as agency, autonomy and responsibility. Central to debates about addiction is the question of its impact upon an individual’s ability to choose not to use drugs. To address this question, Neil Levy examines the effect of addiction on an individual’s autonomy. Cameron Wild and colleagues examine neuroscience research to determine whether coerced treatment of addiction is justified. They review neuroscience evidence regarding the ability of addicted individuals to make treatment decisions, and of the safety and effectiveness of coerced treatment of addiction. Craig Fry and Daniel Buchman review an array of addiction identities: organic, compulsive, constitutive and others. They show how lay descriptive accounts of identity shed light on public and private meanings and experiences of drug use and addiction.

In Section IV: Addiction History and the Media, authors look at how addiction has been understood historically and portrayed over time. Nancy Campbell traces the history of neuroscience pursuits of addiction that has been ongoing for far longer than many of us might imagine. She traces how the neuroscience of addiction is affected by technological change in neuroimaging technologies and in interaction with a succession of neuroscience disciplines, ranging from origins in neurophysiology and neuropsychiatry, through neurochemistry and neuropharmacology, and into today’s cross-disciplinary profession. Julie Robillard and co-Editor Judy Illes explore the media discourse of addiction in the context of reporting at the intersection of law and neuroscience. Joan Leach concludes this section with a chapter on social epistemology, and the various modes of communicating neuroscience research of addiction adopted by different stakeholders, including scientists, clinicians and addicted individuals. Leach discusses the consequence of the dominant modes of neuroscience
communication and suggests ways of communicating neuroscience that may lead to better health outcomes.

Finally, in Section V: Public Policy and Legal Issues, we turn our attention to the very important public health policy and legal implications of addiction neuroscience. Robin Room and Wayne Hall consider the possible impact that neuroscience perspectives on addiction may have on population approaches to reducing problems arising from the use of psychoactive substances such as alcohol, tobacco and drugs subject to the international prohibition regime. They provide a schematic history of ideas and policies on different types of drug use and addiction, discuss the key policy themes often extracted from addiction neuroscience research and consider how they may be used to inform the development of drug policies in the twenty-first century. Stephen Morse reviews the legal issues associated with addiction, such as drug regulation, criminal responsibility and liability, legal competence and treatment in the legal system. He critically examines the impact of current neuroscience research upon these issues; an area that has received significant attention of late. Peter Miller and colleagues describe the ways in which industries that profit from the sale of addictive commodities seek to influence public policy, most recently by funding neuroscience research on addiction. Given the lack of resources available for current treatments of addiction, they also ask whether this expense has been justified and consider some unintended consequences of investing in neuroscience addiction research.

In the final chapter of the volume, Michael Krausz and Edgar Kaiser look to the future of health care and policy for addiction. Challenges for the economy and a new face for a health-care system in one of the world’s superpowers will have a profound impact on prospects for predicting and diagnosing addiction, and providing sustainable medical, psychological, financially sound and likely politically charged interventions. At this intersection of public and private health care, the authors explore what lies ahead.

The issues covered in this volume represent significant ethical and social challenges that need to be considered and balanced in the application of neuroscience knowledge and technologies to addiction. Addiction Neuroethics can provide that guidance. We surely have not covered everything in this volume, but we have made a solid start. Further questions to the ones to which we provide some answers here must be raised and addressed. We fervently believe that the dynamic approach to integrating neuroscience with thoughtful and transparent analysis of ethical and public policy issues represented by this volume is a partnership that is modern, hopeful and a formula for success.
Acknowledgments

Dr. Carter is a National Health and Medical Research Council Postdoctoral Fellow at the University of Queensland Centre for Clinical Research. Dr. Hall is Professorial Fellow and Deputy Director (Policy) at the University of Queensland Centre for Clinical Research, as well as Honorary Fellow at the Queensland Brain Institute, The University of Queensland and the Institute of Psychiatry, King’s College London. His work is supported by a National Health and Medical Research Council Australia Fellowship. Dr. Illes is Canada Research Chair in Neuroethics and Professor of Neurology at the University of British Columbia. Her work is generously supported by the Canadian Institutes of Health Research, The Canada Foundation for Innovation, the British Columbia Knowledge Development Fund, GenomeBC, The National Institutes of Health, The Dana Foundation, The Foundation for Ethics and Technology, and The North Growth Foundation. The Editors also gratefully acknowledge their outstanding research teams and staff, and the International Neuroethics Society whose commitment to the burgeoning area of addiction neuroethics provided a critical foundation for this book.

References


Brain Imaging in Addiction

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Introduction
Neuroimaging Approaches
 Imaging Techniques
  Positron Emission Tomography and Single Photon Emission Computed Tomography
  Magnetic Resonance Imaging
  Structural Magnetic Resonance Imaging
  Functional Magnetic Resonance Imaging
  Arterial Spin Labeling, Diffusion Tensor Imaging and Pharmacomagnetic Resonance Imaging
Neuroimaging and Addiction Research
  The Chemistry of Addiction
  The Brain Circuitry of Addiction
Drug-Related Stimuli
Reward Processing
Cognitive Control
Conclusion
The aim of this chapter is to give the reader a practical understanding of neuroimaging techniques and explain their relevance to understanding addiction. From both psychological and pharmacological aspects, drug (including alcohol) addiction can be seen as a manifestation of pharmacological actions on the brain. However, non-drug or behavioral addictions, especially gambling, show similarities to drug addiction. Therefore, it is sensible to investigate what is happening in the brains of both drug and non-drug addicts to determine what effects substances of abuse have on the brain, as well as the common processes underpinning addiction as a whole.

The evolution of addiction is thought to involve a loss of self-control (Baler & Volkow, 2006). Despite their best efforts and expressed preferences, drug-dependent individuals often appear incapable of exerting sufficient control over their drug urges, their drug-seeking and drug-taking behavior. According to one model, the major neural substrates underlying addiction make up a network of four independent and overlapping circuits in the brain consisting of (1) reward, located within the nucleus accumbens (NAcc) or ventral striatum; (2) motivation and/or drive located in the orbitofrontal cortex; (3) memory and learning, located in the amygdala and hippocampus; and (4) cognitive control, located in the lateral prefrontal and anterior cingulate cortex (Volkow, Fowler, & Wang, 2003). According to this model, the degree of drug “wanting” increases as drug addiction develops and the strength of inhibitory control over reflexive drug-taking behavior is diminished.

An alternative model regarding addiction suggests an imbalance between two separate, but interacting, neural systems (Bechara, 2005). Bechara has postulated that an impulsive amygdala system that signals immediate pain or pleasure, together with a reflective prefrontal cortical system, which signals pain or pleasure further in the future, are the basis for both the development and maintenance of addiction. According to this model, the reflective prefrontal cortical system usually controls the impulsive amygdala system via top–down control. This control, however, is not absolute. Hyperactivity within the impulsive amygdala system may override these reflective top–down executive processes. Drugs of abuse are believed to trigger bottom–up, involuntary signals from the amygdala, which are thought to hijack the goal-driven cognitive control that is required for the normal operations of the reflective prefrontal system. Importantly, Bechara suggests that anomalies within these two systems pre-date the addiction state, and facilitate the progress from drug experimentation to addiction; subsequent chronic use of drugs exacerbates these abnormalities.

These modes indicate that reward, motivation and/or drive, learning and memory and cognitive control are key processes to be understood if
we are to develop pharmacotherapeutic and psychological approaches to preventing and treating addiction. Neuroimaging methods allow us to address such questions as well as test hypotheses about addiction derived from animal experiments and other branches of neuroscience and psychiatry.

**NEUROIMAGING APPROACHES**

There are two main divisions in neuroimaging techniques: structural and functional. The former measures features of brain structure such as its size, shape and density. The latter explores brain function either in terms of blood flow or metabolic activity or in terms of neurochemical measures (e.g. of neurotransmitters and enzymes).

Although neuroimaging approaches are at the cutting edge of neuroscience, interpretation of findings is often difficult for many reasons. One important reason is the fact that many addicts use multiple drugs including legal ones such as alcohol and tobacco, which are likely to contaminate findings. Other medical problems and prior damage such as head trauma may also affect findings. Careful selection of individuals and a good study design can help to mitigate against these confounders, although at the risk of studying individuals who are less representative of general and clinical populations. In addition, although neuroimaging studies can give us much correlational information, they say much less about causality. Longitudinal studies are required to obtain important information regarding causality, although difficulties due to low compliance in the addiction population can lead to high dropout rates and high financial expenditure.

**IMAGING TECHNIQUES**

These fall into two main types: those that use a radioactive tracer or ligand such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), or those that rely on magnetic resonance imaging (MRI) techniques.

**Positron Emission Tomography and Single Photon Emission Computed Tomography**

The basis of these methods is that a radioisotope (usually $^{11}$C or $^{18}$F for PET and $^{125}$I or $^{99m}$Tc for SPECT) is attached to a compound with known pharmacological properties (the ligand) to create a tracer. The tracer is then injected into the bloodstream of an individual so that some
of it enters the brain. Here, the radioactive isotope decays to give off electromagnetic particles that escape from the brain to be detected by crystal detectors, usually arranged in a ring around the brain (the camera or scanner). The radioactive emissions are then sampled over an hour or so to allow calculations to be made regarding where in the brain the original tracer was located. For PET the resolution is about 1 mm$^3$ volume, whereas for SPECT it is about 3 mm$^3$. Although SPECT loses on resolution, it is more widely available and is much cheaper because its tracers are longer lasting and therefore easier to make and transport.

Originally, and before the advent of MRI, PET and SPECT imaging methods were used to measure brain activation and metabolic activity. With PET, radiolabeled water ($[^{15}\text{O}]$water) is used to measure regional cerebral blood flow (rCBF) and $^{18}\text{F}$fluoro)deoxyglucose is used to measure regional cell metabolism. With both of these tracers, an increase in their emission in a particular region reflects increased activity in that region.

Since the widespread availability of MRI, which does not involve the use of radioactivity, PET and SPECT are now predominantly used to measure the binding of tracers to receptor sites in the brain. These include receptors as well as enzymes and neurotransmitter transporters, such as the dopamine and serotonin [5-hydroxytryptamine (5-HT)] uptake sites. In some cases, notably with dopamine, they can also be used to measure changes in levels of the endogenous neurotransmitter. This has proved a very fruitful approach in addiction in showing that many drugs of abuse, particularly stimulants, release dopamine in the human brain in the same ways as in other animals (see below).

**Magnetic Resonance Imaging**

MRI works on the basis that the nuclei of hydrogen atoms (i.e. protons) have magnetic properties that align (i.e. flip) when placed into a magnetic field. A radio signal passed through the magnetic field causes the nuclei to flip back to their original state. When applying this to the brain, the amount of energy from the radio signal required to revert the spins is proportional to the density of the brain matter through which it is passing. This means that the different substrates of the brain [e.g. white matter, gray matter or cerebrospinal fluid (CSF)] can be clearly distinguished in a high definition image. This was a major advance since computed tomography (CT) was not good at distinguishing white from gray matter, thus limiting its use in research. The higher the magnetic field strength, the better the resolution of the image. Magnetic fields are measured in tesla (T), and 1.5T and 3T scanners are in common use for research and clinical purposes, with some facilities now using 5–7T machines. These machines are noisy and claustrophobic, however, which means that a significant proportion of people will not or cannot stay in them.
**Structural Magnetic Resonance Imaging**

This technique measures the volume and shape of the brain with reasonable precision. It can be used to investigate potential structural differences in the brains of certain populations. Such studies usually take a region of interest (ROI) approach (e.g. by examining the size of a predefined brain region such as the hippocampus). A recent popular semi-automated method of comparing groups using structural MRIs is voxel-based morphometry (VBM). This is a voxel-by-voxel method (see below), which can detect structural differences in brain regions in an a priori rather than a hypothesis-led way, each of which has its merits. Structural MRI images are also used for co-registration in PET and MRI studies to more accurately map activity and activation images onto the brain.

**Functional Magnetic Resonance Imaging**

Functional magnetic resonance imaging (fMRI) exploits the fact that the magnetic property of blood changes when oxygen is removed. This can be detected using an MRI paradigm known as the BOLD (blood oxygen level dependent) signal. The strength of this signal in a brain region indicates the relative level of oxygenated to deoxygenated blood at that location. As neuronal activity requires oxygen, changes in the BOLD signal reflect activation at that location. During the same session, a structural MRI is also obtained so that the activation generated during fMRI can be mapped onto a highly anatomically defined image of the brain. fMRI has reasonably good temporal (1–4 s) and spatial resolution (3–6 mm$^3$). Unlike PET or SPECT, fMRI does not involve radioactivity and so repeated scanning sessions are feasible (e.g. mapping changes during recovery). In addition, younger people can be imaged, whereas the use of PET and SPECT is limited or even prohibited because of radioactive exposure.

fMRI has revolutionized studies of brain activation while performing a cognitive task, because it allows those brain regions and circuits that underpin that cognition to be identified. These include motor functioning and speech, memory, planning and impulse control, as well more subjective experiences such as empathy.

**Arterial Spin Labeling, Diffusion Tensor Imaging and Pharmacomagnetic Resonance Imaging**

These recently developed neuroimaging techniques are all based on MRI. Arterial spin labeling (ASL) studies polarize arterial blood in the neck and measure its distribution in the brain. This gives a good absolute measure of blood flow and blood volume in regions of interest, for example, before and after drug administration.

Diffusion tensor imaging (DTI) relies on differences in the properties of water molecules in brain white matter tracts to give high-resolution images of these tracts in vivo. It can demonstrate alterations
in the integrity of the nerve tracts connecting different brain regions and appears to be a very sensitive index of damage to white matter tracts in the brain before atrophy is structurally detectable.

Pharmacomagnetic resonance imaging (phMRI) is essentially the use of pharmacological agents to modulate brain activation and/or cognitive performance in an fMRI study. Drugs are usually given in the form of a challenge test (i.e. as a single dose before the scanning session), although more recently, chronic drug treatment regimens are being used to mimic more closely the clinical outcome of drug administration.

**NEUROIMAGING AND ADDICTION RESEARCH**

PET and SPECT imaging can allow us to ask questions about the chemistry of the brain, how this may predispose some individuals to addiction, and the effects that drugs of addiction have on it. MRI imaging is particularly useful for exploring the circuitry that is activated in addiction-related states, such as craving, reward and attention.

**The Chemistry of Addiction**

As the pharmacology of most drugs of misuse is now understood (Table 1.1) (see Chapter 2 in this volume) it is theoretically possible to explore whether the brain targets for these chemicals are involved in human addiction. PET and SPECT tracers allow the investigation of many of these systems in the human brain, of which the best studied is the dopamine system (Table 1.2). The availability of an appropriate tracer is often the critical limitation in terms of what hypotheses can be tested in humans. For instance, we lack validated PET or SPECT tracers for many glutamate receptors [e.g. N-methyl-D-aspartate (NMDA), metabotropic glutamate 5 (mGLu5)] and tracers with the sensitivity needed to measure changes in endogenous neurotransmitter levels (e.g. 5-HT). Fortunately for studies in addiction, there are a number of well-characterized tracers for the dopamine system, measuring the dopamine transporter (DAT), dopamine D1 and D2 receptors (DRD1/2), as well as one of its metabolizing enzymes, monoamine oxidase (MAO).

Stimulants such as cocaine and methamphetamine (crystal meth) increase dopamine levels. This change can now be measured, as the increase in dopamine displaces some PET tracers that bind to DRD2 receptors (e.g. [11C]raclopride). This method provided the first measurements of neurotransmitter release in humans (Laruelle, 2000). The increase in dopamine produced by stimulants is dose related and correlated with the “high” that people experience (Volkow et al., 1999). These findings, supported by earlier animal studies, show that drugs of addiction increase
dopamine in the nucleus accumbens (ventral striatum). This has led to the view that dopamine release was a necessary, perhaps even sufficient feature, of the addictive potential of drugs. However, recent research has cast doubt on this: heroin and other opioids do not appear to release dopamine (Daglish et al., 2008), and yet are highly rewarding and addictive in humans. In addition, although some of the earlier studies found a large effect of nicotine or cannabis on dopamine release, this has not been replicated in larger studies (Bossong et al., 2009; Brody et al., 2004, 2009; Montgomery, Lingford-Hughes, Egerton, Nutt, & Grasby, 2007; Stokes, Mehta, Curran, Breen, & Grasby, 2009).

### TABLE 1.1 Pharmacology of Drugs of Misuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary target</th>
<th>Main effects/transmitters</th>
<th>Other actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>μ-opiate receptors</td>
<td>Mimic endorphins</td>
<td>κ- and δ-opiate receptors</td>
</tr>
<tr>
<td>Stimulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>DAT</td>
<td>↑ Dopamine and noradrenaline</td>
<td>Local anesthetic</td>
</tr>
<tr>
<td>Amphetamine</td>
<td></td>
<td></td>
<td>↑ Glutamate</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td></td>
<td></td>
<td>↑ Glutamate</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Nicotinic ACh receptor</td>
<td>↑ Dopamine</td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>GABA/glutamate</td>
<td>↑ GABA</td>
<td>Many other systems</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>GABA</td>
<td>↑ GABA</td>
<td></td>
</tr>
<tr>
<td>GHB</td>
<td>GABA</td>
<td>↑ GABA</td>
<td>↑ Dopamine</td>
</tr>
<tr>
<td>Cannabis</td>
<td>CB1 receptors</td>
<td>↑ Dopamine</td>
<td>? Endorphins</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>5-HT transporter</td>
<td>↑ 5-HT; probably ↑ noradrenaline</td>
<td>Some dopamine release</td>
</tr>
<tr>
<td>Ketamine/PCP</td>
<td>NMDA</td>
<td>↑ Glutamate</td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>5-HT₂ receptors</td>
<td></td>
<td>5-HT agonist</td>
</tr>
</tbody>
</table>

GHB: γ-hydroxybutyric acid; PCP: phencyclidine; LSD: lysergic acid diethylamide; DAT: dopamine transporter; ACh: acetylcholine; GABA: γ-aminobutyric acid; CB: cannabinoid; 5-HT: 5-hydroxytryptamine; NMDA: N-methyl-d-aspartate; ↑: increase; ↓: decrease.
The DRD2 may nonetheless play a role in addiction propensity because low levels of receptors are associated with greater reward from stimulants (Volkow et al., 1999) and high levels are possibly protective in alcoholism (Volkow et al., 2006). Since the use of stimulants (cocaine and methamphetamine) lowers dopamine receptor numbers (Dagher et al., 2001; Heinz et al., 2004; Volkow et al., 1996), a vicious cycle of dependence may ensue in those who are most vulnerable (Fig. 1.1).

One of the limitations of PET and SPECT imaging studies is that typically 20 people per group are studied. This may prove too small a number to investigate the impact of clinical variables on tracer binding (e.g. amount of drug use, craving). In addition, it is not possible to use PET or SPECT to image prospectively a large number of young people before drug use and then follow them up to look explicitly at receptors levels and vulnerability. Fortunately, PET can be undertaken in non-human primates and rats, and this translational approach has helped to characterize the contribution of DRD2 levels to drug addiction.

In a landmark study, non-human primates were raised individually and then in groups of four where a dominant–subordinate hierarchy was established (Morgan et al., 2002). Here, an increase in DRD2 levels...
was seen in the striatum of the dominant primate, while lower levels persisted in subordinates. In keeping with the findings in humans, the subordinate primates appeared to find cocaine more rewarding and consumed more than their dominant peers. A later study also reported that cocaine reduced the DRD₂ levels, and the longer it was consumed, the less likely a full recovery in receptor levels was, following abstinence (Nader et al., 2006). It was not clear, however, why full recovery to pre-drug DRD₂ levels occurred in some and not in other animals. In abstinence, prior experience of social dominance was associated with longer latencies to respond to a novel stimulus, a trait that is associated with lower vulnerability to drug misuse in humans (Czoty, Gage, & Nader, 2010). These studies are important, in that they allow us to explore the impact of environmental changes and drug use in ways that are not possible in humans.

A more recent series of studies in rats has similarly established that low levels of DRD₂ in the ventral striatum are associated with the more rewarding effects of cocaine in rats that are highly impulsive (Dalley et al., 2007). However, heroin was not found to be more rewarding, emphasizing that although dopamine is key for the effects of stimulants, it may not be for all substances of abuse.

The endorphin system is the major target for the opioid drugs such as morphine and heroin. It has long been implicated in processes such as interpersonal bonding (e.g. mother–child), love and, when in deficit, pain. Emerging evidence suggests that the craving distress and dysphoria found in early drug abstinence may be associated with alterations in endogenous opioid functioning detected by PET. For instance, there are more opioid receptors available in the brains of individuals in the first few days to weeks of abstinence from opioids (Williams et al., 2007), cocaine (Ghitza et al., 2010) and alcohol (Williams et al., 2009). In some
cases, the increase in their number predicts craving and relapse (Ghitza et al., 2010; Heinz et al., 2005).

A number of abused drugs also boost the functioning of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. These are typically the sedative or “downer” drugs such as alcohol, benzodiazepines, γ-hydroxybutyric acid (GHB) and barbiturates, all of which enhance the actions of the natural neurotransmitter to sedate the brain. Although there are many subtypes of GABA_A or GABA–benzodiazepine receptors, it is now possible to image some of them using PET. For example, flumazenil binds to the majority of subtypes of the receptor and several studies have shown that its binding is lower in abstinent, alcohol-dependent patients (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998, 2010), which is likely to underlie blunted sleep inducing effects of benzodiazepines in alcohol dependence (Lingford-Hughes et al., 2005). This would be consistent with the brain downregulating the receptor to reduce the impact of exogenous sedative drugs on the GABA system. Individuals at risk of alcoholism may also have a pre-existing reduction in GABA activity. Whatever its cause, this decrease would contribute to the hyperexcitable state seen in alcohol withdrawal where anxiety and seizures are very common. Recent work from this group has found that a subtype of the GABA_A receptor (α5) is highly expressed in brain regions that regulate emotion and reward, such as the nucleus accumbens. A reduction in these receptors is also found in alcohol addiction, which may explain why these patients have difficulty in regulating their drug-seeking behavior (Lingford-Hughes et al., 2010).

Many other receptors and neurotransmitters related to brain processes likely to be involved in addiction have yet to be studied using this approach. The limiting factor in this research is the great cost of PET methodology and the lack of suitable radiotracers. In future, we can hope to see tracers that will allow us to image the glutamate and cannabinoid systems in the brain, as both of these systems are almost certainly involved in addiction.

The Brain Circuitry of Addiction

To understand and map the brain circuits in addiction, behavioral tests that examine these domains and which are compatible with neuro-imaging techniques, particularly fMRI, have enabled cognitive neuroscience to examine the role of these processes in addiction in more depth.

One seminal study was that of Breiter et al. (1997), which was probably the first pharmaco-fMRI study in addiction. They gave cocaine to cocaine users and revealed that limbic, orbitofrontal and striatal regions were involved in the neural response to cocaine. These regions are major components of the reward circuitry of the brain. This study also identified
different subregions of this circuitry in which activity was correlated with drug-induced highs and craving. A more recent study used the same approach and identified similar regions that were activated during cocaine craving, including the NAcc, orbitofrontal and anterior cingulate cortex (Risinger et al., 2005).

**DRUG-RELATED STIMULI**

Drug dependence is commonly associated with emotional, cognitive and behavioral reactivity to drug-related stimuli, or to images or events associated with drug use (e.g. needles, settings in which drugs are typically used). Other studies have investigated the neural correlates of cue reactivity and craving using cue-exposure techniques. These studies are ethically less challenging than research that involves giving drugs of abuse (Walker, 2008). Research that examines how drug users react to drug-related stimuli usually employs a simple visual task, whereby people view alternately presented drug-related or neutral (non-drug-related) pictures or videos during fMRI or PET scanning. Examining neural responses in the brain to drug-related stimuli in addiction has particular value. First, according to theories of the underlying neurobiology of drug addiction, the reactivity of neural reward circuits to drug-related cues represents an overvaluation of drug reinforcers (Goldstein & Volkow, 2002). Here, it has been proposed that an attention to drug cues results from, and further reinforces, their significance as a result of dopamine activation within the reward circuitry. It has been suggested, for example, that dopamine systems mediate the significance of rewards, such as drugs, by modulating their motivational value in a manner separable from their hedonic or reward value (Robinson & Berridge, 1993). Importantly, understanding how this system operates is of particular interest, as drug-related cues may increase attentional bias and expectancy of drug delivery in abstinent drug users, potentially providing mechanisms for drug relapse.

Second, understanding the mechanism by which attention is captured by drug-related cues is critical to understanding addiction treatment. The neural mechanisms underlying a drug-related attentional bias may reveal potential targets for therapies in the addictions, whether cognitive (Muraven, 2010; Schoenmakers et al., 2010; Shoptaw et al., 2008) or pharmacological (Anton et al., 2011; Franklin et al., 2011; Goldstein et al., 2010; Longo et al., 2010; Shoptaw et al., 2008), or both. This might be especially important if one could elucidate a distinct neural pattern that reflects successful abstinence in former drug/alcohol abusers, or alternatively predicts prognosis and helps to tailor treatment accordingly.

Brain imaging studies have demonstrated common brain regions [e.g. amygdala, orbitofrontal cortex (OFC) and NAcc/ventral striatum (VS)]
for reactivity and craving in response to drug-related cues in various drug-using populations. For instance, in a study by Franklin et al. (2011), cigarette smokers were imaged during rest and while viewing smoking-related cues before and after either 3 weeks of placebo or varenicline, a prescription medication used to treat nicotine addiction. Smoking cues were initially shown to activate the VS and medial OFC and to elicit subjective craving in all smokers. In those smokers randomized to varenicline treatment for 3 weeks, the VS and medial OFC responses to smoking-related cues were reduced, together with subjective craving (Franklin et al., 2011).

Similar studies have looked at heroin addiction. For instance, exposing heroin addicts to personalized heroin-related auditory memories of craving (cues) increased regional cerebral blood flow in the OFC in proportion to the extent of craving (Daglish et al., 2001). In the anterior cingulate cortex (ACC), by contrast, increases were independent of craving. This suggests that the ACC may be responding more specifically to the cue, while the OFC is more involved in the experience of craving, as has been reported with cocaine cue reactivity and craving (Wexler et al., 2001). Of great interest in the Daglish et al. study was the ancillary finding that the extent of ACC activation increased, rather than decreased, with duration of abstinence. This finding supports the long-held belief that addiction produces enduring, even life-long processes in the brain. It has, therefore, been suggested that increased activity in OFC may reflect hypersensitivity to reward (Bolla et al., 2003), whereas reduced activity in ACC may reflect hyposensitivity to punishment (Garavan & Stout, 2005).

Alcohol-related cues have also been implicated in the maintenance of alcohol addiction. They have been shown in some studies to activate the VS, which is a key part of the dopamine mesolimbic system. Studies have examined the effects of medications, either used in the clinic, or being investigated for their potential to reduce alcohol intake and promote abstinence, in this brain region. Myrick and colleagues have shown that naltrexone (opiate antagonist), ondansetron (5-HT3 antagonist) and aripiprazole (DRD2 partial agonist) all reduced VS activation in response to alcohol-related cues in non-treatment-seeking alcoholics (Myrick, Anton, Henderson, Randall, & Voronin, 2008; Myrick, Randall, Henderson, Voronin, & Anton, 2010).

As described below, PET studies in cocaine abusers have shown decreases in striatal DRD2 levels which, it has been hypothesized, enhance conditioned, phasic dopamine release in brain regions in response to cocaine-related cues that may provoke relapse. Volkow et al. (2010) studied cocaine addicts exposed to videos containing both cocaine-related and neutral cues. Before viewing the videos, subjects were randomly assigned to receive placebo on one occasion and methylphenidate on another. Methylphenidate is a psychostimulant currently used to treat
attention-deficit hyperactive disorder, but which may have some efficacy in the treatment of cocaine addiction. Compared with neutral cues, cocaine cues reduced metabolism in the VS and OFC when cocaine addicts were on placebo, whereas methylphenidate only reduced metabolism in auditory and visual regions of the brain. It appears that methylphenidate blunts cue-induced limbic inhibition over longer periods (Volkow et al., 2010), which means that it may be potentially efficacious in treating cocaine dependence.

There appears, therefore, to be evidence for the development of a conditioned cue-induced neural attentional bias in response to stimuli predictive of drug availability in different drug-using populations. This bias may provoke relapse and maintain addictive behaviors among users attempting to remain abstinent. Significantly, functional brain imaging procedures reliably measure neural responses to drug-related stimuli and, importantly, the effects of medications on these responses. These findings may have important clinical implications for addiction medicine.

REWARD PROCESSING

Motivational theories of drug use make contrasting predictions about how drug use may differentially recruit brain areas, such as the VS, in response to rewards (Bjork, Smith, & Hommer, 2008). The reward deficiency syndrome (RDS) model and the allostatic hypothesis (AH), for example, view addiction as a deficit in dopamine motivational circuitry for non-drug rewards, such that only drugs of abuse are able to normalize dopamine at the VS (Blum et al., 2000; Koob et al., 2004). Alternatively, the impulsivity hypothesis of addiction suggests that in persons vulnerable to, or suffering from addiction, there is excessive approach and reduced inhibitory control of behavior (Bechara, 2005; Bickel, Miller, Kowal, Lindquist, & Pitcock, 2007). This hypothesis is, to some degree, supported by longitudinal studies that have shown that both poor self-control and high novelty seeking in childhood are significant predictors of substance use in adolescence (Ding et al., 2004; Masse & Tremblay, 1997; Myers, Brown, & Mott, 1995) and addiction in later life (Fergusson, Horwood, & Ridder, 2007). Moreover, substance-dependent groups exhibit both impulsive and reward-centered choice behavior, with both cocaine and alcohol dependence associated with an increased preference for small and immediate over larger and delayed rewards (Bechara et al., 2001; Bickel & Marsch, 2001; Bjork, Hommer, Grant, & Danube, 2004; Heil, Johnson, Higgins, & Bickel, 2006). This suggests that in individuals who are both prone to and engage in chronic drug use, there exists a combination of both reward hypersensitivity and deficient inhibitory control (Bechara, 2005; Bickel et al., 2007; Solomon & Corbit, 1974).
The first brain imaging research examining reward neurocircuitry in addiction used PET to measure the DRD$_2$ in mesolimbic regions. This research demonstrated significantly lower numbers of DRD$_2$ in the striatum of people addicted to alcohol, cocaine, heroin and methamphetamine (Volkow, Fowler, Wang, & Swanson, 2004). Other research has revealed that the number of DRD$_2$ does not increase following prolonged abstinence in alcoholics or cocaine addicts (Volkow et al., 1993, 2002). Amphetamine administration in these populations also induces less dopamine release than in drug-naïve subjects (Volkow et al., 1997, 2007). Although this evidence appears to concur with the RDS and AH noted above (Blum et al., 2000; Koob et al., 2004), it does not distinguish between impairment that preceded and followed addiction.

While the evidence from PET research studies may go some way to corroborating a RDS/AH of reward processing in addiction, the results from fMRI studies are more mixed. Most fMRI studies in addiction have examined reward sensitivity using the monetary incentive delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001). This task allows researchers to measure brain activation while a person anticipates and receives a monetary reward or punishment (Fig. 1.2). The person first views a brief visual cue indicating the type of reward trial in which they will participate, followed by a short delay. Following the delay, the person will respond to a target stimulus, before receiving feedback on their response to the target.

**FIGURE 1.2** Task structure for a representative trial in the monetary incentive delay task. Cues used in the different trials indicate whether different amounts of money (number of horizontal lines) could be won or lost or whether there would be no consequences depending on reaction time to the target stimulus (circle, square, triangle). *(Adapted from Beck et al., 2009.)*
fMRI BOLD responses during the MID delay period have been found to correlate with dopamine release in the VS (Wittmann et al., 2005), appearing to substantiate its sensitivity to dopamine reward functioning.

Two research studies in alcoholics have demonstrated blunted VS responses during reward anticipation compared with non-alcoholics (Beck et al., 2009; Wrase et al., 2007), also appearing to support the RDS/AH. In a third study, however, alcoholics did not differ from non-alcoholics during reward anticipation, but did differ in response to reward outcomes (Bjork, Smith, & Hommer, 2008). This is more consistent with the impulsivity hypothesis of addiction. These same divergent results have also been observed in cannabis-using populations. The first of these studies found that cannabis users had a greater BOLD response in the VS compared to drug-naïve controls during reward anticipation (Nestor, Hester, & Garavan, 2010), supporting the impulsivity hypothesis. By contrast, van Hell and colleagues (2010) found that cannabis users had significantly less BOLD activation in the VS compared to non-cigarette smokers, but not cigarette smokers, thus concuring with the RDS/AH. There is only one published study focusing on reward sensitivity in cigarette smokers using a variant of the MID task. This study demonstrated that compared to occasional, non-dependent smokers, dependent smokers have reduced VS activation during cues that signal a chance to respond for monetary reward (Buhler et al., 2010). There has been no research using the MID in cocaine users, although Goldstein et al. (2007) found evidence of dysfunctional PFC activation during an instrumental task.

COGNITIVE CONTROL

Cognitive control can be viewed as flexible, goal-directed behavior, which requires an adaptive cognitive control system for organizing and optimizing processing pathways (Ridderinkhof et al., 2004). Emerging evidence from cognitive neuroscience is now converging on the different contributions of the prefrontal cortex (PFC) in cognitive control. Furthermore, this convergence of evidence is well placed to explain why certain processes may be compromised in addiction, where a loss of cognitive control may be a central component in both initial and continued drug abuse.

Drug addiction is characterized by continued drug use and recurrent drug relapse, despite serious negative consequences, so decrements in cognitive inhibitory control functioning seem likely. Laboratory tests of cognitive inhibitory control usually involve a person withholding a habitual motor response or ignoring the presentation of irrelevant stimuli, while continually updating information and monitoring their performance. These processes of cognitive inhibitory control and monitoring
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have consistently been shown to involve the PFC and ACC (Carter et al., 1998; Garavan, Ross, Murphy, Roche, & Stein, 2002; Garavan, Ross, & Stein, 1999; Ullsperger & von Cramon, 2001). As the ability to inhibit and monitor one’s behavior may be important in the development and maintenance of addiction (Garavan & Stout, 2005), laboratory assessments of cognitive inhibitory control may identify deficits that provide novel targets for treatment intervention.

Preliminary fMRI studies using tests of cognitive inhibitory control and monitoring have provided strong evidence for dysfunctional activity patterns in the prefrontal cortex of people who are dependent on alcohol, cannabis, cocaine, nicotine or opiates, compared with demographically matched drug-naïve subjects. Alterations in the PFC (Sullivan et al., 2003), OFC (Volkow et al., 2007) and ACC (Ridderinkhof et al., 2004) in alcoholism have been shown during inhibitory control. This may reflect neuroadaptations within frontal circuits in these regions. Chronic cocaine users also demonstrate inhibitory and monitoring functional deficits in the ACC and PFC (Garavan, Kaufman, & Hester, 2008; Goldstein et al., 2004, 2010; Hester & Garavan, 2004; Kaufman, Ross, Stein, & Garavan, 2003), which provides evidence for a dysregulation in frontal regions during cognitive control. Importantly, the severity of global cognitive impairment renders cocaine addicts less amenable to behavioral treatment (Aharonovich et al., 2006; Aharonovich, Nunes, & Hasin, 2003), underscoring the importance of cognitive control in addiction rehabilitation.

Cannabis use is also associated with a diminished capacity to monitor behavior, with reduced functioning in the ACC in tasks requiring people to indicate their error awareness (Hester, Nestor, & Garavan, 2009). Chronic opiate use is also associated with irregular neural functioning in the ACC during error monitoring tasks (Forman et al., 2004). Notably, previous research in early cocaine and methamphetamine abstinence has additionally shown cortical neural deficits during verbal and visuospatial memory (Kubler, Murphy, & Garavan, 2005), working memory (Moeller et al., 2010; Tomasi et al., 2007) and decision-making processes (Hoffman et al., 2008; Monterosso, Ainslie, Cordova, Domier, & London, 2007). These findings support the hypothesis that prefrontal circuits, which are important for flexible, goal-directed behavior, may be disrupted in addiction. In non-abstinent cigarette smokers, similar functional deficits have also been observed during inhibitory control, particularly in the lateral PFC and ACC (Nestor, McCabe, Jones, Clancy, & Garavan, 2011). This study also looked at ex-smokers who had been abstinent for more than 1 year. It found that they had increased lateral PFC activation compared with both smokers and nicotine-naïve participants, suggesting that this may be an important characteristic of successfully remaining abstinent. Even if these functional deficits pre-date and contribute
to the initiation of drug use, prefrontal differences during higher order cognitive functioning may have potential implications for the integrity of optimal cognitive control functioning and, consequently, for treatment outcome.

CONCLUSION

Neuroimaging has revolutionized our ability to probe the neurobiology of drug use and addiction in humans. We can now image and track, depending on the technique used, circuits and neurotransmitters associated with addiction vulnerability, drug consumption and abstinence, and processes such as reward and impulsivity. The use of animal imaging allows more hypotheses to be tested. Nevertheless, although different or deregulated brain circuits of chemicals have been identified, these are not currently so different that a brain scan could be used to diagnose addiction. The overlap between “drug” and “control” groups can be considerable. Currently, neuroimaging has been used as a research tool, although concerns have been raised about its future use in a clinical or legal forum (see Chapter 6). For instance, although current techniques would not be able to identify individuals—or children, from their parents—who are likely to develop drug misuse or addiction, how should neuroimaging be used, and by whom if it could? Similarly, while the majority of changes seen in the brain scan of an addict are unlikely to absolve them of responsibility for their actions, particularly the consumption of drugs, would this remain the case if more definitive circuits were identified? How would such findings alter the way that we treat and deal with addiction? See Chapters 7 and 14 in this volume for a deeper analysis of these important ethical issues. The major application and strength of neuroimaging will continue to be used as a powerful research tool to characterize the underlying neurobiology of addiction vulnerability, the impact of drug use, abstinence and treatment.

References


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I. BRAIN IMAGING IN ADDICTION


INTRODUCTION

Addiction has been defined as compulsive drug-seeking and taking that continues despite significant negative consequences (Hyman & Malenka, 2001). However, the development of an addicted state is complex and multifactorial, being influenced by (epi)genetic, biological...
and environmental factors that give rise to individual variability in the vulnerability to develop addiction following drug use (Belin, Berson, Balado, Piazza, & Deroche-Gamonet, 2011; Piazza, Deminiere, Le Moal, & Simon, 1989). Each of the common drugs of abuse (e.g. alcohol, amphetamines, cocaine, heroin, nicotine) has a differing pharmacological profile, can be administered via different routes and has different effects on the brain and resultant behavior after both acute and ongoing drug use. Drug use is normally initiated via experimentation. In a minority of users, this may escalate to continued use and the appearance of tolerance, whereby increasing amounts of the drug are needed to reach the “high” originally produced by lower doses (Bradberry, 2002). Over time this may lead to uncontrolled drug use resulting in changes in the brain, and consequently behavior, that extends beyond the initial neuropharmacological actions of the drug.

Addicted individuals typically display an increased motivation to obtain and continue using a drug. Their hedonic (pleasure) set-point increases, they become depressed, stressed and anxious upon withdrawal and display a high degree of resistance to ceasing drug seeking. There is also an awareness of the emotional consequences of engaging in drug use and a link to environments associated with accessing or using the drug. Although some addicts may try to abstain from further drug use, this is often followed by repeated bouts of relapse. The driving force to continue drug-seeking behaviors is, in part, believed to occur as a result of neuroadaptive changes in pathways in the brain (Feltenstein & See, 2008; Kalivas & Volkow, 2005). Consequently, the progression from casual drug use to an addicted state, through abstinence and relapse, often occurs in a cyclic manner, commonly referred to as the cycle of addiction.

The aim of this chapter is to provide an overview of the current knowledge base regarding the (epi)genetic, molecular and cellular mechanisms linked to substance abuse. The chapter highlights some of the initial responses in the brain following experimentation and the key processes that are believed to drive continued drug use. As in-depth exploration of the literature relating to these topics for all drugs of abuse is beyond the scope of a chapter, basic concepts will be introduced and then specific examples provided from animal data that model aspects of addiction. For the purpose of this review, the focus will be on the acute and chronic effects following exposure to cocaine, one of the most highly reinforcing and addictive drugs commonly used in developed societies.

ADDITION AND THE BRAIN: CIRCUITS AND TRANSMITTERS

Communication in the brain is facilitated by neurotransmitters, which are released primarily from neurons at synapses where they interact as
ligands with protein complexes called receptors on the surface of other cells, predominantly at the postsynaptic membrane. Binding of a neurotransmitter to a receptor transduces a chemical signal that transfers activity-dependent information. The neurotransmitter can then be either taken back up by the cell for future use by transporters or degraded and removed from the system. In the brain, pathways are typically complex integrative systems that contain numerous neurons/nuclei that relay information throughout a circuit and which can be acted on by other neurotransmitter systems that also integrate with that region.

Dopamine

While drugs of abuse have diverse pharmacological profiles, their acute actions converge primarily on the mesocorticolimbic dopaminergic system (Fig. 2.1). This pathway originates in the ventral tegmental area (VTA) located in the midbrain and projects to the nucleus accumbens (NAcc), striatum and forebrain, in particular the prefrontal cortex. Stimulation of the VTA activates dopaminergic neurons, the dominant neuron type in this region, which increases release of dopamine in these projection sites. The VTA receives excitatory glutamatergic inputs from the prefrontal cortex, and inhibitory γ-aminobutyric acid (GABA)ergic inputs from the NAcc, both of which can form feedback loops to regulate activity in the VTA. The VTA can also be influenced by other connections from regions such as the lateral dorsal tegmental nucleus, lateral hypothalamus and bed nucleus of the stria terminalis, to name just a few. The NAcc receives a large number of excitatory inputs, including those from the prefrontal cortex, amygdala, thalamus and hippocampus. It contains predominantly medium spiny GABAergic neurons (MSNs) that project not only to the VTA, but also to other nuclei associated with this pathway (Feltenstein & See, 2008; Kauer & Malenka, 2007).

The prefrontal cortex coordinates cognitive processes and actions aimed at an internal goal (so called goal-directed behavior), while the NAcc is believed to integrate information, synthesize the appropriate response, and control the motivational value of stimuli and reward reinforcement. The NAcc serves as an interface between the limbic (processing of new and learnt information) and motor (task performance) pathways. It is hypothesized that impaired neurotransmission reduces the ability of the limbic pathway to process the adverse consequences of drug taking, leading to the maintenance of drug-seeking behaviors (Kalivas, 2009). The MSNs integrate mesostriatal dopaminergic signals and glutamatergic inputs from cortical and limbic regions. There are two classes of MSN: dopamine D1 receptor-expressing MSNs form part of the direct pathway that results in neuronal excitation, while dopamine D2 receptor-expressing MSNs form part of the indirect pathway that results in neuronal inhibition.
Consequently, modulation of the direct and indirect pathways determines which signals are reinforced and which are suppressed, thereby differentially contributing to pathological behaviors (Bateup et al., 2010).

Immediately after initial exposure to a drug, extracellular levels of accumbal dopamine increase. This is facilitated in different ways by different drugs. Some enhance dopamine release from presynaptic terminals primarily as a consequence of increased neuronal activity in the VTA (e.g. alcohol, nicotine, opiates and cannabis) (Fig. 2.2) while others inhibit the presynaptic uptake by the dopamine transporter (DAT) primarily in the NAcc (e.g. cocaine and amphetamines) (Fig. 2.3). Over time, the extracellular levels of dopamine return to baseline to maintain homeostatic regulation. Significantly, addictive drugs, such as cocaine, produce a larger dopamine release that is maintained for longer than that of natural rewards (Willuhn, Wanat, Clark, & Phillips, 2010). If exposure to the drug continues, there may be a loss of homeostatic regulation: a progressive increase in basal levels of dopamine is accompanied by a reduction in the lesser response to the drug, resulting in the appearance of tolerance to
During acute withdrawal, the levels of dopamine rebound to below basal levels so re-exposure to the drug or a drug-related cue is often sufficient to increase dopamine levels again. This dopamine response has been hypothesized to contribute to relapse. While dopamine release may modulate the acute rewarding effects of drugs it does not solely mediate drug-seeking behaviors and persistent drug taking. Exposure to a drug can have either a direct or an indirect effect on numerous neurotransmitter systems, including the serotonergic (Filip, Alenina, Bader, & Przegalinski, 2010), noradrenergic (Sofuoglu & Sewell, 2009), glutamatergic (Duncan & Lawrence, 2011; Kalivas, 2009) and GABAergic (Filip & Frankowska, 2008) systems. Activation of these neurotransmitter systems can either excite (serotonin, glutamate and noradrenaline) or inhibit (GABA) their targets. These neurotransmitter systems are closely associated, facilitating each others’ release. Their responses are believed to fine-tune signal transmission, with the resultant behavior being driven by an integration of all incoming signals. Unlike dopamine, which facilitates the response to initial drug use, these additional neurotransmitter systems are hypothesized to play a greater role in mediating persistent drug taking, contributing to the inability to
Glutamate

Glutamatergic inputs from the prefrontal cortex, amygdala, hippocampus and other brain regions modulate activity in the NAcc either directly or by their influence on the VTA (Fig. 2.1). Like dopamine, initial exposure to a psychostimulant increases extracellular levels of glutamate in the NAcc (McFarland, Lapish, & Kalivas, 2003), prefrontal cortex (Reid, Hsu, & Berger, 1997) and to a lesser degree the VTA (Kalivas & Duffy, 1998). Unlike dopamine, however, this response increases the sensitivity of the receptors that bind glutamate to the effects of subsequent exposures to lower doses of the drug (Reid & Berger, 1996). This leads to reduced extracellular glutamate levels and decreased glutamate-driven activity over time. Upon re-exposure to the drug, or a drug-associated cue, there is enhanced synaptic glutamate release that possibly drives continued drug-seeking behavior (Kalivas, 2009).

Dysregulation of the glutamatergic system is sufficient to alter drug-induced behaviors even in the face of normal dopaminergic responses to stop drug use and relapse after a period of abstinence. The role that glutamate may play in addiction is highlighted below.
NEUROADAPTATIONS

In 2007, a study by Porrino and colleagues reported a change in the functional activity of the brain in rhesus monkeys that had been taught to self-administer cocaine. After five sessions the changes in function were restricted to regions mediating motivation and reward-related cocaine in the NAcc (Morishima et al., 2005). This imbalance in the glutamatergic regulation of corticostriatal transmission has been named the glutamate hypothesis of addiction, which has been suggested as playing a key role in mediating relapse (Kalivas, 2009). This hypothesis is supported by studies showing that reinstatement of cocaine-seeking can be prevented using the procysteine drug N-acetylcysteine (NAC) (Reichel, Moussawi, Do, Kalivas, & See, 2011). NAC increases glutathione synthesis, which restores glutamatergic signaling (Kalivas, 2009; Moran, McFarland, Melendez, Kalivas, & Seamans, 2005). Treatment with NAC is also able to restore prefrontal driven long-term potentiation (LTP) and long-term depression (LTD) (see below) in the NAcc, which are normally impaired during withdrawal (Moussawi et al., 2009). The therapeutic potential of NAC in cocaine addiction is currently being trialed in preclinical human studies, where it has been shown to reduce the desire to use cocaine (LaRowe et al., 2007) and marijuana (Gray, Watson, Carpenter, & Larowe, 2010).

Astrocytes express the sodium-dependent glutamate transporter, GLT1, which is responsible for removal of over 90% of glutamate from the extracellular space. Overexpression of GLT1 in the prefrontal cortex and the NAcc during extinction training is sufficient to inhibit cue-induced reinstatement to cocaine self-administration, most likely by inhibiting the excess extracellular glutamate that normally occurs upon re-exposure to a drug (Sari, Smith, Ali, & Rebec, 2009). Beyond relapse, imbalances in glutamatergic transmission have been hypothesized to mediate responses to cocaine including self-administration, reward learning (Novak et al., 2010), extinction (Gass & Olive, 2009; Knackstedt et al., 2010) and behavioral sensitization (increased sensitivity to a drug after repeated exposures), which in animal models is manifested by increased psychomotor activity. In the NAcc, the modulation of glutamatergic inputs onto MSNs expressing D1 dopamine receptors plays an integral role in the development of sensitization to cocaine (Heusner & Palmiter, 2005). Thus, an allostatic shift (an adaptive effort in a regulatory system in response to a chronic deviation from “normal” that establishes a new set-point) toward augmented glutamatergic function may contribute to the transition from controlled drug use to a compulsive and uncontrolled drug-dependent state and the high incidence of relapse.

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stimuli, such as the ventromedial prefrontal cortex and ventral striatum including the NAcc. The spatial extent and intensity of these changes expanded after 100 sessions to encompass not only the structures affected following acute exposure, but also areas involved in emotion and cognitive processing, thus intensifying the impact of cocaine on corticostriatal projections (Porrino, Smith, Nader, & Beveridge, 2007). The changes to functional activity in these same regions remained after 1 month of abstinence. Similarly, in rats the change in the resting activity of prefrontal cortical neurons persists during abstinence from cocaine (Trantham, Szumlinski, McFarland, Kalivas, & Lavin, 2002). These data have potentially important clinical implications because they suggest that drug-induced changes in the brain may not be reversed by abstinence alone (Fig. 2.4). This suggests the need for pharmacological interventions (e.g. substitution treatments) in addiction.

Not all individuals who experiment with psychostimulants become addicted. The transition from first drug use to an addicted state is believed to be due to neuroadaptations that occur in the brain. This term
refers to changes that occur in neural systems, at the cellular, molecular and/or (epi)genetic level, in response to a drug that changes the ability of the system to function normally. These changes are thought to become resistant to alteration and have been suggested as providing the biological basis of the transition to, and enduring nature of, an addicted state. They are also believed to contribute to other issues associated with drug taking such as anxiety, impulsivity, psychosis and paranoia. While the concept of neuroadaptations contributing to addiction is not new, our understanding of mechanisms mediating these adaptations, and the need for clinical treatments to address them, is growing rapidly.

Synaptic Plasticity

To date, one of the best understood neuroadaptations to take place after exposure to psychostimulants occurs at the synapse between two neurons. Synaptic plasticity includes changes to receptor expression, signal transduction or the structure of synapses. The density and morphology of dendritic spines, the point at where presynaptic neurons connect to their target, greatly influence this plasticity and are responsive to change in an activity-dependent manner. After 1 month of abstinence from repeated cocaine exposure there is an increase in the number of dendritic branches and spines of MSNs (Robinson, Gorny, Mitton, & Kolb, 2001). A similar increase is also observed at layer V pyramidal neurons in the prefrontal cortex. Cocaine exposure is also sufficient to alter the expression of axon guidance molecules that regulate the formation of axon–target connections (Bahi & Dreyer, 2005). Alterations to dendritic morphology following cocaine leads to synaptic rearrangement and possibly altered excitation of these cells. Following repeated cocaine exposure, there is an increase in spine density in MSNs expressing D1 receptors, but not D2 receptors, that corresponds to changes in the membrane excitability in these neurons (Kim, Park, Lee, Park, & Kim, 2011). Furthermore, prior exposure to cocaine is sufficient to retard the ability of later stimuli, such as environmental enrichment, to induce this form of plasticity (Kolb, Gorny, Li, Samaha, & Robinson, 2003).

Stimulation of receptors located on the surface of dendritic spines, including glutamate (Verpelli et al., 2010) and dopamine (Smith, Starck, Roberts, & Schuman, 2005) receptors, leads to local protein synthesis within the spine itself, which ultimately regulates synaptic changes. One protein, brain-derived neurotrophic factor (BDNF), is believed to play a major role in mediating the activity-dependent structural changes to dendritic spines (Tanaka et al., 2008). Increased BDNF levels produce long-lasting molecular neuroadaptations (Lu, Grimm, Shaham, & Hope, 2003). During withdrawal an increase in response to drugs or drug-paired cues is correlated with a progressive increase in BDNF in reward-associated...
nuclei (Grimm et al., 2003). This finding implicates BDNF in persistent cocaine-seeking behaviors (Lu, Dempsey, Liu, Bossert, & Shaham, 2004). Indeed, drug-seeking often progressively increases over time, so-called “incubation of craving”, a complex phenomenon associated not only with exposure to the drug but also with drug-associated cues. This incubation is accompanied by long-term changes in gene and presumably protein expression (Freeman et al., 2008).

BDNF also plays a critical role in modulating activity-dependent signal transmission between neurons (Huang et al., 2011). Two markers of long-term activity-dependent signal transmission are LTP and LTD. LTP refers to a long-lasting enhancement of signals between neurons that is associated with a strengthening of synapses. LTD refers to suppressed signaling that is associated with the weakening and elimination of synapses. Following exposure to a drug of abuse, the combined actions of LTP and LTD refine and consolidate adaptive changes to neuronal circuits (Kauer & Malenka, 2007; Malenka & Bear, 2004). Within hours of a single exposure to cocaine there is an induction of LTP at excitatory inputs onto dopaminergic neurons in the VTA. While repeated exposure leads to reduced dopaminergic responses, there is a potentiation of LTP that can last for several days. Potentiation can still be detected months after withdrawal, possibly driving downstream adaptations in the NAcc and other projection sites. Mameli and colleagues (2011) have recently shown that exposure to cocaine inverts the processes that lead to the generation of LTP (synaptic adaptation) in dopaminergic neurons. Under normal circumstances LTP is associated with depolarization; however, after exposure to cocaine it was found that LTP is associated with hyperpolarization (Mameli, Bellone, Brown, & Luscher, 2011).

Self-administration experimental paradigms permit animals access to a drug that they can voluntarily consume, if they perform a task such as pressing a lever. Access to the drug is normally associated with a conditioned stimulus, such as a light cue, that becomes associated with the drug reward. The conditioned stimulus is used to mimic the effect of environmental associations with drug use that exist in drug-addicted humans. Self-administration of cocaine results in the persistent potentiation (LTP) of excitatory synapses in the VTA above that of natural rewards such as food, the effects of which persist into abstinence (Chen et al., 2008). The same effect is not observed if cocaine is simply given to the animal or if it is not paired with a conditioned stimulus. This indicates that the pharmacological properties of the drug alone are not sufficient to drive continued drug-seeking behaviors. Rather, this is an associative process in which an environmental stimulus that is paired with a reward acquires both predictive (availability/location) and incentive (acquisition and conditioned reinforcement) properties. This incentive learning process appears to involve MSNs expressing D1 receptors, at least for cue-induced reinstatement of cocaine-seeking (Novak et al., 2010).
Recently, research has focused on the role of corticostriatal LTD in maintaining drug-seeking behaviors. A single presentation of the pharmacological compounds 1-aminocyclopentane-1,3-dicarboxylic acid [a metabotropic glutamate receptor (mGluR) agonist] and 2-amino-5-phosphonovalerate [an N-methyl-D-aspartate (NMDA) receptor antagonist] is sufficient to stimulate LTD, which normally dissipates within 24 hours. (An agonist binds to a receptor, initiating a response, whereas an antagonist binds to a receptor but does not initiate a response.) However, repeated stimulations lead to persistent LTD (Shinoda, Kamikubo, Egashira, Tominaga-Yoshino, & Ogura, 2005). Evidence now suggests that an enduring impairment in LTD may maintain an addicted state. In a study by Kasanetz et al. (2010), corticostriatal LTD was not impaired during the initial phase of learning in a cocaine self-administration paradigm. However, after medium-term cocaine use, LTD was suppressed at corticostriatal synapses in the NAcc. In some animals the LTD deficit progressively recovered despite continued drug use, whereas LTD was persistently suppressed in animals that developed characteristic addictive behaviors (Kasanetz et al., 2010). These findings suggest that the transition to addiction may, at least in part, reflect a state of anaplasticity, or the persistent loss of neuronal plasticity, within the corticostriatal synapse, thus impairing processes that actively control drug intake. In this regard, there is growing animal evidence of the effectiveness of extinction training in maintaining abstinence; that is, when drug-seeking actions do not yield a drug, removing the adaptive value of drug-seeking (comparable to cue-exposure therapy during rehabilitation in humans). After abstinence from cocaine (either passive withdrawal or extinction training), there was reduced LTP in the NAcc core, although LTD was only blunted in animals that had undergone extinction training. In these rats there was an increase in the expression of postsynaptic proteins and a reduction in the expression of mGlu5 receptors (Knackstedt et al., 2010). This suggests that extinction-induced neuroadaptations may be required to recruit new pathways that consolidate the experience of “no drug”, thereby contributing to the suppression of drug-seeking and maintaining abstinence.

**ADDICTION AND THE BRAIN: NEUROPEPTIDES**

There are vast numbers of neuropeptides and their receptors present in pathways that mediate addiction. Most neurons typically express both neuropeptides and primary neurotransmitters. Our understanding of the role of neuropeptides in addictive processes is rapidly advancing, although their full explanation is beyond the scope of this section (selected examples and references are given in Table 2.1). The role
<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>Receptor</th>
<th>Highest expression in the CNS (peptide or receptor)</th>
<th>Primary function</th>
<th>Role in addiction</th>
<th>Suggested site of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>CCK-A and CCK-B</td>
<td>Cortex, NAcc, VTA, amygdala, hypothalamus, septum, limbic regions and spinal cord</td>
<td>Modulation of appetite, memory, anxiety, thermoregulation and sexual behavior</td>
<td>Role in reward, motivation, self-administration and behavioral sensitization. Also modulation of stress responses</td>
<td>Acute effects via CCK-B, while chronic effects via activation of CCK-A receptors in the NAcc which facilitates the effects of dopamine</td>
<td>Rotzinger &amp; Vaccarino (2003)</td>
</tr>
<tr>
<td>Neurotensin (NT)</td>
<td>NT-1 (low affinity), NT-2 and NT-3 (both high affinity)</td>
<td>Hypothalamus and basal forebrain</td>
<td>Modulation of locomotion, stress and pain</td>
<td>Role in locomotor activity and behavioral sensitization</td>
<td>Enhances extracellular dopamine levels in the NAcc and medial prefrontal cortex</td>
<td>Geisler, Berod, Zahm, &amp; Rostene (2006)</td>
</tr>
<tr>
<td>Substance P</td>
<td>Neurokinin 1 (NK1) preferentially; possible cross-talk with NK2 and NK3</td>
<td>Hypothalamus, amygdala, and periaqueductal gray. Coexists with glutamatergic, GABAergic, serotoninergic and cholinergic axons</td>
<td>Member of the tachykinin family involved in the modulation of pain, inflammatory processes, anxiety and stress</td>
<td>Role in reward, motivation and behavioral sensitization, especially of opiates</td>
<td>Activation of MSNs via cholinergic neurons and modulation of serotonergic and noradrenergic nuclei in the brainstem</td>
<td>Commons (2010)</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Y1 and Y2 (CNS), and Y4 and Y5</td>
<td>Cortical, limbic and hypothalamic regions</td>
<td>Regulates food intake and energy balance, memory and learning, emotion regulation, anxiety and stress</td>
<td>Regulation of alcohol intake</td>
<td>Stimulation of Y2 receptors</td>
<td>Ciccolioppo et al. (2009)</td>
</tr>
<tr>
<td>Galanin (Gal)</td>
<td>GalR1, GalR2 and GalR3</td>
<td>Hippocampus, amygdala, thalamus and VTA</td>
<td>Promotes appetite and the analgesic properties of opiates</td>
<td>Role in opiate reward, withdrawal and locomotor activity</td>
<td>Decreases dopamine release and the firing rate of noradrenergic neurons</td>
<td>Picciotto (2010)</td>
</tr>
</tbody>
</table>
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### ADDICTION AND THE BRAIN: NEUROPEPTIDES

<table>
<thead>
<tr>
<th>Neuropeptide</th>
<th>Receptor</th>
<th>Localization</th>
<th>Functions</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynorphin</td>
<td>κ-Opioid receptor (primarily), μ-opioid receptor and δ-opioid receptor</td>
<td>Hypothalamus, amygdala, hippocampus and spinal cord</td>
<td>Opioid peptide involved in the modulation of pain, neuroendocrine regulation, motor activity, respiration, appetite and stress</td>
<td>Inhibitory effects on reward and reinforcement and mediates reinstatement through stress-like effects</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Interacts with the dopaminergic–CREB system and via the stress system</td>
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<td>Wee &amp; Koob (2010)</td>
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<td></td>
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<tr>
<td>Endorphin</td>
<td>μ-Opioid receptor (primarily), κ-opioid receptor and δ-opioid receptor</td>
<td>Pituitary gland, hypothalamus, NAcc, VTA, amygdala, cortex and brainstem</td>
<td>Opioid peptide involved in the regulation of feelings of pleasure and excitement, pain, stress, feeding and immune responses</td>
<td>Role in the feelings of euphoria, reward and reinforcement and regulation of stress during maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increases dopamine release via inhibiting GABA release, which disinhibits the dopaminergic system</td>
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<tr>
<td>Roth-Deri, Green-Sadan, &amp; Yadid (2008)</td>
<td></td>
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<tr>
<td>Neuropeptide S</td>
<td>Neuropeptide S receptor</td>
<td>Amygdala, Barrington nucleus, parabrachial nuclei, and hypothalamus</td>
<td>Suppresses anxiety and appetite, induces alertness and hyperactivity</td>
<td>Mediates conditioned reinstatement of cocaine</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Activation of orexin/hypocretin neurons in the lateral hypothalamus</td>
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<tr>
<td>Kallupi et al. (2010)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cocaine- and amphetamine-regulated transcript (CART) peptides</td>
<td>No specific receptor currently identified. Hypothesized to bind to a G protein-coupled receptor coupled to Gi/Go which results in increased intracellular ERK release</td>
<td>VTA, NAcc, hypothalamus and ventral pallidum</td>
<td>Role in feeding, reward and stress</td>
<td>Role in mediating locomotor activity and sensitization, especially for cocaine and amphetamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Upregulated by CREB and released upon repeated exposures to act locally in the NAcc to oppose increased dopamine signaling</td>
</tr>
<tr>
<td>Hubert, Jones, Moffett, Rogge, &amp; Kuhar (2008)</td>
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<tr>
<td>Oxytocin</td>
<td>Oxytocin receptor (OXTR)</td>
<td>NAcc, amygdala and hippocampus</td>
<td>Modulation of female reproduction, stress, anxiety, social recognition and sexual behaviors</td>
<td>Role in tolerance, dependence, self-administration and withdrawal syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreases dopamine utilization in the NAcc and mesencephalon. Chronically decreases dopamine binding sites in the forebrain</td>
</tr>
<tr>
<td>Sarnyai &amp; Kovacs (1994)</td>
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<table>
<thead>
<tr>
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<th>Suggested site of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotrophin-releasing factor (CRF)</td>
<td>CRF1 (highest affinity) and CRF2 receptors, and/or the CRF-binding protein</td>
<td>Hypothalamus, paraventricular nucleus, amygdala, VTA, septum and bed nucleus of the stria terminalis</td>
<td>Activates the HPA and mediates stress responses</td>
<td>Perpetuates stress-induced relapse and mediates drug-induced synaptic plasticity</td>
<td>Modulation of the glutamatergic and subsequently the dopaminergic systems</td>
<td>Wang, Shaham, Zitzman, Azari, Wise, &amp; You (2005)</td>
</tr>
<tr>
<td>Urocortin (U1, U2 or U3)</td>
<td>CRF1 (U1) and CRF2 (U1, U2, U3) receptors, and/or the CRF-binding protein</td>
<td>Edinger–Westphal nucleus, lateral superior olive, lateral septum, dorsal raphé and spinal cord</td>
<td>Member of the CRF family. Regulates stress-related feeding activity, feeding-related motor activity and blood pressure</td>
<td>Mediates alcohol preference and self-administration during acquisition</td>
<td>Stimulation of CRF2 receptors in the lateral septum</td>
<td>Ciccolioppo et al. (2009)</td>
</tr>
<tr>
<td>Orexin (hypocretin: Hcrt)</td>
<td>Hcrt-1 and Hcrt-2</td>
<td>Hypothalamus, VTA, NAcc, central amygdala and brainstem</td>
<td>Regulates feeding, metabolism, arousal and stress responses</td>
<td>Role in reward function (including motivation) and drug-seeking behaviors</td>
<td>Acquired preferential role in mediating reward stimuli over repeated exposures</td>
<td>Ciccolioppo et al. (2009), Martin-Fardon, Zorrilla, Ciccolioppo, &amp; Weiss (2010)</td>
</tr>
<tr>
<td>Nociceptin/orphanin FQ</td>
<td>Nociceptin receptor (NOP), also known as the orphanin FQ or κ-type 3 opioid receptor</td>
<td>Amygdala, prefrontal cortex, VTA, NAcc, lateral hypothalamus and brainstem</td>
<td>Mediates algesia and stress responses</td>
<td>Modifies drug reinforcement, preference and behavioral sensitization</td>
<td>Modulates dopamine releases in the NAcc</td>
<td>Ciccolioppo et al. (2009), Martin-Fardon et al. (2010)</td>
</tr>
</tbody>
</table>

*Note: NMDA: N-methyl-D-aspartate; VTA: ventral tegmental area; NAcc: nucleus accumbens; GABA: γ-aminobutyric acid; HPA: hypothalamic–pituitary axis; MSN: medium spiny neurons; CREB: cyclic adenosine monophosphate (cAMP) response element binding protein.*
of corticotropin-releasing factor (CRF) is highlighted as an example of the intricate role that neuropeptides may play in mediating addictive behaviors.

Stress, either in the environment or due to drug withdrawal, can induce drug craving, which leads to relapse. The system mediating stress responses incorporates the hypothalamic–pituitary axis (HPA) and extrahypothalamic regions (such as the extended amygdala). CRF is a neuropeptide that is responsible for activating the HPA, where it plays a role in mediating the hormonal, autonomic, emotional and behavioral responses to stress. Initial exposure to a drug engages the HPA but this response becomes blunted with repeated exposures via feedback systems in response to circulating hormones. There is evidence that HPA–CRF-mediated stress responses do not contribute to stress-induced reinstatement, at least for heroin (Shaham et al., 1997) or cocaine (Erb, Shaham, & Stewart, 1998). CRF-mediated actions on addictive behaviors apparently depend on their action at extrahypothalamic sites in these cases (Shalev, Erb, & Shaham, 2010). These extrahypothalamic regions become sensitized to CRF after repeated exposures to drugs of abuse. During withdrawal, these regions become engaged and hyperactive, thereby increasing local CRF levels and perpetuating a negative state of stress (see Koob, 2010, for review). While stress is sufficient to increase CRF levels in the VTA, it is the neuroadaptive changes induced by prior cocaine use that enable CRF to control local glutamate release, subsequently activating the dopaminergic system and perpetuating stress-induced relapse to drug-seeking behaviors (Wang et al., 2005).

There is still debate about the specific site of action of CRF beyond the HPA. CRF acts primarily through either CRF1 or CRF2 receptors, both of which are widely distributed throughout the brain. CRF1 receptors have been hypothesized to play a role in sensitization and relapse. A CRF1 receptor antagonist was sufficient to decrease reinstatement of cocaine-seeking after an abstinent animal was given cocaine (Przegalinski, Filip, Frankowska, Zaniewska, & Papla, 2005) (abstinent animals are often primed or given a drug to examine whether drug-seeking behaviors are reinstated), although more recent studies support the role of CRF1 receptors in active drug taking (Specio et al., 2008). Chronic inhibition of CRF1 receptors is also sufficient to induce long-term adaptations to the dopaminergic system, including reducing the density of dopaminergic projections in the striatum and increasing dopamine receptor expression in a subtype-specific manner (Lawrence et al., 2005). In comparison, stress-induced reinstatement to cocaine can be prevented by infusions of a CRF2 receptor antagonist into the VTA. This most likely reflects inhibition of glutamate and dopamine release, even though CRF1 receptors are the dominant receptors in this region (Wise & Morales, 2010). The presence of CRF is sufficient to induce synaptic plasticity, including LTP, which is mediated via CRF1 and glutamate receptors. However, prior
exposure to cocaine alters the receptors mediating this response via the recruitment of dopamine receptors, whose expression increases during withdrawal in the amygdala (Krishnan et al., 2010). Antagonism of CRF1 receptors has a non-specific effect on LTP while antagonism of CRF2 receptors attenuates LTP specifically in cocaine-withdrawn animals (Guan, Wang, Chen, Guan, & Li, 2010). As highlighted above, there is growing evidence that neuropeptides play a complex role in the modulation of addictive behaviors, the intricacies of which are only just beginning to be understood (see Table 2.1 for a summary).

GENES AND ADDICTION

Human Genetic Links To Dependence

As humans, each of our cells contains approximately 30,000 genes, although they are differentially expressed throughout our bodies. These genes contain instructions that guide development (including passing on heritable traits) and maintain the ability of our cells to function. Unlike disorders such as cystic fibrosis, there is no single gene that predisposes individuals to develop addictive behaviors. Nor does the inheritance of addiction follow a clear Mendelian pattern. Genetic background nonetheless strongly influences addiction liability, as shown by heritability estimates of 40–70% and a high degree of overlap in genetic vulnerability to different drugs of abuse (Ho et al., 2010). Mutations in “genetic vulnerability” genes do not ensure that an individual will become addicted, but increase their vulnerability if they use drugs of abuse. These genes can be classified into those related to the initial stages of experimentation and those related to neuroadaptations following continued exposure. This effect appears additive, with the more mutations an individual has the greater their vulnerability to becoming addicted.

Our understanding of genes related to human addiction has come from twin and adoption studies that use either genome-wide association methods [screening of single nucleotide polymorphisms (SNPs) and chromosomal regions correlated with addiction risk] or candidate gene methods (that assess associations between addiction risk and specific genes of interest). Potential targets responsive to drugs can then be investigated in animal models that include gene knockout and transgenic mice (bred to include a human gene) to increase our understanding of the functional roles of a gene in modulating addiction-related neuronal circuits and behaviors. (Gene knockout animals are selectively bred to remove a certain gene. In comparison, transgenic animals are selectively bred to express an exogenously introduced gene. The function of these genes can then be investigated.)
To date, variations in genes relating to the risk of alcoholism are probably the best understood and so are used as an example. Heritability of genes that predispose an individual to becoming alcohol dependent ranges from 50 to 70% (Ho et al., 2010). An SNP (a change in a single nucleotide in a gene) in the catalytic enzymes for alcohol metabolism, alcohol dehydrogenase-1B (ADH1B) and aldehyde dehydrogenase-2 (ALDH2), is sufficient to reduce the risk for alcoholism (Muramatsu et al., 1995). Individuals with genetic variations in dopamine D2 receptors may show younger onset and severity of drinking (Luo, Hou, Wu, Zhang, & Wan, 2005). Mutations in genes encoding the NR2A subunit of NMDA, or mGlul receptors, may lead to a higher risk of developing alcohol dependence (Schumann et al., 2008). Findings such as these provide novel targets and a potential shortlist of candidate genes to aid in refining treatment strategies. However, substance abuse is a complex polygenic disorder involving interactions between biological, environmental and psychological factors. Many psychiatric disorders, including depression and anxiety, coexist with substance abuse disorders, making understanding the genetics and neurobiology complicated and treatment difficult.

Gene Expression

Genes are sections of DNA that are expressed as mRNA and translated into proteins that are used by cells to maintain their function. Dysregulation of gene expression patterns within the brain via polymorphisms may underlie the long-term behavioral and structural changes that lead to the persistent effects of an addicted state. In support of this hypothesis, Brown, Flynn, Smith, and Dayas (2010) demonstrated that there is a persistent downregulation of genes related to synaptic plasticity in the striatum of animals that are vulnerable to relapse to cocaine-seeking. Indeed, from human postmortem studies it has been well documented that exposure to cocaine alters the expression of numerous genes, in a region-specific manner. These genes can be subcharacterized into those relating to the extracellular matrix, synaptic plasticity and efficacy, receptors, ion channels and transporters, signal transduction and cell death, among others (see Lull, Freeman, Vrana, & Mash, 2008, for an extensive list).

Drugs of abuse have differential effects on gene expression patterns. Exposure to cocaine, for example, may transiently alter the expression of some genes, with levels returning to normal expression patterns should exposure cease (Lull et al., 2009). In other genes, the cocaine-induced changes may persist into abstinence. The expression of additional genes that had not previously been responsive to cocaine may also show altered expression during abstinence once the effects of cocaine have been removed (Freeman et al., 2010).
Understanding the impact of altered gene expression in response to a drug is complicated by the possibility of gene splicing. Proteins are not derived from continual sequences in the gene but are pieced together from coding sequences called exons, which are separated by non-coding sequences called introns. Splicing occurs when the exons of the RNA are reconnected in different ways, producing different isoforms of the same protein. These different protein isoforms show a specific, but differential, expression pattern in the brain and respond differently upon exposure to drugs of abuse. For example, the gene encoding BDNF in humans has seven exons, while BDNF in rodents has eight exons that can be spliced to produce eight BDNF isoforms made up of two-part transcripts (e.g. exons VI and VII) and one isoform made up of a three-part transcript (e.g. exons VI, VII and VIII). All splice variants are expressed at high levels in the hippocampus, with splice variants for BDNF4 and 5 also being high in the striatum. Four hours after acute exposure to cocaine, the mRNA for BDNF4 in the striatum and frontal cortex is increased several fold and the splice variant for BDNF1 is also increased in the cortex (Liu et al., 2006). However, there is no difference in the expression of any splice variant following exposure to cocaine for 10 days or following up to 3 months of abstinence (Liu et al., 2006). This is in contrast to the observation that there is a progressive increase in BDNF protein expression in the striatum during cocaine withdrawal (Grimm et al., 2003), suggesting that additional factors may be acting to regulate the translation of mRNA to protein.

Patterns of gene expression are regulated by transcription factors. Data from microarray studies indicate two transcription factors commonly associated with addiction. The first, cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), is stimulated by activation of the cAMP pathway in response to activation of receptors or ion channels, which leads to phosphorylation of CREB and activation of gene transcription. A second transcription factor, ΔFosB, is a member of the immediate early gene family (i.e. they are induced rapidly in response to a stimulus). The unique feature of transcription factors is that they remain within the cell at which they are produced, being transiently expressed to act locally to regulate the gene expression patterns of that cell specifically. CREB is expressed at high levels throughout the brain (Walters, Kuo, & Blendy, 2003) and targets genes including c-fos, BDNF and prodynorphin. The activation of CREB via phosphorylation is rapidly, yet transiently, elevated following exposure to cocaine. Manipulation of the expression of CREB in the NAcc in animal models is sufficient to alter drug-related behaviors, including a decreased reward value of cocaine (Carlezon et al., 1998) and tolerance, being influential in early drug-seeking behaviors (McQuown & Wood, 2010). In comparison, the motivational properties of cocaine appear driven by CREB-mediated mechanisms in glutamatergic cortical neurons (McPherson, Mantamadiotis, Tan, & Lawrence, 2010).
In response to drugs of abuse, the expression of ΔFosB is increased primarily in the NAcc and striatum, but expression may also be induced following cocaine in other regions including the prefrontal cortex, VTA and amygdala (McClung et al., 2004). Chronic drug exposure results in a slow and sustained increase in ΔFosB-dependent gene expression (Hope et al., 1994). ΔFosB has the ability to mediate over 100 different changes to gene expression, contributing to 25% of the changes to gene expression in the NAcc following chronic cocaine exposure specifically in the MSNs of the direct pathway (McClung et al., 2004; Nestler, 2005). Consequently, ΔFosB has been linked to positive drug reward and sensitization (reviewed in McQuown & Wood, 2010) and it has been hypothesized that this gradual accumulation over repeated exposures plays a role in mediating drug craving. Indeed, ΔFosB accumulates in the NAcc in response to cocaine and its presence increases the rewarding effects (Kelz et al., 1999); overexpression of ΔFosB facilitates acquisition of cocaine self-administration and the motivational drive to gain the drug (Colby, Whisler, Steffen, Nestler, & Self, 2003). These effects presumably occur by ΔFosB’s ability to modulate the transcription of the genes for 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) Glu2 receptor subunits and cyclin-dependent kinase-5 (Cdk5, a member of the cyclin-dependent kinase family), among others, acting as a molecular switch that leads to downstream consequences on altered protein expression, structural changes and ultimately function.

**Epigenetics**

Epigenetics refers to post-translational modifications that control heritable changes to phenotypes that are not dependent on changes in the DNA sequence itself. Epigenetic changes establish and maintain different gene expression programs in specific cell types (Ng & Gurdon, 2008). These changes are primarily controlled through remodeling of the chromatin, which consists of the histone proteins around which the DNA is wrapped. Enhanced or suppressed regulation of the transcription of genes to proteins is influenced by the summation of post-translational modifications to histones or changes to DNA itself (such as acetylation, phosphorylation, ubiquitination, sumoylation and methylation) (see Renthal & Nestler, 2008, for a review). Drug-induced neuroadaptations can lead to stable changes in gene expression that explain the persistence of addictive behaviors (Pandey, Ugale, Zhang, Tang, & Prakash, 2008; Pascual, Boix, Felipo, & Guerri, 2009; Schroeder et al., 2008). For example, the genes encoding the dopamine D1 and D2 receptors show increased methylation after cocaine self-administration (Glausier, Khan, & Muly, 2009).

Drug-induced epigenetic changes can be assessed across the whole genome (genome-wide assay) or by assessing individual changes to chromatin at specific genes. From studies to date, histone modification
has been implicated as one of the primary mechanisms mediating epigenetic changes related to addiction. Histones, which are the chief protein components of chromatin, comprise six classes (H1, H2A, H2B, H3, H4 and H5). Histone acetylation is a sign of activated chromatin (Schroeder et al., 2008). Drugs of abuse induce specific histone modifications at different genes in the same region. Genome-wide studies after cocaine exposure suggest that most genes are activated acutely by acetylation at H4 and chronically by acetylation at H3 (Renthal & Nestler, 2008). Acute exposure to cocaine induces H4 acetylation at the cFos promoter in the NAcc within 30 minutes, but this response disappears by 3 hours post exposure and no further change occurs with repeated exposures. In contrast, repeated (but not acute) cocaine exposure increases H3 acetylation at the BDNF and Cdk5 promoter in the NAcc for 1–7 days after the final dose (Kumar et al., 2005). Changes in the prefrontal cortex last for up to 2 weeks (Renthal & Nestler, 2008). While drug-induced changes in acetylation appear to depend on the frequency of exposure, little is known about the stability of these changes after a period of abstinence. Furthermore, epigenetic changes can precede their downstream results. For example, chronic self-administration of cocaine increases acetylation of the promoter for BDNF in the NAcc within 24 hours after the last exposure (Kumar et al., 2005). However, BDNF protein is not elevated until a week after cocaine withdrawal (Grimm et al., 2003), suggesting that epigenetic changes may play a role in priming genes for subsequent induction. Understanding the impact of epigenetic modifications is complicated by the fact that these modifications are potentially reversible and can be mediated by other processes.

MicroRNA

MicroRNAs (miRNAs) are short non-coding RNAs (ranging in size from 19 to 24 nucleotides) that fine-tune post-transcriptional gene expression, by inhibiting protein synthesis (Filipowicz, Bhattacharyya, & Sonenberg, 2008; Jackson & Standart, 2007; Standart & Jackson, 2007). There is growing interest in the role that miRNAs play in addiction because of their role in neurogenesis, synaptogenesis and plasticity. They can also regulate receptor expression (Karr et al., 2009) and function (Kocerha et al., 2009) and have been shown to play a role in regulating LTP and LTD (Wibrand et al., 2010), especially in hippocampal mediated memory and learning (Konopka et al., 2010). The complexity of miRNAs is amplified by the fact that any one miRNA has multiple targets, and more than one miRNA can regulate the same mRNA.

While drugs of abuse are able to alter gene expression via miRNA-mediated pathways (Huang & Li, 2009b), the role of miRNAs in regulating drug-induced changes in the mesocorticolimbic pathway is only beginning.
to be explored. Indeed, dopamine D₄ receptor expression can be regulated by miRNAs in a miRNA-specific manner (Huang & Li, 2009a) and miRNAs have been shown to regulate the fine-tuning of dopaminergic neurons and dopaminergic mediated behaviors such as locomotion via a negative feedback circuit (Kim et al., 2007). Cocaine treatment can induce alterations (both up and down) in the expression of miRNAs in a miRNA- and region-specific manner, including in the NAcc, dorsal striatum and hippocampus (Chandrasekar & Dreyer, 2009). These can lead to alterations in receptor expression (Chandrasekar & Dreyer, 2009), have downstream consequences for signaling pathways (Hollander et al., 2010) and result in altered levels of BDNF (Chandrasekar & Dreyer, 2009). MicroRNA-mediated changes to BDNF are able to affect dendritic spine morphology (Schratt et al., 2006), while BDNF itself can alter the expression of miRNAs that regulate the expression of glutamate receptors (Kawashima et al., 2010). Furthermore, CREB-mediated transcription may also induce specific miRNAs (Nudelman et al., 2010). Alterations to miRNAs appear sufficient to drive specific aspects of behavior as the expression of certain miRNAs in the NAcc can enhance or attenuate the reinforcing properties of cocaine (Chandrasekar & Dreyer, 2011), while different miRNAs are linked to driving the motivational properties of cocaine (Hollander et al., 2010). These data suggest that miRNAs control intricate feedback loops regulating the expression of proteins involved in drug-induced neuroadaptations. Thus, it is possible that drug-induced modulation of miRNAs could result in enhancement or silencing of genes critical for the induction and maintenance of addictive behaviors. Deficits in miRNA signaling may increase an individual’s vulnerability to addiction.

CONCLUSION

This chapter has presented data from animal models to support the hypothesis that exposure to drugs of abuse can have long-lasting effects on the (epi)genetic, molecular and cellular aspects of the brain. These neuroadaptations are believed to underlie the transition from initial drug use to an addicted state and to facilitate and maintain addictive behaviors. While different classes of drugs may result in different adaptations in the brain, those reviewed for cocaine are likely to represent recurring themes across many drugs of abuse. However, addiction is a highly integrated process complicated by individual variation, genetic and environmental factors. Drug-induced neuroadaptations including synaptic plasticity are complex. They may become persistent and contribute to the biological basis for the transition to, and enduring nature of, an addicted state. As a consequence, drug-seeking behaviors are maintained, leading to relapse even after protracted abstinence (Jupp, Krstew, Dezsi, &
Thus, a major challenge is elucidation of the molecular identities of factors implicated in the development and maintenance of an addicted brain.

Acknowledgments

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INTRODUCTION

A modern version of the Hippocratic Oath reads: “I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism” (Lasagna, 1964). Medical ethics is not merely a matter of differing values, but must deal with data and critical reflection about the benefits and limitations of treatment, and the extent to which a practitioner’s interests may conflict with the patient’s interests.

Opioid substitution treatment (OST) involves prescribing opioids [e.g. methadone, buprenorphine, in some countries long-acting oral morphine, and in some situations, diamorphine (pharmaceutical heroin)] to patients who are opioid dependent, usually on heroin. It is alternatively described as maintenance or replacement therapy. Ethical concerns over OST begin with the concern that conceptualizing heroin addiction as a disease is a form of medicalization, redefining deviance or misfortune as a disease. From this perspective, OST exploits heroin addicts’ craving for opioid drugs, offering them a safe, controlled supply of what is otherwise a proscribed substance, not primarily in the interests of their own health, but as a way of reducing social nuisance from drug-related crime. Rather than being the legitimate and necessary treatment of a disease, it is argued that OST is a form of social engineering in which doctors should not ethically engage, as it is not primarily about treating or preventing illness.

Ethical concerns over OST go further. Prescribing opioids to heroin addicts is counterintuitive, and from its inception has challenged the dominant paradigm of addiction treatment, which is based on the principle that abstinence is necessary for recovery from addiction. Consequently, OST has been dogged by controversy regarding what constitutes valid goals of treatment (Newman, 1987). Remaining on OST medication, in good mental and physical health, and fulfilling a social role, is accepted as a satisfactory outcome of treatment by many treatment providers. But for others, such an outcome is unacceptable and is of far less value than achieving a drug-free state.

Consumers in the UK (Neale, 1998) and the USA (Hunt, Lipton, Goldsmith, Strug, & Spunt (1985–86)) share the concern that OST will prolong their dependency on drugs, and that their quality of life will be negatively impacted by participating in treatment. UK patients on methadone also expressed concern at what they perceived as the poor quality of treatment delivered in some methadone clinics.

These are questions of conscience for clinical practitioners, but they are also issues central to drug policy. In many jurisdictions, such as Russia, methadone treatment is not available because it is not seen as a legitimate medical intervention. In jurisdictions where OST is supported, it is more
highly regulated than other forms of medical practice, and political support for it fluctuates (Allison & Hubbard, 1985; Bell, 2000). This analysis of the ethics of OST begins with a brief history of opioid prescribing, and how attitudes to opioid dependence have evolved. It then analyzes whether addiction can appropriately be called a disease, and whether OST is a form of medical treatment justified in terms of effectiveness in improving quality of life. This includes analysis of factors contributing to and detracting from the quality of treatment.

Finally, the chapter examines the extent to which treatment is primarily driven by the patient’s best interests, as opposed to the interests of government, the treatment industry and the pharmaceutical industry. This is the critical issue in the ethics of OST, because individuals with addictive disorders tend to act in ways that are harmful to themselves. Indeed, it could even be argued that the false consciousness of the addict, driven by the need to avoid withdrawal, means that dependent users do not possess the capacity for making autonomous decisions about their lives. Specifically, they may lack the capacity to refuse offers of prescribed opioids, and their receipt of a prescription merely prolongs their dependence. This critical ethical issue is a concern of consumers, the community and policy makers.

HISTORICAL EVOLUTION OF ATTITUDES TO OPIOID PRESCRIBING

In the USA, opioids were widely prescribed for pain relief by medical practitioners during the latter half of the nineteenth century, when iatrogenic addiction became increasingly common. The peak of opioid dependence in the USA was 1860–1900 (Terry & Pellens, 1928). At this time, the majority of people addicted to opioids in the USA were white, middle-class, middle-aged females, the majority of whom had been initially prescribed opiates by medical practitioners. Over time, there was increasing discussion of the nation’s drug problem, and attitudes to prescribing opioids hardened. By the 1920s, the number of people using opioids had dropped dramatically, and the characteristics of the users had also changed to those of marginalized, alienated young men (Courtwright, 1982). Correspondingly, heroin addiction came to be seen as a social menace, strongly associated with deviance and criminality.

The Harrison Act (1914) in the USA was interpreted by law enforcement officers to mean that prescribing of opiates to known addicts was illegal (other than for short-term use in detoxification). In the years that followed, legal proceedings were initiated against some doctors who were prescribing opioids for maintenance. UK drug policy tended to be more supportive of such prescribing than US policy. As in the USA, opiate use
was relatively common in the UK in the late nineteenth century, and was not regulated up until about the time of World War I. The UK then went in a different direction from the USA, with the amendments to the 1920 Dangerous Drugs Act following the recommendations of the Rolleston Report (Ministry of Health, 1926) allowing doctors to prescribe opiates legally to addicts for treatment purposes. This humanitarian policy was not controversial, in part because there were small numbers of patients involved and most were iatrogenic addicts, and little involved with crime. It established a medical paradigm for responding to opioid addiction in the UK, in contrast to the law enforcement paradigm of the USA.

The UK policy was challenged in the 1960s, as the opioid-addicted population in the UK began to include more increasingly marginalized, criminally active urban poor. As numbers of addicts being prescribed opioids increased, concerns emerged over the inappropriate prescribing by some doctors. This led to the second Brain Report (Ministry of Health and Scottish Home and Health Department, 1965) and the 1967 Dangerous Drugs Act, which required notification of drug addicts to the Home Office, increased restrictions on prescribing and established specialized drug dependency treatment units. The principle of humane maintenance prescribing remained, but occurred in a more regulated framework.

Over the next two decades, support for maintenance prescribing fluctuated. It was renewed in the late 1980s by concerns over human immunodeficiency virus (HIV) transmission (Stimson, 1995), and in the mid to late 1990s with the objective of reducing drug-related crime (Duke, 2006). Thus, over the past few decades, the original humanitarian basis of a policy permitting maintenance prescribing in the UK has increasingly moved to a pragmatic policy based on reducing social problems related to opioid dependence. Possibly in reaction to this social engineering rationale, the latest UK drug strategy has promoted a “recovery agenda” that does not support indefinite maintenance on OST for most patients (HM Government, 2010).

In both the USA and the UK, there has been at times a perception that some doctors supplied drugs to addicts for profit, with little monitoring and no clear therapeutic rationale, thereby contributing to the maintenance, if not the spread, of addiction (Strang, 1989). This perception—probably not entirely groundless—has contributed to community and professional unease over the ethics of OST and has resulted in OST being treated differently from other areas of medical practice. In neither the USA nor the UK were the professions engaged in designing responses to inappropriate prescribing (e.g. by developing therapeutic guidelines or professional standards of prescribing). Policy, regulation and law enforcement dictated how practice should be conducted, undermining the concept of OST as primarily a medical treatment.

II. TREATMENT
Attitudes to opioids are cyclical, and in the USA the “opiophobia” which prevailed for most of the twentieth century was replaced in the 1990s and 2000s with a new enthusiasm for using opioids to control pain. There has been a spectacular rise in opioid prescribing in the past two decades, primarily on humanitarian grounds to relieve pain, which has always been a legitimate medical use of opioids. However, the diversion of prescribed opioids has contributed to an epidemic of prescription drug misuse and dependence in many developed countries, and to a large increase in the number of people on OST. Rather than being primarily driven by individual doctors prescribing for profit, the explosion in prescription opioid dependence appears to have been driven by the pharmaceutical industry aggressively marketing opioids to practitioners and directly to consumers (Van Zee, 2009).

To summarize, there is a substantial latent demand for opioids (as there is for other reinforcing drugs such as alcohol and tobacco). There is profit to be made from making people addicted, as demonstrated by the British in China in the early nineteenth century (Newman, 1995). When opioids are widely available, the prevalence of opioid dependence increases; when availability is restricted, usage becomes concentrated in a subculture of multiple drug-using, socially marginalized and criminally active individuals. As this occurs, the policy response to opioid dependence becomes increasingly focused on controlling social nuisance rather than treating dependent individuals.

**IS ADDICTION A DISEASE?**

Drug use can be initially considered a matter of personal responsibility and persistent use despite experiencing harms may be considered a failure of personal responsibility. This is how many drug users, families and treatment services see drug use (a key theme in all treatment is encouraging patients to “take responsibility”). However, this view is tempered by the widespread perception that dependent users of drugs have impaired control over their use of drugs, a perception buttressed by genetic and neuroscientific research on addiction (Leshner, 1997; Volkow & Li, 2004). In a phrase that has seemingly become the official US position, Leshner (1997) described addiction as a “chronic, relapsing brain disease”. This view is echoed by the current directors of US National Institutes on Drug Abuse (NIDA) and the National Institute for Alcoholism and Alcohol Abuse (NIAAA) (Gunzerath, Hewitt, Li, & Warren, 2011; Volkow & Li, 2005). The scientific evidence is interpreted on this view as showing that drug dependence is caused by the chronic administration of drugs that produce enduring changes in brain neurotransmitter systems that leave the user vulnerable to relapse after abstinence has been achieved (Volkow & Li, 2005).
In considering the matter of responsibility addressed by different theories of drug abuse, Brickman and colleagues (1982) classified the different theories into the four cells of a two-by-two matrix, as illustrated in Table 3.1 and Fig. 3.1. The four cells are defined according to their high or low attribution of responsibility for the problem on one axis, and high or low attribution of responsibility for the solution on the other axis. Thus, in the “moral model” there are high levels of self-attribution on both axes; whereas with the “medical model” there is generally a low level of attribution to the individual of responsibility for the solution (and also usually for the problem) (Strang, 1992). The compensatory model and the enlightenment model involve attributing responsibility for the solution to someone other than the party who is blamed for the problem (Brickman et al., 1982).

TABLE 3.1  Attribution of Responsibility in Four Models of Helping and Coping. Source: Brickman et al. (1982)

<table>
<thead>
<tr>
<th>Attribution to self of responsibility for problem</th>
<th>Attribution to self of responsibility for solution</th>
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<tbody>
<tr>
<td>High</td>
<td>High</td>
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<tr>
<td>Low, High:</td>
<td>High, High: Compensatory model</td>
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<tr>
<td>Moral model</td>
<td>Enlightenment model</td>
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<tr>
<td>Low</td>
<td>Low, High: Educational model</td>
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</tbody>
</table>

FIGURE 3.1  Attribution of responsibility in four models of helping and coping. Source: Based on Brickman et al. (1982).
There is an inherent tension between implementing a public policy of imposing criminal sanctions on those who use and possess drugs, and accepting that addiction is a brain disease that impairs a patient’s control over his or her behavior. Can people be held responsible for their actions if they have a brain disease that impairs their decision making? Quoting Carter and Hall, “For much of the 20th century, opioid dependent persons were seen as autonomous, self-governing individuals who willfully, knowingly, and voluntarily engaged in criminal and immoral behaviour” (Carter & Hall, 2008, p. 81). However, the policy of prohibiting non-medical use, restricting availability, and punishing use and possession, far from asserting the autonomy and self-governance of opioid addicts, implicitly acknowledges the very considerable risk of addiction arising with use of these drugs. The assumption underlying prohibition is that restricting availability of addictive drugs limits opportunities for users to become or remain addicted. Illegality increases the stigma associated with prohibited drugs, deterring some people from experimenting with them. Prohibitions also have unintended consequences, including the creation of an efficient, unregulated, profitable (and often violent) illicit market. Legal sanctions also intensify the marginalization of those who do become dependent. However, the benefits and costs of prohibition are beyond the scope of the current discussion. The important issue is that there is widespread acknowledgment that people who become dependent on drugs have diminished control over their behavior, and to this extent dependence may be viewed as an acquired disease or disability, for which palliative or curative treatment should be provided.

The Natural History of Heroin Addiction

Studies of opioid-dependent persons in the criminal justice system and those seeking treatment consistently support the proposition that addiction is a chronic, relapsing brain disease. Long-term follow-up studies documenting the natural history of heroin addiction suggest that among subjects who seek treatment, 2–5% per year achieve stable abstinence from opioids (Haastrup & Jepsen, 1984; Vaillant, 1988). For the majority of such subjects, opioid dependence is a long-term, relapsing predicament, with significant social dislocation and an increased risk of death.

There is little evidence that treatments of any kind have an impact on the natural history of heroin addiction. Most people relapse after leaving treatment, whether this is abstinence based or OST. There is some evidence that people receiving OST are less likely to relapse if they have achieved a degree of social reintegration: employment, a stable relationship or community connections. But, even among people who voluntarily withdraw from OST, many relapse or develop other drug problems.
It is on the basis of this type of evidence that OST is regarded as a maintenance intervention.

A study on a non-clinical sample of dependent heroin users challenges the notion of addiction as a “chronic, relapsing brain disease”. The epidemiologist Lee Robins followed up a cohort of veterans who had become addicted to heroin while serving in Vietnam (Robins, Helzer, Hesselbrock, & Wish, 2010). Most in this group described having experienced heroin withdrawal after daily heroin use in Vietnam. On return to the USA, although half the subjects tried heroin at least once, only 12% became readdicted at some time, and usually only briefly. The main predictor of becoming readdicted was pre-exposure deviance (e.g. juvenile offences), suggesting that those who became readdicted have something in common with the civilian, heroin-addicted population. It seems plausible to hypothesize that there is a subpopulation of heroin users that is more likely to take risks, less likely to be deterred by social disapproval or penal sanctions, and particularly vulnerable to developing the chronic, relapsing type of addiction.

Recovery among Vietnam veterans clearly shows that heroin addiction is not always a chronic, relapsing brain disease. Some people can recover, usually without treatment (Robins et al., 2010). But this does not discount the weight of evidence that for most people who seek treatment for heroin addiction, or end up in the criminal justice system, their course tends to involve multiple drug dependency over many years. The fact that some people can recover—the cornerstone of self-help movements—does not prove that all can recover in this way.

Dependence on heroin—and other drugs—greatly exacerbates any pre-existing adjustment difficulties, and contributes to the marginalization and alienation of addicted individuals. Most heroin-dependent people only seek treatment when their circumstances have become desperate. The net result is the growth of a drug-using subculture comprising persons with limited skills and poor impulse control, and lacking access to the rewards arising from employment, personal relationships and family participation. Treating heroin addiction is not just about managing a brain disease; it is also about the rehabilitation of people who have few and often tenuous social connections.

### IS OPIOID SUBSTITUTION TREATMENT REALLY TREATMENT?

While recreational use of drugs is driven by a desire for reinforcing effects, dependent drug use is primarily driven by the need to avoid withdrawal. One pharmacological rationale for methadone and buprenorphine treatment is that a single daily dose of these long-acting opioids...
blocks withdrawal symptoms, freeing the dependent user from the cycle of compulsive drug seeking and drug use. As such, OST allows dependent patients to spend more time and energy on more socially productive pursuits, such as seeking employment and care for family members.

There is consistent evidence that effective methadone treatment requires doses much higher than are required to block withdrawal. The reason is that while low doses reduce the compulsion to use, the learned habit persists, and patients on doses of 40–60 mg of methadone daily—enough to block withdrawal for 24 hours in the great majority of patients—can still experience the reinforcing effects of injecting heroin. Higher doses of methadone induce greater opioid tolerance, making additional heroin use less reinforcing, helping to extinguish the learned habit. High-dose methadone produces pharmacological stabilization, in which the individual experiences little intoxication or withdrawal.

There are many other factors contributing to successful OST. Dole and Nyswander, early pioneers of OST with methadone, offered a dynamic perspective, based on the heroin addict’s process of change on entering treatment; a change summed up in the phrase “from drug addict to patient”. Their theme was that, freed from the cycle of addiction and treated with respect and dignity, heroin users can develop a different image of themselves, and behave with self-respect and dignity. They emphasize that negative assumptions about drug users need to be balanced by a belief in their capacity to change, and a sense of the practitioner’s role in fostering that change (Dole & Nyswander, 1973). Their description of change in methadone treatment anticipates the language of the recovery agenda, with its emphasis on hope and the possibility of sustained change.

Not all entrants to OST are able or willing to take advantage of respite from the need to obtain drugs daily. Many resist the loss of autonomy entailed by entering treatment. Rather than seeing OST as treatment, they see it as a temporary refuge or support while they continue their drug-using lifestyle. Some switch to using other drugs, while some refuse high doses of methadone so that they can continue to use heroin.

Despite this, there are many studies demonstrating that entry to methadone, buprenorphine or diamorphine treatment is associated with rapid and dramatic reduction in illicit drug use, and improvements in well-being. This is perhaps best illustrated by two early randomized controlled trials (RCTs) of methadone treatment. In the first (Dole, Robinson, & Orraca, 1969), 32 prisoners awaiting release were randomized to methadone or to a no-treatment group. Both groups were followed for 12 months from release. Four subjects randomized to methadone maintenance treatment (MMT) did not enter treatment, leaving a treatment group of 12. At 12 months, none of the MMT patients had returned to daily heroin use, whereas all 16 in the no-treatment group had done so. Only three of the
MMT patients had returned to jail; all 16 in the control group had done so. Even on an intention-to-treat analysis (that is, including the poor outcomes in the four who did not enter treatment), the dramatic reduction in heroin use and crime witnessed in the treatment group was statistically significantly better than results in the no-treatment group.

The second, Swedish trial involved randomization of subjects to MMT or to drug-free treatment (in effect, the control group received no treatment, as none accepted drug-free treatment). MMT patients received intensive psychosocial support as well as methadone, and could remain in residential treatment for up to 6 months. Patients were randomized sequentially to the two groups until significant differences in outcomes could be detected. This occurred after 36 subjects were so allocated, 17 of whom received MMT. Thereafter, those who had entered the trial were followed for 2 years. At the end of that time, 12 out of 17 MMT subjects were not using heroin regularly, and were employed or undertaking education. The remaining five subjects had been discharged from the program for continuing drug abuse. Two subjects were excluded from the control group as they entered MMT in another program. Of the remaining 17, one was drug free, 12 were abusing opioids, two were in jail and two were dead. The Swedish study, which included intensive psychosocial input, including vocational retraining, is one of few studies demonstrating that methadone treatment improved social reintegration (Gunne & Grondbladh, 1981).

The results of these RCTs are sufficiently impressive to suggest that it would not be ethical to undertake further trials using no-treatment controls. In the short term, methadone treatment is much more effective than no treatment. However, there are two important caveats. First, once a treatment becomes widely practiced, there are often deviations from the treatment model in directions that produce poorer outcomes (e.g. lower methadone doses, time-limited treatment, punitive responses to illicit opioid use). Second, short-term studies provide no information about the long-term consequences of treatment. This is particularly worrying in relation to OST, as there is some limited evidence that most of the benefits of treatment occur in the first 2–3 months, with little further improvement over time. For example, one of the few studies to investigate changes in quality of life found that entrants to treatment report a prompt improvement in quality of life, but no further improvement after the first 2–3 months (Reno & Aiken, 1993).

One public health argument for offering OST is that it attracts and retains a greater proportion of heroin addicts than other modalities of treatment of heroin addiction. Since, in the short-term, OST offers marked improvement over no treatment, and these benefits are sustained while people remain in treatment, the principle of maintenance
treatment seems straightforward. But it is arguable that offering OST to an addict in withdrawal is a powerful immediate inducement to participate. Rather than renouncing heroin use and experiencing the short-term distress of withdrawal, entry to OST is an easier option, for which the cost may be years of institutionalized treatment.

**Does Opioid Substitution Treatment Impede Recovery?**

Most entrants to OST drop in and out of treatment, often cycling between episodes of OST (Bell, Burrell, Indig, & Gilmour, 2006). What is the effect of such prolonged, episodic participation in treatment? Does participation in OST reduce the likelihood of long-term abstinence, as feared by consumers?

Results of a long-term follow-up of a cohort of heroin addicts entering treatment give a picture of the long-term impact of treatment (Maddux & Desmond, 1992a). The investigators identified a group comprising 77 heroin addicts who over a 10-year period had less than 12 months in methadone treatment (the non-MMT group), and a group of 95 subjects each of whom had a minimum of 12 months’ MMT (mean 54 months). Both groups were followed with serial interviews and data were collected from a variety of official records (including arrests, treatment episodes and deaths). In summary, patients with prolonged exposure to MMT tended to have better social outcomes (significantly less crime and more employment), but at the price that fewer patients achieved sustained abstinence from heroin. At follow-up, the proportion identified as problem drinkers was high and similar in the two cohorts (64% and 72%, respectively). The mean duration of daily heroin use in the two groups was similar (14 and 12 months, respectively, out of the 10 years), but the methadone group reported much longer periods of occasional heroin use (usually during methadone treatment) than the non-MMT group.

The same investigators also undertook a review of long-term outcomes in patients entering MMT and in patients entering drug-free residential rehabilitation. From five follow-up studies of patients entering MMT, they found that the proportion of patients voluntarily abstinent from opioids ranged from 9 to 21%. From six follow-up studies of patients treated in drug-free treatment, the percentage who were voluntarily abstinent ranged from 10 to 19% (Maddux & Desmond, 1992b).

These results present a somewhat depressing picture of the outcomes of heroin addiction, whether treated with OST or in abstinence-based programs. It supports the conclusion that heroin addiction is indeed a chronic and relapsing disorder, associated with alcohol misuse and poor social adjustment.
Is Indefinite Maintenance Therapeutic Nihilism?

The concept that some individuals are at lifetime risk of relapse is not restricted to opioid dependence. Among the fundamental articles of faith in Alcoholics Anonymous (AA) are that alcoholism is a “disease”, albeit a “moral and spiritual disease” rather than a physical one, that the risk of relapse to drinking is life-long and that long-term affiliation with the fellowship is needed to sustain recovery. The latter claim is empirically false: some problem drinkers never relapse, despite not affiliating with AA, while others can return to controlled drinking (Vaillant, 1988, 2003). However, this does not outweigh the evidence that for many people, dependence on alcohol or drugs is a chronic predicament, with a long-term risk of relapse and a need for long-term support.

Some addicted individuals are happier to accept the need for lifelong abstinence and affiliation with a fellowship than they are to accept the need for long-term OST. The public, professionals and many patients believe that abstinence is preferable to being maintained on an opioid. One critic of OST invoked the concept of “subclinical euphoria” (Ausubel, 1983) to describe the state induced by methadone (a claim which suggests that the author has never visited a methadone clinic, where the prevailing mood is dysphoria). If methadone did induce a state of euphoria, would this be unethical? Beneath this cloak of outrage at “subclinical euphoria” lies the suspicion that rather than being unwell, people in treatment are pursuing pleasure, and so not deserving of public spending on health care.

It is difficult to argue that indefinite maintenance is inherently unethical. A different, more valid question is whether indefinite maintenance produces sustained health benefits. Evidence on this point is not strong, and the tentative conclusion on current data is that indefinite maintenance produces no better or worse outcomes than abstinence-oriented treatment.

Is Much Opioid Substitution Treatment of Poor Quality?

Divergence from Evidence-based Treatment

While early RCTs produced dramatic evidence of effectiveness, once OST became industrialized with the widespread roll-out of clinics, there was a loss of fidelity to the original treatment model and a loss of effectiveness (D’Amanda, 1983). Two decades after the widespread introduction of methadone treatment into the USA, much of the treatment provided was inconsistent with the original research protocols that had proved so effective (D’Aunno & Vaughan, 1992). Clinicians introduced low-dose treatment, time-limited treatment, a psychotherapeutic model of treatment in which methadone served primarily as a bait attracting...
people to and retaining them in compulsory counseling sessions, and a contingency model in which people who persisted in using heroin had their methadone doses reduced and were ultimately withdrawn. There were many variations radically departing from the Dole model of high-dose maintenance and a respectful therapeutic relationship.

Probably the most important factor contributing to this diversity of treatment approaches was resistance among health professionals to the two basic tenets of the Dole model: the concept of maintenance prescribing, and the assumption that patients have autonomy in how they respond to treatment. The issue confronting every clinician involved in OST is the extent to which individuals should be treated as autonomous. Should there be a system of rewards and punishments to push people into meeting the clinician’s (and community’s) expectations of them? Specifically, if patients choose to continue misusing drugs while in treatment, should this be tolerated, or should treatment be withdrawn? Should continued drug-seeking be regarded as bad behavior, a failure by the patient to keep their side of the implicit treatment contract? Or should it be regarded as failure of treatment, suggesting the need for different, more reinforcing medicines such as diamorphine?

The Dole model is characterized by tolerance of a degree of ongoing drug use (meaning little pressure to change), and by the assumption of indefinite high-dose maintenance (meaning no pressure on participants to withdraw from treatment). Those staff who distrust patient autonomy and seek to shape patients’ behavior have developed a variety of approaches to treatment, all of which can be classified as “abstinence oriented” or “change oriented”. These approaches assume that patients have to be pushed and encouraged to make changes, with the ultimate goal of withdrawing from methadone. While adaptive treatment on the Dole model arouses community disquiet, and gives rise to the perception of people being “parked on methadone”, studies have consistently demonstrated that adaptive treatment has achieved better outcomes than abstinence-oriented treatment (Ball & Ross, 1991; Ward, Mattick, & Hall, 1998).

Is Much Opioid Substitution Treatment of Poor Quality?
Cost Saving in Delivering Treatment

A divergence of views about the most effective way to use methadone is compatible with the assumption that OST is at least a well-intentioned attempt to improve the health of heroin addicts. However, the self-interest and financial motives of practitioners and clinic operators have also contributed to uneven quality of treatment delivery. During a rapid expansion of methadone treatment in Australia, a study of several private, for-profit clinics noted that clinical records were very poor, and most clinics did not have a treatment ethos: they were largely business-like opioid dispensing...
operations. Staff had little training, little support and little clarity about their roles. Patients were required to attend for too many, very brief medical consultations, a requirement that seemed to be based more on the financial return to the doctor from each visit rather than the welfare of the patient. There was also poor compliance with clinical guidelines on the use of take-home doses (Bell, 2000).

The issue of profit from OST is problematic because supplying opioids generates a continuing need in the recipient. For the British East India Company selling opium to the Chinese, for Dr Feelgood prescribing opioids without asking too many questions of patients, for Pharma aggressively marketing opioids, and for the OST industry, there are profits to be made from distributing opioids. In the case of OST clinics, profits can be enhanced by cutting costs, providing minimal services, and giving as many doses as possible without expensive supervised consumption. Unlike in other areas of health care, recipients of these types of lax treatment are unlikely to complain or take their custom elsewhere.

Such instances of unethical practice do not mean that OST is inherently corrupt. It means that, as in all areas of health care, standards of care need to be clearly defined and subject to clinical audit. It seems likely that the majority of professionals working in OST are committed to optimizing their patients’ chances of recovery. In jurisdictions with publicly funded treatment, a more common problem than cost-cutting for profit is cost-cutting by government that leads to poorly resourced clinics with large caseloads, and minimal support, supervision and training for staff, all of which contribute to suboptimal treatment.

Can Patients Give Informed Consent to Opioid Substitution Treatment?

One of the critical issues at the heart of OST (and especially research trials of OST) is the extent to which patients should be treated as autonomous and able to make decisions. One objection to OST is that a heroin addict in crisis who is offered OST is not able to give informed consent to participate. This issue has gained fresh attention in recent years as a result of clinical trials of injectable diamorphine (heroin) OST for patients who have not responded to other forms of OST. Could a person addicted to heroin ever decline the offer of a prescription of their preferred drug? If they cannot even contemplate refusing, then can they really be considered to be able to give informed consent (Charland, 2002)?

Experience with the clinical trials of heroin prescribing indicates that many heroin addicts can decline an offer of diamorphine. To the frustration, and possibly surprise, of the researchers running clinical trials, it proved more difficult than expected to recruit study participants. All recent trials failed to recruit target numbers, and/or had to extend recruitment and
add new sites, in order to increase recruitment (van den Brink et al., 2003; Haassen et al., 2007; March, Oviedo-Joekes, Perea-Milla, Carrasco, & PEPSA Team, 2006; Oviedo-Joekes et al., 2006; Strang et al., 2010).

There are many reasons why people decline to participate in such trials. The fact that many heroin addicts were not interested in participating does not exclude the possibility that for some patients diamorphine treatment—like all forms of OST—is a powerful inducement. The major reason why drug users are reluctant to enter treatment is that treatment is not perceived to offer them any advantage over their drug-using state (Gerstein & Harwood, 1990). In treating individuals whose motivation system has been deeply influenced by drug dependence, inducements, rewards and punishments become integral to the treatment process.

In addition to the concern that people are induced into treatment, there are other ethical concerns regarding prescribing injectable heroin to heroin addicts. Use of a short-acting, parenteral opioid produces spikes in opioid activity rather than the stability provided by a steady oral dose. This appears to make this form of OST more susceptible to the charge of keeping patients addicted.

The target population for diamorphine treatment is that of long-term heroin addicts who have failed to respond to other forms of treatment. Most participants who enter this form of treatment have lost family support, and are so entrenched in a daily cycle of drug seeking and drug use that they have little other reward in life, and little capacity to hope or imagine that things might ever be different. Injectable diamorphine treatment is highly structured, requiring twice-daily (or more frequent) attendance to administer diamorphine under medical supervision. These onerous requirements deter many heroin-addicted individuals from participating in this treatment, but for others access to diamorphine provides motivation enough to comply with the requirements of treatment. Street addicts with attitude might well see diamorphine treatment as a Faustian bargain of short-term gratification at the price of long-term institutionalization. However, for many demoralized trial participants, the transition (not always smooth) from addict to patient begins a process of social reintegration that is made possible because sufficient incentive is offered to cease street drug use. Quoting one service user, who has written and spoken in the UK media about her experiences of diamorphine treatment, “For me, it’s about being able to lead a normal life and make a positive contribution” (SLAM News, 2009/10).

CONCLUSION

Most expressions of ethical concern over OST can primarily be considered as empirical matters: as to whether treatment is delivered
professionally and achieves good outcomes for the individuals in treatment. The more that discussion of the ethics of OST moves away from evidence, the less ethical is the discussion. As societies and times change, ongoing research and evaluation are necessary to avoid sinking into rigid assumptions.

Evidence on long-term outcomes of OST is limited, but suggests a generally poor outlook for heroin addicts who seek any form of treatment. One consequence of this is the trap of low expectations (therapeutic nihilism), the failure by discouraged staff to foster the possibility of good outcomes, and for treatment to descend to the mechanical issuing of opioid prescriptions. Low expectations may also foster cynical, profit-oriented treatment.

In any area of health care, where outcomes are poor there are always people keen to market optimism. (There has always been a thriving market for alternative therapies in areas such as cancer and serious neurological disease where treatment options are limited.) Therefore, the trap of low expectations is episodically interrupted by people who assert that there is room for optimism, that outcomes can be better even if there is not yet evidence to support this. Optimism about addiction is what patients, their families and politicians want to hear. This, by contrast, may lead to the trap of high expectations that can also be self-defeating, promoting resistance and setting patients up for failure. The ethical challenge in treating heroin (and other forms of) addiction is in finding a balance between excessively low and excessively high expectations in clinical practice and in policy.

References


II. TREATMENT


Addiction Neuroscience and Tobacco Control

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INTRODUCTION

The use of tobacco for its psychoactive effects has a long history within many human societies (Goodman, 1993; Proctor, 2004). Tobacco can be smoked (as cigarettes or cigars, or in a pipe), or used via non-smoked products such as chewing tobacco, oral and nasal snuff. Over the past century, cigarette smoking has become the most common method of tobacco use in most societies (Brandt, 2007; Proctor, 2004). Smoking tobacco is the most harmful form of consumption. Exposure to the by-products of combustion (e.g. fine particulates, carcinogens and noxious gases including carbon monoxide) has been shown to cause numerous diseases including cancers, respiratory diseases and cardiovascular disease (US Department of Health and Human Services, 2004). Until recently, smoking was the leading cause of preventable mortality and disability in high-income countries, such as the UK, the USA and Australia; it was responsible for around 5.4 million deaths globally in 2005. This toll is expected to rise to 6.4 million in 2015 and 8.3 million in 2030 as the prevalence of smoking continues to increase in low-income countries (Mathers & Loncar, 2006).

Tobacco addiction is a complex phenomenon that develops from a combination of positive reinforcing effects of nicotine (such as mood enhancement), avoidance of nicotine withdrawal symptoms and conditioning effects (Benowitz, 2010). It is variously influenced by neurochemical, genetic, behavioral, social and environmental factors. Tobacco use is a behavior usually initiated in adolescence (White & Hayman, 2006). Symptoms of tobacco addiction can develop within days to weeks of initiation, typically before the onset of daily smoking (Di Franza et al., 2000). Tobacco smoke contains thousands of chemicals but nicotine is the substance primarily responsible for dependence (US Department of Health and Human Services, 1988). Other naturally occurring and commercially added substances in tobacco smoke may contribute to the addictive potential of tobacco products (e.g. ammonia and aldehydes).

Compared to other addictive substances, tobacco has a high conversion rate from experimentation to dependence. Of those who initiate use, almost one-third become addicted smokers—a figure substantially higher than many other drugs including heroin, cocaine, alcohol and cannabis (Anthony, Warner, & Kessler, 1994; Upadhyaya, Deas, Brady, & Kruesi, 2002). Tobacco’s status as a legal, widely available and, until recently, socially acceptable and inexpensive consumer product that was aggressively promoted has contributed to this high rate of dependence (Brandt, 2007; Proctor, 2004).
Over the past decade the medical model of tobacco addiction has gained greater acceptance by government and health authorities (Royal College of Physicians of London, 2000; US Department of Health and Human Services, 2000). This is evidenced by the US Surgeon General and the National Institute on Drug Abuse (NIDA) adopting the view that tobacco addiction is “a chronic disease with remission and relapse” (US Department of Health and Human Services, 2000). There are good reasons for treating tobacco addiction in this way. Although most smokers want to quit, and around 90% have attempted to do so (Zhou et al., 2009), only around 5% of quit attempts result in long-term abstinence. The majority of smokers relapse within the first 3 months after quitting (Ockene et al., 2000; Zhou et al., 2009), and a significant proportion of those who are still abstinent after 1 year will relapse (Hawkins, Hollingworth, & Campbell, 2010). Relapse rates are influenced by a number of biological factors, such as severity of nicotine dependence, cigarette craving and withdrawal symptoms (Hyland et al., 2004; Ockene et al., 2000; Zhou et al., 2009).

Neuroscience and genetic research explains why smoking is so appealing and abstaining is so difficult. It suggests that the chronic use of nicotine produces a long-term change in the synaptic connectivity and gene regulation of critical regions of the brain (Benowitz, 2010; Koob, 2000; Launay et al., 2009; Laviolette & van der Kooy, 2004). The main pharmacological effects of nicotine are produced by its binding to neuronal nicotinic acetylcholinergic receptors (nAChRs) (Dajas-Bailador & Wonnacott, 2004), but it also affects other neurotransmitter systems (Berrendero, Robledo, Trigo, Martín-García, & Maldonado, 2010). nAChRs are located throughout the central nervous system and are present in the terminals of most of the neurotransmitter systems (GABAergic, glycineergic glutamatergic, dopaminergic, serotonergic, etc.) [Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2010]. Dopamine, a critical neurotransmitter involved in the rewarding effects of drug use, is released in the mesolimbic area, the corpus striatum and the frontal cortex when nAChRs are activated by nicotine (Benowitz, 2010). Nicotine’s addictive effects are also potentiated by other components of tobacco smoke through monoamine oxidase inhibition, which slows the breakdown of dopamine, norepinephrine (noradrenaline) and serotonin released by nicotine (Berlin & Anthenelli, 2001).

Chronic exposure to nicotine leads to the development of tolerance and dependence by increasing the density of nAChRs in most neurotransmitter systems in the brain (Walsh et al., 2008). Postmortem and functional neuroimaging studies of smokers, ex-smokers and life-long non-smokers suggest that the increased receptor density reverses after
quitting (Breese et al., 1997; Mamede et al., 2007). However, animal models also suggest that nicotine exposure in adolescence can lead to permanent brain changes that increase the severity of addiction (Benowitz, 2010). Some studies have found long-lasting epigenetic modifications in animals exposed to tobacco smoke (Launay et al., 2009). These may explain epidemiological evidence that smokers who start daily smoking at younger ages become heavier smokers and are less likely to quit than those who start as adults (Breslau, 1993; Breslau, Fenn, & Peterson, 1993; Breslau & Peterson, 1996).

### HOW MIGHT NEUROSCIENCE RESEARCH INFLUENCE THE BEHAVIOR OF SMOKERS?

Nicotine addiction is increasingly described by neuroscientists as a “brain disease” that arises from the effects of sustained heavy drug use on brain functioning and makes it difficult for users to quit without pharmacological assistance (Leshner, 1997). Many public health experts have also endorsed the brain disease model of nicotine addiction. Neurobiological explanations for nicotine addiction are now widely reported in the popular media, in commercial advertising for smoking cessation aids and in government-funded public education materials. Within the brain disease and medical models of tobacco addiction, pharmacological treatments such as nicotine replacement therapy (NRT), bupropion or varenicline are primarily aimed at addressing neurobiological factors. These pharmacological therapies are highly cost-effective health interventions (Bertram, Lim, Wallace, & Vos, 2007; Song et al., 2002; Woolacott et al., 2002).

There are conflicting predictions about how smokers’ acceptance of neurobiological theories of nicotine addiction may influence their attitudes and behavior. Neurobiological explanations for nicotine addiction could, for example, assist quitting if they led to greater use of effective cessation methods that increased quitting success (Nides, 2008). Alternatively, this information may be interpreted by smokers in ways that undermine individual agency and autonomy and reduce the effectiveness of public health strategies that aim to encourage smokers to quit (Chapman & MacKenzie, 2010).

### Addiction as a “Brain Disease”: A Reason to Quit, or an Excuse for Failure?

Confidence in one’s ability to quit smoking—cessation self-efficacy—has a reliable association with future abstinence from smoking (Gwaltney, Metrik, Kahler, & Shiffman, 2009). Acceptance of the
neurobiological model of addiction (what some call the brain disease model) could increase cessation self-efficacy if smokers believe that addiction can be overcome with medical cessation aids. However, it is also possible that acceptance of the neurobiological model of addiction could erode some smokers’ confidence in their ability to quit because they may view neurobiological factors as inherently unchangeable, thereby discouraging them from making attempts to quit. Studies have shown that smokers who attribute a failure to quit to unchangeable intrinsic factors such as personal characteristics have lower personal quitting intentions and lower quitting self-efficacy (Harackiewicz, 1987).

NEUROSCIENTIFIC APPROACHES TO REDUCING SMOKING PREVALENCE

Tobacco control policies (such as high taxation, advertising bans and restrictions on smoking) in high-income countries such as Australia, Canada and the USA have reduced smoking prevalence among adults to around 20%. How can the prevalence of smoking be further reduced? Suggested options have included a complete or de facto ban on tobacco smoking, and severe restrictions on the sale of smoked tobacco products, including plain packaging. But what should be done for smokers who cannot or will not quit? A range of technologically oriented approaches have been advocated that are based on neuroscience research and the medical model of addiction.

If Nicotine Addiction is a “Brain Disease”, What is the Best Way to Quit?

Acceptance of neuroscientific explanations of addiction could affect the types of cessation treatments that smokers seek (Nides, 2008). Popular acceptance of the brain disease view of nicotine addiction could, for example, promote medical treatments such as NRT, and drugs such as buproprion or varenicline (Laviolette & van der Kooy, 2004; Volkow & Li, 2005). Pharmacological therapies advocated by the brain disease model of addiction have been shown to improve smoking cessation outcomes in randomized controlled trials. However, some worry that handing the responsibility for quitting over to medical professionals could also lead some smokers to abdicate personal responsibility for continuing to smoke. This could reduce smokers’ self-efficacy and motivation to help themselves (Carlsten & Burke, 2006). There is as yet little evidence on whether neurobiological views of addiction have influenced the methods that smokers use to quit.
Neurobiology and Novel Treatments for Addiction

A criticism of the neurobiological model of addiction is that it medicalizes human behavior and overemphasizes the biological bases of addictive behavior at the expense of social and psychological influences (Conrad, 1992; Press, 2006; Verweij, 1999). These critics argue that depicting nicotine addiction as heavily influenced by neurobiology privileges the development and use of expensive and sometimes risky medical interventions (e.g. deep brain stimulation) (Caron, Karkazis, Raffin, Swan, & Koenig, 2005) while neglecting proven social policies such as higher taxes on tobacco, reduced access to under-18-year-olds and tight controls on tobacco promotion (Carlsten & Burke, 2006; Caron et al., 2005; Chapman & MacKenzie, 2010). The idea that tobacco addiction is rooted in a person’s neurobiology and genes may also lend itself to the view that the minority of people who are susceptible to tobacco addiction and tobacco-related disease should be identified and subjected to individually focused preventive measures.

The following text will briefly outline a range of novel approaches that are considered to be high-technology and that are aimed at the cessation or prevention of smoking that could arise from neuroscience and genetic research: the use of predictive genetics and pharmacogenetics, vaccinations and neurosurgical interventions. Following on from these, more low-technology approaches to reducing smoking prevalence are outlined, such as NRT, tobacco harm reduction policies and pharmacological treatments.

Predictive Genetic Testing and Pharmacogenetics

Given the heritability of many aspects of smoking behavior, the early identification of individuals who are genetically most at risk of becoming smokers could facilitate prevention of uptake. Genetic information could also be used to match smokers to the treatment that is most likely to assist them to become abstinent (pharmacogenetics).

At least 30 genetic association studies have examined differential response to smoking cessation treatment according to genotype; however, many have not been replicated (Hall, Gartner, & Carter, 2008). Modeling based on the modest effect sizes observed in genetic association studies of smoking shows that this is also unlikely to produce a universal screening test that could identify people at risk of tobacco dependency with acceptable sensitivity and specificity (Gartner, Barendregt, & Hall, 2009). This is because only a small proportion of the population will be at very high or low genetic risk of nicotine dependence, with the majority of the population at average risk.

It is unclear in any case whether knowing that one is at a greater genetic risk of addiction provides a greater disincentive to smoke than
simply knowing that tobacco is addictive. Most smokers underestimate their personal risk of developing a tobacco-related disease (Weinstein, Marcus, & Moser, 2005). The belief that providing information on personal genetic susceptibility will improve motivation to quit assumes that people will act upon such advice. The trials to date of providing people with feedback about their genetic susceptibility to common tobacco-related diseases have not found that this information reduces smoking in the long term (Carpenter et al., 2007; Ito et al., 2006; Lerman et al., 1997; McBride et al., 2002).

Nicotine Vaccines

Nicotine vaccines induce the immune system to produce antibodies that bind to nicotine molecules in the bloodstream to form a molecule that is too large to cross the blood–brain barrier and produce its rewarding effects (Maurer & Bachmann, 2006). A nicotine vaccine has potential advantages over NRT, bupropion and varenicline as a cessation aid: it may have fewer adverse effects than drugs that act on the central nervous system (Cerny & Cerny, 2008), it can be administered in only five or six doses to produce effects that last for several months (Cerny & Cerny, 2008), and it may be more effective at preventing relapse by blocking the rewarding effects of a temporary lapse. However, a nicotine vaccine could be circumvented by using a larger dose of nicotine, by smoking more cigarettes in rapid succession or by smoking while wearing a nicotine patch. The term vaccine also raises expectations of preventive use to prevent smoking uptake in adolescents. However, there are major ethical and practical obstacles to such an application (Hall & Gartner, 2011).

Neurosurgical Interventions

Various cortical regions of the brain have been implicated in the maintenance of drug addiction, leading some authors to suggest deep brain stimulation (DBS) as a treatment of addiction including for smoking cessation (Kuhn et al., 2009; Mantione, van de Brink, Schuurman, & Denys, 2010). Functional imaging studies show that drug-related cues can activate these cortical regions, and a retrospective review of smokers who had suffered brain injury found that those who sustained damage to the left or right insula were much more likely to quit smoking easily, to remain abstinent and to lose their urge to smoke than smokers who suffered damage to other brain regions (Naqvi, Rudrauf, Damasio, & Bechara, 2007). Case reviews of patients treated with DBS of the nucleus accumbens for Tourette’s syndrome, obsessive–compulsive disorders or anxiety disorders have reported greater quitting than in the general
population and an absence of cigarette cravings and withdrawal symptoms on cessation (Kuhn et al., 2009; Mantione et al., 2010).

However, the use of neurosurgical techniques such as DBS for nicotine addiction is highly contentious given the ethical and safety considerations involved (Carter, Racine, Bird, & Hall, 2010). Neurosurgery is an expensive, invasive and risky medical procedure for a condition that may be effectively treated using simpler and safer methods. Although promising, it is not clear that any of these options are more effective at reducing smoking prevalence than other less technologically oriented options. Current evidence for their feasibility and effectiveness is somewhat limited, and there are doubts over whether they represent a good allocation of resources (e.g. why should DBS be given to smokers when there are patients with other more suitable conditions for DBS treatment, such as Parkinson’s disease, on waiting lists for treatment?). For these reasons, DBS is unlikely to be a realistic treatment for most smokers (see Chapter 5).

Nicotine Replacement Therapy for Tobacco Addiction

A range of pharmacological treatments (e.g. NRT, bupropion, varenicline) is currently used for tobacco dependence. NRT is a partial replacement for the nicotine in cigarettes that reduces withdrawal effects during abstinence. NRT products include transdermal patches, gum, lozenges, microtabs, inhalers, nasal sprays and oral pouches. They have been designed to have low dependence-forming potential by delivering a relatively small dose of nicotine over a long time (compared to smoking). They are only intended for short-term use (8–12 weeks). Bupropion (Zyban) is an antidepressant medication used as a smoking cessation aid because it reduces nicotine withdrawal symptoms and cigarette cravings. The mechanism by which it increases smoking cessation success is not fully understood, but it likely acts by inhibiting catecholamine (noradrenaline and dopamine) reuptake and as a non-competitive antagonist at nAChRs (Benowitz, 2010; Hughes, Stead, & Lancaster, 2007). Varenicline is a partial nAChR agonist that reduces nicotine craving and withdrawal symptoms by maintaining moderate levels of dopamine (acting as an agonist) and also reduces smoking satisfaction (acting as an antagonist) (Cahill, Stead, & Lancaster, 2008). However, the efficacy of all currently available pharmacological cessation aids is modest (1.5–3-fold increased chance of quitting compared to unaided quitting), relapse is common and uptake by smokers remains low.

Reducing the Addictiveness of Cigarettes

An understanding of the neuroscientific basis of addiction might also raise the possibility of developing less addictive or less harmful tobacco
products. So-called light or low nicotine/tar cigarettes were first marketed by the industry in response to health concerns and were encouraged by government and non-government public health organizations in the mistaken belief that lowering the tar and nicotine yields of cigarettes would reduce health risks for smokers (King, Carter, Borland, Chapman, & Gray, 2003). These cigarettes proved to be popular with smokers but failed to reduce harm or addiction because of compensatory smoking, such as inhaling more deeply, smoking more cigarettes and more of each cigarette, and blocking ventilation holes designed to dilute smoke exposure (National Cancer Institute, 2001; Stratton, Shetty, Wallace, & Bondurant, 2001). It is now known that the industry designed these cigarettes to produce low nicotine yields when smoked in a Federal Trade Commission (FTC) smoking machine, while knowing from internal research that smokers would compensate to obtain their usual level of nicotine (National Cancer Institute, 2001).

There has been renewed interest in regulating cigarettes to make them less addictive by lowering their nicotine content to a level that would not sustain smoking. Unlike light cigarettes, it is possible to produce cigarettes with genuinely reduced nicotine content. An example of one such product that was marketed as a quitting aid was Vector Tobacco’s Quest cigarette, which was produced with genetically modified tobacco plants. These were available in doses of 0.6 mg, 0.3 mg and 0.05 mg of nicotine, allowing the smoker to move gradually from their regular cigarette to the denicotinized version. These and other examples of reduced or denicotinized cigarettes, such as Philip Morris’ Next cigarettes, appear to have been market failures, probably because smokers found them unattractive.

There are several potential risks with a strategy of reducing the nicotine content of cigarettes. First, there is still likely to be some compensatory smoking that could result in greater exposure to the harmful constituents of tobacco smoke (Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007). One study found increased carbon monoxide exposure in those randomized to a 0.3 mg nicotine cigarette, suggesting compensatory smoking, but reduced exposure and greater quitting among those randomized to one with only trace nicotine levels (0.05 mg) (Hatsukami, Kotlyar, et al., 2010). Other studies have found only minimal smoking compensation with reduced or denicotinized cigarettes (Hatsukami, Perkins et al., 2010; Walker, Bullen, & McRobbie, 2009).

Second, there are few data on the level of nicotine in cigarettes needed to develop or sustain addiction (Hatsukami, Perkins et al., 2010). Studies of adolescents suggest that dependence can develop at low levels of nicotine exposure and before onset of daily use (DiFranza et al., 2000). Relatively brief or low-level exposure to nicotine also appears to produce neurobiological effects in adults such as desensitization of nAChRs
and long-term potentiation of the excitatory transmission to the brain reward centers (Hatsukami, Perkins et al., 2010). There is also likely to be substantial individual variability due to genetic, metabolic and social factors in the threshold dose required for nicotine’s reinforcing effects (Hatsukami, Perkins et al., 2010). Third, if addicted smokers do not find these cigarettes satisfying, they may turn to black market tobacco with higher nicotine content (West & Hall, 2008).

**Tobacco Harm Reduction**

If addiction produces neurobiological changes that make quitting difficult or even unachievable then there is a strong case for attempting to reduce the harm caused by tobacco addiction by encouraging smokers who are unable or unwilling to quit to switch to less harmful ways of using nicotine. The most promising such substitutes for cigarettes are NRT products (e.g. gum, lozenge, microtab, inhaler, oral pouch), electronic nicotine delivery systems (ENDS; e.g. e-cigarettes) and low-nitrosamine varieties of smokeless tobacco (SLT) (e.g. Swedish snus) (Gartner & Hall, 2010).

The health risks of SLT are probably larger than those for NRT because they may include an increased risk of some cancers (Luo et al., 2007), and only limited data are available about the potential health effects of ENDS (Laugesen, 2008; Laugesen, Thornley, McRobbie, & Bullen, 2008; Vansickle, Cobb, Weaver, & Eissenberg, 2010). All these alternative sources of nicotine avoid exposing the user or bystanders to the combustion products of smoked tobacco. They also contain much lower levels of tobacco-specific nitrosamines, the main carcinogens in tobacco products. There is good evidence that individual smokers who switch from cigarettes to these products achieve large health gains from the lower risk of lung and other cancers including oral cancer, respiratory diseases such as chronic obstructive pulmonary disease and cardiovascular disease (Broadstock, 2007; Gartner, Hall, Vos, et al., 2007; Lee & Hamling, 2009; Lee, 2007; SCENIHR, 2008). Evidence from Sweden also suggests that tobacco harm reduction policies have reduced tobacco-related disease at the population level (Foulds, Ramström, Burke, & Fagerström, 2003).

These non-abstinence-based tobacco policies remain controversial, largely because of the past experience with “light” cigarettes. Some tobacco control advocates reject any policy goal other than the elimination of nicotine use, often on moral grounds, because these policies may perpetuate nicotine dependence (Ritter, 2004; Swedish Network for Tobacco Prevention, 2006). Some critics of harm reduction believe that any health risk from continued use of less harmful nicotine substitutes, no matter how small, is too great for its use to be encouraged. However, a requirement of zero risk is an unrealistic standard that is not applied
to other health interventions, such as using seatbelts and airbags in automobiles, diagnostic X-rays or pharmaceutical medications and surgical procedures that simply require evidence that the benefits outweigh the risks (Chapman, 2007).

Those who do not object to tobacco harm reduction in principle may have doubts about the size of the health benefits from persuading smokers to switch to SLT. These critics are often skeptical about the connection between increased snus use in Swedish men and the decline in smoking prevalence and tobacco-related disease observed in Sweden over the past 20 years (Stratton et al., 2001; Warner, 2002). However, the difference in healthy life expectancy and overall mortality risk between smokers who quit using all tobacco products and smokers who switch to low-nitrosamine SLT is likely to be very small (Gartner, Hall, Vos, et al., 2007; Henley et al., 2007). Furthermore, Sweden has achieved substantial reductions in tobacco-attributable mortality despite a high prevalence of snus use among men (Ramström, 2000), suggesting that the risks from snus use are much lower than those from tobacco smoking.

There are also concerns that the reduction in health risk for individual smokers who switch to less harmful nicotine products will be outweighed by adverse effects if SLT is a gateway to smoking in adolescents, deters smokers from quitting or encourages former smokers to resume smoking (Pierce, 2002; Stratton et al., 2001; Warner & Burns, 2003). Currently available NRT products have not been shown to encourage non-smokers to take up smoking (Gerlach, Rohay, Gitchell, & Shiffman, 2008; Klesges, Johnson, Somes, Zbikowski, & Robinson, 2003). In Sweden there have been no increases in smoking among adolescent males, who have been the heaviest users of snus (Foulds et al., 2003). Instead, it is more common for smokers to switch to snus than for snus users to switch to smoking; and snus is a commonly used cessation aid for Swedish male smokers (Fagerström & Schildt, 2003; Gilljam & Galanti, 2003; Ramström & Foulds, 2006).

American studies of SLT have shown more variability. Some echo the Swedish experience (Ault, Ekelund, Jackson, & Saba, 2004; O’Connor, Kozlowski, Flaherty, & Edwards, 2005) but others have reported that more young SLT users graduate to smoking (Haddock et al., 2001). It is challenging to quantify how much smoking is attributable to prior SLT use because it is difficult to determine whether smokers who used SLT before cigarettes would have become smokers in the absence of SLT use. In the USA, such gateway effects may also be unwittingly facilitated by health authorities who claim that the health risks of SLT are not different from those of cigarette smoking (Kozlowski & Edwards, 2005; Kozlowski & O’Connor, 2003; Waterbor et al., 2004).

Some critics of harm reduction are concerned that smokers will use SLT products when they cannot smoke and continue to smoke when they
can, rather than switch completely. Such dual use could deter quitting by removing the motivation to quit provided by public, workplace and household indoor smoking bans (Fichtenberg & Glantz, 2002; Gartner, Hall, Chapman, & Freeman, 2007). However, there is nothing preventing smokers using currently available products, such as NRT, in this way. Similarly, there are claims in the popular media in the UK that the e-cigarette is being used in response to smoking bans in pubs and clubs (Sikora, 2007). However, no studies have examined the patterns of use of regular cigarettes and ENDS to confirm whether these lead to quitting or sustained smoking.

Another concern expressed about tobacco harm reduction policies is that the tobacco industry will use these products to subvert population tobacco control policies and promote cigarette use (Chapman, 2007). There are good reasons to anticipate such subversive use of harm reduction by the industry. The US tobacco industry has been engaged in racketeering behavior in the past (Bonnie, Stratton, & Wallace, 2007; Brandt, 2007). It also deceived the public about the addictiveness and health risks of its products. However, many of the risks of tobacco industry subversion can be minimized through legislative controls.

Some tobacco control advocates have also suggested removing industry involvement in the retail supply of tobacco products by implementing a regulated market model (Borland, 2003). Under such a proposal, a government agency with a mandate to reduce the harm from nicotine use would have full control over how tobacco products are sold to the public. Other alternative proposals include market-based incentives that move the tobacco industry away from producing the most harmful to the least harmful tobacco products. Alternatively, legislation could (1) define a maximum amount of smoked tobacco that could be produced and marketed, gradually reducing this limit over a prescribed span of time (Federal News Service, 2007), (2) progressively reduce the nicotine content of smoked cigarettes to zero (Bonnie et al., 2007; Henningfield et al., 1998), or (3) impose increasingly high rates of taxation on the nicotine content of smoked cigarettes. These strategies would need to be combined with current tobacco control policies to make the use of low-harm, non-smoked tobacco products more attractive to current tobacco users than smoked tobacco.

THE ETHICS OF NICOTINE AND TOBACCO PRODUCT REGULATION

The current regulation of nicotine and tobacco products continues to be inconsistent with what neuroscience research tells us about the relative addictiveness and harmfulness of individual products. The most
harmful and addictive products (smoked tobacco) are still subject to the least regulation; the least harmful (NRT) must conform to the strict requirements covering medicines and therapeutic goods; and products that lie in between these extremes, but closer to the lower end of the risk spectrum (e.g. low-nitrosamine SLT), are subject to varying regulation that ranges from sales bans to regulatory requirements similar to smoked tobacco products.

Regulating smoked tobacco products to reduce harmfulness will face substantial practical obstacles. It will also require significant resources and could cause potentially adverse effects, such as falsely reassuring smokers that cigarettes are safe. A rational approach to tobacco and nicotine product regulation should involve progressively greater taxation and restrictions on the sale of the most harmful products combined with the least regulation and lowest rates of taxation on NRT and low-nitrosamine SLT. Those aspects of smoked tobacco that increase their attractiveness and addictiveness and are more amenable to regulation (e.g. banning the addition of flavorings, packaging and marketing, etc.) should be regulated. As there is good evidence that non-smoked tobacco products can be manufactured to contain lower levels of toxins (Österdahl, Jansson, & Paccou, 2004; Stepanov, Jensen, Hatsukami, & Hecht, 2006), maximum limits on key toxins, such as tobacco-specific nitrosamines and other carcinogens, should be enforced in addition to regulation of factors that contribute to attractiveness and addiction (Gartner, Hall, & McNeill, 2010).

CONCLUSION

Neuroscience research has contributed to the understanding of the reasons for smoking and to the development of new cessation aids. An acceptance of a neurobiological model of addiction could lead to greater smoking cessation if this model increases smokers’ belief in their ability to quit successfully. However, the most successful strategies for reducing smoking prevalence remain in the domain of broad public health measures such as high taxation on tobacco products, anti-smoking counter-advertising campaigns, workplace and public smoking bans, and measures that reduce the visibility and attractiveness of tobacco products, such as retail display bans and mandatory plain packaging laws. Tobacco harm reduction options, such as non-tobacco recreational nicotine products and non-smoked low toxin tobacco products, may also contribute to reducing tobacco-related harm. Researchers and policy makers need to balance the promise of new methods based on a neurobiological understanding of addiction with these other population-wide policies if the harms of tobacco addiction are to be further reduced.
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CONCLUSION
4. ADDICTION NEUROSCIENCE AND TOBACCO CONTROL


II. TREATMENT
CONCLUSION


II. TREATMENT
# 5

Emerging Neurobiological Treatments of Addiction: Ethical and Public Policy Considerations

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## Outline

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Addiction is a neuropsychiatric disorder that shortens life, causes morbidity for affected individuals and can adversely affect others, such as spouses, children, family members, workmates and the community. Relapse rates after treatment are high. Pharmaceutical and other medical assistance markedly improves the likelihood of abstinence, but only 40–60% of patients will achieve 12 months of continuous abstinence after treatment (McLellan, Lewis, O’Brien, & Kleber, 2000). Recent developments in neuroscience (see Chapters 1 and 2 in this volume) promise to substantially improve our ability to assist addicted individuals to abstain from using drugs and, more speculatively, to provide a cure for drug addiction. Technological innovations in neuroimmunology, the development of sustained-release forms of medications and neurosurgery are among the potential candidates. Some of these approaches have been used in limited but often controversial situations. It is the authors’ contention that before they become more widely used, there needs to be a considered analysis of the socio-ethical implications of their use, including their potential misuse and harms that may arise from their use in particular populations. This chapter will also examine prospective neurobiological interventions on the horizon and discuss some of the ethical and social challenges that may arise from their future use.

ETHICAL AND SOCIAL CHALLENGES IN ASSESSING NEW NEUROBIOLOGICAL TREATMENTS OF ADDICTION

There has been significant debate about whether addiction is best understood as an issue of moral impropriety or a medical disorder (Carter, Capps, & Hall, 2009). Some scholars argue that addiction is simply an excuse to justify continued use of illegal and prospectively harmful recreational drugs (Davies, 1997; Szasz, 1975). Others hold that neuroscience research supports a view that addiction is a brain disorder (Dackis & O’Brien, 2005; Leshner, 1997). Neuroscience has shown how the chronic use of addictive drugs produces long-lasting neurochemical changes in regions of the brain thought to be involved in motivation, learning and decision making. These changes are believed to make abstinence from drug use difficult (see Chapter 1 in this volume). This view is most forcefully expressed in the “brain disease” model of addiction (Leshner, 1997).

Addiction is, however, a highly stigmatized condition that causes significant social harm, and elicits strong moral and political responses that discourage the idea of promulgating a medical excuse. This is sometimes called the “choice” or “moral” view (Pescosolido, Monahan, Link,
Both of these responses, along with more moderate views, may influence the type of addiction research that is publicly funded and affect how and to whom new treatment technologies and therapies are made available.

The use of neurobiological treatments for addiction can often serve competing goals. The usual aim of medical treatment is to alleviate or cure an affected person’s condition. However, the public funding of treatment and research in addiction is often motivated by the aim of reducing the burden that addicted drug users impose on society. The result is a conflict between the therapeutic goal of treating a patient and the social aims of reducing the social costs of addiction. Sometimes, the strong political desire to reduce the harm that addiction causes can result in the use of new interventions before their safety and effectiveness have been rigorously assessed. This has been the case, for example, in Australia, where naltrexone implants have been inserted in thousands of opioid-dependent individuals in the absence of clinical trials demonstrating their safety and efficacy (Wodak, Ali, Henry, & Sansom, 2008).

Often the media (BBC News, 2007) and sometimes academics (Caplan, 2008) emphasize the potential social benefits of new neurobiological forms of addiction treatment that have not been comprehensively evaluated in terms of their clinical efficacy or social implications. However, it is important that the safety and efficacy of any new drugs are assessed primarily in terms of their expected benefits for addicted individuals rather than solely for their social benefits, as would be the case for treatments in other areas of medicine. As will be argued below, an overemphasis on the moral model of addiction can lead to unjustified use of treatments under conditions of compulsion and coercion.

An uncritical acceptance of the brain disease model of addiction may also have unintended negative consequences (Carter et al., 2009; Carter & Hall, 2007a, b). An overemphasis on the neurobiological causes of addiction can be seen as a warrant to the use of invasive or risky neurobiological treatments. Neurobiological treatments targeted at the individual may come at the expense of broader social approaches to reduce drug use such as taxation, education and welfare initiatives, or a failure to address the social problems that promote drug use and poor treatment outcomes. A more balanced view may produce a more effective policy on addiction treatment that takes into account the medical and social conditions of addiction. Below, the challenges to addiction policies are outlined and the authors suggest how such a moderate view might be articulated.

Clinicians, researchers and policymakers will also need to consider the opportunity costs in researching and developing new neurotechnologies to treat addiction (see Chapter 15 in this volume). It may make little sense to develop new, expensive forms of treatment that are unlikely to
be more cost-effective than existing treatments that society is unable or unwilling to provide to those who would benefit from them.

Successfully encouraging pharmaceutical companies to invest in developing new drugs to treat addiction is another major challenge. Many companies are unwilling to be involved in addiction research given the stigma associated with its clientele, and doubts arise about whether addicted individuals will have the capacity (or governments the inclination) to pay for any new treatments that are developed. Industry may also not wish to test drugs in the treatment of addiction if they have other potentially more profitable medical uses. There is a possibility that implication in addiction treatment may impact upon these other medical markets (Koob, Lloyd, & Mason, 2009). Given the enormous social cost of drug addiction, there is perhaps an economic and social incentive for governments to invest in developing new pharmacological treatments for addiction. A major hurdle continues to be the lack of political will to accept that treating addiction is complementary, and possibly preferable, to imprisonment. Opinion may be swayed by balanced debates about the current state-of-the-art science, accompanied by a clear understanding of the ethical implications of the kinds of treatment envisaged. Few governments, with the exception of the USA, have allocated the necessary resources to addiction neuroscience. In this respect, partnerships between government and industry may be the key to stimulating this research (Koob et al., 2009).

Below, the most promising new treatments suggested by advances in neuroscience research on addiction are examined to illustrate how these ethical and social challenges may arise and be addressed.

**NOVEL PHARMACOLOGICAL TREATMENTS OF ADDICTION**

The most commonly used pharmacological approaches to treat addiction have involved either drug substitution or relapse prevention. In drug substitution, a patient is prescribed a drug that has similar but less harmful effects than the drug that is abused. This drug is referred to as an agonist. In relapse prevention patients are often given an antagonist, that is, a drug that blocks or attenuates the effects of the abused drug. For some types of addiction, such as psychostimulant addiction, no effective agonist or antagonist drugs have been developed despite significant research conducted in the pursuit of such drugs.

Neuroscientists have more recently begun to look for novel pharmacological interventions that are informed by a more sophisticated understanding of the neurobiology of addiction. Drugs of addiction interfere with key neurotransmitter systems in the brain, such as dopamine, opioids, noradrenaline, γ-aminobutyric acid (GABA) and glutamate, in
ways that lead to the development of tolerance, withdrawal symptoms and drug cravings on cessation of use. The molecular pathways involving these neurotransmitters represent potential pharmacological targets to reduce the symptoms of addiction and harmful effects of addictive drug use. Therapeutic targets include drugs that:

- improve executive control (e.g. modafinil, methylphenidate)
- dampen memories that can trigger craving and relapse (e.g. propranolol)
- reduce or eliminate craving (e.g. acamprosate, bupropion, disulfiram, naltrexone)
- mitigate the aversive or negative affect aspects of drug addiction (e.g. corticotrophin-releasing factor receptor antagonists).

It is not possible in this chapter to evaluate the ethical and policy considerations raised by the 80-plus drugs that are currently under investigation as potential treatments (Nutt, 2008). Interested readers should see Koob et al. (2009), Goodman (2008) or Jupp and Lawrence (2010) for more detailed analyses. Instead, a discussion follows on some of the ethical issues raised by the use of a class of drugs that has attracted recent attention and is illustrative of the ethical concerns of addiction treatment approaches: anti-craving drugs.

**Anti-craving Drugs**

Anti-craving drugs aim to reduce relapse by preventing or reducing the intensity of cravings (O’Brien, 2005). Drugs for which there is some evidence of anti-craving effects, from either animal studies or human clinical trials, include acamprosate, bupropion, disulfiram, ondansetron and naltrexone. One potential problem with anti-craving drugs is that their long-term use may have subtle, but significantly adverse effects on patient mood and motivation. It has already been suggested, for example, that long-term naltrexone use may produce dysphoria and depressive symptoms (Dean et al., 2006; Miotto, McCann, Basch, Rawson, & Ling, 2002), and attenuate the rewarding or hedonic effects of everyday “authentic” activities such as eating (Yeomans & Gray, 2002), sex (Murphy, Checkley, Seckl, & Lightman, 1990) and physical exercise (Daniel, Martin, & Carter, 1992).

The concern with such treatments is that they may change a person’s behavior in unexpected and sometimes unwanted ways. Agents normally act for reasons that coherently interrelate their desires and choices. We are partly motivated by goals and use reason to choose the best means to achieve them. These goals, and our realization of them, have been loosely described as our “sense of self”. It is this purposefulness that gives meaning to our actions. Some bioethicists have voiced concern about drugs that interfere with or undermine this sort of authentic action (Kass, 2003).
While the use of drugs by healthy adults to alter their sense of self may be an important neuroethical concern (Glannon, 2006; Levy, 2007), the situation is arguably very different in the case of addicted individuals who already have a distorted concept of self. Addiction may have significantly affected their choices and constrained the kind of life that is open to them. It also produces significant emotional, physical and psychological harms that limit their choices. A drug that is able to ameliorate these personal conditions could more correctly be seen as enabling, rather than impairing, self-hood.

Some commentators have argued that only drugs that block the agonist action of addictive drugs, such as naltrexone, should be used to treat addiction. The ethical objection is that agonist treatments elicit the same loss of self as the drug of addiction. These critics further argue that using drugs with agonistic or rewarding effects only perpetuates addiction.

A categorical rejection of the therapeutic use of agonist drugs may lead to the use of anti-craving drugs at the expense of more effective treatments, such as methadone and buprenorphine for treating opioid addiction; for example, both of these are prohibited in Russia (Krupitsky, Zvartau, & Woody, 2010) and only offered in a limited manner in many parts of Asia. It is important that medications are selected because they have been shown to reduce the harm that addiction causes—where the benefits outweigh any side-effects – and not because their psychopharmacological action is more morally attractive. The worst kinds of judgments, based on this latter premise, might lead to not treating addiction at all, i.e. relying on purely penal sanctions, or administering ineffectual or even harmful treatments.

NOVEL APPROACHES TO RELAPSE PREVENTION

Relapse to drug use is one of the greatest impediments to successfully overcoming addiction. Once an individual relapses, they often return to chronic and harmful drug use. A significant amount of research has been invested in developing treatments that reduce the length and severity of these relapses. One method has been to provide a prophylaxis against relapse by blocking or attenuating the effects of drugs. There are two technologies that have received significant research attention for this purpose: drug vaccines and sustained-release medications.

Drug Vaccines as a Prophylaxis Against Relapse

Immunotherapies, such as a nicotine vaccine, block the psychoactive effects of a drug either by stimulating the immune system to produce antibodies (active immunization) or through the introduction of synthetic monoclonal antibodies into the bloodstream (passive immunization)
(Harwood & Myers, 2004). These antibodies bind to the target drug, preventing it from acting on receptors in the brain (Kosten & Owens, 2005; Nutt & Lingford-Hughes, 2004). Animal studies have shown that drug vaccines reduce the amount of a drug that reaches the brain. They also reduce the amount of dopamine that is released in the nucleus accumbens (NAcc), the rate of clearance across the blood–brain barrier, the volume of drug distribution and self-administration of the target drug (Kosten & Owens, 2005). Vaccines have a potential advantage over traditional small-molecule pharmacological approaches that require daily dosing (e.g. agonists and antagonists): they are long-lasting, improving treatment compliance; highly specific in their effects; and because they remain in the blood stream, produce no adverse effects on the central nervous system (Kosten & Owens, 2005) as can drugs such as bupropion and varenicline (e.g. suicidal ideation).

Vaccines have been developed against opioids, nicotine, cocaine, methamphetamine and phencyclidine (PCP) (Kantak, 2003), although the majority of research has focused on nicotine (one of the most harmful addictive drugs) and cocaine (where there are no effective pharmacological treatments). Vaccination against nicotine, for example, could reduce relapse to smoking in abstinent smokers during the first few months after quitting, when most smokers relapse (Vocci & Chiang, 2001). Ex-smokers would be given a series of vaccinations during the critical period after cessation when most are vulnerable to relapse, in combination with behavioral programs to reduce the chances that a “slip” will lead to a return to regular cigarette use. While a nicotine vaccine could be circumvented by increasing the dose of nicotine, attenuating the rewarding effects of nicotine may be enough to reduce rates of relapse to daily smoking (Hall, 2002; Vocci & Chiang, 2001).

Several phase II clinical trials for cocaine and nicotine vaccines have been reported (Cornuz et al., 2008; Kosten et al., 2002; Martell et al., 2009). They found that only one-third of participants developed sufficient antibodies against the drug to prevent a relapse to drug use. Those individuals that developed the highest level of antibodies derived the most benefit from the intervention. Increasing the number and/or size of doses may increase immunogenicity and effectiveness, but may also increase any potential side-effects. New formulations of vaccines are currently in development that may provide greater immunoprotection against relapse (Moreno et al., 2010).

**Sustained-Release Treatments: Depot Medications and Drug Implants**

Depot injections (typically oil suspensions that are injected into the muscle) and drug implants (larger polymer-based implants that are
surgically inserted under the skin) are long-acting forms of medications that are used to treat addiction. These slowly release medications to counteract the effects of addictive drugs over weeks and months. Sustained-release technologies most often employ antagonists (e.g. naltrexone) that block the effects of the target addictive drugs (e.g. opioids). Like vaccines, sustained-release medications also have the potential advantage over traditional oral treatment medications of increasing compliance because they only need to be taken monthly or less often.

Several sustained-release preparations of the antagonist naltrexone, for alcohol and opioid dependence (Comer et al., 2002; Kranzler, Modesto-Lowe, & Nuwayser, 1998; Krupitsky & Blokhina, 2010), have been developed. The US Food and Drug Administration (FDA) approved the use of the naltrexone implant Vivitrol for the treatment of alcohol in 2006, and more recently for opioid dependence (FDA, 2010). Several slow-release preparations of the opioid partial agonist buprenorphine have also been trialed for the treatment of opioid dependence (Ling et al., 2010; Sigmon, Moody, Nuwayser, & Bigelow, 2006; Sobel et al., 2004; White et al., 2009). Sustained-release formulations of lofexidine may be used in the treatment of nicotine dependence (Rawson, McCann, Hasson, & Ling, 2000) and implantable flumazenil is being developed to treat benzodiazepine dependence (Nutt & Lingford-Hughes, 2008).

Ethical Issues in Pharmacologically Assisted Relapse Prevention

If broadly effective vaccines and sustained-release drugs are developed, a number of ethical issues ought to be considered before they are routinely used to treat addiction.

First, vaccines and sustained-release drugs may prove counterproductive if an individual attempts to overcome their blocking effects by increasing their drug dose. Drugs such as nicotine and cocaine cause significant physical damage outside their impact on the central nervous system (e.g. cardiovascular disease), and any increase in use is likely to be harmful. Moreover, those who ambivalently agree to vaccination may also switch to using other possibly more dangerous drugs, different and more harmful routes of administration (e.g. intravenous injection) or much higher doses than usual, risking overdoses (Murray, 2004). The extent to which these patterns of drug use will manifest is as yet unanswered. It is possible that readily available and effective vaccines could make experimentation with drugs seem less risky, and therefore unwittingly increase drug use. It is also possible that blocking the rewarding effects of a particular drug may reduce its use.

Second, vaccines and implants do not address problems that may be associated with compulsive drug use and addiction. 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 & Franey, 2004). Thus, while vaccines may find a place in the management of addiction, they are unlikely to be magic bullets. Addiction can be a chronic condition and vaccines, like traditional addiction medications, will need to be used in conjunction with behavioral treatments if life-long abstinence is to be achieved.

Finally, the use of a vaccines or implants may also block the action of agonists or partial agonists (e.g. methadone and buprenorphine for opioid dependence). This would prevent the use of substitution therapies while vaccination remains effective. Vaccines and implants may also block the action of medications used in the treatment of other conditions (e.g. opioid analgesics for pain relief) (Ashcroft & Franey, 2004).

None of these issues precludes the therapeutic and voluntary use of effective vaccines or sustained-release medications to treat addiction and reduce problematic drug use, if they prove safe and effective in clinical trials. They do mean, however, that care is needed in how these treatments are provided outside the conditions of clinical therapy.

Use of Vaccines and Implants Under Legal Coercion

If effective immunotherapies or implants for illicit drugs such as cocaine and heroin are developed, they could be used in situations that are inherently coercive (see Chapter 8 in this volume). Vaccines and implants might be used with addicted persons in the justice system to whom addiction treatment is offered in return for a reduced sentence or avoiding imprisonment. Given the prevalence of drug use in prisons, vaccination could potentially be required when entering prison. Addicted women could be compelled to accept a vaccine or implant in order to protect the fetus during pregnancy from the direct effects of substance use, or to help the mother to remain abstinent to maintain the prospective health of the newborn. These treatments could also be required of addicted parents if they become involved in the child welfare system, with the threat of losing custody of children if they fail to comply.

An even more controversial option would be compulsory use of vaccines or sustained-release medications. For example, Caplan (2008) and others (Marlowe, 2006; Sullivan et al., 2008) have argued that the brain disease model of addiction indicates that addicted individuals lack autonomy regarding decisions to use drugs and so may be compulsorily treated in their best interests (Caplan, 2008; Charland, 2002). However, the claim that addicted individuals are always incapable of making autonomous decisions about their drug use is not supported by behavioral, neuroscientific or social scientific evidence (see Chapter 7 in this
This would make the coercive use of vaccines ethically contentious. At the very least, the safety and effectiveness of these technologies should be established in volunteers before they are trialed in mandated situations.

### PSYCHOPHARMACOLOGICAL HARM REDUCTION

One possible extension of existing forms of harm reduction approaches to addiction treatment, such as methadone maintenance treatment, is engineering safer forms of recreational drugs. Professor David Nutt has suggested that pharmacology and neuroscience be used to engineer a recreational drug that is safer than alcohol: a GABA partial agonist, for example, that possesses most of the socially desirable properties of alcohol without its biological toxicity (Nutt, 2006). There are, however, social implications and regulatory obstacles to such products being introduced.

There are some doubts, as discussed above, about whether the pharmaceutical industry will invest the substantial funds needed to undertake preclinical and clinical research and development on such a drug. 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 perverse regulatory standard that insists upon much tighter regulations for less harmful nicotine products, such as smokeless tobacco (e.g. snus), than are imposed on the far more dangerous smoked tobacco products (Gartner et al., 2007). These regulations provide major disincentives to pharmaceutical investment in harm reduction approaches.

Despite these impediments, safer recreational drugs may still emerge either as a by-product of basic pharmacological research or following therapeutic use for an unrelated indication. Their recreational potential may subsequently be discovered by people who experiment with illicitly sourced or prescribed drugs, as has occurred with most currently used recreational drugs. 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 happened with GHB (γ-hydroxybutyric acid) (Gahlinger, 2004). The experience with GHB suggests that the political and regulatory impulse would be to ban any drug used by young adults by making it a criminal offence to produce, sell or possess it. This outcome would accord with the conservative regulatory climate in the USA and other developed countries such as Australia, Canada and many European nations, which has ensured that no new recreational drug has been approved for use in well over a century.
NEUROSURGICAL "CURES" OF ADDICTION

Drug-addicted individuals are often desperate for an effective and relatively painless end to their addiction, and are therefore susceptible to the promotion of heroic medical cures. Neurobiological rationales for these treatments often lend them a spurious scientific credibility that distracts from the lack of evidence for their safety and efficacy. One example of this has been neurosurgical treatments for addiction. Two kinds of treatment that have been used or advocated as potential cures for addiction are discussed.

Stereotactic Ablative Neurosurgery

A novel and so far rarely used treatment for addiction is neurosurgical ablation of brain structures involved in addiction. Neurosurgery is the most invasive and permanent form of treatment, and is generally considered a treatment of last resort in a few cases of severe, treatment-resistant psychiatric disorders (Hall, 2006; Valenstein, 1986).

Russian and Chinese surgeons have used neurosurgical procedures to treat heroin addiction: 305 patients were reportedly operated on in Russia (Walsh, 2002) and over 500 in China (Xinhua News Agency, 2005). In China, stereotactic surgery was used to destroy the NAcc (Gao et al., 2003), the brain region where the rewarding effects of opioids and other drugs are thought to be mediated (Robbins et al., 2007). Russian neurosurgeons lesioned the cingulate gyrus, a brain region that has previously been removed to treat obsessional disorders (Orellana, 2002). International criticism prompted both countries to abandon the controversial treatment in 2003, but a recent report suggests that clinicians in China have commenced a clinical trial of neurosurgical treatment of opioid addiction (Goff, 2005) and have trialed the same procedure in alcohol-dependent individuals (Wu et al., 2010).

These reports raise a number of important ethical concerns (Hall, 2006). First, there is no compelling medical reason to use neurosurgery to treat heroin addiction. There are effective forms of treatment that substantially reduce illicit opioid use and stabilize the lives of heroin addicts (e.g. substitution or maintenance treatment on methadone or buprenorphine) (Amato et al., 2005; Mattick, Breen, Kimber, & Davoli, 2009). However, methadone maintenance treatment was not readily available in China at that time (Cohen, 2004), and its use is prohibited by law in Russia (Krupitsky et al., 2010).

Second, there are major concerns about the safety and efficacy of these neurosurgical procedures. Stereotaxic neurosurgery is an invasive and permanent 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. While this may be true, these results come from uncontrolled studies that did not properly evaluate the cognitive and behavioral effects of destroying such important neurological regions as the NAcc and anterior cingulate gyrus (Gao et al., 2003; Medvedev, Anichkov, & Poltakov Iu, 2003).

Third, there are major concerns about the effects of producing irreversible lesions in neural centers that are implicated in the control of food intake, sexual behavior and the formation of social bonds. At particular risk are the patient’s responsiveness to reward, their motivation, mood states, risks of depression and suicide, and capacity for planned action. No study to date has adequately assessed such effects.

Finally, there are doubts about whether patients have given free and informed consent because of the circumstances in which neurosurgery has been used (Kleinig, 1985). Chinese policies toward opioid dependence are largely punitive and retributive, with imprisonment and compulsory detoxification as first line responses. In such circumstances it is difficult to obtain free and informed consent without being coercive, particularly where effective treatments are not available.

Deep Brain Stimulation

Deep brain stimulation (DBS) is another form of neurosurgery that has been proposed as a treatment of addiction (Bauer, Pohl, Klosterkotter, & Kuhn, 2008; Krack, Hariz, Baunez, Guridi, & Obeso, 2010; Lu, Wang, & Kosten, 2009). It involves inserting electrodes into specific brain regions to modulate neural activity via a battery-controlled external stimulator in the patient’s chest. DBS has been used to treat intractable cases of Parkinson’s disease for almost three decades, and is being trialed in intractable psychiatric conditions, including Tourette’s syndrome, obsessive–compulsive disorder (OCD) and depression (Krack et al., 2010).

DBS is often described as a reversible alternative to neurosurgery, but is nonetheless an invasive intervention that carries significant risks (Bronstein et al., 2011). Estimates of surgical complications vary markedly, largely due to differences in the competence of the teams and hospitals performing the operation, and variations in the procedure: a recent meta-analysis estimated that approximately 11% of patients have adverse events from surgery (Kleiner-Fisman et al., 2006). Estimates of major adverse surgical outcomes, such as intracerebral hemorrhages and death, range from 0 to 10% (Bronstein et al., 2011). However, a consensus view is that the likely prevalence of intracerebral hemorrhage was probably less
than 2% in most centers (Bronstein et al., 2011). The successful insertion of stimulating electrodes can also cause serious infections and produce cognitive, behavioral, emotional disturbances and irreversible psychosocial harm (Kleiner-Fisman et al., 2006). Given the risks associated with any neurosurgery, there needs to be a careful assessment of the risks and benefits of the procedure before DBS should be used to treat addiction.

DBS of the dopaminergic reward pathway has been shown to reduce the self-administration of addictive drugs in animal models of addiction (Knapp, Tozier, Pak, Ciraulo, & Kornetsky, 2009; Levy et al., 2007; Liu et al., 2008; Rouaud et al., 2010; Vassoler et al., 2008). Evidence on the effects of DBS in humans consists of case studies of its impact on addictive behavior in patients treated for other disorders (Carter, Bell, Racine, & Hall, 2010). While initial reports were positive (Ardouin et al., 2006; Witjas et al., 2005), DBS was found to exacerbate addictive behaviors in others (Lim et al., 2009; Smeding et al., 2007).

There have been five reports of the use of DBS to treat addiction to nicotine, alcohol and heroin (Heinze et al., 2009; Kuhn et al., 2007, 2009; Mantione, van de Brink, Schuurman, & Denys, 2010; Müller et al., 2009). In the first, a woman was unsuccessfully treated for agoraphobia by bilateral DBS of the NAcc, incidentally ameliorating her comorbid alcohol dependence (Kuhn et al., 2007). The same group reported smoking cessation in three of 10 patients who underwent DBS of the NAcc for Tourette’s syndrome, OCD or anxiety, but over two-thirds derived little benefit (Kuhn et al., 2009). A 47-year-old woman treated with DBS of the NAcc for treatment-refractory OCD quit smoking and lost weight after surgery (Mantione et al., 2010). However, these changes emerged 10 months after her OCD symptoms disappeared, suggesting that this may have been an indirect effect of successful treatment of her OCD.

There has only been one report of the effects of DBS used specifically to treat addiction. Craving for alcohol and alcohol consumption were greatly reduced in three long-term, treatment-refractory alcohol-dependent individuals who underwent DBS of the NAcc (Heinze et al., 2009); two were abstinent after 1 year and a third had markedly reduced their drinking (Müller et al., 2009). These were, however, small case studies with short-term follow-up and no comparison group (Carter et al., 2010). The history of neurosurgical treatment in psychiatry cautions against uncritically accepting “positive results” from uncontrolled and often selectively reported clinical case series (Valenstein, 1986).

This is a poor evidence base to support trials of DBS in addiction. The use of DBS in debilitating conditions such as Parkinson’s disease is justified by the severity of the condition and its inexorably deteriorating course. Patients with Parkinson’s disease who no longer respond to pharmacological treatment face a course of irreversible deterioration in motor function and increasing disability. In contrast, addiction does
not usually follow an inexorable path to severe disability and death; it is generally more amenable to pharmacological and psychotherapeutic treatment, so drastic remedies are less justifiable. In fact, many of the failures of addiction treatment are due to inadequate access to well-run and optimally provided forms of existing treatment (Strang et al., 2010); a situation that would be exacerbated by an increased use of DBS to treat drug addiction. This suggests that the very uncertain benefits of DBS in alleviating the symptoms of addiction do not outweigh the known harms associated with the procedure, or the harm of not providing DBS and relying upon currently available treatments provided to the highest standard (Carter & Hall, 2011).

There are other ethical and social issues that would need to be considered in evaluating the use of DBS for addiction. DBS is an extremely expensive procedure, costing about US $50,000 for the operation with US $10,000 ongoing maintenance costs every few years. This would utilize scarce health resources to treat a very small number of addicted patients with the income to pay for it, while failing to treat the majority, and may also impact upon the provision of DBS for other uses, such as Parkinson’s disease, dyskinesia and essential tremor. The opportunity costs of providing DBS, even if it proved to be safe and effective, make such trials a low priority for public funding (Carter et al., 2010; Carter & Hall, 2011).

Managing patient expectations about the limited and uncertain benefit of the treatment is an important challenge (Bell, Mathieu, & Racine, 2009). Addicted individuals are often desperate for a cure, and may have unreasonably high expectations based on uncritical media reports, as has happened with previous psychosurgical enthusiasms (Diefenbach, Diefenbach, Baumeister, & West, 1999). Patients will need to understand that DBS will not be a cure for their addiction; it will not eliminate comorbid psychiatric issues or poor social circumstances and will still require ongoing psychosocial support (Carter et al., 2010).

**CONCLUSION**

Neuroscience has the potential to provide powerful new methods for reducing addictive behavior and the harm that it causes. It is important that these treatments be developed and used in ways that take account of the social context in which addiction treatment is provided (e.g. possible conflicts between the public’s desire to reduce societal harm and punish wrongdoers versus the need to treat a medical condition) and the ambivalence of some addicted individuals to stopping drug use (e.g. justifying the use of coercion). The history of addiction treatment is littered with therapeutic enthusiasms prematurely embraced and widely
disseminated by uncritical proponents before the necessary evidence has been collected to evaluate their safety and efficacy. This has often left the field to discover belatedly that these new treatments are at best no better than placebos and, at worst, harm some of their supposed beneficiaries.

If we are to capture the benefits of emerging new types of addiction treatment, these therapeutic mistakes need to be avoided by rigorous evaluation of the safety and effectiveness of these treatments and an appreciation of the ethical issues that can arise from their use. Many of the failures in addiction treatment are the result of poorly run and resourced treatment programs that fail to provide the necessary social and psychological support. It is important that new technological innovations do not become a surrogate for the obligation to provide the necessary social and financial resources needed to overcome addiction, or a way of achieving other social goals, such as punishing harmful behavior.

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II. TREATMENT
Technical, Ethical and Social Issues in the Bioprediction of Addiction Liability and Treatment Response

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INTRODUCTION

Over the past several decades, increased insights into the genetics and neurobiological bases of addiction have raised the possibility that biomarkers, such as genetic tests and measures of brain functioning, will be used to predict an individual’s liability to develop addiction. In the case of addicted people, these biomarkers may be used to match individuals to treatments to maximize their chances of achieving abstinence (Ho et al., 2010; Hutchison, 2010; Singh & Rose, 2009). This chapter critically evaluates the likelihood of these types of “bioprediction” (Singh & Rose, 2009) being realized and considers the ethical issues that would arise if this were to happen.

The focus is on the predictive use of genomic information. Since this possibility was first described over a decade ago (Collins, 1999) a great deal of research has been undertaken to assess the feasibility of genetic tests being used for bioprediction. Many of the same issues may arise if biomarkers based on brain functioning are developed for predicting future disease risk or selecting treatment, but there has been more limited research on this possibility to date (Singh & Rose, 2009).

PREDICTIVE GENOMIC MEDICINE

In 1999, Francis Collins predicted that genomic medicine would revolutionize medicine in the following decade (Collins, 1999). He foresaw medical professionals using genomic information to identify healthy individuals who were at higher risk of developing common diseases, such as cancers and heart disease, and then intervening with those at higher risk to reduce their chances of developing these diseases by changing their behavior (e.g., exercise, healthy diet) or taking drugs such as statins or antihypertensive agents. Collins also foresaw the use of genomic information to personalize medical treatment by using genomic information to match patients to treatments that gave them the best
chance of a good outcome or that reduced the chances of adverse side-effects. Collins imagined, for example, screening smokers for genetic susceptibility to lung cancer and counseling those at high risk to stop smoking. Similarly, optimistic projections have been made by addiction genetics researchers (Uhl & Grow, 2004).

This chapter evaluates these promises in the case of alcohol and nicotine dependence, two leading avoidable causes of premature death and illness globally (Ezzati & Lopez, 2003). Extensive research has been undertaken on the genetics of alcohol and drug dependence, and researchers have discussed potential clinical and public health applications of this research (e.g. Berrettini & Lerman, 2005; Caron, Karkazis, Raffin, Swan, & Koenig, 2005; Lee & Tyndale, 2006).

THE GENETICS OF ALCOHOL AND NICOTINE DEPENDENCE

Twin and adoption studies indicate that genetic factors play a role in alcohol and nicotine dependence. The heritability of alcohol dependence is estimated to range from 50% to 60% (Agrawal & Lynskey, 2008; Ho et al., 2010) with approximately 44% due to specific environmental factors not shared by family members (Kendler & Prescott, 2006). Heritability estimates for nicotine dependence range from 39% to 80% (Li, Cheng, Ma, & Swan, 2003; Vink, Willemsen, & Boomsma, 2005), indicating that susceptibility is influenced by individual genetic make-up as well as environmental factors. There also appear to be both unique and overlapping genetic factors for initiation of alcohol, nicotine and other types of drug dependence (Fowler et al., 2007; Li & Burmeister, 2009).

One of the paradoxes of genomic research is that it has proven difficult to identify alleles that strongly predict susceptibility to common human disorders (Davey Smith et al., 2005). In addiction studies, many positive findings do not replicate (Ho et al., 2010; Li & Burmeister, 2009; Munafò, 2009b) and the minority that have been replicated very modestly predict an increased risk of disease (Ioannidis, 2003). Typically, people with these alleles are only 1.2–1.5 times more likely to develop these diseases than are those who do not have the allele (Ioannidis, Trikalinos, Nizani, & Contopoulos-Ioannidis, 2003).

Research on specific alleles and chromosomal regions has generally identified weak predictors of addiction liability (Ball, Pembrey, & Stevens, 2007). Exceptions are the family of alleles for the high-activity variants of alcohol dehydrogenase (ADH) and the low-activity variants of aldehyde dehydrogenase (ALDH2). People with at least one of these alleles are much less likely to use alcohol and develop alcohol dependence (Ball et al., 2007; Ho et al., 2010). However, individuals with either
of these alleles do not need a genetic test to discover this fact: the ingestion of even small amounts of alcohol induces nausea, palpitations and facial flushing.

Genome-wide scans have revealed associations between nicotine dependence and chromosomal regions that contain a number of genes of possible biological relevance, such as the $\mu_1$-opioid receptor ($OPRM1$), serotonin receptor 5A, $\alpha_2$-nicotinic acetylcholine receptor ($CHRNA2$), $\alpha_{1A}$-adrenergic receptor ($ADRA1A$) and dopamine receptor ($D_1$) genes (Ho & Tyndale, 2007). Candidate gene studies have also proliferated, with mixed results. One meta-analysis found that the most replicated genetic association (Taq1A allele of the $ANKK1$ gene) conferred a modest increase in risk: people with this allele are 1.3–1.5 times more likely to be regular smokers than those without it (Li, Ma, & Beuten, 2004; Munafò, Clark, Johnstone, Murphy, & Walton, 2004). However, the results of another analysis were more equivocal (Munafò, Timpson, David, Ebrahim, & Lawlor, 2009). More recently, a cluster of genes coding for multiple alpha and beta nicotinic acetylcholine receptors, $CHRNA3$, $CHRNA5$ and $CHRNB4$, has been implicated in nicotine dependence, and this association has been well replicated (Greenbaum & Lerer, 2009). However, smokers with risk alleles within this cluster of genes were only about 1.4 times more likely to develop nicotine dependence, and their average daily intake differed by only one to two cigarettes per day.

The most plausible explanation of these data is that alcohol and nicotine dependence are polygenic disorders, i.e. multiple susceptibility alleles of modest effect are involved, and their effects depend on interactions with other genes and with environmental exposures (Davey Smith et al., 2005; Khoury, 2003; Uhl & Grow, 2004). The genes likely to be involved in addiction affect different dimensions of human behavior. They probably include, for example, genes that influence the propensity to take risks or act impulsively, both of which may increase the likelihood of trying these drugs at an early age (Ho et al., 2010). Genes that influence drug metabolism are also involved in alcohol (e.g. $ALDH2$) and nicotine dependence (e.g. $CYP2A6$) (Li & Burmeister, 2009). So too are genes that affect how rewarding individuals find the effects of different drugs; these likely act by influencing the number of brain receptors and levels of neurotransmitters acting on reward centers in the brain (Goldman, Oroszi, & Ducci, 2005; Ho et al., 2010).

**Genomic Prediction of Addiction Liability**

Single alleles are poor predictors of addiction risk (Khoury, Yang, Gwinn, Little, & Flanders, 2004), but prediction could be improved by testing for multiple genetic variants (Khoury, 2003; Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005) and combining the test results to produce a
Using Genetic Information to Increase Quitting

Francis Collins' assumption that people would be more likely to comply with advice not to smoke if they have been told that they are at increased genetic risk of developing tobacco-related diseases has not been supported by research. Randomized trials of personalized feedback about genetic susceptibility to tobacco-related disease have failed to find improvements in long-term smoking cessation rates (Carpenter et al., 2007; Ito et al., 2006; Lerman et al., 1997; McBride et al., 2002). Smokers who were advised that they had a positive test result for genetic susceptibility to lung cancer (CYP2D6 status) were no more likely to attempt to quit, nor were they more likely to succeed in quitting, than smokers who were not advised of their genetic risk (Audrain et al., 1997; Lerman et al., 1997). In one study, smokers who were told they had a greater genetic susceptibility to chronic obstructive pulmonary disease were more likely to attempt to quit and use cessation aids than those who tested negative (Carpenter et al., 2007) and marginally more likely to be abstinent at 3 months (12% versus 4%). Another study, which provided nicotine replacement therapy (NRT) and telephone counseling for all participants, did not find any difference in cessation rates between smokers advised of a positive or negative genetic test result (McBride et al., 2002).
An additional concern is that smokers who are told that they are at lower genetic risk of tobacco-related diseases may be less motivated to quit (Marteau & Lerman, 2001; Wilfond, Geller, Lerman, Audrain-McGovern, & Shields, 2002). There is limited evidence on this issue. Studies of the effects of hypothetical genetic feedback on smokers have found lower motivation to quit among those given a “low-risk” result (Hoff, Evers-Casey, Weibel, Patkar, & Leone, 2005). One randomized trial found that smokers who were told that they were at low risk of tobacco-related diseases had lower smoking cessation rates than those not given any genetic risk information (Ito et al., 2006). A more recent randomized controlled trial, however, found some evidence of a beneficial effect of genetic tailoring on adherence and no evidence of reduced motivation in those who failed to quit (Marteau et al., 2010).

Genetic testing of children and adolescents to discourage smoking initiation has also been proposed. Such testing poses additional ethical concerns. The potential impact of labeling a child or an adolescent as being at increased risk of addiction is unknown, but could be damaging to self-image (Wilfond et al., 2002). These issues require careful consideration because some providers of adolescent medicine have expressed an interest in genetic testing of their patients for nicotine addiction susceptibility (Tercyak, Peshkin, Abraham, Wine, & Walker, 2007). Some have also asked adolescents about their interest in having such genetic tests (Tercyak, Peshkin, Wine, & Walker, 2006).

**GENETICALLY PERSONALIZED TREATMENT: ADDICTION PHARMACOGENETICS**

Genetic information could also be used to select the most effective treatment for people who are alcohol or nicotine dependent (Ho et al., 2010; Hutchison, 2010). For example, genetic information about nicotine metabolism or dopamine response to nicotine could be used to match smokers to the treatment that was most likely to produce abstinence (Munafò, Shields, Berrettini, Patterson, & Lerman, 2005). This use of genetic information is less ethically problematic than screening healthy adults for addiction risk because individuals are seeking treatment for alcohol or nicotine dependence and the testing may improve treatment outcome.

Nonetheless, in order for addiction pharmacogenetics to be of clinical utility, evidence is needed (1) that there are alleles that predict different responses to different smoking cessation and alcohol dependence treatments, and (2) that genetic matching is more cost-effective than giving everyone the treatment that is the most effective regardless of genotype (Hall, 2007). If pharmacogenetics is to be cost-effective, the genotypes
identified must reliably predict a differential response to treatment that is of sufficient size to justify the additional costs of genetic testing and counseling (Flowers & Veenstra, 2004).

**Pharmacogenetics of Smoking**

Pharmacogenetic studies of smoking cessation have examined a variety of polymorphisms, for example in *DRD2* (e.g. Berlin, Covey, Jiang, & Hamer, 2005; Lerman et al., 2006), *OPRM1* (Munafò, Elliot, Murphy, Walton, & Johnstone, 2007), *CYP2B6* (Lerman et al., 2002), *SLC6A3* (Lerman et al., 2003), *SLC6A4* (David, Munafò, Murphy, Walton, & Johnstone, 2007; Munafò et al., 2006), *DBH* (Johnstone et al., 2004), *FREQ* (Dahl et al., 2006) and *COMT* (Berrettini et al., 2007). Some trials have reported a differential response to treatment (typically to NRT or bupropion compared to placebo), but the differences have been small, have often weakened over time, and most findings have not been replicated (e.g. David et al., 2007; Lerman et al., 2004; Munafò, Elliot et al., 2007; Munafò et al., 2006). The positive results are also of doubtful utility because the polymorphisms tested (Lee & Tyndale, 2006) are not single nucleotide polymorphisms (SNPs) and are therefore not as straightforward to genotype.

Munafò (2009a) argues that to be useful, genes need to have a high prevalence and be highly predictive of differential treatment response. As he notes, this is an uncommon combination: the more prevalent alleles in the population typically confer only a modest increase in risk while more predictive alleles are generally rare. Modeling suggests that a hypothetical genetic test to match smokers to treatment may not be cost-effective (Welton, Johnstone, David, & Munafò, 2008), and that at the very least the cost-effectiveness of such tests should not be assumed and will require evaluation. It is uncertain how much advantage there may be in combining multiple alleles because, as shown by Gartner and colleagues’ (2009) modeling, few individuals are likely to have combinations of risk alleles that predict large differential treatment outcomes (Munafò, 2009a).

Evaluations of pharmacogenetics will also need to assess the effects of genetic information on smokers’ beliefs about their likelihood of quitting. Two studies suggest that smokers interpret genetic risk information to mean that they can only quit, if at all, using biological interventions (Cappella, Lerman, Romantan, & Baruh, 2005; Wright, Weinman, & Marteau, 2003). In these studies, smokers who accepted that genetic factors contributed to cigarette smoking were less confident about quitting and more likely to believe that they needed a biological intervention to quit. Researchers will also need to assess whether giving genetic risk information discourages future quit attempts in those who try and fail to quit. This would be undesirable because most smokers only achieve
abstinence after a number of failed quit attempts (John, Meyer, Hapke, Rumpf, & Schumanna, 2004).

Pharmacogenetics of Alcohol Dependence

The application of pharmacogenetics to improve alcohol dependence treatment efficacy is potentially important because pharmacological and psychological interventions have at best, modest efficacy: 12 month abstinence rates range from 17% to 35% for drug treatments such as naltrexone and for psychosocial treatments that include 12-step programs, motivational enhancement therapy and cognitive behavior therapy (Miller, Walters, & Bennett, 2001). Rates of relapse after treatment completion are also high. In the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence Study (COMBINE), approximately 80% of all alcohol-dependent patients had a heavy drinking day in the 12 months after treatment (Anton et al., 2006). Targeting treatments to those who are most responsive to them may increase overall treatment effectiveness.

Studies have found that the Asp40 allele of the gene encoding the \( \mu \)-opioid type 1 receptor in the brain (\( OPRM1 \)) predicts response to the opioid antagonist naltrexone (e.g. Ray & Hutchison, 2007). One small study reported that variants in \( GABRA2/GABRA6 \) predicted responses to acamprosate (Ooteman et al., 2009), but this result has not been replicated. An SNP in intron 9 of the glutamate receptor 5 (GluR5) gene (\( GR1K1 \)) has also been shown to predict side-effects in people with alcohol dependence treated with topiramate, an anti-convulsant drug that reduces craving (Ray et al., 2009). Genetic variants may also predict responses to psychological therapies for alcohol dependence, such as motivational enhancement therapy (Feldstein Ewing, LaChance, Bryan, & Hutchison, 2009).

Effective use of pharmacogenetics to personalize treatment of alcohol dependence also requires highly prevalent genes that are strongly predictive of treatment response. The Asp40 allele of the \( OPRM1 \) gene is the most promising candidate to date as a pharmacogenetic test for naltrexone. Asp40 is found in 15–18% of Caucasian Americans, around 48% of people of Asian descent, but less than 5% of African–Americans (Kuehn, 2009). Clinical trials have shown people with Asp40 are three times more likely to respond to naltrexone than those homozygous for the Asn40 allele (Anton et al., 2008; Oroszi et al., 2009; Oslin, Berrettini, & O’Brien, 2006). Cost-effectiveness analyses are needed to determine whether using this test provides a sufficient gain in treatment outcome to justify its cost in the whole population because there is a lower prevalence of this gene variant in Caucasian Americans and African–Americans than in those of Asian descent. If the test does prove to be cost-effective and acceptable to both clinicians and patients, it will provide a good model of how a pharmacogenetic test may be used in the addictions field.
ETHICAL AND POLICY CONCERNS

Medicalization of Addictive Behavior

Social scientists criticize addiction genetics for "medicalizing" human behavior (Ashcroft, Campbell, & Capps, 2007; Conrad, 1992; Press, 2006; Verweij, 1999). Medicalization is seen as overemphasizing the biological, and particularly genetic, origins of addictive behavior, at the expense of social and psychological explanations, in ways that may adversely affect people who engage in these socially stigmatized forms of behavior (Caron et al., 2005). If addictions are seen as genetic disorders, these critics argue, more resources will be spent on medical interventions and less on effective social policies, such as imposing higher taxes, banning promotions and restricting access to under-18-year-olds (Carlsten & Burke, 2006; Chapman & MacKenzie, 2010; Evans, Meslin, Marteau, & Caulfield, 2011; Hall & Chikritzhs, 2011; Merikangas & Risch, 2003).

Medicalization could also potentially affect the types of cessation treatments that are made available. Pharmacogenetic tests have been marketed to smokers in the absence of evidence of their effectiveness. This was the case with NicoTest (www.nicotest.com). It was marketed to smokers as guiding their choice of either NRT or bupropion for smoking cessation before its clinical utility had been evaluated (De Francesco, 2006; GeneWatch UK, 2004), but has since been withdrawn from the market.

Critics also argue that behavior genetics may affect thinking about alcohol and nicotine dependence in ways that reduce the ability of smokers and problem drinkers to quit (Backlar, 1996; Caron et al., 2005). Such a view could further stigmatize those who possess particular genetic alleles or mutations, or genetic markers associated with alcohol and nicotine dependence (Caron et al., 2005). On this view, behavior genetics could lead to both institutionalized discrimination, by employers (who may decline to employ people at increased genetic risk) and health and life insurers (who may decline to cover those at increased genetic risk) (Anderlik & Rothstein, 2001; Geppert & Roberts, 2005; Greely, 2001; Hall & Rich, 2000; Rothenberg et al., 1997).

Third Party Uses of Genetic Information

Genetic information on addiction risk may potentially be used by insurance companies, employers and educators, and the courts. This information may affect not only individuals being tested but also their close relatives. This raises questions 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

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with whom (Anderlik & Rothstein, 2001; Rothstein, 1998; Rothstein & Anderlik, 2001)?

It is not clear to what extent bioethicists’ concerns about the ethical and policy implications of genetic testing apply to addiction liability. Many of their analyses have focused on genetic testing for Mendelian disorders such as Huntington’s disease (Marteau & Richards, 1996). Because the mutations that cause this severe neurological disease are strongly predictive of risk and there is no effective treatment, genetic testing can create significant ethical dilemmas for affected individuals and family members (Marteau & Richards, 1996). It also raises real concerns about the discriminatory use of genetic risk information by health and life insurers and employers (Billings et al., 1992; Munafò et al., 2005; Taylor, 1998). It is difficult to estimate the prevalence of genetic discrimination from case studies and anecdotal reports. However, a recent Australian survey of around 2600 people who were genetically predisposed but asymptomatic for mature-onset neurological (e.g. Huntington’s disease) and familial cancers showed that discriminatory treatment occurred in as many as 10% of cases (Taylor, Treloar, Barlow-Stewart, Stranger, & Otlowski, 2008).

As indicated above, however, monogenic disorders such as Huntington’s disease provide a poor model for addictive disorders, which are most likely to be polygenic disorders. This means that genetic testing will, at best, only modestly improve upon the predictive value of family history. If the critics of genetic research on addiction are correct, then the ethical and policy issues identified by bioethicists will not arise because we will not see genetic screening of whole populations for addiction risk.

Genes expressed in the central nervous system and associated with complex behavioral phenotypes are likely to influence multiple phenotypes (a phenomenon known as genetic pleiotropy). Therefore, genes associated with addiction may also carry information about the risk of developing other mental disorders. It is not clear how this collateral information would be handled following genetic testing.

Fear of genetic discrimination may still deter people with family histories of addictive disorders from having genetic tests that may benefit them. Similar fears may also deter individuals from participating in genetic research on addictive disorders, thereby impeding the acquisition of scientific knowledge about the genetics of these disorders. A research priority should be assessing whether community concerns about third party use of genetic information will prove to be a barrier to addiction genomic research and its future medical applications.

Society can, of course, eliminate the risks of third party use of genetic information by banning all genetic tests. However, such a policy would prevent the realization of the benefits that genetic testing may bring and it would also be highly paternalistic. A better approach would be to look
for safeguards to prevent individuals’ privacy and confidentiality from being unfairly compromised. The challenge will then 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 minimizing stigmatization and discrimination.

The USA has taken steps in this direction by enacting the Genetic Information Non-Discrimination Act in 2009. The Act protects people with a genetic mutation, but who are not yet symptomatic, from being discriminated against by health insurers and employers. Under the Act, health insurers are not allowed to request genetic information from clients or to request that they undergo genetic testing (Appelbaum, 2010). They are also not permitted to use genetic information to decide whether they will insure clients or to set their insurance premiums. Employers are prohibited from using genetic information to make decisions about hiring, promoting or firing an employee, and requesting genetic testing under any circumstances.

The definition of genetic information in the Act is broad. It includes genetic tests performed on individuals or their family members, as well as “family history” information about a disorder (Appelbaum, 2010). However, the law does not cover life, long-term care or disability insurance. Nor is it applicable to people who have clinical manifestations of genetically based disease. Consequently, there is still potential for genetic discrimination under these circumstances (Van Hoyweghen & Horstman, 2008). The legislation has also yet to be tested in the courts, so it is not clear what level of protection the Act offers against genetic discrimination and what impact it will have on public anxieties about such discrimination (Rothstein, 2008; Van Hoyweghen & Horstman, 2008). The same is true of moratoria and legislative bans on genetic discrimination in life insurance that have been introduced in many European countries (Joly, Braker, & Le Huynh, 2010).

Premature Commercialization of Genetic Testing

Third party misuse of genetic information may also arise from the premature marketing directly to consumers (DTC) of genetic tests that have not yet been clinically validated. Even though genetic tests for alcohol and nicotine dependence are not yet available in clinical practice, some commercial companies are selling putative genetic tests for addiction susceptibility DTC. Five companies offer testing for nicotine dependence (23-and-me, deCODE, Gene Planet, Biomarker Pharmaceuticals and Lumigenix), four for alcohol flush response (23-and-me, deCODE, Gene Planet and Lumigenix) and three for alcohol dependence (23-and-me, Biomarker Pharmaceuticals and Lumigenix). One company, 23-and-me, also offers pharmacogenetic testing for naltrexone response. The tests are accessible over the internet. Consumers send the company a swab of
cells from the inside wall of their cheek, which are subsequently sent to
the company’s laboratories for genetic testing, in some cases for as little
as US $200 (e.g. 23-and-me).

Ethical concerns are raised by the absence of any regulation of DTC
genetic testing and the wide variations between companies in the esti-
mates of the genetic risk for the same diseases (Ng, Murray, Levy, &
Venter, 2009). The US Food and Drug Administration (FDA) has pro-
posed that it be regulated in the USA because of concerns about the
questionable validity and clinical utility of the alleles tested. With the
exception of the variant for alcohol flush reaction, the genes tested are
only weakly predictive of addiction risk. None of the other DTC genetic
tests for addiction liability provides the consumer with actionable infor-
mation: they will typically be told that they are at average, above average
or below average risk of disease. If DTC genetic tests were to be regu-
lated, an immediate priority should be to set minimum standards for the
clinical validity and utility of tests. These standards would need to be
met before a test could be made available for purchase by consumers.

The pharmacogenetic test for naltrexone response does have the
potential to provide actionable information, assuming the consumer can
correctly interpret the test result. Most of these companies assert that
their tests are intended purely for research and educational purposes and
are not to be used diagnostically. Consequently, most provide genetic
risk information in the absence of genetic counseling either before or
after testing. Navigenics is one exception, although it does not offer test-
ing for alcohol or nicotine dependence. Given the limited genetic liter-
acy of the general public, consumers may incorrectly interpret their risk
of disease. Mandatory pre- and post-test genetic counseling could be
enforced through regulation of DTC genetic tests by the FDA.

Developing standards to protect the privacy of consumers’ genetic
information should be a priority for policy makers. DTC tests raise
greater privacy concerns than laboratory-based tests, given that they
are purchased over the internet and genetic information can be shared
with others (e.g. 23-and-me). The potential for surreptitious testing via
these companies (i.e. family members of individuals collecting a sam-
ple of DNA without their permission) is an emerging privacy concern,
although it is not clear how common this may be (Udesky, 2010). It is
vital to develop measures to safeguard the privacy of genetic information
derived through DTC genetic testing by preventing surreptitious testing
(e.g. of minors in the case of disputed paternity).

Challenges for Public Understanding

Popular understanding of the role of genetics expressed in the media
is often deterministic. They sometimes suggest that genetic research
has identified “the gene for addiction” (BBC, 2004; Doyle, 2004), that people with the gene are very likely to develop that disorder, and that those who do not have it are at low risk of doing so (Khoury et al., 2000). Popular media reporting of NicoTest, for example, described it as a test for the “smoker’s gene” or the “addiction gene” (BBC, 2004; Doyle, 2004). Research is needed to better understand how these framings of genetics affect public attitudes and behavior (McBride et al., 2010).

These views probably reflect the media’s focus on Mendelian disorders such as Huntington’s disease, cystic fibrosis and Tay–Sachs disease (Khoury et al., 2000). The challenge for public education will be to better explain 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 (McBride et al., 2010). If successful, such public education could allay anxieties about the third party misunderstanding of genetic information.

Public education will also need to avoid any unintended message that public health alcohol and tobacco strategies can be replaced by high-risk genomic medicine strategies (Carlsten & Burke, 2006; Merikangas & Risch, 2003; Willett, 2002). Population-based tobacco control strategies such as taxing cigarettes and reducing the opportunities to smoke have halved cigarette smoking rates in Australia (White, Hill, Siahpush, & Bobevski, 2003) and the USA (Pierce et al., 1998) over the past three decades. It makes more policy sense to reduce cigarette smoking by increasing taxes on tobacco products, banning cigarette advertising and restricting opportunities to smoke than it does to spend resources on identifying those at higher genetic risk of becoming nicotine dependent or developing tobacco-related diseases, if they smoke tobacco (Hall, Madden, & Lynskey, 2002; Khoury et al., 2004).

Subversive Uses of Genomic Risk Information

Public health professionals are also concerned about the potential misuse of genetic risk information by industries that wish to promote harmful forms of consumption (Gundle, Dingel, & Koenig, 2010). These industries are likely to use genetic risk information to undermine support for public health policies that will reduce the use of their products in the population (Hall, Gartner, & Carter, 2008).

Tobacco industry documents (Gundle et al., 2010) show that the industry funded genetic research on smoking and tobacco-related disease in the 1970s and 1980s in order to promote genetic explanations of tobacco-related disease. The aim was to locate the risks of smoking in the genome of the smoker and exonerate tobacco smoking as a cause of disease (Gundle et al., 2010). The alcohol industry also promotes the idea that alcohol-related problems are the province of a minority of
genetically vulnerable drinkers (Hall, 2005). It argues that these problems are addressed by intervening with problem drinkers rather than adopting strategies to reduce population-level alcohol consumption, such as increased taxation and reduced availability of alcohol (Babor, Miller, & Edwards, 2010). The gambling industry has recently funded research into the genetics and neurobiology of problem gambling (Vrekko, 2008), which one can hypothesize may be for similar strategic reasons.

**CHALLENGES FOR PREDICTIVE USE OF BIOMARKERS OF BRAIN FUNCTION**

Some neuroscientists have made optimistic predictions about the future predictive utility of neuroimaging and measures of brain functioning in determining risks of psychiatric and neurological diseases as well as the course and outcomes of these diseases (Singh & Rose, 2009).

For instance, suggestions have been made that brain scans of children or adolescents that identify poorly functioning inhibitory control circuits or a highly responsive reward system may predict an increased risk of addiction later in adult life, particularly if the individual uses drugs when young (Volkow & Li, 2005). However, at present, it is not possible to determine whether such neurobiological changes occur before chronic drug use and therefore are predictive of future drug abuse, or are a consequence of chronic drug use (Paulus, 2005).

Forecasts about the predictive utility of neuroimaging should be treated with similar caution to those made about the predictive utility of genetics for a number of reasons. First, neuroimaging research is at risk of repeating the early experience in studies of disease genomics: promising results are reported in small study samples that may not be replicated in larger studies. Indeed, a recent meta-analysis of studies of brain volume abnormalities in people with psychiatric disorders found an excess of statistically significant results that was strongly suggestive of publication bias (Ioannidis, 2011).

Second, given the comparative costs and ease of using genotyping versus neuroimaging, it will be much more logistically difficult and expensive to conduct the large-scale studies required to test the predictive utility of neuroimaging than is now true of genome-wide association studies. The cost of functional magnetic resonance imaging (fMRI) and positron emission topography (PET) scans is unlikely to come down as quickly as the cost of genome scans has; these procedures also require attendance at a specialist imaging facility, which attracts more costs than taking a blood or saliva sample in a clinic or the field.

Third, it is a reasonable hypothesis that, as with genomics, biomarkers of brain functioning may have more utility in clinical populations.
when used for the purposes of diagnosis and matching addicted individuals to treatment. For instance, Paulus, Tapert, and Schuckit (2005) showed brain activation patterns obtained using fMRI were able to predict relapse in people with methamphetamine dependence. However, it remains unclear whether these results would translate to other forms of substance dependence. Schutz (2008) examined the potential utility of using neuroimaging to predict relapse in smokers and suggested that while initial results appear to be encouraging, it needs to be studied further to establish its utility.

The high cost of neuroimaging will potentially be a barrier to its application to treatment matching and relapse prediction in addiction, even if its effectiveness is to be demonstrated across all forms of addiction. Neurocognitive tests such as tests of attentional bias toward drug use, impulsivity or the ability to resist immediate rewards are a less expensive option that appear to have equal if not superior efficacy to neuroimaging in identifying susceptibility to relapse to drug use (Cox, Hogan, Kristian, & Race, 2002; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008; Paulus et al., 2005). Like neuroimaging, the use of neurocognitive tests to inform treatment decisions will require further investigation to establish its clinical and scientific validity before it is routinely integrated into clinical practice.

CONCLUSION

Despite good evidence that genes contribute to addiction susceptibility, substantial challenges remain before Francis Collins’ predictions about genomic medicine can be realized in the field of addiction. A major challenge has been the lack of commonly occurring, susceptibility alleles that strongly predict addiction risk. Multiple alleles may better predict individual risk but the costs of screening and counseling large numbers of individuals in order to identify the small number at high risk of addiction may be difficult to justify in the absence of effective preventive strategies. Population health strategies such as increased taxation and reduced opportunities to smoke or drink alcohol are likely to remain more efficient preventive strategies by reducing cigarette smoking and risky alcohol use.

Any future predictive use of genomic information on addiction risk will need to address ethical and policy issues such as community concerns about privacy and the third party use of genetic information. Public education will be needed about the implications of the genetics of alcohol and nicotine dependence. Research is needed on how best to present genetic information to motivate desired behavioral change and avoid undermining successful public health strategies for reducing
addiction and disease risk (McBride et al., 2010). Evaluations of the utility of genetic, pharmacogenetic and neuroimaging prediction in the field of addiction still require substantial investments in research and development and health services evaluation.

References


II. TREATMENT


INTRODUCTION

From a legal and moral perspective, addiction is perplexing. Courts, philosophers and ordinary people find themselves torn when they consider the behavior of people with addiction disorders such as alcoholism, illicit drug use and disordered gambling: should we think of it as free and responsible behavior, or instead as unfree (coerced or compelled, perhaps)? The question arises especially acutely when addicts engage in illegal behavior that seems to arise from their addiction, whether consuming the drug in jurisdictions where the drug is legally proscribed, or engaging in illegal acts to procure the money for drugs. Should we respond to such acts with the full force of the law, or should we instead respond with compassion, treating the behaviors as symptoms of a disease? Intuitively, these two perspectives seem to map on to the distinction between two ways of understanding the behaviors characteristic of addiction. We might see these behaviors as either chosen or compelled.
Chosen behaviors are voluntary and, so it seems, for what we do voluntarily we are morally responsible. However, behaviors that are compelled are not voluntary and not morally responsible actions.

For the past three decades, a disease model of addiction has been in the ascendancy among knowledgeable professionals. The disease model, which understands addiction as a mental illness, seems to powerfully support one side of the debate over the moral responsibility of addicts. The symptoms of a disease are not chosen, and therefore they are not phenomena for which agents are morally responsible. Recently, however, the disease model of addiction has come under withering attack from several quarters. According to the rival view, presented most vociferously by Gene Heyman (2009), the behaviors characteristic of addiction are voluntary. Though Heyman does not address whether this entails that addicts are responsible for their behavior, it seems to be the obvious conclusion. This seems to be how most reviewers have understood Heyman’s book, with those who support a more punitive approach to addiction seeing in the book support for their view, while those who support a non-punitive approach have been sharply critical of it.

In this chapter, it will be argued that the claim that the behaviors characteristic of addiction are (in some sense) voluntary does not entail either that the disease model of addiction is wrong or that addicts are (fully) responsible for their actions. Behaviors can be chosen and yet not free in the manner required for moral responsibility; for a wide range of the behaviors characteristic of addiction, it is suggested, both these things are true. The responsibility of the addict will be approached via a consideration of her (or his) autonomy. Though autonomy and moral responsibility are not equivalent concepts, the impairment of autonomy can significantly undermine moral responsibility.

**UNDERSTANDING AUTONOMY**

Autonomy is a term with multiple meanings. There is a maximal sense of autonomy, according to which an autonomous being has only the desires and beliefs they want to have and makes choices uninfluenced by any factor they have not chosen or endorsed. Autonomy, in this sense, is not a goal that human beings can hope to achieve. Finite beings like us must strive for something much less grandiose. Clearly, if addiction threatens autonomy (as it is commonly thought to do), it must be some less extravagant notion of autonomy that it undermines.

In a minimal sense (a sense suggested by the etymology of the word: *auto*, self; *nomos*, rule), autonomy is simply self-government. Just as an autonomous nation is one that is able to make major decisions of internal and external policy without undue interference from foreign powers,
so an autonomous agent is one capable of governing herself: setting her own ends, short and long term, and choosing the best means of achieving these ends. Once again, we must be careful not to overinflate this conception of autonomy. The fact that I have to work does not represent an infringement of my autonomy (so long as the conditions under which I work are reasonable and I am free to seek other employment), even though this fact means that my time is not necessarily my own, and that I must pursue goals that I would not choose to pursue otherwise. If my work leaves me free, and enables me to pursue the ends I most value (say personal relationships and family), then it does not infringe my autonomy. Of course, for some people the most important ends are internal to work, such as wealth or reputation.

If autonomy is best thought of as self-rule, then how should we understand the loss of autonomy? The most obvious situation in which self-rule is compromised or lost is when the self is ruled by another. In the political domain, complaints of the loss of autonomy refer exclusively to this phenomenon. This same kind of phenomenon can occur, more or less dramatically, in the individual case as well. A slave, for instance, whose life is entirely in the hands of another, is a dramatic instance of the phenomenon, while a dispositionally subservient person might represent a less dramatic instance of a partial loss of autonomy.

Addiction does not seem to involve the loss of autonomy in this sense. The addict who suffers from a loss of autonomy is not under the control of another person, even partially; at least, not necessarily. An addict might be excessively subservient to the person who supplies her drugs or the money for her drugs, and therefore have her autonomy compromised by the rule of another. However, if her autonomy is compromised in this way, this is a consequence of an initial loss of autonomy that is characteristic of addiction. This initial loss of autonomy left her vulnerable to this subservience, since it is her addiction that gives the person who controls her undue influence over her.

Moreover, there need not be any other person exercising undue influence over the addict for her to experience a diminution of her autonomy. The person who is able to supply her habit herself—and such people are plentiful, as brief reflection on tobacco addiction makes obvious—is not likely to be in thrall to another person as a consequence of her addiction. It is sometimes claimed that addicts are in thrall to their drug. Carl Elliott, for instance, writes that the addict “must go where her addiction leads her, because the addiction holds the leash” (Elliott, 2002, p. 48). Clearly, however, and putting aside for the moment whether Elliott overdramatizes the loss of autonomy involved in addiction, this can only be a metaphor. An addiction cannot hold a leash: it is not an agent, and has no desires or goals of its own. Rather, if addiction involves a loss of autonomy it must somehow undercut the addict’s own ability to pursue her
goals. Addicts, it is suggested here, have compromised self-government even though they are not under the strict rule of anyone else.

**MYTHS AND PUZZLES**

Carl Elliott’s claim that addicts are in thrall to their addiction echoes a long tradition of theorizing about addiction. According to this myth, addiction involves an almost complete loss of control over drug-seeking and consuming behavior. This myth is widespread, even among knowledgeable people, and can be found repeated in the writings of philosophers, psychologists and medical doctors. For Louis Charland, for instance, “the brain of a heroin addict has almost literally been hijacked by the drug” (Charland, 2002, p. 43); for Alan Leshner (a former Director of the US National Institute on Drug Abuse), the initially voluntary behavior of drug-taking gradually transforms into “involuntary drug taking, ultimately to the point that the behavior is driven by a compulsive craving for the drug” (Leshner, 1999, p. 1315); for the influential philosopher Harry Frankfurt, the unwilling addict struggles against his desires to no avail for he is always “helplessly violated by his own desires” (Frankfurt, 1971, p. 12). For these thinkers, addiction is compulsive, which is to say that addicts are forced to act as they do by an irresistible desire.

Desires are irresistible when they are so powerful as to overwhelm an agent’s abilities to overcome or circumvent them (Mele, 1990). So addiction is compulsive, according to the myth, because it produces desires that are so powerful that the addict cannot resist them. This conception of how addiction functions dates back at least to William James. Commenting on “dipsomania” (a medical term popular in the nineteenth century to describe various alcohol use disorders), James commented that:

*The craving for a drink in real dipsomaniacs, or for opium or chloral in those subjugated, is of a strength of which normal persons can form no conception. “Were a keg of rum in one corner of a room and were a cannon constantly discharging balls between me and it, I could not refrain from passing before that cannon in order to get the rum”; “If a bottle of brandy stood at one hand and the pit of hell yawned at the other, and I were convinced that I should be pushed in as sure as I took one glass, I could not refrain”: such statements abound in dipsomaniacs’ mouths. (James, 1890, p. 543).*

For all its popularity, however, this characterization of addiction seems to be false. Addiction may indeed produce powerful desires, on occasion, yet there is ample evidence that their power is not so strong as to overwhelm agents in the manner pictured.
We can measure the strength of a desire by examining the behavior of people who are subject to it. It is this test for strength, indeed, which underlies the claims above: proponents of the compulsion conception of addiction think of it in this manner because they are impressed by the lengths addicts will go to in order to procure their drugs. They will engage in risky and degrading activities or steal and lie. Most impressively, they spend time and effort not only in pursuit of their drugs, but also in attempts to stop consuming the drug (Ross, Sharp, Vuchinich, & Spurrett, 2008) —behavior which clearly indicates that (no matter what else is true of them) at least on many occasions they genuinely desire to give up their drugs. However, though proponents of the myth are right to think that the behavioral evidence clearly indicates that addicts have impaired autonomy, addicts’ behavior does not fit the profile we would expect were they subject to irresistible desires.

An agent subject to the irresistible desire to pursue a goal will pursue that goal across a very broad range of circumstances, so long as she is able to engage in any voluntary action: she will pursue the goal (almost) no matter what. Only a countervailing incentive that is itself of comparable power will prevent the behavior. Hence, the fact that an addict might refrain from consuming her drug with the policeman at her elbow is not evidence that her desire is not irresistible; but were she to refrain for much smaller incentives —because she prefers to spend her money on food, though she is not at risk of starvation, or in order to schedule it for a more convenient time—then she is not compelled, on this understanding of compulsion. The evidence available clearly demonstrates that actual addicts’ behavior is sensitive to incentives that are not extraordinary in nature, and that therefore they are not subject to irresistible desires.

Price increases affect the amount of drugs consumed by addicts (Elster, 1999; Neale, 2002). Alcoholics are sensitive to the cost of alcohol even after a priming drink (Fingarette, 1988). Moreover, many addicts give up their drug, often without outside help. When given a powerful reason to abstain permanently, addicts typically succeed in overcoming their addiction. New mothers, for instance, are often able to give up their addiction in order to care better for their child (Heyman, 2009). Heyman has recently emphasized that addicts can be treated by bringing to bear incentives, positive and negative. Heyman cites the work of Steve Higgins, who has successfully used rewards in the form of vouchers in the treatment of cocaine addiction. The vouchers were paid to addicts in return for clean urine tests, with the value of the vouchers increasing over time if the person remained abstinent. The value of the vouchers did not exceed US $12 per day, and was sometimes significantly lower than this figure. As Heyman notes, this is considerably less than the subjects were routinely spending on cocaine. Yet the treatment modality was effective in
encouraging the majority to abstain. Other treatment programs used negative incentives: Heyman cites programs that drug tested physicians and airline pilots, who were threatened with loss of their jobs if they failed a drugs test. Recovery rates were extraordinarily high. Again, the data suggest that incentives are effective at treating addiction.

This evidence clearly shows that addicts are not subject to irresistible desires to consume their drugs. Other evidence indicates that they may not be subject to desires to take their drugs at all, at least on one understanding of the nature of desires, according to which we necessarily have a positive attitude toward what we desire. Drugs may apparently be “wanted”, that is, they may have high incentive salience, without being “liked” at all (Robinson & Berridge, 2003). Balfour (2004) has identified the neural basis for this dissociation between the causal strength of a desire and the liking of its object as a consequence of the effects of dopamine on different regions of the nucleus accumbens. One region is involved in the subjective feelings of reward associated with a drug, while the other confers incentive salience on the stimulus, independently of its being pleasurable.

How should we respond to this evidence? Heyman himself responds by describing addiction as a “disorder of choice”. By this phrase, he means two things: addiction is a syndrome in which choice is disordered, but also, and especially, that addiction is a syndrome in which dysfunctional behavior is chosen. This is a conclusion that, prima facie at least, seems to imply that we ought to treat the behaviors characteristic of addiction—the behaviors involved in procuring and using drugs, most focally—in the same way we treat other voluntary actions. For instance, it seems to imply that we should regard this behavior as chosen and morally responsible behavior, to which it is appropriate to respond by punishing addicts. If behavior is chosen—if it is responsive to incentives of ordinary strength—then it seems to be sufficiently autonomous to count as a locus of moral responsibility.

Though this line of thought is tempting, it may be far too hasty. Autonomy comes in degrees: it is not an all-or-nothing phenomenon. An agent may be capable of choice and suffer from diminished autonomy. Heyman is right to hold that addicts choose to act as they do; nevertheless, close attention to their choices reveals that their autonomy is significantly impaired.

The addict need not be in thrall to anyone else, but it is clear that she fails to adequately govern herself. Addicts have the greatest of difficulty in imposing their will on themselves, not in the manner that proponents of the myth imagine—because they find themselves forced to act, against their will, by overwhelming desires—but because though they may identify with their moment-to-moment choices, they cannot effectively pursue plans and projects. As Michael Bratman (2006) has emphasized, the
ability to coordinate one’s own behavior over time is essential to agency. The person who cannot impose their will over themselves across time continually frustrates her own plans, and makes many, perhaps most, of her own actions futile. A great deal of what we do is worthwhile only because it is a component in an ongoing series of actions, aimed at an end. We save money for distant goals; we eat well and exercise to preserve our health, we get enough sleep to ensure that tomorrow we will be able to work, and we work to achieve career goals or a reputation that can be secured only through many repeated actions. If we are unable to impose our own agency across time, these activities would be pointless. If I knew that at the end of the day I would delete everything I wrote, I would not write. If I knew that tomorrow I would gorge myself on chocolate cake, cigarettes and amphetamines I would not abstain from dessert tonight, and if I knew that I would spend all my money at the casino next week, I would not bother saving this week. It is only because I trust myself sufficiently not to do these things that I am motivated to act prudently now.

There is a growing body of evidence that addicts cannot trust themselves to act prudently in these ways. Though the addict may choose to do what she does when she does it, she is subject to regular and predictable preference reversals, which undercut her ability to impose her will on her own behavior across time.

Recall the evidence mentioned above that addicts’ behavior is inconsistent: addicts expend a great deal of time and effort in procuring the opportunity to consume their drugs, but they also put a lot of effort into attempting to free themselves of their addiction (Ross et al., 2008). This pattern of behavior is evidence of ambivalence on the part of addicts. The experimental and behavioral evidence clearly demonstrates that for many addicts—those who make an effort to rid themselves of their addiction—this ambivalence is manifested in an oscillating preference structure: addicts alternate between preferring consumption and preferring abstention.

George Ainslie (2000, 2001) has provided some of the theoretical apparatus we need to understand the preferences of addicts. Ainslie claims that we can understand failures of self-control in general by reference to agents’ discount curves. Humans and other animals are hyperbolic discounters. We do not discount future goods at a steady rate, as classical economics suggests that we ought; instead, our discount function varies according to the immediacy of opportunities for consumption.

When tempting goods are immediately available, we often overvalue them relative to the value we placed on them previously; as a consequence, our discount curves for competing goods may cross. This can cause problems in planning. Goods compete when achieving one good depends on abstaining or avoiding opportunities for another. This
kind of conflict is common for us, perhaps because we live in environments that differ markedly from those for which we are adapted. In the environment of evolutionary adaptiveness, for instance, opportunities for consuming food were relatively rare, and we therefore have an evolved disposition to take these opportunities. Today, however, at least for those of us in prosperous nations, opportunities for consuming food are pervasive, and as a consequence the good of eating can compete with the good of health.

For a hyperbolic discounter, this conflict makes achieving the good of continued good health very difficult. Whenever the opportunity to consume food arises, she will find herself preferring consumption over abstention, and behave accordingly, even though at all times that food is not immediately available she prefers eating moderately and therefore forgoing most opportunities to consume. Her preferences oscillate, and the plans she enacts for her future behavior are continually frustrated by her own actions.

As the example just given illustrates, self-control is a continual problem for all of us. However, the problem is much more acute for addicts than it is for non-addicts. Addicts have steeper discount curves than non-addicts, though the extent to which this fact is a cause of addiction or instead a consequence of it remains controversial. Longitudinal studies, for instance, have shown that inability to delay gratification in children is predictive of addictive behavior later in life (Vitaro, Arseneault, & Tremblay, 1999). However, drinking alcoholics discount more steeply than non-alcoholics or abstaining alcoholics (Petry, 2001), and the discount rates of former smokers are lower than those of current smokers (Bickel, Odum, & Madden, 1999), which suggests either that smoking and drinking cause steepness of discount rate, or that smokers and drinkers with reduced discount rates are more likely to quit.

Though it is likely that some people are more vulnerable to addiction than others (as the high heritability of substance misuse disorders suggests), contemporary neuroscience has produced a substantial body of evidence of changes in the brain that together suggest that addicts’ discount curves alter as a consequence of the chronic use of addictive substances. There is evidence that stimuli associated with the substances to which a subject is addicted are highly motivating for them in ways that bypass capacities for conscious control. The motivational salience of a cue for consumption of any good seems to be encoded as, or to be caused by, a surge in dopamine from the ventral tegmental area. As the subject habituates to a reward, this dopamine signal tends to attenuate. This attenuation fails to occur with regard to drugs of addiction, and also to gambling rewards, which may explain why their motivational salience increases, even while the degree to which the subject likes the drug tends to fall (Hyman, 2005, 2007). Dopamine causes a focus on predictors of
reward and primes the motor system for action, leading to judgments that are difficult to revise and behavior that is difficult to inhibit (Ross et al., 2008). At the same time as these mechanisms cause judgments and behavior that it would be hard for a well-functioning person to inhibit, addiction causes neuroadaptations that weaken the efficacy of the frontal mechanisms that regulate behavior. As Ross et al. (2008) put it, “[i]n effect, addiction first hijacks the reward system below decks, then commits mutiny on the bridge by sabotaging the cognitive systems that would otherwise check its influence” (p. 156).

Whereas these adaptations increase the motivational salience of the drug, others reduce the ability of the agent to resist. There is evidence that decision making by addicts is impaired globally, not only with regard to their drug. Perhaps some of these deficits reflect pre-existing vulnerabilities in decision-making mechanisms, rather than neuroadaptations caused by persistent substance abuse. Some of these deficits in decision making are clearly problems with translating desires into action. On tasks requiring subjects to inhibit prepotent responses, addicts perform poorly relative to controls (Garavan & Stout, 2005). Yet other neuroadaptations affect addicts’ abilities to properly assess their options. Neuroadaptations increasing the reward value of the drug are likely to influence addicts’ evaluation of the choice-worthiness of consumption, as well as (or sometimes instead of) increasing the desire for it independent of such evaluations. Some cognitive evaluations bias addicts’ memories, making them more likely to recall positive outcomes of consumption than negative, or leading them to miscategorize alike situations as unlike (or vice versa). For instance, a gambling addict might erroneously distinguish situations predictive of reward from situations predictive of losses (Redish, Jensen, & Johnson, 2008). Adverse consequences may be less salient to addicts, perhaps owing to impaired somatic marker systems, as a result of which they may fail to generate the anticipatory autonomic system responses seen in non-addicted individuals (Bechara, 2005). Other neuroadaptations do not directly affect the evaluation of consumption, but bias attention, such that drug-related cues are very salient to addicts (Lubman, Peters, Mogg, Bradley, & Deakin, 2000). Further, addicts may find it difficult to avoid ruminating obsessively on courses of action that would lead to drug consumption (Redish et al., 2008).

All these neuroadaptations help to explain why addicts who sincerely claim that they wish to abstain from their drug nevertheless find it extremely difficult to inhibit their responses to drug-related cues, and therefore frequently find themselves acting accordingly. These neuroadaptations help to explain the inconsistency in behavior characteristic of addiction. Work in social psychology has demonstrated the existence of what may be a separate pathway whereby addicts may come to find themselves oscillating from preferring abstention to consumption and back again. This work, on the phenomenon that has come to be called
ego depletion, suggests that the cognitive resources that agents use to assess their options and to inhibit prepotent responses are depletable: utilizing these resources leaves fewer available for subsequent self-control tasks and therefore makes such tasks more difficult.

The evidence here comes from comparing the performance of subjects who have recently engaged in self-control tasks to that of subjects who have engaged in other tasks matched for perceived difficulty, but which do not require very much self-control. The consistent finding is that subjects in the former group perform worse at a subsequent self-control task than subjects in the latter group. This apparently indicates that self-control is a depletable resource (Baumeister, Bratslavsky, Muraven, & Tice, 1998; Baumeister, 2002). It is likely that ego depletion helps to explain the oscillation of preferences experienced by addicts. Repeated or sustained contact with drug-related cues is thought to draw down the self-control resources of addicts, making abstention increasingly difficult. Importantly, loss of control seems to be mediated by judgment shift: the agent comes to judge that they have better reason to give in and consume the tempting good than to abstain (Levy, 2011). Thus, ego depletion gives rise to the oscillation of preferences observed in addicts: when self-control resources are plentiful, the agent judges that abstention is best, but as they are depleted he or she experiences judgment shift.

It may be that ego depletion functions independently of the neuroadaptations that make addicts vulnerable to relapse, or it may be that the neuroadaptations are best understood as vulnerabilities to ego depletion: neuroadaptations that increase the reward value of drugs may increase the degree to which resisting consumption depletes self-control resources, while adaptations that make drug-related cues salient to addicts may make it difficult for addicts to replenish their self-control resources by redirecting their attention. There is some direct evidence that ego depletion is at least part of the explanation for the failures of self-control seen in addiction. Muraven (Muraven, Collins, & Nienhaus, 2002; Muraven & Shmueli, 2006) has shown that resisting the temptation to drink depletes self-control reserves and that ego depletion leads to higher alcohol consumption. This work needs to be replicated with addicts, rather than the heavy drinkers who were the subjects of the study; nevertheless, it strongly suggests that ego depletion plays a role in the behavior characteristic of addiction.

**AUTONOMY, RESPONSIBILITY AND THE OSCILLATION OF PREFERENCE**

Insofar as addicts are subject to oscillations in preferences, they find it especially difficult to govern themselves. They face obstacles to self-rule
that do not confront most other agents. Anyone who is subjected to strong temptations that persist long enough will give in to them; that is the upshot of the finding that self-control is a limited resource. Addicts probably experience such temptations more frequently and with greater intensity than other agents. Their attention is captured by drug-related stimuli, which are motivationally extremely salient for them. They may also have fewer self-control resources to call upon. They are therefore subject to preference reversals more often, and more significantly, than others. To that extent, their autonomy is significantly impaired.

It is not impossible for an addict to resist taking the substance to which they are addicted. Were that the case, the fact that most addicts mature out of addiction (Heyman, 2009) would be mysterious. Any addict will be able to resist the temptation constituted by their drug for some period of time. How long will depend on what other incentives are available, positive and negative, and on what other options they have. The most effective way of resisting a temptation is to remove oneself from it, or to remove one’s own power to respond to it. We commonly use this kind of self-binding strategy to avoid behaviors we wish to avoid; for example, by putting our money in a fixed-term account so that we cannot spend it no matter how tempted we are (or, for accounts that impose large penalties for early withdrawal, to change our incentive structure to ensure that we act as we believe we ought). Addicts frequently find it difficult to impose these kinds of constraints on themselves: their chaotic lifestyles and typical lack of resources, cognitive and financial, make it difficult for them to remove themselves from the cues that trigger temptation for them.

Autonomy and moral responsibility are not the same thing. Nevertheless, lack of autonomy is typically correlated with lack of moral responsibility. If an agent is not able to govern themselves, then they are not capable of ensuring that they refrain from certain actions. The impairment of autonomy to which addicts are typically subject is sufficient to excuse or heavily mitigate their moral responsibility for their actions. The greater the difficulty a particular addict has in maintaining control over their behavior across time, the smaller their degree of moral responsibility for that action. It is an empirical question as to what extent a particular addict’s autonomy is impaired. The neuroadaptations that make drug-related cues salient and tempting for an addict, the cognitive impairments to which some addicts are subject and impairments of the inhibitory mechanisms characteristic of addiction all come in degrees. The smaller the degree of impairment to which an addict is subject, the greater the degree of moral responsibility they bear for their behavior, other things being equal. Features of the context in which agents act also vary in ways that will affect an addict’s degree of moral responsibility: some addicts have the financial resources to remove themselves from neighborhoods in which they frequently encounter drug-related cues, for instance, and some do not.
These factors suggest a general principle: to the extent to which it is reasonable to expect a particular addict to refrain from behaving in a particular way on a particular occasion, that addict is morally responsible for their behavior. It should be noted that it is not only facts about agents and their context that make it more or less difficult for them to act in particular ways that are relevant to the reasonableness of our expectations. It is also facts about the significance of the action. We expect people to try harder to resist performing seriously immoral acts than relatively trivial acts and this expectation seems to be a reasonable one. When subjects are reminded of their values, or offered cash incentives, they are able to hold out against the urge to succumb longer than otherwise (Baumeister, Sparks, Stillman, & Vohs, 2008). We expect that the thought of engaging in a seriously immoral act, such as mugging someone to procure the money to buy drugs, will automatically remind agents of their values and therefore make available more cognitive resources for resistance.

Given the right circumstances, however—circumstances involving repeated or persistent temptations and significantly impaired cognitive and inhibitory mechanisms, say—it is likely that addicts’ responsibility even for seriously wrong actions is significantly mitigated. Though addiction might sometimes be used illegitimately as an excuse for bad behavior, sometimes agents are appropriately excused. Their actions are the product of choices: each action is produced by a process that is sensitive to incentives, and is therefore, in one central sense of the term, voluntary. However, mere voluntariness is sufficient neither for autonomy nor for moral responsibility.

References


III. PHILOSOPHICAL REFLECTIONS
INTRODUCTION: WHAT EVIDENCE IS NEEDED TO LEGITIMIZE MANDATORY TREATMENT

Addictive behaviors clearly undermine individual and population health (Ezzati, Lopez, Rodgers, Vander Hoorn, & Murray, 2002), and exact
an enormous economic cost on societies across the world (Lewin Group, 2004; Rehm, Baliunas, & Brochu, 2006). Clinicians, researchers, policy makers and the public at large are thus eager to implement effective policies and programs to reduce the social, health and economic burdens of addiction. Treatment is one important response to these burdens. Addiction treatment programs have traditionally adopted the view that clients are sufficiently impaired and concerned by their problems to seek help voluntarily. However, the case-mix has shifted over time, and mandatory treatment pathways are becoming increasingly entrenched in addiction treatment programs and policies around the world (Wild, 2006). These pathways include legal mandates from the criminal justice system, formal mandates from employers and social assistance agencies, and informal mandates (e.g. threats, ultimatums, interventions) issued by family and friends, all compelling people with addiction problems to seek treatment (Gerdner & Holmberg, 2000; Gregoire & Burke, 2004; Polcin & Weisner, 1999; Rush & Wild, 2003; Wild, 2006). Mandated treatment policies and programs have been argued to be cost-effective and rehabilitative adjuncts to voluntary treatment (Marlowe, Glass et al., 2001) and justifiable public health measures (Gostin, 1991), akin to seatbelt laws or mass immunization programs.

The rationale for mandatory addiction treatment has recently been broadened to emphasize findings from neuroscience research. Evidence of impairments in decision making (Bechara, 2005; Bechara, Dolan, & Hindes, 2002) and behavioral control (Goldstein & Volkow, 2002) in people with histories of substance abuse and gambling disorders has been used to argue that people with such neurocognitive deficiencies cannot reasonably be assumed to be capable of informed consent. Some have extended this argument further by proposing that mandated addiction treatment should be used to restore patient autonomy (Caplan, 2008) and is therefore justifiable on humanitarian grounds.

In this chapter, it is suggested that any proposals in favor of mandatory treatment policies and programs must provide reasonable evidence that: (1) people experiencing addictions are incapable of making treatment decisions; (2) treatment provided under mandates is effective; (3) there are no iatrogenic effects of mandatory treatment; and (4) negative effects of not providing mandatory treatment are likely. In the following sections, it is argued that neuroscientific findings are currently insufficient to support (1), and that neuroscience cannot, in principle, provide compelling evidence with respect to (2), (3) and (4). Moreover, addiction research outside the neuroscience area has not provided sufficient evidence to support criteria (2), (3) and (4). Consequently, it is concluded that mandatory addiction treatment policies and programs—despite their appeal as a useful approach for reducing the health, economic and social costs of addiction—do not currently warrant widespread support.
Impaired control over voluntary behavior is a key feature in emerging neurobiological explanations of addiction (Hyman, 2005, 2007), in clinical and diagnostic accounts (Martin, Filmore, Chung, Easdon, & Miczek, 2006) and in debates about addiction nosology (Potenza, 2006). There is growing evidence that chronic, sustained abuse of alcohol and other drugs is associated with neurocognitive changes and deficits, as revealed by neuroimaging studies (Bolla et al., 2003; Goldstein & Volkow, 2002) and neuropsychological testing (Ersche & Sahakian, 2007). Goldstein and Volkow (2002) and others propose that chronic exposure to drugs of abuse sets in motion neurobiological processes that result in an overvaluing of the reinforcing properties of a substance or behavior and an undervaluing of natural reinforcers (e.g. food, relationships, work). These processes are associated with impaired voluntary control over one’s behavior. Similarly, Bechara’s (2005) review of multiple lines of research on the neurocognitive systems implicated in addiction concludes that people experiencing an addiction have neurological impairments that weaken their ability to make voluntary decisions in the service of long-term outcomes. Despite cautionary assertions that “it is still difficult to make any substantive generalizations or conclusions about the neuropsychological and neurobiological correlates of chronic drug use, due largely to the fact that the findings are not always consistent in the nature or extent of deficits observed” (Yucel & Lubman, 2007, p. 34), results from neuroscientific studies have been used to argue that mandated treatment is not only justified, but should be employed in order, paradoxically, to restore free will (Caplan, 2006, 2008). Caplan argues that cravings are such “irresistible” and “powerful ... physiological forces” (Caplan, 2006, p. 119) that someone with an addiction is not capable of acting autonomously when the decision involves denying their cravings.

There are several fundamental problems with this argument. First, laboratory procedures used to assess capacity for decision making bear little resemblance to real-life treatment-related decisions faced by people experiencing addictions. Consider the experimental tasks used by neuroscientists to make inferences about impaired behavioral control. Imaging studies and neuropsychological testing procedures typically used in addiction studies involve respondents making low-level decisions in language-based tasks (e.g. go/no-go responses in lexical decision tasks, reaction time responses in word recognition tasks). Although these procedures lend themselves well to experimental control and precise measurement, they are hardly externally valid with respect to the behavioral phenotypes of interest to proponents of mandated treatment, i.e. denial
of cravings in the process of entering treatment and/or decision making related to therapeutic alternatives and goals within treatment programs. Even tasks that explicitly attempt to model impaired voluntary behavioral control and decision making in the laboratory exhibit this problem. For example, the Iowa Gambling Task assesses decision-making capacities in a procedure that requires respondents to weigh both short-term and long-term potential gains in the course of making behavioral responses in the presence of mixed reward and punishment contingencies (Bechara, Damasio, Tranel, & Damasio, 1997). People with a history of addiction are biased toward short-term gains over long-term losses when performing this task (Grant, Cortoreggi, & London, 2000; Rogers & Robbins, 2001), possibly owing to decreased attention to the non-reinforcing consequences of a behavior or losses associated with that behavior (Garavan & Stout, 2005). However, it is problematic to extrapolate these findings to treatment decision-making contexts because the laboratory procedures and stimuli involve monetary decisions rather than treatment decisions.

Even if such laboratory-based procedures afforded an ecologically valid assessment of voluntary behavioral control, a second problem is that performance using these tasks has not been systematically mapped against the full phenotypic heterogeneity exhibited by people entering addiction treatment. On the contrary, laboratory studies designed to model impaired voluntary behavioral control by examining performance on neuroimaging and neuropsychological tasks typically study recently abstinent long-term drug misusers (usually stimulant misusers), carefully selected to exclude polydrug use and comorbid medical, neurological and psychiatric conditions. However, addictive behaviors exhibit substantial heterogeneity and comorbidity within individuals over time, and between individuals over levels of severity (Leri et al., 2005; Swendsen & Le Moal, 2011), and have proven to be difficult to subtype (Babor & Caetano, 2006). Treatment-seeking populations similarly exhibit wide within-person variation (e.g. differences between intoxication at treatment intake and short-term abstinence) as well as between-person heterogeneity with respect to drug use (type, duration, frequency, patterning, polydrug involvement), demographic characteristics (education, socioeconomic status), and—of particular interest to the present topic—route of referral (legal, formal, informal treatment mandates, voluntary treatment entry) (Rush & Wild, 2003).

Laboratory-based investigations of impaired voluntary behavioral control have not examined neuroimaging results and neuropsychological performance on tasks assessing capacity for voluntary behavioral control in relation to such heterogeneity, nor is there a robust literature relating laboratory performance on these tasks to changes in response to pharmacological or psychosocial addiction treatments. These observations raise
significant concerns about the extent to which findings documenting statistically significant differences in performance on decisional tasks with low external validity can support inferences about impaired capacity for treatment decision making. Advocates of mandatory treatment using neuroscience findings thus need to develop a more robust evidentiary base that addresses the problem of phenotypic heterogeneity before neuroscientific findings can be meaningfully brought to bear on discussions about decision-making capacity in addiction treatment.

A third problem is that neuroscientific research on impaired behavioral control among people experiencing addictions has yet to be reconciled with evidence demonstrating that capacity for voluntary behavioral control and decision making—among individuals unencumbered by addictions—is also variable within and across people and is reliably influenced by contextual factors outside the individual (Bargh & Chartrand, 1999; Baumeister, Heatherton, & Tice, 1994; Deci & Ryan, 2002). Exclusive focus on substance-induced reductions of capacity for voluntary behavioral control in the neuroscientific addiction literature thus downplays contextual influences on voluntary decision-making capacity. If, as suggested by this parallel literature, voluntary behavioral control is indeed influenced by forces external to the individual in addition to the impact of chronic alcohol and other drug exposure on neurobiological processes, it would be misguided to try to “restore” autonomy by imposing a treatment targeting only one possible determinant of voluntary behavioral control.

All of these problems call into question the claim that people experiencing addictions are incapable of choosing to enter treatment in accordance with their long-term goals. In fact, many people who experience problems in relation to addictive behaviors (and who presumably are experiencing cravings or urges to engage in the problem behavior) do seek treatment voluntarily (Rush & Wild, 2003). In conclusion, there is currently an absence of appropriate neuroscientific evidence supporting claims that impairments in decision making are persistent and pervasive across the full spectrum of addictive behaviors, justifying the imposition of treatment.

**CRITERION 2: TREATMENT PROVIDED UNDER MANDATES IS EFFECTIVE**

Imagine that there were a body of replicated neuroscience findings supporting robust, ecologically valid inferences about deficits associated with voluntary behavioral control in the context of treatment decision making across the full diversity inherent in addiction phenotypes. Would this evidence be sufficient for supporting mandated treatment policies
and programs? It is argued here that it would not because, first, other criteria must be met to justify mandated treatment, and second, neuroscience research cannot, in principle, provide relevant evidence to satisfy these other criteria. For example, advocates of mandated treatment would need to demonstrate that such treatment is effective in comparison to receiving no treatment, being incarcerated without access to treatment or voluntary treatment seeking. Addiction neuroscience research designed to identify mechanisms of impaired control and decision making cannot provide relevant evidence on this score, but several recent reviews and meta-analyses outside the neuroscience literature have examined whether mandated addiction treatment is effective (Broadstock, Brinson, & Weston, 2008; Harvey, Shakeshaft, Hetherington, Sannibale, & Mattick, 2007; Klag, O’Callaghan, & Creed, 2005; Parhar, Wormith, Derken, & Beauregard, 2008; Stevens et al., 2005; Urbanoski, 2010; Wild, 2006; Wild, Roberts, & Cooper, 2002; Wilson, Mitchell, & MacKenzie, 2006).

These reviews have reached several common conclusions. First, all of them acknowledge the paucity of research in this area relative to general research on addiction treatment. The limited scholarly literature that does focus on mandated treatment is further constrained because it is primarily non-empirical, focusing on unsystematic clinical observations and legal and ethical opinions (Klag et al., 2005; Wild et al., 2002). Moreover, empirical research that does assess the effectiveness of mandated treatment focuses primarily on legal mandates, with little research examining the role of formal and informal mandates to attend treatment (Broadstock et al., 2008; Wild et al., 2002), despite the widespread use of such social control tactics to compel people to seek treatment. Finally, virtually all of these studies compare mandated treatment participants to those seeking treatment voluntarily, and do not include untreated comparison groups.

An examination of the meager empirical literature on the effectiveness of legal, formal and informal mandates to receive treatment indicates that the scientific literature has reached an impasse. Some reviews have concluded that coerced addiction treatment “works” (Anglin, 1988; Farabee, Prendergast, & Anglin, 1998; Harvey et al., 2007; Lurigo, 2000; Leukefeld & Tims, 1988; O’Brien & Cornish, 2006; Parhar et al., 2008), while other reviews have pointed to inconclusive findings and methodological problems supporting a neutral and even critical stance (Klag et al., 2005; Stevens et al., 2005; Urbanoski, 2010; Wild et al., 2002; Wilson et al., 2006). More recent empirical studies in this area provide little new evidence to resolve this impasse. For example, Copeland and Maxwell (2007) examined treatment outcomes for a group of legally mandated cannabis users in relation to their voluntary peers. They found that those in the mandated group were more likely to complete treatment and remain abstinent from cannabis at follow-up. Schaub and colleagues (2010) examined legally
mandated and voluntary addiction treatment clients across five European countries. Their analysis indicated that clients mandated into treatment achieved similar reductions in substance use and reoffending as the comparison group in post-treatment follow-ups, and concluded that mandated treatment is as effective as voluntary treatment for reducing substance use and crime. In contrast, Rengifo and Stemen (2010) used propensity score matching to study recidivism rates among offenders in legally mandated treatment programs and a comparison group receiving other sanctions. They found that those in the mandated treatment group were more likely to reoffend. Finally, Brecht, Anglin and Dylan (2005) examined treatment and patient outcomes among a sample of legally mandated methamphetamine users. Despite finding no significant differences in treatment and short-term substance use outcomes for mandated versus voluntary clients, a 6-month follow-up found that relapse outcomes were significantly worse for those reporting legal pressures to seek treatment.

These mixed findings are rooted in persistent conceptual and methodological problems in this research area. Conceptually, just as addictive behaviors themselves are a heterogeneous phenotype, so too is terminology used to describe mandated addictions treatment. The terms “coerced”, “compulsory”, “mandated”, “involuntary”, “legal or external pressure”, “criminal justice referral”, “social control” and “quasi-compulsory” can all be found in the literature (Prendergast, Greenwell, Farabee, & Hser, 2008, p. 173). Although the concept of treatment “mandates” is relatively clear, implying legal, formal and/or informal social control processes compelling people to enter treatment (Wild, 2006), “coercion” has not been clearly defined and is difficult to operationalize as a dichotomous variable (Klag et al., 2005). Adding to this confusion is the fact that the scholarship in this area spans multiple disciplines: criminology, health services, sociology, psychology, epidemiology, health ethics, legal scholarship, criminology and health policy studies. Researchers trained in these disciplines have divergent “fundamental assumptions, theoretical approaches and research strategies” (Wild, 2006, p. 41). Consequently, studies employ different research designs and define successful treatment “outcomes” differently, rendering effectiveness inferences problematic when using meta-analytic techniques. (A recurring problem in this area is the identification of appropriate comparison groups for mandated treatment. Those interested in recidivism tend to compare mandated treatment to incarceration, whereas those interested in substance misuse tend to compare mandated treatment to either no treatment or to voluntary treatment. Whether relative cost-effectiveness and cost–benefit are the most appropriate outcome criteria, or whether the impact on civil liberties implied by mandated treatment requires a demonstration of its relative superiority in comparison to other options such as incarceration, no treatment, or voluntary treatment, is also rarely debated.)
A common measurement problem in this area is a tendency to conflate objective social pressures (mandates) to seek treatment with client perceptions of coercion (Prendergast et al., 2008; Urbanoski, 2010; Wild et al., 2002). Past studies have primarily employed objective measures, such as referral source, to make inferences about “coercion” in treatment. However, this approach ignores the “ample empirical evidence supporting the lack of a direct, or one-to-one correspondence between objective pressure strategies (e.g. a court order, probationary condition, employment contingency, etc.) and perceptions of coercion” (Urbanoski, 2010, p. 3). Even individuals given the choice between treatment and incarceration may not necessarily perceive or believe that they are being coerced to enter treatment (Urbanoski, 2010). Conversely, a sizeable number of clients who identify as “self-referred” perceive and believe that treatment is nonetheless a coercive imposition (Wild, Newton-Taylor, & Alleto, 1998). Research using both types of measure has found that objective mandates do not predict client engagement early in treatment, whereas perceived coercion and self-reported reasons for seeking treatment do predict client engagement (Wild, Cunningham, & Ryan, 2006). Even if one accepts the view that addiction treatment options should be expanded via mandated referral mechanisms, there are good theoretical and methodological arguments, along with a substantial empirical literature, supporting the notion that we should reject treatment policies, programs and associated practices that may be experienced by clients as coercive (Wild, 2006).

Recent studies have tried to account for client perceptions in measuring coercion (McSweeney, Stevens, Hunt & Turnbull, 2007; Prendergast et al., 2008; Schaub et al., 2010). Yet studies of coerced addiction treatment continue to labor under other methodological problems. Although longitudinal designs are common, the nature of mandated treatment often necessitates the use of non-equivalent comparison groups (Wild et al., 2002; Urbanoski, 2010). Evidence indicates that at treatment entry, mandated clients often differ from self-referred clients with respect to age, problem severity, personal characteristics, criminality, employment and motivation for treatment (Copeland & Maxwell, 2007; Klag et al., 2005; Rush & Wild, 2003; Urbanoski, 2010). Thus, we can reasonably assume that these groups’ recovery processes, trajectories and prognoses are likely to differ as well (Urbanoski, 2010). Systematic pretreatment group differences confound and distort comparisons of treatment effects (Klag et al., 2005), making attributions of effectiveness for mandatory treatment problematic (Wild et al., 2002).

Research in this area typically examines treatment compliance rather than treatment engagement in making inferences about effectiveness, as shown by reliance on attendance as the most commonly used outcome variable in this literature (Wild et al., 2006). However, this preference is
problematic because treatment retention is not synonymous with treatment engagement or treatment success. Indeed, there is some research indicating that legal pressures to seek treatment are linked with poorer levels of commitment to the treatment process and problems within the client–provider therapeutic alliance (Urbanoski, 2010). For example, treatment systems that include programs handling high proportions of clients experiencing legal social controls exhibit greater rates of failure to comply with treatment plans than programs with lower proportions of legally mandated clients (Howard & McCaughrin, 1996). Moreover, when substance use or recovery outcomes are formulated, they tend toward measures of abstinence in the short term. Recoveries, like addiction careers, are not homogeneous. While abstinence may be an appropriate goal or outcome for some, it is not necessary for others. Thus, more nuanced outcome measures may contribute to more accurate assessments of efficacy in the long run. Finally, research examining the efficacy of mandated treatment has been criticized for de-emphasizing treatment context and other covariates beyond mandates per se that can explain or mask differences across comparison groups (Parhar et al., 2008; Wild, 2006; Wild et al., 2002; Wild & Wolfe, 2009). For example, Cosden and colleagues (2006) found that client-reported motivation accounted for little variance in treatment program completion within a drug court program. Instead, they found that prior employment and previous incarceration were more important predictors of treatment outcomes.

In summary, despite widespread use, relatively few empirical studies have examined whether mandated addiction treatment is effective, relative to the large amount of research conducted on efficacy and effectiveness of addiction treatment generally. Research investigating the effectiveness of mandated addiction treatment is marred by a number of conceptual and methodological problems, suggesting that there is a poor evidentiary basis for this criterion.

**CRITERION 3: THERE ARE NO IATROGENIC EFFECTS OF MANDATORY TREATMENT**

Even if a compelling body of evidence clearly demonstrated the equivalence or even superiority of mandated treatment relative to no treatment, incarceration or self-referral into treatment, advocates of these policies and practices would need to demonstrate that any unintended negative consequences of providing mandated treatment at either the individual level (e.g. harming the therapeutic relationship between client and counselor) or the system level (e.g. introducing shifts in the case-mix that addiction treatment systems are ill-equipped to manage) are outweighed by its benefits. As with criterion 2, neuroscience per se
cannot address these issues, and there is insufficient evidence outside the neuroscience literature on addiction treatment to support this third criterion.

**Impact on Quality of Treatment**

Studies show that client–counselor rapport, therapeutic alliance and peer relationships are important predictors of client engagement, retention and outcomes (Lebow, Kelly, Knobloch, & Moos, 2006; Simpson & Joe, 2004). There are findings demonstrating that legal and formal mandates prolong retention in treatment (Anglin, Brecht, & Maddahian, 1989; Brecht, Anglin, & Wang, 1993; Collins & Allison, 1983; Grichting, Uchtenhagen, & Rehm, 2002; Kelly, Finney, & Moos, 2005; Leukefeld & Tims, 1988; Polcin, 2001), which predicts positive post-treatment outcomes at least in the short term (Brecht, Angling, & Dylan, 2005; Collins & Allison, 1983; Grichting, Uchtenhagen, & Rehm, 2002; Knight, Hiller, Broome, & Simpson, 2000; Leukefeld & Tims, 1988; Young, 2002; Young & Belenko, 2002). However, other data indicate that mandated treatment undermines the quality of therapeutic relationships, compliance and confidence in treatment (Joe, Simpson, & Broome, 1999; Marlowe, Merikle, Kirby, Festinger, & McLellan, 2001; Marshall & Hser, 2002) and that benefits of treatment under social controls do not persist after legal, institutional and/or family sanctions are lifted (Anglin, 1988; Anglin & Hser, 1991; Stevens et al., 2005; Weisner, 1990).

**Impact on Service System Capacity**

Only a minority of individuals who need specialized alcohol or other drug treatment actually receive it, whether in the general population (Cartwright & Solano, 2005) or in prisons (Belenko & Peugh, 2005). A fundamental consideration is whether a shift to mandated treatment as a preferred mechanism for referring individuals to addiction treatment displaces treatment capacity away from those seeking treatment voluntarily (Rush & Wild, 2003). Thus, an analysis of the increased mandated treatment would need to consider iatrogenic effects on those seeking voluntary treatment.

The use of mandated treatment mechanisms could be argued to be an effective early case-finding strategy, bringing people into treatment before their addictive behaviors and related health and social problems become severe (Marlowe, Patapis, & DeMatteo, 2003; Sowers & Daley, 1993). Consistent with this claim, research has pointed to important differences in the characteristics of those entering treatment under a mandate and those seeking treatment voluntarily. People who are referred to addiction treatment by legal and formal routes tend to be younger, and
less severely dependent on alcohol and other drugs, and are less likely to have previous treatment experience than others seeking treatment (Brecht et al., 2005; Grichting et al., 2002; Friedmann, Lemon, Stein, & D’Aunno, 2003; Kelly et al., 2005; Kline, 1997; Leukefeld & Tims, 1988; Marshall & Hser, 2002; Polcin & Weisner, 1999; Rush & Wild, 2003). However, when policies shift from treating those with severe alcohol or drug dependence (e.g. those who may have “hit bottom” and recognize a need for treatment) to treating drinkers and drug users who may not believe that their substance use contributes to their health and social problems, programs must accommodate a new client base, which may have different needs.

Paradoxically, these findings imply that mandated policies and programs may in practice bring people into treatment who are systematically less likely to exhibit the purported neurobiological impairments that might justify the suspension of patient rights and individual autonomy over treatment entry. To the extent that this “net widening” occurs, mandated treatment policies and programs could become institutional mechanisms of deviance control (Archer, 1985; Hendershott, 2002), which carries its own risk for societal harm, rather than a set of practices designed to have therapeutic benefit.

Finally, notwithstanding the problem of phenotypic heterogeneity discussed earlier, whether increased use of mandated treatment will increase or decrease the overall success rate and cost-effectiveness of treatment programs remains to be seen. In sum, far from presenting a compelling case that mandated treatment is associated with either no iatrogenic effects or minimal negative effects relative to benefits, the evidence reviewed in this section suggests, at best, that there is insufficient evidence on this score, and at worst, that iatrogenic effects for individuals seeking treatment and the capacity of treatment systems to deliver quality care to those seeking help are probable.

**CRITERION 4: NEGATIVE EFFECTS OF NOT PROVIDING MANDATORY TREATMENT ARE LIKELY**

It is incumbent upon advocates of mandated treatment to address whether treatment under legal, formal and informal mandates is better than exposure to no treatment at all. Thus, policy makers and treatment providers must take into account the sizeable body of research that has accumulated documenting remission of addictive behaviors without treatment intervention. An early review of the literature on natural recovery from alcohol and other drug dependence published before the end of 1997 cited 30 studies of natural recovery from alcohol misuse; three focused on cocaine, nine on heroin, one on marijuana and five on other substances (Sobell, Ellingstad, & Sobell, 2000). A follow-up to
this review of the literature published between 1999 and 2005 found 18 additional publications addressing natural recovery from alcohol; five focused on cocaine, five on heroin, seven on marijuana and six on other substances (Carballo et al., 2006).

Several studies have investigated rates of natural recovery among alcohol users, drug users and gamblers (Hodgins & el Guebaly, 2000; Slutske, 2006). A Canadian study of more than 12,000 individuals over the age of 15 who reported using an illicit substance more than once addressed natural recovery from use of marijuana, cocaine, LSD, speed and heroin (Cunningham, 1999). Among those who had no reported use in the past year, most indicated that they had never sought “any services or help” (Cunningham, 1999, p. 268) for their drug use. Untreated remission was reported among 94% of former marijuana users, 91% of former regular marijuana users, 86% of former LSD users, 84% of former cocaine users, 80% of former speed users and 66% of former heroin users. This study, however, did not classify former users according to whether their use met criteria for dependence.

A later study by the same author employed more stringent criteria to classify drug dependence in a general population sample using a cluster of indicators of DSM IV criteria (Cunningham, 2000). In this study, many drug users who met the criteria for dependence at some point in their lifetime, but did not meet the criteria within the past year, were found to have accessed some form of treatment for their drug misuse. Among those who had a lifetime diagnosis of dependence for a substance but did not qualify as being dependent on that same drug within the last year, between 9% and 57% reported never having sought treatment. Untreated remission from the original drug of abuse was most common among those who had been dependent on cannabis (57%) and least common among those who had been dependent on heroin (9%). Similarly, among those who met the criteria for a lifetime drug dependence but who currently did not meet the criteria for any kind of drug dependence, between 8% and 57% indicated that they had never accessed addiction treatment. This is consistent with other research showing that untreated remitters tend to have lower problem severity compared to those who obtain treatment (Sobell, Sobell, Toneatto, & Leo, 1993; Tucker & Gladsjo, 1993).

Studies of problem gamblers have also shown that natural recovery is a common outcome. In a population study, Slutske (2006) reports that 36–39% of individuals identified as having a lifetime history of problem gambling did not meet criteria for having a past year gambling problem, but only 7–12% of the population of lifetime problem gamblers had obtained formal treatment. This means that about one-third of problem gamblers can be classified as natural remitters. Among alcohol users, rates of natural recovery vary across studies, depending on sampling and criteria used to define “recovery”. For example, based on two
large representative samples of Canadian adults, about three-quarters of those who experienced recovery from an alcohol problem did so without formal treatment (Sobell, Cunningham, & Sobell, 1996). Rumpf and colleagues (2006) reported that natural recovery is stable in many individuals, with 92% of those who had evidenced remission from alcohol use without treatment remaining abstinent 2 years later (Rumpf, Bischof, Hapke, Meyer, & John, 2006).

Taken together, these results have several implications for the mandated treatment debate. First, it is important to distinguish between drug use, misuse and dependence, i.e. phenotypic heterogeneity must be kept in mind. It might be expected that mandated treatment policies and programs would be reserved for the most severe addiction problems. However, research indicates either that treatment mandates are unrelated to problem severity (Polcin & Weisner, 1999) or that mandated clients have less severe clinical profiles at treatment entry (Bischof, Rumpf, Hapke, Meyer, & John, 2001; Kelly et al., 2005). Cessation or reduction of addictive behaviors without the aid of treatment is quite common when considering the full range of users (those who do and do not meet criteria for dependence), although it is less common only when considering those who meet dependence criteria. Second, drug of choice is an important consideration. The studies reviewed in this section indicate that spontaneous remission is more common for some drugs than for others. This highlights the need for judgments about whether treatment mandates should be made on an individual basis, taking into consideration patterns of drug use and the considerable heterogeneity among people experiencing addictions (Klag et al., 2005). In sum, the literatures on natural recovery and phenotypic heterogeneity both suggest that we should be cautious about claims supporting mandated treatment that rely on the argument that negative consequences are probable if treatment is withheld.

**TOWARD A MODEL OF INFORMED CONSENT FOR ADDICTION TREATMENT—WITH OR WITHOUT MANDATES**

This chapter began with the argument that proposals to suspend clients’ right to informed consent in addiction treatment would require solid evidence on four key criteria: (1) people experiencing addictions are incapable of making treatment decisions; (2) treatment provided under mandates is effective; (3) there are no iatrogenic effects of mandatory treatment for the individual or society; and (4) negative effects of not providing mandatory treatment are likely. To date, addiction studies—whether framed from a neuroscientific perspective or from psychosocial
and health services research traditions—have not yet produced an evidentiary basis to satisfy these four proposed criteria. Thus, there appears to be no reasonable justification at present for overriding or suspending potential clients’ right to informed consent in the provision of addiction treatment. On the contrary, the authors support emerging guidelines for obtaining informed consent to participate in addiction treatment, which include providing clients with a clear, lay-language description of their diagnosis; information about treatment recommendations and a rationale for the recommended course; information on the risks and benefits of treatment, including financial costs and alternatives; and freedom to refuse or choose between treatment options (Walker, Logan, Clark, & Leukefeld, 2005). These guidelines are consistent with theory and empirical evidence on the beneficial role of perceived autonomy support and client choice in the context of addiction treatment and health behavior change (Wild, 2006).

As argued throughout this chapter, it is as problematic to assume that those exhibiting addictive behaviors are a homogeneous group, as it is for those with other mental health problems (Usher & Arthur, 1998). Clients presenting for treatment should be expected to show variation in their histories of exposure to alcohol and other drugs, pre-existing or co-occurring cognitive capacities, and resilience or vulnerabilities to the effects of addiction. White and Kurtz (2005) reviewed the ways in which recovery from substance abuse problems are experienced, which include variability in terms of scope of recovery, depth of recovery (e.g., partial, full and enriched), types of recovery (abstinence-based, moderation-based, medication-assisted) and recovery stability/durability. Prochaska and colleagues (1991) further emphasized the instability and non-sequential path of recovery. The authors reported data on 544 participants who completed standard measures of stages of change every 6 months over a 2-year period. Individuals were classified on five occasions as being in the precontemplation, contemplation, action or maintenance stages (Prochaska, Velicer, Guadagnoli, Rossi, & DiClemente, 1991). Results revealed that consistent and sequential progression through the theoretically predicted stages was infrequently observed. Only 16% of participants progressed stably over the 2 years, while 12% moved backwards one or two stages over time and 36% showed no change at all. The issue of stability or durability of recovery has also been addressed in a study of 229 US veterans seeking treatment for cocaine misuse (Siegel, Li, & Rapp, 2002). In this sample, only 31% showed a pattern of stable abstinence over the 18 months following admission to treatment. The remaining participants were classified as either consistent users (28.8%) or inconsistent users (40.2%) based on their self-reported patterns of behavior at three separate time-points. This study may have overestimated the proportion of individuals who were stably abstinent,
as only those who could be contacted for each follow-up were included in the study. McLellan and colleagues (2000) argue that drug addiction is best viewed as a chronic medical condition, akin to diabetes or hypertension. They remind the reader that among those who seek treatment, relapse rates typically range between 40% and 60% (McLellan, O’Brien, Lewis, & Kleber, 2000). Although neuroscience research has not gone so far as to assess whether such interindividual and intraindividual differences are associated with concomitant variations in the effects of addiction on the neurobiological mechanisms’ underlying capacity for voluntary decision making, it is reasonable to expect that such differences would exist.

On the whole, these findings imply that assessment of competence to make an informed choice about treatment is necessary and, in fact, that competence should be regularly reassessed after a mandatory treatment measure is imposed to detect at the first opportunity when competence is restored. Currently, there are no published guidelines about assessing competence to consent in people with addictions. However, mental health researchers offer a model for how the consent process can be handled so as to ensure that personal autonomy is protected under such circumstances. Standardized tools, designed to assist practitioners in assessing competence to provide informed consent for mental health treatment, have been designed and tested by a number of authors largely since the early 1990s. A review of the instruments and protocols reported in the literature between 1980 and 2004 found 15 tools specifically designed for treatment contexts (Dunn, Nowrangi, Palmer, Jeste, & Saks, 2006). Instruments varied in the extent which they included assessment of four domains: understanding, reasoning, appreciation and expression of choice. The authors identify the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) as one of the best of those reviewed, owing to its coverage and psychometric quality. The reliability of this tool has been assessed and shows good interrater consistency (Cairns et al., 2005). Grisso and colleagues (1997) created a semi-structured interview procedure aimed at guiding the clinician and client through information disclosure and assessment of decisional capacity (Grisso, Appelbaum, & Hill-Fotouhi, 1997). Understanding is assessed by having the client paraphrase the information provided to the individual; reasoning is assessed by probing the rationale underlying the client’s choices (e.g. making appropriate comparisons, generating consequences); appreciation is assessed by guided questioning to uncover whether the client comprehends that the disclosed information applies to him or her and whether the client accepts that treatment may be of some benefit; and ability to express a choice is determined by whether the individual overtly states a preference for or against treatment. Importantly, the authors stipulate that a lack of appreciation must be evidenced by delusional or distorted
thinking, rather than simply treatment refusal or a reasonable difference in opinion from that of the clinician.

A more systematic procedure to assess multiple dimensions of competency could be supplemented by an approach to informed consent first developed for qualitative research. In qualitative research where the researcher has an ongoing and evolving relationship with the participants, it is often the case that the risks to the participant change over time. In such situations, some have argued that consent should occur not just once at the beginning of the study, but continuously as the research progresses (Usher & Arthur, 1998). Others have developed a corrected feedback approach for use in research contexts whereby consent information is delivered and then the recipient is asked questions to assess his or her understanding of the key elements. Misunderstandings can then be corrected, and in some cases reassessment and correction continue until mastery is achieved (Festinger, Dugosh, Croft, Arabia, & Marlowe, 2010). Such a “process consent” framework views the relationship among actors as a partnership requiring ongoing consultation and team decision making. It also involves an ongoing process of determining the patient’s competency, regardless of what the initial determination might be. On this view, informed consent is seen as a collaborative process, rather than a one-time authoritative judgment made about the client. The introduction of systematic assessment of competency and principles of process consent are foundational steps needed to move the clinical addiction field toward making individualized, evidence-based decisions about client needs for treatment.

CONCLUSION

In this chapter, it has been argued that a neuroscientific explication of the mechanisms underlying addictive behavior is, at best, incomplete at this time. Further, a fully realized neurobiological model of addiction would constitute an insufficient basis for suspending rights to self-determination in the context of treatment decision making (Kalant, 2010). The authors advocate an approach whereby neuroscience informs but does not necessarily dictate conceptualizations of mandated treatment, nor our practical responses to it. This approach is consistent with calls for evidence-based ethical practice (Anderson & DuBois, 2007) wherein policy and clinical procedures are guided by a critical examination of the totality of our current knowledge, while also acknowledging the limits of what we currently know. This approach also guards against the tendency of neuroscience approaches and findings to be reified in relation to other scholarly traditions in addiction studies, and to be used as the sole, or most valued, justification for mandated treatment.
Additional research is needed to explore how neurocognitive impairments vary in relation to phenotypic heterogeneity with respect to context of drug use, addiction history, treatment history and time. It will also be important to investigate the shift to a more process-oriented approach of competency assessment, and evaluate what impact such an approach might have on the development of client–counselor rapport and client outcomes in treatment. Finally, in studies examining effectiveness of mandated treatment, researchers should consider potential unintended adverse consequences of treatment mandates. Treatment system research also needs to determine the potential impact of the increasing use of mandated treatment on system capacity and case-mix. The authors advocate continued discussion about the ethical implications of coercion in the addiction treatment field and believe that such a discussion will be vastly improved by broadening the evidence base in such ways.

References


CONCLUSION


8. CONSENT AND COERCION IN ADDICTION TREATMENT


III. PHILOSOPHICAL REFLECTIONS


INTRODUCTION

[If the history of addiction research reveals anything, it is that science is a fundamentally social activity taking place within a structure of beliefs about productive citizenship, public health and technoscience as a route to pharmacological fixes and ultimately to social progress. (Campbell, 2010, p. 102)
Drug consumption and beliefs about morality, identity, responsibility and self-control are inextricably linked. Since the nineteenth century, influential models of drug use and addiction either as a moral decision (intentional and controllable) or as a medical disease (chronic, relapsing and compulsive) have emerged. For better or worse, these have informed public, private and state responses to the “drug problem”.

There are other accounts of drug use and “addiction” identities. These include more liberal stances that reject the idea of drug addiction, and define drug use as pleasure seeking akin to other consumption behaviors (Foddy & Savulescu, 2006; Szasz, 1975). Functional and constitutive addiction identities are also available from popular culture (be it literature, film, music and other areas of the arts) and in the narrative accounts of drug users themselves. “Addicted” individuals have occupied prominent political, social and cultural positions for as long as we have debated the place of drugs and psychoactive substances in our societies.

Both moral and disease models of addiction are criticized because they present an identity that is fundamentally deficient, where the drug user is “wrong”, “weak”, “out of control” or “deviant” (Reith, 2004). The current dominance of this deficit idea is problematic because it serves to restrict the social identities that are available to drug users; identities that perhaps are already limited because they are expert defined in academic and professional discourse and practices.

Such framings of drug use and addiction give rise to and perpetuate stigmatized conceptions of self-identity, as well as the negative judgments of others (Ross & Darke, 1992; Simmonds & Coomber, 2009), and may undermine the impact of prevention and treatment efforts. This is illustrated by studies of supervised methadone maintenance therapy (MMT) dispensing and client identity (Fraser & Valentine, 2008; Anstice, Strike, & Brands, 2009).

Anstice and colleagues (2009) showed that dispensing settings can help MMT clients to manage their identity by assisting them in “passing as normal” in the public, while other clients found that certain dispensaries reinforced a stigmatized “user” identity, which in turn discouraged them from accessing services. Other studies show that the adoption of biological explanations for chronic health conditions like mental illness can lead to stigmatization and negative identity assessments (Marie & Miles, 2008; Mehta & Farina, 1997; Phelan, Cruz-Rojas, & Reiff, 2002; Phelan, 2005). Some warn that deficit accounts of drug use and addiction “inevitably lead[s] to a sense of hopelessness and pessimism about the likelihood of effective treatment” (Fitzgerald, 1998, p. 79).

An alternative account of drug use and addiction is possible, in the form of how drug users and addicted individuals identify themselves, thereby creating or at least describing their own identities. Taking seriously the perspectives of drug users and drug-dependent individuals on
such topics as identity, agency and capacities for choice and control can help us to test the identity and capacity assumptions and claims made in contemporary models of drug addiction. Lay perspectives provide a possible counter to the dominance of deficit accounts of drug addiction and, perhaps more importantly, help to highlight capacities for recovering from, living well with, or as Mitchell says, “developing an appreciation of ourselves as capable of modifying addictive tendencies expressed in everyday living” (2007b, p. 236).

Recent advances in clarifying the neurobiology of drug dependence, and its role in brain function and decisions about drug use and other behavior, have reinvigorated academic, practitioner and policy debates around the impact of addiction on agency, identity, and capacities for choice and control. As shown by other chapters in this collection, innovations in neuroscience have in turn given rise to a specialized focus of bioethics known as neuroethics, within which an examination of the ethical and social implications of addiction neuroscience is emerging (e.g. Illes, 2006; Levy, 2007).

Currently, the dominant perspectives in addiction neuroethics are those from neuroscience, philosophy, psychology and the law. Pervading much of the debate is the assumption that drug addiction is fundamentally harmful to self and other, and that treatment seeking, spontaneous recovery and self-change in “addicted” people is a universal goal that is motivated by either a dislike of the drug(s) to which they are addicted, or the negative things they experience as a consequence of use (e.g. punishment, blame, stigma, health harms).

It is worth considering how the way we think about drug use and addiction and the above assumptions might change if we examined seriously the lay perspectives and lived experience of drug users or “drug-addicted” people. Fry and others (2005) have argued that one way to reframe existing power relations in the addictions field is by the clarification of stakeholder values through “community input (in this case from “drug users” and representative organizations) on their own values, ethics and interests” (p. 457). In their view this would help to “define a positive new territory of authority for drug users” and progress the community consultation and participation project “beyond disputes over technical expertise” (Fry, Treloar, & Maher, 2005, p. 457).

Would an equitable admission of lay perspectives to addiction neuroethics yield positive outcomes, or are these too destined to be co-opted, regulated and returned to “normal” (Reith, 2004)? Is epistemic humility possible in the knowledge translation of addiction neuroscience? Or would dominant expert voices prevail through continued “knowledge deficit” assumptions (Brunk, 2006) about the worth of lay contributions to public policy debates? To address such questions it is necessary to examine drug use and addiction identity more closely.

III. PHILOSOPHICAL REFLECTIONS
The idea of identity is important in both addiction and addiction neuroethics, but is a complex construct to clarify. The aims in this chapter are to highlight some of the key accounts of identity that are relevant to drug use and addiction, and to discuss how descriptive definitions of addicted identities (or lay, folk psychological or narrative understandings, as they are also known) offer an important alternative account.

**DRUG USE AND ADDICTION IDENTITIES**

Many of the scholarly contributions on identity from the humanities and social sciences focus on personal identity, or the questions that arise about what or who an individual is. This includes discussions about the conditions of personhood, moral and practical identity, moral agency, and temporal questions such as what it means for one person to exist at time A and at time B. Aspects of these discussions focus on the determinants of how individuals live by (or practice) their values, goals and plans (Sayers, 1999; Atkins & MacKenzie, 2008).

Addiction is a paradigmatic case in contemporary philosophical discussions on issues of identity, self, agency and responsibility. For example, Frankfurt’s (1971) portrayal of the “addict” distinguished actions that the agent reflectively endorses, from those where the agent is helpless—moved by “a force other than his own” (p. 13). The individual who acts upon a desire (to consume drugs) that she does not endorse is thereby said to be unwilling and lacks agency. A central focus in philosophical examinations of drug use and addiction has been the question of whether addiction is compelled or determined biologically, or the result of human choices that are morally suspect (Husak, 2004; Wallace, 1999).

**LIBERAL ACCOUNTS**

Liberal theorists such as Szasz (1971) and Foddy and Savulescu (2006, 2010) are concerned about the impact of determinist accounts of addiction upon our ideas about autonomy and agency. Foddy and Savulescu’s (2006, 2010) liberal account of drug addiction holds that “to get at the truth about the nature of addiction, we need to allow each person to hold his own set of desires and values” (Foddy & Savulescu, 2010, p. 18). The authors define pleasure seeking as a normal human behavior, and are skeptical that medical models of addiction will remove the individual’s responsibility for the consequences of their drug use. They acknowledge that such individuals may possess poor self-control and act recklessly, but contend that poor self-control and reckless behavior are not diseases (Foddy & Savulescu, 2006, 2010).
For Foddy and Savulescu, “[a] full and correct account of addiction would take seriously the claim that pleasure as a sensation can be a part of an autonomous and even rational life plan” (2010, p. 20). But others have argued that “[t]o explain drug use as merely pleasure-seeking is to ignore, or dismiss as unimportant, the emotional world of the drug user” (Fitzgerald, 1998, p. 83); and so there may be room for liberal accounts to be developed even further.

Indeed, Fitzgerald’s focus on the commonality of the emotional regulation challenge is suggestive of a more positive view of drug addiction: “All humans struggle to a lesser or greater extent with emotional regulation and self-care issues. The emotional regulation perspective encourages a compassionate and thoughtful response to problem drug use: the individual is not seen as morally weak, hedonistic, or hopelessly suicidal, but instead is understood to be struggling to manage a complex and difficult emotional life” (Fitzgerald, 1998, p. 83).

Some who adopt a liberal view endorse the notion of personal responsibility and that the “person, not his autonomous brain, is the instigator of relapse and the agent of recovery” (Satel, 1999, p. 861). Here, the addiction-related actions of such individuals are regarded as prima facie autonomous (intentional and voluntary), and as such may be subjected to moral scrutiny.

The aim of liberal accounts is arguably to avoid the creation of addiction as “other”, and implicitly allow that drug users have the capacity to choose otherwise. In this view, drug use and addiction can be defined as choices we are responsible for; responsible in the sense that we have the capacity to reverse or avoid such choices. This frames drug use and addiction as accepted identities where the capacity for autonomous agency, control and decision making is not completely undermined; an assessment that need not lead us to abstinence- and prohibition-based policy responses.

**MEDICALIZATION AND DISEASE**

Clinically, addiction is characterized by a loss of control over drug use as indicated by continued use despite negative consequences (APA, 2000). In the emerging neurobiological framework, addiction is understood as “a chronic, relapsing disease of the brain” (Leshner, 1997, p. 46). The brain disease framework has three main objectives. The first is to produce effective therapeutic strategies, such as pharmacotherapies that will eliminate craving and vaccines that block drug euphoria. The second is to strengthen the medical perspective of addiction that contrasts with willpower-based views of addiction that place moral or criminal blame on addicted individuals. The third aim, a political consequence of the
medicalization of addiction, is to encourage more humane treatment of addicted individuals.

Neuroscientific explanations of addiction appear to promise less punitive treatment of those with addiction, given the diminished control of the addict (Carter & Hall, 2007). Yet some caution that the potential misuses of an overly deterministic view of identity and behavior can include legally coerced treatments, emphasis on medical over social and public health interventions, issues of consent, use of treatments and diagnostics of uncertain efficacy, and further stigma and discrimination (Academy of Medical Sciences, 2008; Buchman, Skinner, & Illes, 2010; Carter & Hall, 2007; Nutt, Robbins, Stimson, Ince, & Jackson, 2007).

It is argued that “the failure to recognize addiction as a disease” (Goldstein et al., 2009, p. 372), and continuing to see addiction as a character flaw, have resulted in increased societal stigma toward addicted individuals, creating barriers in accessing services, and retributive or punitive drug policies (e.g. incarceration). Dackis and O’Brien (2005) state that “pejorative views toward addicted individuals also exist and contribute to policies that would be simply unacceptable if applied to ‘real’ medical disorders” (p. 1431, quotes in original).

Because it is believed that addicted individuals often do not desire to continuously consume their drug, some scholars suggest that they are coerced to consume by their mental states. Debates over whether brain states “coerce” addicted persons into an uncontrollable compulsion have gained considerable momentum in the research ethics literature, particularly whether or not such states impair addicted individuals’ capacity to consent to research involving their drug of addiction. See, for example, Carter and Hall (2008), Charland (2002), Cohen (2002), Elliott (2002), and Hall, Carter, and Morely (2003). Given that autonomy requires freedom from coercion, this view of internal coercion has led some philosophers, bio/neuroethicists and health-care workers to argue the addicted individual is not a “fully free, autonomous agent” (Caplan, 2008, p. 1919).

Contemporary addiction neuroscience has been a key recent player in relocating addiction from the social body to the brain (Campbell, 2010). However, even among brain disease supporters, the issue of voluntary control is far from resolved. While many would agree that addiction impairs the capacity to make decisions about drug use, others argue this “loss of control is not complete or simple” (Hyman, 2007, p. 8).

Since the mid-twentieth century, a developing view from both inside and outside research programs in the brain and behavioral sciences has been that knowledge about the brain will uncover the essence of what it means to be a human being. Some argue that there is a historical trend in this area in the form of the “old and powerful idea that we acquire knowledge of humanity by replacing human kinds by physiological or mechanical or neuroelectrical or biomechanical ones” (Hacking, 1995, p. 353).
HACKING’S (1995, 2007) discusions of “human kinds” and “making up people” are valuable illustrations of the ways in which identity might become closely tied to an essentialist neurobiological constitution of self in addiction. Human kinds are classification systems that describe a specific kind of person and their behavior, and are often contrasted with natural kinds, things such as chemical elements, trees or quarks that do not change in response to the ways they are classified (Hacking, 1995).

Unlike natural kinds, human kinds are said to interact with the ways in which they are described via “looping effects”. For example, an individual diagnosed with a particular disorder acts in accordance with the expectations cultivated by that classification. The concept of human kinds points toward the ways in which expert explanations and systems of classification become malleable once adopted by non-experts who are the subject of the classification.

Explanatory narratives for addiction such as the “dopamine hypothesis”, brain-targeting treatments (e.g. buprenorphine and naltrexone) and the brain disease model of addiction in popular news outlets (see Chapter 11 in this volume) have been particularly persuasive in classifying the individual who is addicted to drugs as a “neurobiological human kind” (Vrecko, 2006). For instance, the drug user as being a diseased brain is represented and reinforced in the National Institute on Drug Abuse’s (NIDA) widely disseminated publication *Drugs, brains, and behavior: The science of addiction* (2010), currently in its third revision. Maintaining consistency with their message of addiction as a disease of the brain throughout, the publication is complete with images of pathological brains labeled as “drug abuser” contrasted with images of non-dysfunctional brains of “healthy persons”.

Addiction then becomes a kind of neurobiological otherness, where the agent’s identity, experiences and behaviors are intimately connected to the functioning of his or her neurobiology (Vrecko, 2010). These links between neurobiology and identity reinforce the perception that, because of a diseased brain, the individual living with addiction is a certain kind of person. Hence, the brain disease framework emphasizes the difference between “addicts” and “normals” in their respective neurological identities.

Neuroessentialist claims about addiction should not be dismissed outright, particularly when there is a paucity of evidence about how addicted individuals actually interpret these new types of classification. For instance, believing that one is neurobiologically dysfunctional may hold symbolic value for the drug user and those close to them. That is, a neurobiological human kind might reinforce the idea that addiction has a “family resemblance” to other medical diseases, and necessitates treatment.
Although there is limited work in this area, recent research suggests that individuals with mental disorders have begun to speak of themselves in neurobiological terms (Cohn, 2010; Martin, 2007), and in some cases, hope that a neurobiological identity will help to reduce social distance and fear (e.g. Cohn, 2010; Martin, 2007). Indeed, a recent American study suggests that although the public is increasingly embracing a neurobiological understanding of schizophrenia, depression and alcohol dependence, this does not translate into reduced stigma or social distancing (Pescosolido et al., 2010). Important for the present discussion is that if we make the empirical judgment that an individual’s neurobiology is functioning in an abnormal manner, a co-occurring normative judgment is also made about that individual, in terms of behavior, well-being and, in particular, identity.

Hence, concepts that are associated with a brain disease (e.g. a diseased brain, a neurochemical imbalance, defective genes) may allow the individual to construct an illness narrative in which they can connect their present and past experiences to the development of their addiction, finding meaning in their story and ways in which they may develop knowledge and understand themselves (Buchman, Illes, & Reiner, 2010).

Neuroscience may well have identified “some of the cellular and molecular mechanisms involved in tolerance, neural resensitization, withdrawal, and dependence” (Buchman & Reiner, 2009, p. 18), but there is an important unanswered question about whether or not these neurobiological facts, even though they may be said to exist in the person, are really lived or consciously experienced by the people in whom they exist. How can the cellular and molecular aspects of drug addiction be said to be part of the addiction identity if these processes are unavailable to our conscious experience?

Of course, our vocabulary for explaining our lived experiences is shaped by the received expert language and practices (Larkin, Wood, & Griffiths, 2006), and by popular culture (Ross, 2007). Expert academic and professional claims about the role of the brain in addiction, and the impact of drugs upon brain function, human decisions and behavior, give rise to important questions about autonomy, identity and self-understanding. They also have a wider relevance for public policy and the treatment of drug users.

Some of the central claims of addiction neuroscience that have “identity” implications include the following: our decisions and actions have precognitive antecedents; drugs can impair and damage the brain; drug addiction and related mental states can be imaged and predicted; addiction impairs memory, self-control, cognition and emotion; drug addiction can be transformed or changed (e.g. pharmacotherapy, vaccines, neurosurgery); and drug addiction can be regulated (e.g. policy, surveillance,
treatment) (e.g. European Monitoring Centre for Drugs and Drug Addiction, 2009; Nutt et al., 2007; World Health Organization, 2004).

The potential problem that emerges from an absence of knowledge about drug user identity and self-understanding in relation to addiction (or “lived experience”, as it is referred to in the social sciences) is two-fold. First, greater clarity on drug user identity and self-understanding is crucial for establishing ethical and effective public policy and practice in this field. Second, without this understanding important questions remain unanswered around issues of responsibility, autonomy and, perhaps most importantly, the “addicted” individual’s capacity to be otherwise (or recovered).

**DESCRIPTIVE “FOLK” UNDERSTANDINGS OF ADDICTION**

Folk psychology has been characterized as the idea that there is a real me or “self” that resides in my body and is the subject of my experiences. The term is used by many functionalist philosophers and cognitive scientists to refer to an internal theory of human psychology used to predict behavior: a theory of mind in everyday talk about mental states and behaviors (Stich & Ravenscroft, 1994).

Folk psychology as a lay theory of mind is a descriptive theory derived inductively from the process(es) of describing the experience of human behavior (including thoughts or cognition). Folk accounts contrast with a long tradition in neurophilosophy of attempting to eliminate the subjective through an approach called eliminative materialism. On this account, proponents argue that folk psychology is a misguided theory for explaining and attributing human mental states; the neurosciences provide a more appropriate alternative (Churchland, 1981, 1986). Eliminativists believe that behavior can be entirely accounted for in terms of brain states, and so they hope that neuroscience will eliminate folk psychology from scientific discourse.

Despite the influence of such arguments, the subjective has persisted in health and medical domains, and the value of “introspective accounts” for informing neuroimaging studies (Shaw, Senior, Peel, Cooke, & Donnelly, 2008) and neuropsychopharmacology research (Langlitz, 2010) is starting to be acknowledged.

The field of addiction studies is another area in which the influence of folk perspectives can be seen. For example, as part of the UK Foresight Project on Brain Science, Addiction and Drugs, Hurwitz and colleagues undertook a review of addiction narratives (Hurwitz, Tapping & Vickers, 2005, 2007) in the post-1950 literature. Following from the work of Arthur Frank (1995), they identified three common narrative types: the Restitution/Recovery narrative, where good health (the aspirational norm)
is disrupted and regained with the assistance of external expertise rather than individual changes as told by the addicted person; the *Chaos narrative*, which focuses on the drug impacts on individuals who remain addicted; and the *Quest narrative*, where drug use is a journey along which addiction is an illness to be treated to reveal true identity, and the addicted person attempts to restore health.

Folk psychological perspectives are thus one form of the lay descriptive accounts of addiction identity highlighted here. Such perspectives from individuals who are experiencing drug addiction can fulfill an important role as a narrative practice that enhances our understanding of defined health problems (Hutto, 2009). They help to reveal previously hidden aspects of the experience of human behavior, as well as highlighting the areas in which the beliefs and behaviors of “patients”, “consumers” or “users” may differ from those of biomedicine.

Indeed, Hurwitz and colleagues (2005) have shown that “Many addiction narratives move beyond a strictly scientific view of addiction. The addict’s illness is perceived as a psychological and emotional journey in which the sickness of the physical body gathers less significance. Addiction narratives inherently tend to moralise the experience of addictive processes, diminishing in the process consideration of the physical or physiological aspects of addiction” (p. 4).

While there have indeed been attempts in the addiction studies area to emphasize “the importance of the individual constructing a non-addict identity for themselves” (McIntosh & McKeganey, 2000, p. 1501), we are still without a compelling positive narrative in this area that can serve as an alternative to the deficit accounts that dominate biomedical, 12-step and many psychosocial treatment approaches. McIntosh and McKeganey’s (2000) research in this area has shown that narratives of recovery can function to construct “non-addict” identities through a reframing of self and “drug using lifestyles”. However, they suspect that these new identities are themselves developed in collaboration with expert professional perspectives in the drug treatment field.

The importance of the narrative turn through the humanities, psychology, medicine and other health sciences has been long acknowledged, where “[a] now widespread conception of the self or identity as narrative construction is challenging the traditional view of a natural self with its own existence” (Ville & Khlat, 2007, p. 1004). The narratives of recovery and the others highlighted above provide an insight into how some individuals shed illness or addicted identities by striving to adopt others (Hänninen & Koski-Jännes, 1999; McIntosh & McKeganey, 2000; Weegmann, 2010). These identities may therefore be seen as alternatives to the dominant addiction as biomedical illness identity, even though the transition between identities is not always easy for those who use drugs (Doukas, 2011).
It has been said that “narratives reveal a truth—not an objective truth, but the truth of experience” (Riessman, 1993). This is an important point about the nature of lay descriptive perspectives, especially in the case of drug addiction. Others have cautioned, “any information that we garner concerning the self-conception of addicts in this way must be carefully evaluated, weighed against other accounts, and, in general, treated as no more epistemically important than any other information we have on this matter” (Ross, 2007, p. 229).

However, the point is these “other accounts” (e.g. from science and the health professions) are at present given greater epistemic weight. “Addicted” self-conceptions (whatever these may be) are epistemically undervalued in the hierarchy of knowledge about addiction. The current dominant view in mainstream philosophy and cognitive science is that such accounts are less valid or mistaken, less reliable or dishonest, or too subjective.

In health terms, drug addiction (and a steadily expanding group of other “addictions”) is regarded by many as a complex affliction that can take the form of a range of disapproved or contested identities. These include being overly intoxicated, addicted or overconsuming, being at risk and engaging in non-compliant behavior (e.g. in the treatment context, chosen locations of drug consumption, or in the failure to be healthy) (Fry, 2010). In relation to drug addiction as we have illustrated, lay or folk health conceptions are also contested.

This set of health identities is in direct contrast with what are regarded as accepted identities in the health sphere (e.g. health seeking, rational, expert, professional, vulnerable) (Fry, 2010). Foucauldian governmentality scholars would argue that these types of health identity are defined by expert professions in a regulatory process that constructs “particular categories of identity and … forms of subjectivity in ways that are consonant with prevalent cultural values and social institutions” (Reith, 2004, p. 294).

There is a tradition of valuing lay perspectives in the wider field of health and medicine, with work in psychology, literary studies, sociology, psychiatry, medical anthropology and bioethics (Charon et al., 1995; Ville & Khlat, 2007). This is evident in the patient-centered paradigm in clinical research and medical care, where it is acknowledged that including the “authentic voices of patients as collaborators at every stage of development will help to resolve conflicts, build trust, recruit trial participants, and accelerate new therapies” (Cohen, Herman, Jedlinski, Willocks, & Wittekind, 2007, p. 537).

There is a steadily growing literature on the core themes of identity, self-understanding, narrative accounts and illness beliefs in relation to health and medical problems, particularly in relation to prevalent chronic
diseases such as obesity, cancer, diabetes and asthma. By contrast, there have been few first person empirical studies of what drug addiction means to the afflicted drug user. First person narrative or descriptive accounts provide the opportunity for the reintegration of disrupted selves, and to inform others about lived experiences (Frank, 1995). They present a way of reconciling scientific and humanistic views about who drug addicted people are, and what the focus, content and processes of health and other social polices in the addictions area should be.

“Identity” is a key concept that has informed participatory approaches in health (Kelleher & Leavey, 2004) and has been the focus of public understanding of science research in recent times (Scott, 2008). Research on self-concept, identity and health and illness beliefs has been crucial for understanding the impact of a wide range of health issues, including HIV/AIDS prevention and mental health (Fox & Ward, 2008; Haller, Sanci, Sawyer, & Patton, 2008).

In some specialty areas of addiction and related studies, there has been a long commitment to including consumer perspectives in the design and evaluation of treatment, prevention and research policy and program initiatives (Rhodes, 2010). For example, it is recognized that many innovations in the harm reduction field of public health have been facilitated by the perspectives and participation of drug-using communities such as the establishment of needle and syringe exchange programs, advocacy for MMT programs, supervised injecting facilities and HIV/AIDS prevention responses in many countries (Southwell, 2010).

However, for the most part, the attitudes and experiences of drug users on the important questions of identity and capacity prompted by addiction neuroscience have been largely absent. There has been a notable lack of published research on drug-user knowledge and opinions about addiction neuroscience and the public and private implications of advances in this field. Nor has there been significant research on the perspectives of drug users and drug-addicted individuals on questions of identity and self-hood in relation to their addiction and its impacts.

Individuals living with addictions are epistemically suspect. By virtue of their membership in the group of “addicts”—aside from the cognitive challenges brought on by chronic substance use—individuals are not always trusted as reliable historians about their symptoms and drug use, or as being able to accurately represent their quality of life and well-being. Further reliance on addiction neuroscience as a superior way of knowing the addicted self might lead to further cases of epistemic disenfranchizing (Scheman, 2009).

One crucial challenge for addiction neuroethics will be to define the possible relationships between normative and descriptive accounts of drug use and addiction. A key question here is: do the claims of impaired agency from addiction neuroscience match the lived experience of
“addicts” and their own identity conceptions? It is encouraging that there is a wider emerging literature examining public engagement and the identity implications of neuroscience research generally (e.g. Academy of Medical Sciences, 2008; Borgelt, Buchman, & Illes, 2011; Cohen et al., 2007; Hurwitz et al., 2007; Illes et al., 2005; Illes, Lombera, Rosenberg, & Arnow, 2009; Rose, 2003; Timpane, 2004). The possibility of enhancing addiction recovery or rehabilitation through non-expert clarification of identity and self-conception has been acknowledged (Barker & Hunt, 2007; Mitchell, 2007a), but we are yet to see an “identity” focus in addiction neuroscience studies.

Choudhury, Nagel, and Slaby (2009) remind us that “the reduction of psychiatry to neurobiology tends to neglect phenomenological insights, biographical accounts of the person and the meaning—that is, the social, cultural, moral or spiritual significances—of mental illness or interventions” (p. 71). While many clinicians in this field have long known this, this wisdom has not penetrated other domains.

The challenge, then, for neuroethics is to develop a more naturalized account of identity and self in addiction. To do so, one must look not only to neurological function, but at the stereotypes, the status loss, the alienation, lack of recognition, invisibility, and the multitude of ways that power relations inflect the perspectives of individuals living with chronic addiction and mental health issues. As neuroethics develops its own disciplinary identity, there is an opportunity to engage with some of the thinking from both critical bioethics (e.g. Hedgecoe, 2004) and critical neuroscience (Choudhury, Nagel, & Slaby, 2009) literatures. The descriptive lived experience of addicted people could emerge in this context can help to challenge the assumptions made by scientists and neuroethicists about identity and self in addiction.

**CONCLUSION**

Recent advances in addiction neuroscience are further clarifying the role of the brain in drug addiction and the impact of drug use on brain function, decision making, self-control and behavior. The hope is that these findings can inform new addiction treatment and prevention programs and alleviate the associated health burdens. These findings warrant fresh attention to the impact of addiction on the lives of users: their agency, identity, and capacities for choice and control. The perspective of the drug user or “drug addicted” as an agenda-guiding or defining voice in discussions of neuroscience research has largely been absent. A critical and interdisciplinary understanding of these issues, and epistemic humility, will be crucial in establishing ethical and effective public policies and practices in the addictions field.
The clarification of lay descriptive accounts of addicted life will be central to this task. The meanings and understandings given by drug users to their lives (e.g. decisions, actions, experiences) are important because in these descriptions resides the situated normative assessment of these lives (van der Scheer & Widdershoven, 2004). A focus on the lived subjective truth of addiction is warranted because drug use and addiction are fundamentally social and political in how they are experienced and understood.

Such accounts may also be useful for informing science and other professional domains and understandings, providing a critical reimagining of current epistemic hierarchies (notions of who has valid “expertise”) in defining and responding to drug addiction. Some hope that advances in neuroscience will prove that the brain is a deterministic system, and thereby allow us to reject “folk” beliefs in identity and free will, and moral responsibility (Greene & Cohen, 2004; Libet, Gleason, Wright, & Pearl, 1983; Spence, 1996). However, in the twenty-first century, science is just one form of knowledge informing policy in health and social domains. Blurred boundaries are becoming increasingly apparent between science and politics and these have profound implications for how health, illness and disease are defined and regulated (Gottweis, 2008). Lay descriptive accounts of addiction also have an important role to play in this process.

Following the classic demonstration of the value of believing in free will (Vohs & Schooler, 2008), Vohs and Baumeister (2009) argue for a view of addiction that encourages individuals to retain a belief in free will for the purpose of taking responsibility for their choices and actions. There is likely to be a similar functionalist value in believing in positive and constitutive ideas and capacities of drug use and addiction identity, irrespective of whether or not these capacities actually exist or can be seen in neurobiological terms and regardless of whether or not these are undermined or impaired in certain instances.

What should come with such a belief is a commitment to multiple levels of analysis and perspectives in understanding the lived experience of drug addiction (Buchman, Illes & Reiner, 2010). Fry has previously framed such an approach as a “social neuroethics orientation (in the social science and social justice sense) … [which requires that] … we are critical and reflexive about, and inclusive of, the diverse perspectives that are possible on the question of how identity and self-understanding (‘embodied subjectivity’) are conceived of and practiced by people in the real world” (Fry, 2008, p. 16).

Some have argued that the ultimate goal of neuroethics must be to recognize the relational and distinctive nature of human identity and activity (Gillett, 2009). Important questions remain about what are the conceptual, theoretical and empirical means through which this goal may be best achieved, and for what ends (i.e. theory, practice, policy) (Fry, 2009).
this sense, the tools of neuroethics are still emerging, and the epistemic hierarchies around the methods, evidence and accepted expertise that are brought to bear in discovering the truth of phenomena such as drug addiction are still being negotiated.

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### III. PHILOSOPHICAL REFLECTIONS

9. TOWARD A LAY DESCRIPTIVE ACCOUNT OF IDENTITY


The history of scientific research on addiction has contemporary relevance for neuroethics, the unfolding “examination of how we want to deal with the social issues of disease, normality, mortality, lifestyle, and the philosophy of living informed by our understanding of underlying brain mechanisms” (Gazzaniga, 2005, p. xv). Addiction research was one
of the earliest arenas in which a seemingly social problem was understood as a neuroscientific problem. Initially this insight was confined to a small cadre of researchers in the US Public Health Service (USPHS), and a handful of global drug control policy makers who were informed by these path-breaking scientists. The problem of narcotic drug addiction had emerged with such force by the 1920s in large US cities that US political elites—initially in the philanthropic sector and later in the quasi-public sector—sought to bring the power of science to curb the number of addicted people through prevention and explore possible “cures”, including pharmacotherapy. However, the underlying neurophysiology was not well understood, and the dominant psychoanalytic and psychodynamic frameworks of the time foreclosed widespread diffusion of this idea. The study of the social, political, psychological and economic factors that shaped narcotic addiction occupied the arena, driving neuroscientific theories and neurobiochemical explanations to the periphery. Because the debate was framed as biological versus social, serious exploration of biosocial interactions emerged only gradually as pharmacological models, neuroimaging technologies and neuropharmacological techniques evolved in the late twentieth century. Ethical questions arose for early twentieth century neurobiological addiction researchers in direct relation to their need for human subjects who had significant social and neurophysiological experience with narcotic drugs. This chapter explores the relevance of this history for the ethical questions embedded in contemporary neuroscience theories of addiction.

NEUROPHYSIOLOGICAL STUDIES OF NARCOTIC ADDICTION AT THE US NARCOTIC FARM

Elucidation of the neural mechanisms underlying narcotic addiction was the goal of empirical and experimental studies carried out at the US Public Health Service Narcotics Hospital in Lexington, Kentucky, from 1935 to the late 1970s. The knowledge base upon which rest today’s neuroscientific studies of addiction as a chronic, relapsing brain disease consists of countless experiments in which dependence-causing drugs were administered to “postaddicts”, as abstinent, formerly addicted human subjects participating in this research were called.

The US Narcotic Farm was one of two large institutions serving narcotic addicts that were operated jointly by the USPHS and the federal Bureau of Prisons (BOP) in Lexington, Kentucky, and Fort Worth, Texas. In 1929, the US Congress authorized construction of the narcotic farms, and included a research mandate designed to create a knowledge base for preventing, treating and ultimately curing addiction. The congressional mandate was carried out in the laboratory at Lexington, known
as the National Institutes of Mental Health (NIMH) Addiction Research Center (ARC) after 1948. This laboratory was the forerunner of the intramural research branch of the National Institute of Drug Abuse (NIDA), the National Institutes of Health (NIH) institute currently charged with bringing the power of science to bear on drug abuse and addiction. From its inception, the laboratory’s research priorities were set by the Committee on Drug Addiction (CDA), later known as the Committee on Drug Addiction and Narcotics (CDAN), and later still as the Committee on Problems of Drug Dependence (CPDD). Until 1977, the committee was part of the National Academies of Science/National Research Council’s efforts to identify a non-addicting analgesic and compounds to substitute for legitimate medical uses of morphine (Acker, 2002; Eddy, 1973).

ARC studies on experimental readdiction were published in top clinical and pharmacological journals; Congress was briefed annually about the laboratory’s operation; and data so generated was so well respected by those involved in international drug diplomacy that the committee’s actions and opinions on drug scheduling were often translated into law. Despite this, the human and animal studies conducted at Lexington raised ethical issues from their inception. These became clamorous during the tumultuous period after public disclosure of the USPHS studies of untreated syphilis and the research ethics scandals of the 1970s (Reverby, 2009). This chapter tells a condensed story of how neuroscientific theories of addiction arose in the laboratory at Lexington, while attending to conversations about the ethics of neuroscientific research conducted there.

ETHICAL ISSUES IN RESEARCH WITH POSTADDICTS

One prominent ethical dilemma that arose immediately concerned the dual-pronged nature of the institution within which experimentation occurred. Treatment proponents saw the primary purpose of the narcotic farm as rehabilitation. The 1200-bed institution was placed under the clinical direction of Lawrence C. Kolb, Sr, who conducted early animal research on opiate addiction at the Hygienic Laboratory, forerunner of the NIH (Kolb & DuMez, 1931). How appropriate was it to conduct research on drug addiction within the context of a treatment facility? Discussion of research ethics took place prior to Lexington’s opening. One of the main proponents of the narcotic farm approach, Assistant Surgeon General Walter S. Treadway, wrote in 1930, “It is not assumed that Federal prisoners should be used as experimental animals for the furtherance of medical knowledge. However, a large prison may be regarded as analogous to a laboratory, subject to control, where
observations and scientific studies should be made possible” (quoted in Campbell, 2007, p. 54). Lexington was intended not primarily as a research environment, but as a way to get narcotic addicts out of the US prison system.

Two-thirds of the population at the narcotic farm had been sentenced to the institution by the criminal justice system; human subjects were drawn from a population of felons at a time when prison research was widely tolerated. They had to meet health criteria and be “seasoned” addicts who had failed several “cures” (Campbell, 2007). Study sizes generally consisted of six subjects until the late 1940s. The one-third of the population that voluntarily sought treatment—including women, who were admitted after 1941—was never experimented upon.

Experimentation began prior to Lexington’s opening in May 1935. A young, commissioned USPHS officer, Clifton K. Himmelsbach, was groomed to direct the laboratory. He had studied morphine tolerance in rats at Western Reserve University, a technique that he later refined in monkeys at the University of Michigan with Nathan B. Eddy, who moved to NIH in 1938 when the USPHS established a chemotherapy unit. Eddy headed CDA, which became a US government responsibility administered through NAS in 1939. Under CDA auspices, Himmelsbach’s clinical research commenced in 1933 at Fort Leavenworth Prison in Kansas, at a US Army disciplinary barracks housing several thousand addicts. Himmelsbach set up a small laboratory to conduct research on biochemical and physiological changes in humans during tolerance, addiction and withdrawal. Although no law required procedures for informing subjects participating in research, Himmelsbach implemented them (see his remarks at the 1963 conference on research ethics at the Boston University Law–Medicine Research Institute; quoted in Campbell, 2007, p. 72). Having moved the research operation to Lexington, Himmelsbach hired the first generation of physicians and scientists who were destined to become one of the world’s only multidisciplinary research teams devoted to the scientific study of drug addiction in the mid-1930s.

Research objectives included “new treatment and substitution techniques, intensive study of physicochemical, psychiatric, and psychological changes resulting from single therapeutic and repeated doses of morphine in the nontolerant individual, during stabilized addiction, and in the postaddiction state” (Eddy, 1973, p. 30). Initial studies were pharmacological, physiological, biochemical and biophysical. Himmelsbach investigated the relationship of chemical structure to addictiveness (1941a, b, 1944), creating a point-score system to track the “Morphine Abstinence Syndrome” (1941c). Building on results published by Light and Torrance (1929), who had studied stably maintained opiate addicts at Philadelphia General Hospital (Acker, 2002, p. 50; Isbell, 1958, p. 123), Himmelsbach
charted the abstinence syndrome. He found that individuals took 2–6 months to regain physiological stability after withdrawal from opiate maintenance. Based on close observation of 65 cases, Himmelsbach (1943) generated hourly and daily point scores and a method for calculating the intensity of abstinence and predicting its course. Patients served as their own controls while passing through cycles of tolerance, addiction and withdrawal or “abstinence”.

One of the most important outcomes of the early research was Himmelsbach’s hypothesis that “tolerance and physical dependence are due to changes in the activity of homeostatic mechanisms mediated via central (mainly hypothalamic) regions of the brain” (Isbell, 1958, p. 123). After visiting physiologist Walter Cannon (Acker, 2002, p. 205), whose concept of homeostasis forged an early link between neurophysiology and behavior, Himmelsbach hypothesized a model for the physiology of both tolerance and abstinence. “For Himmelsbach, it appeared that chronic administration of opiates offset the body’s internal homeostatic norm …, but when drug use stopped, the measures that had compensated for the drug’s presence were still in force, and a period of adjustment was required to reset the homeostatic center” (Acker, 2002, p. 205). Himmelsbach’s theory was that morphine affected the brain by “call[ing] into play autonomic responses which tend to restore homeostasis by opposing the effects of morphine”, a series of adaptive responses enhanced with repetition that required greater doses of morphine to overcome (Isbell, 1958, p. 123). He demonstrated that these adaptations proceeded despite discontinuation of morphine.

During World War II, addiction research activities were put into abeyance; scientific personnel at Lexington were called to Washington, DC; and the committee suspended operation from 1941 to 1947, when it was reconstituted as the CDAN. The committee’s first order of business was testing a German pharmaceutical innovation confiscated by the Allied forces. Methadone (then called amidone) was tested at Lexington beginning in 1946, in the ARC’s first larger scale studies. These investigations of a synthetic analgesic initiated what the second research director of the laboratory, Harris Isbell, referred to as the “synthetic flood” of chemical subtypes of analgesics (1978, p. 32). From 1950 to 1970, the Committee screened over 1600 pharmaceutical compounds for addiction liability. The aim of the laboratory was less about developing a non-addicting analgesic and more about preventing “the introduction of drugs possessing dependence liability of the morphine type into general use without proper control” (Isbell, 1978, p. 32). However, this empirical work provided a continuous basis for the ongoing conceptual work that was the ARC’s hallmark and became the career-long focus of the scientists who trained there and who increasingly self-identified as “neuropharmacologists”.

IV. ADDICTION HISTORY AND THE MEDIA
CREATING CONCEPTUAL FRAMEWORKS FOR STUDYING ADDICTION

Scientific determinations of whether or not novel analgesic compounds acted in “morphine-like” manner and were thus “addictive” should not be viewed as simply applied science. Such empirical work contributed greatly to the highly conceptual and theoretical work that ultimately led to an understanding of how opioid receptors and peptides work in brain. Downs and Eddy (1928a, b) showed cross-tolerance between morphine, codeine and heroin in the dog. Himmelsbach (1978) reasoned that where there was cross-tolerance, there would also be cross-dependence. He demonstrated the practical uses of this insight in the so-called Lexington test or substitution technique. Himmelsbach’s findings on cross-tolerance of morphine congeners were also essential decades later to the “suggestion that opioid receptors differed in the intimate details of their configuration from one species to another” (Martin, 1983; Martin & Jasinski, 1977). This explained Himmelsbach’s early, disappointing results with desomorphine, one of the Committee’s most promising candidate drugs, which did not produce dependence in the monkey but did so in humans. Reflecting on contributions made by the laboratory at Lexington reveals continuities between early findings and later theoretical work on the underlying neural mechanisms through which drug addiction worked. The question facing addiction researchers at Lexington was not only how to study subjective drug effects but also how to interpret the meaning of their findings.

One of the main contributions of the laboratory at Lexington was technological innovation and the application of innovation specifically to addiction. For instance, soon after Lexington opened, one of the psychiatrists working there, Robert H. Felix (founding director of NIMH), had become persuaded that the newly invented neuroimaging technology of his day, the electroencephalograph (EEG), could be used to study the effects of addiction on the brain. He went to Providence, Rhode Island, for training and convinced biophysicist Howard L. Andrews to move to Lexington, build and install an EEG machine, and study “postaddicts” (Kay, 1978, pp. 140–154). Andrews departed in 1942 “with a distinct sense of disappointment and personal failure” because the technology had not enabled him to draw any conclusions of basic significance about addiction (Andrews, 1978, p. 153).

Despite these disappointments in studies of brain structure and function, in advancing the homeostasis hypothesis, Himmelsbach made a critical move toward a neurobiology of addiction, and his work is still cited today (Koob & Le Moal, 2006, p. 451). While the significance of abstinence symptoms in addiction is still debated, researchers at Lexington were
particularly puzzled over the long-lasting character of the neurophysiological changes they were studying. In a 1975 retrospective published on the occasion of their 35th anniversary, Andrews recalled his EEG finding that morphine addiction led to a “high alpha state” that persisted more than a year after withdrawal (1941). According to Himmelsbach, the research team had known that this observation was significant, but “found the nut much too tough for us to crack” (1978, p. 22).

The puzzle of persistence—and its possible role in relapse—occupied Andrews’ successor in the neuropsychiatric laboratory, Abraham Wikler. When he took the reins, Wikler expanded the facility with a government surplus ink-writing EEG machine that he used to study sleep patterns, metabolic and tissue tolerance, and the effects of lysergic acid diethylamide (LSD), mescaline, psilocybin and other non-opioid drugs. In seeking to specify the mode of action of these drugs, Wikler hoped to elucidate an organic basis for the psychopathological or sociopathological behaviors involved in narcotic addiction.

Defining the most basic neurophysiological mechanisms of drug addiction required a laboratory model that mimicked the process of addiction. Wikler refined this throughout his scientific career. Working with rats, dogs and human subjects, Wikler found that unconditioned responses could be “conditioned to various situations or memories associated with taking the drug, thereby evoking subjective experiences similar to those associated with morphine withdrawal, namely anxiety with craving for the drug” (Wikler, 1948, p. 337). Conditioning—or learned adaptation to drug effects—could account for addicts’ oft-noted vulnerability to relapse long after withdrawal (Wikler, 1965). Working from his human subjects’ recollections of the precise circumstances surrounding previous relapses in their home environments, Wikler’s conditioning hypothesis explained relapse as a response to environmental stimuli or cues (Wikler, 1948; 1978, p. 80). Wikler tested his hypothesis in rat studies and showed that symptoms of abstinence could be classically conditioned in combination with operant conditioning of opioid-seeking behavior (Wikler & Pescor, 1967, 1970; Wikler, Pescor, Miller, & Norrell, 1971). Wikler foresaw that these studies (1978, p. 83) had implications for human postaddicts because relapse could be triggered by single doses of their drug; by what he called “interoceptive” states arising from illness or anxiety; and even by aspects of the environment in “maintenance” and treatment programs, including those based on pharmacotherapy with methadone or narcotic antagonists.

During the 1950s, Wikler had become increasingly critical of neuroanatomical theories of brain localization, in which “anatomically defined ‘centers’ with specified functions, were ‘selectively’ acted upon by agents’ thereby altering the balance of excitation and inhibition of the nervous system, and either disturbing or restoring ‘homeostasis’” (Wikler, 1950;
1957, p. 126, quotations in the original). He thought that such theories endowed neuroanatomical structures with the “powers of psychological constructs” and predicted that one day his fellow neuropsychopharmacologists would replace the “mechanisms of psychodynamics … by statements about synaptic transmission, facilitation and inhibition in specific neural pathways within and between such ‘centers’” (Wikler, 1957, p. 126). One of the world’s leading proponents of a neurophysiological theory of addiction, Wikler remained chary about drawing correspondences between structure and function “regardless of the biography of the organism, the object of its activities, the stimulus arrangements and the conditions of the internal and external environment” (Wikler, 1957, p. 127). He adapted Sir Charles S. Sherrington’s “spinal dog” preparation—following it up in a “spinal man” (Wikler & Rayport, 1954)—to show that “processes underlying physical dependence are diffuse throughout the central nervous system, and that hyperirritability in reflexes mediated through multineuron arcs appears during addiction” (Livingston, 1958, p. 128). These experiments revealed that morphine was not a general central nervous system depressant but a selective one. This paved the way for researchers to use specific but differential central nervous system effects to classify compounds (Martin, Sloan, & Eades, 1978, p. 104).

ARC researchers avoided the language of psychoanalysis and psychodynamics, seeking to characterize the processes they were studying in a neurophysiological vocabulary. At a 1958 NIMH symposium, Isbell dismissed psychoanalysis as a “toxic theory”, and advanced a neurophysiological explanation for addiction that centered on the brain:

> The brain is the instrument governing social as well as individual physiological integration. We need to know particularly about the limits and opportunities of an addicted person’s behavior, his internal value system of appetites, rewards and punishments relating to narcotic drug abuse, the predisposing factors, the relationship of addiction to his past experiences and future prospects, the internal and external lures and deterrents as seen from his point of view (Isbell in Livingston, 1958, p. 185).

Addiction researchers advanced the study of the underlying neural mechanisms of behavior by developing bioassays and statistical techniques for assessing subjective effects (Fraser & Isbell, 1960). They quantitatively characterized the pharmacological profile of a drug by comparing the potency of its subjective effects to those of other drugs in its class or category. The scales that eventually comprised the Addiction Research Center Inventory (ARCI) gave researchers a basis for comparison beyond Himmelsbach’s scoring of the intensity of the abstinence syndrome, because the ARCI scales could be used to score dose-related changes in subjective effects (Hill et al., 1963). The scales yielded an
important finding directly related to the neuronal basis of addiction: “feelings of improved self-image, efficiency, and popularity [or the opposite] were changed in a dose-related manner” on the morphine scale, and the “subjective syndromes” produced by different drugs could be distinguished from one another using the ARCI. Isbell encouraged the refinement of the scales to address CDAN’s need to screen compounds produced in the laboratories of academia, the NIH and the pharmaceutical industry for addiction liability.

NEUROPHARMACOLOGICAL EXPLANATIONS FOR ADDICTION

Upon retiring from the ARC in 1963, Isbell and Wikler handed the reins over to neuropharmacologist William R. Martin, who embarked on a career-long study of the role of neurotransmitters in the neural mechanisms of addiction (Martin & Sloan, 1977). He used the scales data and the “synthetic efforts” of chemists Sydney Archer, Jack Fishman, John Lewis and Everett May in a highly original way (Martin, 1988, p. 18). Unlike Himmelsbach, Isbell and Wikler, all physicians who became clinical researchers as a result of USPHS assignment, Martin was a physician who held a PhD in pharmacology from the University of Illinois. A World War II Army veteran, Martin was trained by neuropsychopharmacologist Klaus R. Unna who, while working for Merck, had discovered nalorphine, a narcotic antagonist observed to “prevent or abolish the action of morphine” (Unna, 1943). While in graduate school, Martin became interested in catecholamine neurotransmitters and, once he arrived at Lexington in 1957, gravitated toward neurochemistry and was groomed to become director of the ARC in 1963.

Possessing little prior knowledge of addiction, Martin immersed himself in the laboratory’s early findings, including Himmelsbach’s early work on the role of homeostasis. Martin became convinced that tolerance was extremely complex, and in studies with chemist Anna J. Eisenman, one of the first women to graduate from Yale, he advanced a homeostatic theory of tolerance and dependence. Working also with Jewell W. Sloan, he set out to understand the “neuronal events that are responsible for morphine’s action as well as for a development of physical dependence and the emergence of the phenomena of early and protracted abstinence” (Martin et al., 1978, p. 108). Martin believed that his studies presented solid neuropharmacological evidence that “psychiatric manifestations” predisposing addicts to drug use were at base neurological.

The ARC was a unique environment with constant access to new analgesic compounds facilitated by the Committee, which was designed to minimize conflicts of interest. USPHS researchers were responsible
entirely to it and not to the pharmaceutical industry or the national drug control apparatus. CDAN’s charge to develop a non-addicting analgesic had shifted across the several decades of its existence. By the mid-1960s, its goals had expanded to include finding a pharmacotherapy for addiction treatment and relapse prevention. While Martin felt that the narcotic antagonists were the best potential candidates, a series of scientific events in the 1960s and early 1970s led him to a different view. Martin observed that the new analgesic cyclazocine produced a different type of physical dependence than did morphine (Martin, 1989, p. 3; Martin, Fraser, Gorodetzky, & Rosenbert, 1965). According to chemist Sydney Archer (1983), Martin was the first to suggest that cyclazocine might be used as a “modality for preventing recidivism in ex-heroin addicts” (p. 6), thereby ushering in a new method for treating opiate addiction.

Martin noticed that nalorphine was competitive with morphine, but worked through a different mode of action. To make sense of this observation, he introduced the concept of receptor dualism (Martin, 1967). He gained his first clues to the existence of multiple opioids and multiple opiate receptor subtypes from experiments using the chronic spinal dog model (1967), later confirmed in a series of pharmacological observations in humans (Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Although he argued the concept of “pharmacologic dualism” using several different lines of evidence—quantified subjective effects, observed effects of different types of dependence and biphasic dose–response curves—the notion that there were multiple opioid receptors was not, he recalled in a 1989 interview, well received in the scientific community. For a variety of reasons, he did not return to the problems of opioid receptors until 1972, when he found himself “trying to reconcile some perplexing observations concerning agonist–antagonists” in hopes of developing “safer analgesics” (Martin, 1989, p. 6).

As Martin put it late in the 1980s, the opioid neurotransmitter–receptor system on which he had spent his career was so complicated that it was difficult to determine its physiological, pharmacological and psychopathological role in drug addiction. By then Martin had another piece of the puzzle owing to the laboratory’s interest in the long-lasting effects of abstinence. This was what appeared to be a “secondary” or “protracted” abstinence syndrome (Martin & Jasinski, 1969) that differed from Himmelsbach’s “explosive, early abstinence syndrome” (Martin, 1984, p. 2). Tracing the lineage of “protracted abstinence” from Himmelsbach (1942), Martin noted that he and Wikler had demonstrated it in rats in the 1960s, and extended their findings to dogs and humans in the 1970s. Martin and Jasinski (1969) traced the contours of the persistent abstinence syndrome, finding that its characteristics varied between individuals but fell within the range of normal physiological variables, characteristics that made it extremely difficult to diagnose. However, the
ARCI yielded more data because it could trace changes in feeling states that accompanied protracted abstinence.

Martin’s initial observations about subjects’ negative attitudes and feelings were casual at first, arising from conversations with the six subjects involved in his initial 18-month study of protracted abstinence. The research ward at Lexington was small, promoting almost daily contact between researchers and subjects. As Martin put it in his Eddy Award acceptance speech, “I came to know them quite well. As I came to understand these patients, I was increasingly impressed with their poor self-image. Initially this seemed incongruous with their egocentricity and self-concern ... [they] felt they were unpopular, unwanted, incompetent, and unappreciated” (Martin, 1977). Noting that he often found such individuals manipulative and difficult to work with, Martin began to take an interest in these attitudes and the feeling states accompanying them because he recognized that these subjective states were unique to the population he was studying. They resembled depression, but differed in some important respects. He called these feeling states “hypophoria” and argued that abstinent narcotic addicts displayed an affective disorder. “Feeling states”, he argued, “may be under the control of proven neurohumors for we know that narcotic analgesics share many features with brain peptides, the enkephalins and endorphins, that amphetamines release dopamine, that the LSD-like hallucinogens mimic the effects of tryptamine and serotonin, both of which are endogenous brain transmitters, and that the barbiturate prolonged the action of the inhibitory transmitter GABA” (Martin, 1983, 1984). Speculating that hypophoric patients might have “minor imbalances in neurotransmitter–receptor systems which modulate or determine feeling states”, Martin speculated that these “deficiency states” were minute but correctable imbalances lodged at the basis of “sociopathic behavior” and “personality disorder” (Martin, 1983, p. 10; 1984, p. 6). Rapid development of the neurosciences would, Martin believed, not only make possible better identification and diagnosis of these “mental health disorders”, but also enable the design of “specific chemotherapy” through “appropriate and selective” mixtures of narcotic agonists and antagonists. He predicted that neuroscience would overtake the “preoccupation with the concept that sociopathy and drug abuse are primarily social, ethical and legal issues”. Martin believed that this idea had had a “devastating effect on innovative thinking about these diseases” (Martin, 1983, p. 10).

As a neuropharmacologist, Martin brought to bear a new way of thinking about addictive or sociopathic behaviors, which he saw as based upon neurochemical state. These “feeling states” were sometimes (mis)diagnosed as “personality disorders” or “mental disorders”. Martin argued, as he accepted the highly coveted Nathan B. Eddy Award, that the “diathesis of the drug abuser is associated with a deviance in brain
function and metabolism” that he believed would ultimately prove to be treatable through specific chemotherapeutics (Martin, 1977). He suggested that the “possibility of having such feelings may be determined by the activity of functional systems in the brain” (Martin, 1977, p. 4). In specifying the model of affective disease or disorder from which addicts and alcoholics suffered, Martin remained optimistic that further developments in neuroscience would result in specific pharmacotherapeutics of addiction.

THE CENTRALITY OF “POSTADDICTS” AND HISTORICAL NEUROETHICS

Groundwork for the neurosciences of addiction was laid at Lexington, where the ARC played a formative role in constituting addiction research as a specialized neuroscientific enterprise. It was the only place where experienced drug users regularly came into contact with clinicians and researchers. Elsewhere, addicts were turned away from both treatment and research. At Lexington, researchers enjoyed close proximity with “postaddict” subjects, and their neurophysiological theories about drug effects were formulated in explicit rejection of psychogenic theories. ARC researchers made clear to Congress that they were in the business of readdicting prisoners who were both patients and human subjects (Wikler, 1960). Findings were published in top-flight clinical and scientific journals, and the expertise and data of the ARC were sought for the sake of international global drug control. They willingly spoke to the press during journalists’ periodic visits. Reporters sometimes filed sensationalistic stories of “gruesome experiments on voluntary guinea pig patients” (Mowery, 1951), but more typically there was a climate of acceptance of such research that shifted gradually during the 1960s and abruptly after the disclosures of the major research ethics scandals of the 1970s.

ARC studies involved a high degree of prisoner–patient participation by experienced and knowledgeable subjects, who appear to have been aware of what was happening to them. Drugs were never tested on “unwitting” subjects (Himmelsbach, 1972, 1994). The indigenous morality (Halpern, 2004, pp. 9–10) of the ARC placed such importance on consent that a brief note on voluntary participation appeared in many of its scientific publications from its inception, prior to the development of the Nuremberg Code after World War II. Research participants “volunteered” through the same routes that they “volunteered” for work assignments, vocational education or recreational activities. “There was no dearth of people who wanted to be subjects”, Conan Kornetsky recalled (personal communication, July 28, 2006). Questions of what
motivated people to “volunteer”, and whether “true voluntarism” was possible in coercive prison or military contexts, were only asked in retrospect.

Addicts were understood to have already “voluntarily” subjected themselves to risk outside the laboratory. Acceptance of voluntary risk is generally higher than acceptance of involuntary risk among the American public (Halpern, 2004, p. 97). Prisoner–patients at Lexington could easily avoid taking on experimental risk, and the vast majority did by neither participating in nor being recruited to participate in experiments. Those who did “get on the program” (i.e. participate in research studies) did so largely through seeking drugs to break their everyday institutional routines. They were self-identified “dope fiends” whose prime objective was to get high. The latter objective was convergent with the ARC’s scientific goals, which could only be met by studying serious, seasoned, long-term opiate addicts with a demonstrated tendency to relapse. Most subjects had been admitted many times and possessed a wide range of extrainstitutional drug-using experiences.

Within the ARC’s indigenous morality, knowledgeable former drug users were considered not only the best source of comparative data but also as the only ethical subjects. As Isbell remarked to the CDAN, “An addict takes all he can get; he does not stay down to the therapeutic level of the dose” … “regarding the question of primary vs. secondary addiction, it is not ethical to determine the addiction liability of drugs in people who have not already been addicted. Former addicts are probably the best subjects in any case, because they are known to be susceptible” (Minutes of the CDAN, 1949, p. 75). Like many elements of the ARC’s research protocols, this statement would not now pass scrutiny because rehabilitation was the institution’s primary goal and chronic drug exposure of the sort required in ARC studies violated that most basic principle. Since the 1970s, research on prisoners has been considered to be inherently coercive. However, Martin argued against that view in the 1970s in hopes of preserving ARC practices, and because he believed that prisoners—and postaddicts—retained not only civil rights but legal competence to decide to participate in research. Martin and Isbell testified unsuccessfully to continue neuroscientific work with postaddict populations in Washington, DC, at public hearings and also lobbied behind the scenes with other neuropharmacologists.

Conventional historiography of bioethics—and the reduction of ethical concerns to regulation—is currently being re-examined in light of evidence that some laboratories conducting research with human subjects prior to regulation operated within ethical bounds. Renee Fox, Susan E. Lederer and Sydney Halpern point to informal social controls that were adopted within these research networks; the “indigenous moralities” that enable or constrain scientific practices and “moral traditions
for handling investigatory risk” (Halpern, 2004, pp. 41, 124). Campbell (2007) concludes that ARC research was undertaken by knowledgeable subjects who were informed to the greatest extent possible about the experiments in which they participated. The few notable exceptions included ethically questionable experiments designed to document the dangers of barbiturates (Isbell, 1950) and rule out the use of frontal lobotomy as a treatment for narcotic addiction (Wikler, Pescor, Kalbaugh, & Angelucci, 1952), and single-subject studies designed to document the “natural course” of addiction by offering subjects ad libitum access to rum (Isbell, 1958) and morphine (Wikler, 1952) and then abruptly arresting intake. It is also evident that standards governing human experimentation since 1966 in the NIH and since the 1979 Belmont Report were not always met in the days before the current bioethical cultural and regulatory regime was put into place. As with much research conducted during the mid-twentieth century, the ethics of the situation demands attention to historical specificity.

References


The Diction of Addiction at the Intersection of Law and Neuroscience

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INTRODUCTION

Innovations in neuroscience are increasingly broadening the understanding of human brain function and contributing to knowledge about mental health and addiction. Consequently, results from
neurotechnological innovations quickly enter into policy making, law and public attitudes (Dietrich, Heider, Matschinger, & Angermeyer, 2006; McClure, Puhl, & Heuer, 2010). The media serves as a primary purveyor of neuroscience findings into the public sphere and, in its role as an intermediary, has its own set of disciplinary techniques and reporting standards. Its influence is powerful: studies have highlighted the weight attributed to neuroscience findings in defining how people see themselves (Racine, Waldman, Rosenberg, & Illes, 2010), how hype can create a public health hazard (Offit & Coffin, 2003; Singh, Hallmayer, & Illes, 2007) and how miscommunication can jeopardize the advancement of meritorious science (Elvevåg, Wynn, & Covington, 2011). The goal of this chapter is specifically to explore media discourse of addiction in the context of reporting at the intersection of law and neuroscience.

Decades of research into the neuronal networks underlying drug abuse have led to an improved understanding of the neurobiological basis of addiction (Leshner, 2002). As a result, addiction is increasingly viewed as a chronic, relapsing disease of the brain (Koob & Volkow, 2010; Leshner, 1997). However, some argue that this simplistic view has substantial policy implications. As a result, new integrative approaches are emerging, tackling addiction from all angles that range from molecular targets to the psychosocial environment (Buchman, Skinner, & Illes, 2010; Carter & Hall, 2010). In order to be successful, such an integrative approach will rely on effective communication on the part of researchers, policy makers and journalists, and on a media discourse that promotes the approach.

These considerations also come at an important time for the new field of neurolaw that is emerging at the intersection of neuroscience and justice systems. Neurolaw encompasses a growing list of legal domains on which neuroscience research may have an impact (Wolf, 2008), and of which substance abuse is significant one. While the term is new, the debate is old: philosophers, legal minds and neuroscientists have long discussed the influence of brain sciences on notions of free will and the role of brain pathology in criminal responsibility. Little is known about how the interaction of neuroscience and law is communicated to the public. The links between these critical pillars—neuroscience, law and media—are particularly relevant in addiction where stigma is a part of public attitudes. Dominant discourses and narratives in the media shape socio-cultural constructions of addiction (Moore & Rhodes, 2004). Discourses, in turn, lead to social roles or subject positions that may be denied a voice in the narrative. Multiple discourses of addiction—from popular to expert—have been identified, and all have implications for concepts of power and identity (Bailey, 2005; Bright, Marsh, Smith, & Bishop, 2008). Inevitably, over the past century, these constructions have been actively incorporated into policy.
The importance and impact of popular discourses of addiction require further investigation. To understand and characterize the phenomenon of addiction in media reports discussing both neuroscience and law, we carried out: two studies (1) an analysis of headlines containing addiction terms; and (2) a content analysis of press articles. The specific aim was to quantify and qualify addiction content in popular media and analyze the occurrence of addiction in the context of press articles at the intersection of neuroscience and law.

**HEADLINES**

**Approach**

To acquire first metrics of attention to addiction in the press, the LexisNexis® Academic News Search engine was used to retrieve headlines in major international newspapers for a 12-year period between October 17, 1997 and October 17, 2009. Headlines are given great attention by readers, even more than text, are more likely to be remembered and are highly influential in shaping perspectives (Sillup & Porth, 2008). The beginning date for this analysis was chosen deliberately to coincide with Alan Leshner’s pivotal paper “Addiction is a brain disease, and it matters” (Leshner, 1997). The end date for data collection gave a complete 12-year window to discover: (1) the use of headlines as a rapid device to communicate messages about addiction; (2) the quantity and quality of messages about addiction as a disorder of the brain or a failure of moral constitution; and (3) references to technology, neuroimaging in particular, as one approach to validating claims about brain biology and addiction.

The news category, English full text, and terms and connectors were searched using the LexisNexis truncation operator (!) with [Addict!] in headline AND [brain OR mind] in document AND [disease!] in document AND [imag! OR picture OR scan!] in document, and the 1197 headlines returned were manually curated for duplication and relevance. The final sample comprised 413 unique newspaper headlines for analysis. These were classified then according to geographical origin of the newspaper, and coded for type of addiction, treatment, neurotechnology, and brain disease or moral disorder.

**Results**

News articles were retrieved from 14 countries: the USA (51% of the sample), the UK (27%), Australia (11%), Canada (5%), and Ireland, New Zealand, South Africa, Malaysia, Asia, Argentina, India, Israel, Russia and Singapore with one to three articles each in the period of study.
Of the 413 headlines, 40% (n = 161/413) made no reference to the type of addiction. In the remaining 60% (n = 252/413), a wide range of addictive behaviors was found: opiates (28%), stimulants (24%), references to gambling, the internet, alcohol and “drugs” (15–20%), and anxiolytics, “pills”, exercise, television, sports and marijuana (<5%). For example:

The happiness addicts missing out on a melancholy miracle [The Age (Australia), March 1, 2008]
A “porn again” Christian fights curse of addiction [Cape Argus (South Africa), June 25, 2009]
Eating addictions on the rise [The Age (Australia), March 5, 1998]
Are you addicted to chocolate? Is that Easter egg you’re eating actually a drug? [Sunday Mirror (UK), April 11, 2004].

By contrast, the content analysis for treatment yielded little salient information. Treatment was not mentioned in 87% of the headlines. In 2%, the headline made reference to rehabilitation. In the remaining 11%, headlines referred to martial arts, methadone, therapists, nutritionists, body-image specialists, vaccines, acupuncture, brain surgery, diet, hypnosis and pets (lamb) as approaches to intervention for addiction. For example:

This woman has spent a decade addicted to drugs prescribed by her doctors. So why does the medical profession still think we’re undermedicated? [The Australian Magazine (Australia), May 17, 2008]
“Shut them down,” says former addict. “Use of clinics panned” [City North News (Australia), May 8, 2008]
Drug addicts swear by brain surgery [The Moscow Times (Russia), March 18, 2000].

In an era in which brain scanning with functional magnetic resonance imaging (fMRI) and other neuroimaging techniques are rapidly rising and in which trends in media coverage parallel this growth (Racine, Bar-Ilan, & Illes, 2005), the extent to which brain imaging is invoked in this sample was explored. In a complete divergence from predicted trends, there was no mention of brain imaging in 99% (n = 409/413) of the headlines. We found only four references to “brain scans”, one to “scan brains” and one to “medical imaging”. Three examples of these are:

Brain scans of addicts reveal drug’s effects [The Record (Canada), January 5, 1998]
Brain scans of addicts “revealing” [Deseret News (USA), October 1, 2000]
Medical imaging shows addiction alters brain’s perception [Daily Utah Chronicle (USA), September 25, 2000].
The vast majority of headlines (95%) did not suggest that addiction is a brain disease, disorder or dysfunction. While this may seem surprising given the scientific literature, the short nature of headlines may not allow for this concept to emerge. However, the 5% of headlines that did suggest that addiction is a brain disease were explicit in doing so. For example:

*Often dismissed as being weak, compulsive gamblers may have a brain malfunction* … [St. Louis Post-Dispatch (USA), February 6, 2000]

*Brain’s wiring may work against recovering addicts* … [San Jose Mercury News (USA), May 4, 2001]

*Brain link to addiction* [Geelong Advertiser (Australia), February 27, 2008]

*Addicts may be wired not to stop* [Courier Mail (Australia), February 23, 2005].

A similar proportion of headlines explicitly referred to addiction as a deficit in character traits or a moral problem:

*Don’t forget the addict’s role in addiction* [The New York Times (USA), April 4, 1998]

*Addiction isn’t a brain disease; fatalistic rhetoric diminishes personal responsibility, but it’s not a hopeless condition, and like a bad habit, can be broken* [Chicago Sun Times (USA), July 29, 2007]

*Alcohol, drug addiction: “a hole in soul”* [The Denver Post (USA), April 6, 2009].

**Summary**

Overall, we found that headlines generally convey little substantive information to the reader, but when they do, the assertions are strong. This is the case both for claims that addiction is a brain disease and claims that it is a moral condition. The US media is dominant. References to imaging technology are essentially absent.

While this was a limited and descriptive study, the messages contained in the headlines nonetheless suggest that change would benefit the culture of communication, starting with empirical research on the public communication of issues of addiction, as well as a cultural shift that rewards public outreach (Illes et al., 2010). Indeed, for improving well-being and policy making for addiction, this quote from Australia says it all:

*Sensationalism is not the way to fight drug addiction* [The Age (Australia), March 20, 2007].
CONTENT ANALYSIS OF PRESS ARTICLES

Approach

The sample for this content analysis of press articles was generated using LexisNexis Academic. We conducted a search for full-length articles in the English language between January 1, 2000 and December 31, 2009. To retrieve a full set of relevant articles at the intersection of law and neuroscience, we carried out a keyword search using the LexisNexis truncation operator (!) and the following terms: ((brain! OR neuro! OR mind!) AND (legal! OR law! OR justice OR judici! OR crime OR crimin!)). The search was performed on headlines, lead paragraphs and text body to maximize the yield. Articles were retrieved in three different news categories from the USA as defined by the LexisNexis Academic database: general news (major newspapers such as the New York Times), magazines (such as Oprah! Magazine) and legal news (such as Lawyers USA). Once all the articles had been collected, we discarded duplicates arising from the frequent republication of articles and articles that did not discuss neuroscience themes.

One coder analyzed all articles from the final sample (n = 168 newspapers, n = 99 magazines and n = 229 legal news) according to the instructions contained in a detailed coding guide. The coding guide was developed for this specific study based on the research objectives and a pilot analysis of the content. Individual codes represent the units of analysis for this study. The coding structure included the identification of: (1) the general features of the article (e.g. year, type of content, category of information reported); and (2) themes (e.g. technology, mind reading, criminal responsibility). A rich coding strategy was used to code content of articles that appropriately corresponded to more than one category. Following this first level of coding, all newspapers and magazine articles containing the substance abuse theme were retrieved (newspapers: n = 39/168, magazines: n = 6/99) for a total yield of 45 articles. A second, independent coder analyzed a random 20% of the total to ensure coding reproducibility.

To gain an in-depth insight about the concepts of addiction in the articles, a second level coding strategy was applied to the subset of articles that mentioned substance abuse. For this subset of articles (n = 45), the coding structure included: (1) the addiction content of the articles; (2) substances mentioned; (3) the context of addiction content; (4) the link between substance abuse and responsibility; and (5) the occurrence of substance abuse-related themes (e.g. driving under the influence, drug courts).

For both sets of analyses, we used descriptive statistics to characterize the composition and the properties of the sample.
Results

Quantitative Features of the Data Set

The number of retrieved articles from newspapers and magazines meeting the inclusion criteria increased substantially between the first (2000–2004, one article per year on average) and second (2005–2010, seven articles per year on average) periods of the study. There was a large increase in the number of articles on addiction specifically beginning in 2008. The variables driving the reporting of addiction varied widely (Fig. 11.1). Nearly half of all articles (49%) focused on a single case (e.g. a murder or a drunk driving incident). Another large proportion of the articles (29%) featured discussions of the legal system (e.g. drug courts). Articles also reported on legal proceedings such as the adoption of a new law (16%) and on advances in research and technology related to addiction (7%). In terms of the specific addiction content of the articles, the sample could be clearly divided into two categories: (1) articles entirely dedicated to addiction where the main subject of the article was addiction or substance abuse (20%), and (2) articles with at least one mention of addiction or substance abuse but where the main subject of the article was unrelated to addiction as a whole (80%).

To gain an understanding of the addiction landscape specifically, we coded each article for substances mentioned (Fig. 11.2). Nearly half of all articles (49%) did not refer to a specific substance, using instead the terms “drugs” or “drugs and alcohol”. Alcohol was the sole substance mentioned in 24% of all articles. Other substances mentioned were amphetamines, marijuana, methamphetamines, cocaine, heroin, crack and painkillers.

Each article was further coded for the specific framework in which addiction or substance abuse was described (Fig. 11.3). The context was

![FIGURE 11.1 Content drivers (%, n = 45).](image-url)
responsibility (e.g. drunk driving causing an accident) in 44% of the sample, and treating addiction as a part of dealing with prison populations in 24%. Law making, law enforcement and scientific research into addiction and treatments were other contexts encountered. For the context of responsibility, we assessed the weight of substance abuse or addiction as a cause of the outcome (e.g. aggressive behavior, accident) (Fig. 11.4). In a majority of articles (61%), the responsibility for a given outcome (e.g. a murder) was shared between substance abuse or addiction and one or more other factors such as mental illness. In 22% of articles, responsibility was specifically attributed to substance abuse or addiction. In the remainder of the articles (17%), substance abuse or addiction was mentioned, but not specifically linked to the outcome.
In addition to criminal responsibility, we identified seven main emergent and recurrent themes in discussions of addiction or substance abuse in the sample: (1) addiction is a brain disease; (2) driving under the influence; (3) costs of addiction to society; (4) drug courts; (5) juvenile justice; (6) veterans; and (7) harm reduction (Fig. 11.5).

**Qualitative Features of the Data Set**

To examine the discursive context in which addiction issues are constructed in the press, we used a qualitative approach we used to explore the medical, legal, economic, moral, political and glamour content of the sample, following the model described by Bright and colleagues (2008).

**MEDICAL DISCOURSE**

The medical discourse encompasses the theory that addiction is a brain disease, and that psychoactive substances are dangerous...
Examples from this type of discourse in the sample often used technical medical language, as illustrated by the following quote:

> Dr. Davis continued, “It is imperative that the process of recovery begin by focusing on the dysfunction of the brain and the neurological impairment that occurs as a result of chemical dependency” (Business Wire, October 11, 2004).

Another way of conceptualizing addiction as a disease of the brain is by comparing addiction with other unrelated pathologies, thereby legitimizing the disease theory but also implying passive agency for drug users:

> “Today we know that mental illness and addiction is a disease of the brain,” White said. “The brain is not working correctly, just like the body doesn’t work correctly when someone has diabetes. If we locked up people with diabetes there would be a public outcry” (The Daily Oklahoman, January 16, 2009).

The medical framework of addiction leads to the emergence of two clear and opposite subject positions: experts (often doctors or researchers) and patients or drug users. This is illustrated by the following example:

> Dr. Hyman Gross, a neurologist whose medical practice is in Santa Monica, testified that Varnum’s blood alcohol level of .23 percent—nearly three times the level at which a driver is presumed drunk—coupled with a history of head injuries may have contributed to Varnum being in a state of unconsciousness even though he appeared awake and was doing things (Ventura County Star, July 3, 2009).

**LEGAL DISCOURSE**

The legal discourse can be recognized through language: judicial terms are used to identify substances or behaviors as legal or illegal. This discourse can arise from both illegal drug use and illegal behaviors associated with the use of legal drugs. Similar to the medical discourse, the legal discourse gives rise to two clearly defined subject positions: that of the legal professional (judge, lawyer, police officer) and that of people who are affected by the law (though not necessarily people who are breaking the law). This is exemplified in the following quote:

> The St. Louis County Attorney’s Office has filed notice that it intends to seek a longer-than-guideline sentence for the driver of an SUV accused of driving away drunk after hitting two pedestrians walking along Rice Lake Road last month (Duluth News, November 25, 2009).
The legal discourse also lends itself to the classification of substances, creating a licit/illicit dichotomy:

[Amphetamines are] also used illegally as a recreational drug, such as those at dance clubs or raves, and as an athletic performance enhancer (Chicago Tribune, January 3, 2008).

**MORAL DISCOURSE**

Addiction at its core represents a moral concept: it embodies the dualist concept of the relationship between the mind and the body, and it is often seen as a failure of self-control over desires and functions (Bailey, 2005). The moral discourse surrounding addiction attempts to delineate right from wrong, but also places substance use as a source of identity (du Gay, 1995), with addiction lying at one extreme of the spectrum of consumption identity.

While the moral discourse is distinct from the legal discourse in that the appropriate conduct is defined by ideology rather than by law, the moral discourse and the legal discourse go hand in hand: the use of an illicit substance or an illicit behavior while using a licit substance are considered wrong because they are illegal in nature but also because they can be perceived to represent behaviors that are morally wrong (Bright et al., 2008). In the case of the moral discourse, morality is seen as a virtue of character, and addiction as a weakness of this character:

Veterans returning from war often have difficult transitions, Daley said. They can develop problems in their personal relationships or jobs. They often self medicate with alcohol or drugs, Daley said, and their addictions can get them in trouble (The Janesville Gazette, September 20, 2009).

Like medical and legal discourses, the moral discourse lends itself to two subject positions: that of the righteous, and that of the deviant and irresponsible user, as exemplified in this quote:

I battle crime every day, and I defend myself every day, too. I’m a black prosecutor in Louisville, KY. I have presented cases before juries, but from my first day on the job I have felt that I have been on trial in the court of public opinion. Even my maternal grandmother once asked if I was a Republican (I’m not), while others just asked the ultimate question: how can you put our black men in jail?

Depending on my mood, the answer can be a three-part speech on the decay of moral values, educational-attainment levels and teenage motherhood. Other times I simply tell them the defendants put themselves in the penitentiary and I facilitated their exodus from the community. Or better yet, my favorite answer: I didn’t put the crack in their pocket and a gun in the other (Newsweek, April 14, 2008, emphasis added).
Taken together, the medical, legal and moral discourses suggest a contradiction in how addiction is portrayed in the press: both as an organic, normal phenomenon and as a behavior that is dangerous and pathological (Brodie & Redfield, 2002).

ECONOMIC DISCOURSE

Previous analyses of the economic discourse around addiction suggest that it is often framed in a capitalist ideology where drugs represent consumer goods (Bright et al., 2008). This specific framework tends to apply primarily to alcohol and tobacco, reflecting the licit industry surrounding those substances. In this context, drugs represent commodities, and substance users make decisions to become consumers, and as such have significant agency (Heather, Greeley, & Miller, 1991), unlike substance users described in medical, legal or moral discourse. While we did not find any discourse relating to decision making or choices associated with psychoactive substances such as consumer goods, we did find instances of concern over fiscal issues when these issues pertain to society:

*Failure to treat incarcerated drug abusers can lead to higher crime rates and re-incarceration, says to a report from the National Institute on Drug Abuse (NIDA), and the costs of treatment are not nearly as high as the costs to society when drug abuse is ignored (The Washington Times, July 25, 2006).*

Unlike other media studies (Bright et al., 2008), we did not find discussions of normalization or delegitimizing substance in this sample.

POLITICAL DISCOURSE

The political discourse revolves around discussions of policy and governance. Like other discourses, it lends itself to two subject positions, that of the politician (the primary subject, considered an expert) and that of the community. Because government institutions and politicians are naturally interested in appealing to the community, the political discourse tends to mirror whichever discourse is dominant during a given period (e.g. following the discovery of a neurobiological basis for addiction, the dominant discourse may be medical). In the present sample, it was found that the political discourse was situated around specific events:

*The new direction was made clear last week, as [Bobby] Scott hosted a National Crime Policy Summit aimed at laying the ideological groundwork for future legislation. [...]*

“I really appreciate Bobby’s doing this forum,” said Rep. Patrick Kennedy, D-R.I., who came to urge the creation of drug courts that keep drug users out of the traditional court system (Newport News, June 25, 2007).
GLAMOUR DISCOURSE

In their systematic analysis of the dominant discourses within Australian society with regard to substance use, Bright et al. (2008) found instances of a glamour discourse that combines reality and fiction and pertains mostly to celebrities. In this discourse, drugs of abuse are framed as mysterious and fascinating. No instances of such discourse were found in this US-based print media sample, although this may be an artifact of the focus on addiction in the context of law and neuroscience.

DISCUSSION AND CONCLUSION

Overall, we found that headlines paint a vague picture of addiction, with few mentions of specific substances, few references to treatment and little content value. By contrast, full articles both closely link addiction to criminal responsibility, and create a dichotomy between subject positions: the addict on the one hand, and a person of some power on the other. As discourses represent implicit and explicit rules about what may or may not be communicated, this dichotomy may present a threat to the contribution of an addicted person’s own account to the discourse.

Some discrepancies were found between the content of headlines about addiction and the content of articles at the intersection of neuroscience and law with a mention of addiction. As expected, while full articles all contained a mention of a substance, even if vague (e.g. “drugs”), this was not the case in over a third of headlines. While most headlines with a mention of substance focused on opiates and stimulants, the full articles mentioned alcohol and drugs more in general. There was a strong focus on alcohol in the full article sample, likely due to the nature of the study: by selecting articles in the context of law, a bias for themes such as driving under the influence was naturally introduced.

The analysis of addiction specifically in the framework of law in the media here revealed, for the first time, links between addiction or substance abuse and context of criminal responsibility. Such representations may lead to the promulgation of stigmatizing messages about mental illness through a variety of mechanisms including choice of vocabulary and framing of issues (Francis, Pirkis, Dunt, & Blood, 2001). The idea that certain conditions such as brain-related illnesses can decrease a person’s responsibility is not new. The Prussian General State Laws of 1794 stated: “Everything that increases or diminishes a person’s ability to act freely and deliberately, increases or diminishes the degree of culpability” (Kroeber, 2007). The debate now continues with new evidence from neuroscience. Initially, neurochemical models of impulsive violence and aggression led to debates on whether violent criminal offenders are responsible for their conduct if it is the result of deterministic processes
in the brain (Siegel & Douard, 2011). New insights from neuroimaging and cognitive neuroscience hold the promise of an even greater understanding of the biological causes of criminal behavior (Eastman & Campbell, 2006) and further fuel the responsibility debate among philosophers, legal scholars and neuroscientists. These developments may well have a transformative effect on criminal law and several models are emerging as to how this shift will take shape (Chorvat & McCabe, 2004; Greene & Cohen, 2004; Reider, 1998; Roskies, 2006).

In the past three decades, advances in neuroscience have promised to change the understanding of addiction among scientists, health-care providers, policy makers and the public alike (Carter & Hall, 2010; Leshner, 1997). New insights into neural networks and behavioral systems as well as new technologies have advanced our knowledge of the addicted individual’s brain tremendously and these trends are reflected in the present analysis. Although few headlines characterized addiction as a brain disease, nearly a third of all full articles from the content analysis alluded to this view. As such, there is an implicit assumption that medical institutions may halt substance abuse through treatments and cures (Bright et al., 2008). Yet, we found very few references to treatment or harm reduction in either of the studies presented here. In full-length articles, treatment was most often discussed in the context of reducing or managing prison populations and only minimally discussed in the context of public health. Further work will be required to investigate the motivators to discuss or not discuss treatment in the media and how the press presents issues surrounding the treatment of addiction.

Understanding how the media frames discourses of addiction as a whole can further affect public health strategies (Bailey, 2005; Bright et al., 2008). The close ties between substance abuse and criminal responsibility in the press, combined with the improved understanding of the biological underpinnings of addiction challenge, at least to some extent, notions of autonomy and free will, and may change the way that courts and the public think about criminal policy. Furthermore, implicit and explicit representations of a link between substance abuse and criminal behavior may contribute to dueling subject positions and stigma against people living with addiction. Overall, the data presented here support the imminent need to bring neuroscientists, journalists, legal scholars and the public into interactive dialogue.

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References


Social Epistemology: Communicating Neuroscience

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OUTLINE

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INTRODUCTION

Serious discussions of social impact, public understanding and engagement, and public debate emerge strongly in current discourses about the sciences. Neuroscience is second only to genetics in foregrounding such concerns by inventing an interdisciplinary space, “neuroethics”, in which social discourses of neuroscience are considered within an ethical framework (Carter, Capps, Nutt, ter Muelen, Ashcroft, & Hall, 2009; Moreno, 2003). Adjacent to the interests in ethics, and many times superseded by them, issues of communication and knowledge circulation have become increasingly important in scientific fields, including neuroscience (Illes et al., 2010). The goal of this chapter is to suggest a social epistemology of neuroscience, with a special focus on the communication of addiction neuroscience. It sets social epistemology in a complementary relation to neuroethics, as part of this important interdisciplinary space.
where issues of knowledge circulation and science communication are foregrounded.

Social epistemology is the study of how knowledge is constituted, defined and circulated in social groups—as opposed to how individuals come to knowledge. [Of course, as in many academic disciplines, this definition is not unproblematic. There is at least one version of social epistemology that suggests that “the social” is what is being analyzed by epistemology, not where knowledge resides (Goldman, 2010).] It was invented as a category of library science by the philosophically and sociologically minded Jesse Shera at the University of Chicago in the 1960s (Shera, 1968). His insight was that, with the rapid proliferation of knowledge and the introduction of information technology, librarianship was about to be transformed. Access to knowledge, as he saw it, was going to become a bigger problem not only for people not involved in its production but also for the knowledge producers themselves. Thus, he saw a need for a specialist area, social epistemology, to study and resolve issues of access to knowledge and mediate between the skills of librarianship and those of information technology. Like many good ideas, it escaped its initial formulation. “Social epistemology” has been used to describe all sorts of knowledge mediation enterprises in philosophy, sociology, education and elsewhere (Baba & Walsh, 2010; Downer, 2010; Fagan, 2010; Lundqvist, Almqvist, & Ostman, 2009; Warner, 2008).

Like traditional epistemology, social epistemology has been strongly normative, attempting not only to describe the circulation and constitution of knowledge, but also to assist social groups to obtain knowledge that is best for them (Fuller, 2002). As Steve Fuller has put it, the difference between social epistemology and traditional epistemology is whether one focuses on “knowledge” as a noun or the verb “to know” (Fuller, 2007, p. 177). For social epistemologists whose focus is on the social aspect of epistemology, the key interest is in knowledge, the noun, and not individual knowledge acquisition. For mainstream epistemology, with its emphasis on knowledge acquisition, the “coming of neuroscience” has been profoundly unsettling; social epistemologists find the terrain more exciting. [The representative anecdote indicating the degree of discord between neuroscience and traditional epistemology is Patricia Smith Churchland’s (1987, p. 545) Journal of Philosophy article, where she opines that with the coming of neuroscience, “most of the questions which used to preoccupy us as graduate students and whose answers seemed necessary to advancing the general program of epistemology, now look either peripheral or misguided, and the general program itself looks troubled”.] A social epistemologist, then, might even see an account of knowledge acquisition as a problem for neuroscience itself. This is important because an approach from social epistemology is happy to use neuroscience to naturalize questions of cognitive function or individual
knowledge acquisition. It is more likely, however, to naturalize questions of knowledge circulation to philosophy, sociology, education, communication studies and other analytic fields in the humanities and social sciences.

**SCIENCE COMMUNICATION: BEYOND MEDIA TRAINING**

What makes the terrain of neuroscience exciting for the social epistemologist is the priority that the field has given to science communication. There is a range of professed reasons why neuroscientists want to communicate that imply a diversity of communication modes and genres through which this might happen (Table 12.1).

These and other motivations for science communication in neuroscience are an indication of the broad range of reasons why communication has emerged as a central topic. On the one hand, there is general interest in communicating to a broad range of audiences in the mode and genres of popular neuroscience. On the other, ethical discussions of emerging neuroscience applications (neuroenhancement, neuromarketing) create spaces in which neurorhetoric can thrive. Thus, the term “science communication” covers a wide range of practical applications of communication in science as well as a nascent discipline that studies communication in those fields (Logan, 2001).

“Science communication” also refers to the process whereby scientific knowledge is communicated from inside science to a range of audiences and the processes by which audiences demand knowledge, engage it, contribute to it and respond to it (variously known as science popularization, citizen science and public engagement). The field of science communication has a somewhat chequered history in engaging with multiple communication contexts in a coherent fashion (Bauer & Bucchi, 2007; Logan, 2001). That pattern seems to be continuing in addiction neuroethics, where professional and clinical communication are seen as separate practices from ethical discussion and identity work. Thus, it is possible, even likely, to find neuroscientific communication fragmented among researchers who are undergoing media training, clinicians working through scenarios of doctor–patient communication, and public relations officers well-schooled in issuing press releases touting research breakthroughs. Each of these communication scenarios might be effective and useful communication practices in itself, but taken together, they can operate in a counter-productive fashion, if the goal is the communication of knowledge.

A recent example of this is the emergence of neuromarketing. The *New York Times* (popular science) covered the recent acquisition by
### TABLE 12.1 Multiple Modes and Media of Science Communication

<table>
<thead>
<tr>
<th>Clinical communication</th>
<th>Neuroscience as clinical practice: Neuroscience has a clinical component and patients are an important group with whom to communicate (Bell, Mathieu, &amp; Racine, 2009; Gilbert &amp; Ovadia, 2011; Pluta, Perazza, &amp; Golub, 2011; Sachdev, 2011; Schermer, 2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical discussion</td>
<td>Neuroscience as problematic practice: Neuroscience involves new scientific techniques whose ethical or social status is not yet clear. Communicating about these techniques may pre-empt controversy, generate ethical discussion and raise awareness of the emergence of new knowledge practices (Illes et al., 2010)</td>
</tr>
<tr>
<td>Professional communication</td>
<td>Neuroscience as interdisciplinary practice: Neuroscience research spans disciplines as well as theoretical, applied and clinical settings. Thus, the need for transparent communication is central to research having impact and the generation of interdisciplinary knowledge (Leshner, 1997)</td>
</tr>
<tr>
<td>Identity work</td>
<td>Neuroscience as social game-changer: Neuroscience has implications for questions of individual and social identity. Communication to audiences with a stake in these questions is core business for such a field (Dumit, 2004); see Fry and Buchman (This volume, Chapter 9)</td>
</tr>
<tr>
<td>Multimodal communication</td>
<td>Neuroscience and multimodal communication: Imaging techniques in neuroscience (Berns, Capra, Moore, &amp; Noussair, 2010) produce novel ways to conduct and report neuroscience research. Communication through these modes is both popular and difficult territory (Joyce, 2005)</td>
</tr>
<tr>
<td>Cannot not communicate</td>
<td>Neuroscience as “normal science”: Neuroscience is coming of age in an era where science communication is expected and public relations must be managed (Bubela et al., 2009)</td>
</tr>
<tr>
<td>Neurorhetoric</td>
<td>Neuroscience advocacy: Areas such as neuromarketing, addiction treatment programs and drug policy draw advocates and critics, both producing neurorhetoric for public and professional consideration (Jack, 2010)</td>
</tr>
<tr>
<td>Popular neuroscience</td>
<td>Popular neuroscience: There is a general interest in neuroscience that can be satisfied with various forms of popular mediation, from news, blogs, websites, paperback books and advertising to business analysis and documentary</td>
</tr>
</tbody>
</table>
Nielsen of NeuroFocus, a leading neuromarketing company. NeuroFocus was also of interest to The New York Times because they had ignored the policy guidelines of the Advertising Research Foundation on the ethical use of neuromarketing. The paper reported the views of other neuromarketers and neuroethicists on this development (ethical discussion). Meanwhile, on blogs, in popular science and in professional forums, neuroscience researchers have been characterizing neuromarketing as “junk science” or an “area of concern” (professional communication). Given that much of the technology of neuromarketing results in the interpretation of images (multimodal communication), some marketers are skeptical about the value of neuromarketing (neurorhetoric) apart from the persuasive images it produces. Finally, neuroethicists have worried, that if successful, neuromarketing could raise serious ethical problems by targeting “stealth neuromarketing” at audiences who were unaware that marketing was taking place (more ethical discussion) (Murphy, Illes, & Reiner, 2008). Thus, there is a tremendous variety of communication modes and interests involved in assessing one emerging area of applied neuroscience. Tackling this issue solely by suggesting that neuroscientists undergo media training or any other one-mode or genre solution is unlikely to be successful. This is because the audiences for neuroscience have already shown themselves to be multiple (inter alia, patients, critics, fellow professionals).

Examining science communication, then, can be a much more multifaceted activity than understanding how the media works or being able to parse the interests of various actors in a controversy. Being able to analyze the various communication modes at play is a first step in understanding how knowledge is circulated among various communities. In the example above, one relevant audience is Nielsen shareholders. Another is the large community of marketers curious about the possibilities of neuromarketing research. What do they know about neuroscience after this episode? Do they find the claims of NeuroFocus credible enough to jump on the neuromarketing bandwagon? What, if any, is the impact of increased popular discussion of neuromarketing on opinions or beliefs about other forms of neuroscience? These are questions of knowledge circulation and of the cumulative effects of multiple communication modes and genres.

COMMUNICATION EXPECTATIONS

What can more or better communication achieve for neuroscience? Those in the fields of neuroscience and neuroethics have begun to answer that question. Jonathan Moreno (2003), for example, posits that “some neuroscientific discoveries, once they become more widely appreciated,
are likely to become objects of popular imagination”. He goes on to conclude that:

many of those engaged in these efforts [neuroscientific research] will find themselves the subjects of the sort of public attention that was previously experienced by their colleagues in nuclear physics and genetics. Neuroscientists will increasingly be challenged to explain the significance of their work in moral as well as scientific terms.

The burden of discovery in neuroscience, from this point of view, is that people outside the field will engage with new discoveries, perhaps coming away with ideas not sanctioned by their discoverers. Further, the specter of moral controversy is raised to underscore the need for neuroscientists and neuroethicists to justify themselves and their research to a skeptical or worried audience. In short, faced with potentially problematic findings, the neuroscientist will be forced to communicate. Or, in the terms laid out in Table 12.1, faced with an accusation that neuroscience is a problematic practice, neuroscientists cannot not communicate; they will have to engage in ethical discussion. This formulation raises questions about the general expectations for what communication can achieve and what other formulations for motivating communication might be.

In observing researchers’ attitudes to science communication, three rather clear stances are taken, with the same people sometimes occupying different stances for different occasions and purposes. That is, neuroscience and neuroethics researchers can encourage or discourage others from attempting to engage in science communication by taking rhetorical stances about the possibility of success. First, there are science communication optimists. They claim that communication will make a substantial difference to the way knowledge is constituted and circulated and in ways that produce positive social outcomes. Inside neuroscience, optimists are best represented by Alan Leshner (1997) in his well-cited editorial “Addiction is a brain disease, and it matters”. While Leshner is dubious about other social mechanisms that negatively impact knowledge circulation such as “ingrained ideology”, he says, “I believe we can and must bridge this informational disconnection if we are going to make any real progress in controlling drug abuse and addiction”. Despite the infelicitous term “informational disconnection”, for Leshner it seems clear that improved science communication is how the field must progress. Note that Leshner seems to be directing his attention to science communication in professional circles. It is the professional and clinical audiences who need to worry most about communication (one-way, “informational” communication) because confusion about the definition and quality of addiction in professional circles has, in his view, made the successful treatment of addiction more difficult. Successful communication
in this view is a range of experts speaking with a unified voice to express a scientific consensus. (For expressions of “scientific optimism” from leading addiction neuroscientists including current and recent directors of US national research institutes on illicit drugs and alcohol, see Baler & Volkow, 2011; Dackis & O’Brien, 2005; Shurtleff, Liu, & Sasek, 2009; Volkow & Li, 2004, 2005; Volkow, Fowler, Wang, Baler, & Telang, 2009; for critical reviews, see Campbell, 2010; Courtwright, 2010; Vrecko, 2010.)

Science communication pessimists, by contrast, worry that science communication is futile, or worse, that communication (especially journalism) can have negative social consequences. In neuroethics, pessimists can be represented by the view that science communication in the field is rife with misrepresentation which, at least in some cases, is worse than not communicating at all (e.g. Gonan, Bezard, & Boraud, 2011). Criticisms of neurorealism, the idea that some neuroscience findings appear more real or true because they are associated with images (typically functional magnetic resonance imaging scans) are also suggestive of this stance (Racine, Bar-Ilan, & Illes, 2005). While the images themselves are a source of media appeal, their effects may have emphasized the standing of the wrong research or provided inferential leaps to claims that “hysteria is real” or autism is caused by a “super-male brain”. A more ambivalent form of pessimism is framed by Illes and colleagues (2010, p. 61):

*Neuroscience is among several scientific disciplines that are particularly prone to misinformation and inaccurate reporting. Sensational media headlines that evoke mind reading, a neurogenetic basis for fidelity or voting patterns, memory boosters for the healthy, and miracle cures for sensory and movement disorders are but a few examples. Without accurate and sufficient background information or context, the public—who are naturally interested in diseases and cures, especially with regard to common and serious brain disorders—may accept these simplistic messages uncritically.*

While pessimistic about current public communication of science, Illes et al. retain a modicum of optimism about the possibilities for science communication to have a positive social impact. This requires an overhaul of the media, a cultural transformation inside neuroscience circles and more empirical research on public understandings. Indeed, they write “with an even stronger commitment to communication, the neuroscience community and its partners will mitigate or avoid the public backlash and funding freezes that have taken other areas of science by surprise …” (Illes et al., 2010, p. 68).

Of course, there are also pessimists about professional communication in neuroscience. The anonymous author of an editorial in *Nature Neuroscience* (2000) throws up his or her hands at the end of an essay, describing professional communication of neuroscience as “pomposity”,

IV. ADDICTION HISTORY AND THE MEDIA
“ineffective communication solutions”, “vapid statements” and a “culture of bad writing”. They conclude that “perhaps the solution is for graduate programs to place more emphasis on formal instruction in scientific writing, but this will only happen if scientists appreciate the need for better communication and understand the steps that can be taken to achieve it”. The pessimistic implication is that scientists do not and will not communicate effectively.

These stances are rhetorical strategies, and whether you are an optimist or a pessimist radically changes your strategy. A typical pattern for researchers is to be optimistic about scientific communication, but pessimistic about public communication of science. A more nuanced view holds that there is something about neuroscience, or even reflexively, about ourselves, that makes neuroscience more difficult to communicate about, or for the public to understand or engage with it. Also, there is more than a bit of threat, of fear, in each of these rhetorical stances about communicating neuroscience. Moreno presents the image of public attention, sweeping like a spotlight from physics to genetics before it finally rests upon neuroscience. Will neuroscientists be able to perform in that spotlight? Leshner sets the communication bar quite high: can clinicians and researchers forge a common language in order to make any impact on the suffering of addiction? Illes et al. create the specter of a public beguiled by neurohype before challenging their audience of neuroscientists to engage in direct (and sober) communication with an interested public. The anonymous editorial writer leaves us with the threat of unending unreadable prose, opaque to public and professional alike.

Even the optimists see communication as difficult at best, and scary too because the threat of misunderstanding and skepticism is real, and the stakes are high. Those who succeed in communicating are duly congratulated for scaling this high rhetorical wall. As Stephen Hilgartner (1990) pointed out in relation to science popularization, this “scary” view of public communication “serves scientists (and others who derive their authority from science) as a political resource in public discourse”. It ensures flexibility in the face of mistakes and failures of communication, and provides an excuse when controversy prevents open communication. Thus, talk of “science communication” is not necessarily to be taken at face value; it also needs to be seen as a part of a larger set of questions about how knowledge in neuroscience circulates.

SOCIAL EPISTEMOLOGY AND SCIENCE COMMUNICATION, ALONGSIDE NEUROETHICS

Neuroethicists aim to identify, analyze and provide possible solutions or guidance for ethical problems arising in neuroscience; the science
communicator and the social epistemologist have related tasks. Communication modes, tools, techniques and genres can be used in service of ethical debate and even their resolution. However, there are other goals for science communication that an approach from social epistemology can help to articulate alongside a research program to answer the questions of communication raised in the previous two sections. First, given the rhetorical quality of appeals for more and better science communication, what would count as successful neuroscientific communication? While some neuroethicists have acknowledged the “two-way nature” of public engagement and dialogue (Illes et al., 2010, p. 62), the venues suggested for this to happen have been limited to “café scientifique” discussions and online interaction, both still focused on professional communication with lay audiences. If a goal for such communication is a larger social engagement with neuroscientific research, audiences will need also to feel some responsibility for or at least affinity with the research. Currently identified as “citizen science” (Irwin, 1995), this approach advocates a position of audiences, not as passive witnesses to scientific or ethical arguments, but as active participants in the definition and creation of new scientific knowledge. The flagship successes of this approach have been in ecology and conservation biology (Evans et al., 2005; Jenkins, 1999), where participants in the research make observations that would be impossible for researchers to achieve by themselves. This has also expanded to genetics and biotechnology, where non-scientists can make observations and contribute to the formation of research projects (Swan, Hathaway, Hogg, McCauley, & Vollrath, 2010). Medical researchers have approached this way of bringing lay expertise to bear on clinical questions. As citizen science projects typically ease funding restrictions on research by using volunteers to carry out research, they can be attractive projects for researchers pursuing large-scale research that otherwise would not be done. Neuroscience is an area where such an approach could also prove fruitful.

A recent editorial in *Nature Neuroscience* (2010) reinterprets citizen science as an opportunity for bringing funders and researchers together:

*Several new funding initiatives that encourage the public to fund science directly with their pocket change … Such microfinance efforts will not make an immediate dent in systemic problems of insufficient funding, but increased personal investment in scientific research could help improve scientific literacy and enthusiasm for science and, ultimately, win stronger backing for federal support of scientific research.*

Reformulating citizen science in this way replaces intellectual engagement and direct dialogue with personal investment and risks undermining any trust that has been gained already by neuroscientists discussing ethical issues and promoting open communication. It also points to
the slipperiness of the goals of science communication. From a social epistemology perspective, an important goal of science communication is the more equal distribution of knowledge and the more active engagement of participants in its production, not solving the funding crisis for neuroscience. In this instance, there is a worrying trend to replace knowledge policy with economic policy for science, using “science communication” as a convenient excuse for the exchange. The criteria for measuring successful science communication, then, need to be clearly articulated. Is it increased science literacy? Is it increased support for neuroscience? Is it creating a more engaged audience for neuroscientific research? Also, how and by whom will these goals be set?

A second perspective on science communication from social epistemology argues for a joined-up approach to science communication. This is especially true in addiction neuroscience. Hall, Carter, and Morley (2004) have sympathetically characterized drug-dependent people, arguing that, “addiction needs to be seen, in part, as the result of choices that are not always wisely made by young people who operate with a short time perspective, a sense of personal invulnerability and skepticism toward elders’ advice about the risks of drug use”. Alongside this characterization of addicted drug users rests the problem of representations of neuroscience in mediated contexts. Hall et al. write, citing Colin Blakemore:

*Given the public interest in neuroscience research, potential misunderstandings may rebound to the detriment of neuroscience and genetics. Neuroscientists and geneticists arguably have a moral responsibility to be proactive in their dealings with the media (Blakemore, 2002).*

There are a few common communication facets to these two problems. First, ignorance, skepticism and misunderstanding are common threads to these two characterizations, if not to the people they may apply to. However, it is worth seeing ignorance, skepticism and misunderstanding not as the simple “lack” of the right knowledge, but as the result of a state of affairs that has been actively produced by a lack of communication. This more positive account of ignorance as a product of ineffective activity, or none at all, provides a target for improving communication activity. It is already a mainstay of public health messaging for families that open communication channels and proactive communication with teens are prophylactic for adolescent drug abuse; Anderson’s recent study (2010) documents the continuing popularity of this governing idea despite problems demonstrating its effectiveness. As this chapter has demonstrated in a few examples, it is becoming a common trope of neuroethics that open communication channels and proactive communication with interested
publics for neuroscience are necessary to resolve emerging ethical dilemmas. The key issue, however, is to see these two situations (the skeptical drug-dependent user and the misunderstanding public) as related figures who have been, in part, rhetorically characterized by the communication practices of neuroscience in order to give itself a communication problem to solve. Also, that problem is seen as one of “lack;” a lack of communication or a lack of understanding to which communication becomes a remedy. Communication misunderstandings can always be blamed on the receiving end of the communication. The challenge is to place the communication burden on neuroscience. The injunction to “communicate or there will be misunderstandings”, emphasizing “lack” in both communication and knowledge terms, is changed to “your communication practices are not working; try something else”, which emphasizes the goals of communication.

In summary, science communication is an important area for neuroscience and neuroethics that can all too readily be identified with its modes and genres instead of its goals and purposes. The use of a framework from social epistemology that is more concerned with how knowledge circulates can provide efforts to improve communication with a more appropriate focus. In addition, this approach suggests a series of research questions that can provide solutions for practical communication problems (e.g. what is the best way to explain synapses to a person considering taking an antidepressant such as a serotonin reuptake inhibitor?) as well as address larger normative issues about the goals of science communication in neuroscience (e.g. to aid in scientifically formed public debates about ethical issues raised by neuroscience). An overemphasis on certain genres of communication in neuroscience, for example media training, can distract attention from the wide variety of pressing communication concerns of clinical, ethical and epistemic significance. It is therefore important that discussion of science communication is not centered on only one mode or genre. Popular neuroscience, in the form of expert media commentary is only one possible way that neuroscientists and neuroethicists communicate. Indeed, if the pessimistic editorialist quoted above is to be believed, professional communication needs as much attention as communication with lay audiences.

It is worth concluding on a note of qualified optimism, inspired by the qualified pessimism of Illes et al. (2010). Neuroscientists might yet be able to engage with questions of the public good, if they take communication seriously, if they are rewarded for communication interventions that, by clear criteria, work, if neuroscientists continue to examine their relationship with social mediation, and if a social epistemology research framework can generate good answers to some complicated empirical questions of knowledge circulation.
Acknowledgments

I would like to thank Wayne Hall and Judy Illes for inviting me to talk about science communication in neuroscience at “Introducing Neuroethics”, a conference at the University of Queensland, April 2010. I would also like to thank Sarah Yeates as a model of social epistemology in action, from library to neuroethics.

References


Population Approaches to Alcohol, Tobacco and Drugs: Effectiveness, Ethics and Interplay with Addiction Neuroscience

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INTRODUCTION

This chapter considers the possible implications that neuroscience perspectives on addiction may have for population approaches to reducing problems arising from the use of psychoactive substances such as alcohol, tobacco and drugs subject to the international prohibition regime (often called “illicit drugs”). Population approaches mean policies and strategies that aim to affect rates of drug use in the population as a whole by affecting all potential users without targeting interventions at heavy or problem users. The chapter first provides a schematic history of ideas about and policies toward different types of drug use and addiction. This is followed by a discussion of the key policy themes often extracted from addiction neuroscience research and a consideration of how they may be used to inform the development of drug policies in the twenty-first century.

A SCHEMATIC HISTORY OF PSYCHOACTIVE SUBSTANCE USE

Throughout recorded history, humans have used psychoactive substances—substances taken into the body that affect brain function, cognition and mood. There have been a wide variety of reasons for such use. Often initial uses were medicinal (Bruun, 1986), but users found that these substances had a variety of other human use values that arose from their psychoactive and physical properties. These could include intoxication, increased wakefulness or endurance, elevated mood, nutrition, as a solvent, as a symbol of sociability and commensality, as a sacrament, as an indication of lifestyle, and so on (Mäkelä, 1983; Room et al., 2002, p. 82).

In traditional and village societies, the supply of psychoactive substances was usually limited by seasonal scarcity. Supplies were accumulated or prepared for occasional use, often on festival days, or scarce supplies were reserved for the use of those in powerful or special social roles. Depending on the cultural circumstances, there were often some users who were recognized as habitual heavy users and who might, as a result, be socially marginalized as figures of fun. The concept of addictive drug use only became common in the wake of the European Enlightenment and industrialization of the production of psychoactive drugs, such as distilled spirits.

The industrialization, commercialization and globalization that accompanied the expansion of European empires in the last 500 years radically changed the distribution and availability of psychoactive substances (Courtwright, 2001). European empires and settler societies for a long time supported the expansion of the availability and marketing of
psychoactive substances, even though overuse of these substances was well recognized to produce health and social problems in some users.

Psychoactive substances have been accurately described as the “glue of empires” (Courtwright, 2001; Room, 1985). In European home markets, excise taxes on alcohol and tobacco were the mainstays of state finances in the days before income tax. In most places, spirits, fortified wines and tobacco were “trade goods” exploited for commercial and imperial advantage. In Asia, the opium trade was the principal source of revenue for the British government of India, and a profitable business in all colonial empires in Asia.

The Emergence of a Modern Response in the Late Nineteenth Century

Until the middle of the nineteenth century, imperial governments’ main interest in controlling the market in psychoactive substances was in extracting the maximum revenue (the “surplus value”) from their human use via taxation. Things began to change with the advent of grassroots temperance movements. These movements were initially concerned with alcohol, particularly in Britain and its settler societies, such as the USA. The initial temperance impulse took the form of mutual help for problem users among craftsmen but quite quickly the movement began to see government policies as facilitating intemperance and also as potential instruments for producing temperance (Blocker, 1988). By the late nineteenth century, the attention of the temperance movement in Britain and the USA had expanded to other psychoactive substances, specifically the opium trade that Britain had forced on China after the Opium Wars in the early part of the nineteenth century (Gerritsen, 2000).

Around this time, ideas that anticipated some of today’s neuroscience approaches to psychoactive substances began to appear. Early family studies found that there were apparently inherited dispositions to develop “inebriety” (habitual drunkenness). This prompted hypotheses that there were individual differences in the biological ability to “handle” intoxicating substances (Crowe, 1985). Related investigations found large differences between ethnic groups in rates of inebriety, for instance in the urban USA of the 1890s (Room, 1968). Social Darwinist and racialist ideas of the time often distinguished between “civilized” and “primitive” peoples, defining the latter as requiring protective restrictions on access to alcohol or other drugs (Lind, 1917). Meanwhile, other lines of research suggested that the human brain and other organs were susceptible to be damaged by long-term heavy alcohol use.

A century ago, then, two competing themes were already established in biomedical studies of the effects of alcohol and other drug use. On the one hand, there was the idea that humans shared a general susceptibility
to be damaged by using alcohol and other psychoactive substances. This suggested the need for policy measures that applied to everyone. On the other hand, the identification of individual differences in susceptibility to alcohol tended to suggest that policy measures to reduce drug-related harm need apply only to some. Some temperance thinkers attempted to resolve the issue by arguing that the most ethical approach was for the insusceptible to deny themselves the use of these drugs, as a model for or in the interest of protecting their “weaker brothers” (Akin, 2010).

**Two Population-Based Approaches: Prohibitory and Regulatory**

**The Prohibitory Approach**

The second half of the nineteenth century saw the emergence of two rival ideologies about the state’s role in reducing harm from psychoactive substances: prohibition and regulation (often called “control”). These were approximately aligned with the two themes noted in the biomedical literature.

The prohibition approach argued that the one sure way to rid human-kind of problems arising from the use of any particular psychoactive substance was to ban its use for any purpose other than as a medicine, where this was warranted. This whole-population approach was first developed for alcohol. It made its first breakthrough when the US state of Maine adopted a prohibition law in 1851. In the later nineteenth century, the prohibition solution became established as the policy for colonized peoples in European colonies and settler societies, particularly in Africa, North America, Australia and Oceania. The first international drug control treaty, adopted in 1889–90, prohibited the supply of “trade spirits” to native peoples in a wide central band of Africa (Bruun, Pan, & Rexed, 1975).

In the 1910s and 1920s national alcohol prohibition was adopted in 13 self-governing countries, partly as an extension of wartime restrictions on alcohol production and sale (Schrad, 2010). It was abandoned in the 1920s and 1930s in one country after another, although it left behind in many places “dry” states, provinces or counties, a few of which remain so today. A second wave of state alcohol prohibition, much less discussed, occurred in Muslim societies as they became self-governing in the last 65 years.

Apart from in Muslim societies, the movement for alcohol prohibition failed politically in the long run. The huge illicit markets and other social disruption that prohibition generated came to be seen as outweighing the health gains, at least in the short term, that alcohol prohibition brought (Gerstein, 1981, p. 195; Hall, 2010; Levine, 1985).

By 1900 the temperance movement’s concerns about psychoactive substances had extended beyond alcohol to tobacco. Here, too, prohibitions of cigarettes were introduced in the early 1900s, but only in a few
US states, and not for long. Temperance advocates had more success with other psychoactive substances, particularly the opiates. An initial international treaty in 1912 on opium and its derivatives, which was at least in part motivated by desires to rein in European empire building (Carstairs, 2005), provided the base for the construction of an international prohibition regime in the succeeding century.

Until the 1960s this regime focused on drugs derived from three plants—opium poppies, coca bushes and cannabis plants—all of which were grown and primarily used in poor countries. In response to the rise of drug-using youth cultures in wealthy industrialized countries, the international drug control regime was extended to industrially synthesized drugs by a 1971 treaty. By 1995, the international prohibition regime had expanded to include 282 psychoactive substances and precursor substances (Bayer & Ghodse, 1999). It has since further expanded its scope.

Between 1928 and 1938, the size of recorded world trade in opium derivatives and cocaine fell substantially (Donnelly, 1992). This was arguably a success of the prohibition system, although the global depression and a general decline in international trade are alternative explanations. The fully developed system of the last half-century cannot be regarded as a success, if the criteria are eliminating non-medical use of controlled substances or decreasing the size of the illicit market (Babor, Caulkins, et al., 2010, pp. 218–219).

The primary activities of the international system have come to be defined around the criminalization of illicit markets and enforcement of these laws. It is very hard to show any lasting effects of this strategy (Babor, Caulkins, et al., 2010, pp. 139–162). Meanwhile, those incarcerated for drug law offenses have become a large proportion of the prison population in many countries, imposing large burdens of privation and marginalization. Given the lack of evidence that the toughness with which prohibition laws against use are enforced reduces rates of use or addiction, it is hard to see how reductions in harms from drug use outweigh the misery caused by such responses to drug use in any cost–benefit assessment of the international prohibition regime.

The main lesson from global experience with prohibitions of psychoactive substances seems to be that legal prohibitions of use across broad populations and geography are most successful when there is widespread and strong social support for the community norm of abstinence from the substance. However, if such normative consensus exists, there are doubts about the need for prohibitions on use, although prohibitions on marketing and promotion may be needed to buttress social norms. In Muslim parts of the former Soviet Union, for example, there was little drinking despite the lack of any prohibition on alcohol use.

The experience with alcohol also suggests that local prohibitions may produce good results in particular circumstances in local areas, if the
area is geographically isolated (Room et al., 2002, pp. 192–200). Such arrangements are, however, often politically unstable.

**The Market Regulation Approach**

State regulation of the markets for psychoactive substances with the primary objectives of protecting public health or well-being also emerged in the second half of the nineteenth century. As noted, there were already long traditions of states regulating alcohol and tobacco markets with a primary aim of gathering excise revenue. There was also a long tradition, for instance in Britain, of local alcohol licensing controls that were primarily oriented to protecting public order (Nicholls, 2009). What was new in the later nineteenth century was the new primary objective of policy.

In the case of alcohol, this period saw the implementation of high tax regimes, and restrictions on the number of outlets and hours and days of sale as ways of limiting population-level consumption. In some places, government monopoly retail shops, and monopolies on production and wholesaling, were the means used to implement these limits (Room, 1993). In other places the limits were imposed through a licensing system on private sellers (Babor, Caetano et al., 2010, pp. 128–138).

In the case of psychoactive substances available from apothecaries or pharmacists, the nineteenth century also saw the beginnings of prescription systems. These required certification by a doctor that the patient had a medical need for the substance. These systems were not fully implemented in most countries until the twentieth century and remain to be implemented in some developing countries (Babor, Caulkins et al., 2010).

What these various measures share is the aim of controlling (or eliminating) commercial interests in the market rather than attempting to control the individual drinker or drug taker. A tavern-keeper could be persuaded to limit sales on threat of losing his or her livelihood if the license to sell was withdrawn. Such administrative controls tend to be more effective, in part because they are easier to enforce than attempting to control drinking problems by threatening to punish individual drinkers. The evidence from the modern research literature is that raising alcohol taxes and limiting the availability of alcohol are at least moderately effective in reducing levels of alcohol consumption and rates of alcohol-related problems (Babor, Caetano et al., 2010, pp. 109–138). The effectiveness of regulatory controls on licensed retail sellers has also been shown in experience with the Dutch “coffee shops” as retail sellers of cannabis (MacCoun & Reuter, 2001, pp. 238–264), in pharmacist sales of over-the-counter drugs (Babor, Caulkins et al., 2010, pp. 182–183), and in regulatory controls on smoking in bars and restaurants.

A common objection to these relatively “soft” measures is that they solely or primarily affect moderate users, and have no effect on heavy
users or “addicts”. The argument is usually made on a priori grounds, rather than based on evidence. An individual who is “addicted” is seen as being inherently unresponsive to environmental cues or nudges. The evidence indicates that the contrary is the case: there is strong evidence from a variety of sources, including early experiments which showed that the drinking of inpatient alcoholics was responsive to economic incentives (Mello & Mendelson, 1972). More recent evidence from a variety of economic analyses supports this position (Babor, Caetano et al., 2010, pp. 121–124).

The major drawback to a regulatory system through licensing is that the commercial interests it controls have a deep interest in limiting the activities and effectiveness of the system. Such systems operate under threat of “regulatory capture” by the interests that they are designed to regulate; their effectiveness depends on vigilance and a preparedness by governments to “push back” in the general public interest.

Individualized Population Approaches

There is also a long history of various measures that aim to control or punish (and thus deter) individual substance users from harming themselves or others. The objectives of these approaches may vary from limiting alcohol consumption to preventing alcohol-related harms. Included in this category are such measures as drink-driving and drugged-driving laws and laws against public substance use or intoxication, with criminal penalties for failure to comply. Also included are banning individuals from using drugs or restrictions on their right to purchase or use drugs.

There is a rich history and variety of such measures. They have often been seen as offering the path of least political resistance for legislators who wish to be seen to be “doing something” about expressing community concerns about specific types of substance use.

In the case of drink-driving, the evidence is strong that deterrence—setting a maximum allowed blood-alcohol level routinely enforced by police—is effective in reducing rates of driving injuries and deaths (Babor, Caetano et al., 2010, pp. 169–174). This is assumed to be true for drugged-driving, although so far in the absence of direct evidence. In the societies in which the studies have been done, the majority of automobile drivers who might be inclined to drink and drive are adults with a considerable stake in protecting their reputations and their jobs. These will be most easily deterred by threats of criminal processing.

There is much less supportive evidence for the efficacy of laws against public intoxication or substance use. A large proportion of people arrested for public drunkenness in many places consists of socially marginalized, often homeless street drinkers, who are not significantly deterred by threats of being further marginalized. Public drunkenness
was made a criminal offense in many European and English-speaking countries in the course of the nineteenth century; as a result, in many places arrests for public drunkenness became and remained for many years the most common type of arrest.

In the 1960s and 1970s, policies changed. Police and judges handling public drunkenness arrests became disturbed by the futility of the “revolving door” of arrest and release. They made common cause with civil liberties campaigners in many places to decriminalize public drunkenness (for the USA, see Room, 1976). There was no consistent evidence that these changes caused any perturbation in rates of public intoxication. Likewise, the available evidence suggests that neither decriminalization nor recriminalization of illicit drug possession and use appears to affect population rates of use (Babor, Caulkins et al., 2010, pp. 167–177; Room, Fischer, Hall, Lenton, & Reuter, 2010, pp. 109–124).

Prescription systems may be regarded as an administrative individualized control system in which psychoactive substances are available only on prescription. The doctor or other prescriber is licensed by the state to control the individual patient’s access to the substance by agreeing that the person has a valid health-enhancing reason to use the drug. As in the case of alcohol controls, there is good evidence that doctors’ prescribing behavior can be influenced by regulatory incentives. Evidence is scant on the effectiveness of the often-preferred alternative approach of trying to deter patients from “doctor-shopping” (Babor, Caulkins et al., 2010, pp. 183–197).

Administrative individualized control systems were also used in a number of regulatory systems for alcohol that were set up as alternatives to or replacements for prohibition between the 1910s and the 1940s. Some of these systems continued into the 1960s or 1970s. Sweden, for example, had an alcohol rationing system in which each potential purchaser of alcohol was evaluated and assigned a monthly maximum amount of spirits which could be purchased in the range of 0–4 liters. Evaluations were based on drinking history, as well as affluence, gender and marital status (Bruun & Frånberg, 1985). Finland had a less bureaucratized version of “buyer surveillance” which included home visits by social workers to establish whether and what limit on purchases should be imposed (Järvinen, 1981). In Ontario’s system, individualized bans or limits could be imposed by inspectors and other store personnel and enforced through the use of an IBM computer-card recording and tracking system (Thompson & Genosko, 2009). Evaluations of the effectiveness of these individualized controls are sparse, although there was a substantial rise in liver cirrhosis deaths after Sweden’s system of setting a maximum monthly ration of spirits was abolished (Norström, 1987).

The effectiveness of individualized approaches to influencing population alcohol and drug use is quite mixed. There is strong evidence of the
effectiveness of drink-driving enforcement, but enforcement of restrictions on public intoxication or substance use at best moves the public nuisance around while having little effect on patterns or amounts of use. For individualized regulatory controls, where the state controlled access to the cheapest form of alcohol, as in the retail-monopoly systems of Sweden, Finland and Ontario, there is evidence of the effectiveness of rationing amounts allowed (see also Schechter, 1986), but the effectiveness of individualized bans on purchasing alcohol is more open to question.

Ethics and Population Approaches

Many ethical assumptions underlie public health approaches to controlling psychoactive substance use. By and large, these policies take no account of the pleasure and psychological benefit derived from drug use. The emphasis is solely on minimizing the harms of use. This emphasis can be justified so long as governments do not actively interfere with individual decisions about whether to use a drug or not. The government’s responsibility, it can be argued, is to preserve health and well-being by minimizing these harms; it is not to intervene in individuals’ decisions about how to lead the good life (Room, 2000). Public health policies are much harder to justify when the government actively intervenes to prevent individuals making choices, for instance by criminalizing the use of some substances.

In global burden of disease (GBD) calculations, addiction (“dependence”, in the current terminology) is assumed to be an unmitigated evil. Dependence is measured in general population studies by responses to questions about what psychiatrists have defined as criteria for dependence; for instance, the respondent reports using more of the substance than formerly to get the same effect, continuing to use the substance despite knowledge that it has caused harm, having given up some other activities because of substance use, and so on. For a 25-year-old university graduate with a demanding job, these answers may primarily indicate a series of lifestyle choices. But in the GBD context, positive answers to three or more of these questions qualify the respondent as drug dependent. A substantially impaired quality of life score is then assigned, on the assumption that people meeting the criteria for “dependence” in a general population sample have the same quality of life as the highly marginalized inpatients in alcohol and drug treatment services. These technical procedures have built into them ethical assumptions and choices that may markedly differ from the way that the respondent may see his or her life situation.

On the other hand, population perspectives on alcohol and other drug use in the modern era have ethical considerations built into them that are easily forgotten by those approaching substance use policies from
a clinical or a free-market perspective. Researchers with sociological or criminological training played an important role in producing the paradigm shift in alcohol policy discourse from a focus on “alcoholism” to the “total consumption” or “new public health” perspective (Room, 2009). In the 1960s and 1970s, a major criticism of social policy by sociologists and criminologists was that the process of singling individuals out for special treatment because of their deviant behavior was a negative form of social labeling that often led to stigmatization. Terms such as “secondary deviance” encapsulated the sociological insight that the individualized processing and labeling of some drug users in itself contributed to the further alienation of the individual from “normality”.

These issues remain alive in social attitudes toward psychoactive substance use. In a World Health Organization (WHO) collaborative international study in 14 societies, drug addiction was universally ranked among the most stigmatized of the 18 disabilities or disease conditions considered. Alcoholism was almost universally stigmatized (Room, Rehm, Trotter, Paglia, & Üstün, 2001, p. 276). Potential clients often resist attending specialized alcohol or drug treatment services because they believe that the knowledge that they have entered such treatment will add to the stigma (Room, 2005).

The new total consumption perspective was put forward in the 1970s on ethical grounds rather than only on the basis of the potential effectiveness of such measures. Regulatory controls were seen as having the advantage of a “focus on the population at large, rather than on single individuals”, in “contrast with criminal-law and treatment strategies”.

Strategies that single out individuals—whether for correction, treatment or rehabilitation—tend to involve the large and continuing costs of state-funded agencies and professional personnel. The labeling of individuals as part of such strategies also carries social costs in that it tends to be applied to those with the fewest social resources to protect themselves (Bruun, Edwards et al., 1975, p. 67).

The main argument offered against population-wide policies is that such policies are unfair to the moderate trouble-free drinker, who is asked to pay more or travel farther to get his or her supplies. People should be allowed to make their choices in a free and untrammeled market, according to arguments that appeal to “consumer sovereignty”. The preferred alternative is to enforce criminal penalties against those whose choices transgress social boundaries. As Catlin pointed out 80 years ago, these arguments are especially congenial to alcohol industry interests:

Associations representative of the brewing and distilling interests have repeatedly urged that nothing would give them more satisfaction than to see the penalties increased against drunkards whose topings only serve to bring a legitimate trade
into disrepute, but that the honest man should be free to have his glass of beer or whisky unhampered.…

As Catlin puts the counter-argument:

*It is probably not equitable moral practice and it is certainly not effective law to penalize a man solely and severely for overstepping a boundary line which not even the medical profession is able to define with any precision and which varies from individual to individual* (Catlin, 1931, p. 244).

**The Interplay of Population Perspectives and Neuroscience**

Neuroscience research on addiction proceeds from two alternative premises, with rather little interplay between the respective research literatures (WHO, 2004). Studies of the neural pathways on which psychoactive substances act in the brain tend to assume the psychic unity of humankind (and implicitly that of mammals in general, since much of this research depends on animal models of human addiction). In this perspective, all humans share common biological pathways on which psychoactive substances act, and presumably are similarly vulnerable to their adverse effects. A crucial contribution of this literature to ethical discussions of psychoactive substances and drug policy is its finding that the pathways of action for psychoactive substances are shared by a variety of other rewarding human activities that support individual and species survival: eating, feeling affection, and sexuality. Although official anti-drug rhetoric often characterizes these findings as evidence that drugs “hijack” the pleasure centers of the brain, the findings have also been used by those of more liberal inclination to normalize drug use by arguing that psychoactive substance use is just one among many activities in which humans find pleasure.

The other premise of much genetic research on psychoactive substances is that individuals differ in their responses to them, and in their susceptibility to experience any adverse consequences of their use. This is the premise of a large literature on genetic differences in addiction risk and responses to the effects of psychoactive substances. The ethical implications of this aspect of neuroscience research are more troublesome from a sociological or population-level perspective. These findings seem to invite efforts to genetically type individuals and single out those at higher risk for special treatment. Such differentiations are open to the sociological criticisms of the adverse social effects that differential handling and treatment can have. They also are congenial to the views of some drug users that “I should be able to use this substance, because I can handle it, while you cannot”; views that raise serious ethical questions.
Until recently, there was a third characteristic of the neuroscience literature relevant to population perspectives and to thinking about drug policies. Psychopharmacologists and others interested in the neuroscience of psychoactive substances showed little scientific interest in the international drug control system or in legislation nearly everywhere that distinguished between alcohol and tobacco and illicit drugs, those controlled by the international system whose use was forbidden on pain of imprisonment. The last attempt by psychopharmacologists to provide a science-based justification for what drugs were controlled was in the Report of the WHO Expert Committee on Drug Dependence for 1955. After that, all such efforts were abandoned (Room, 1998).

For many years thereafter, psychopharmacologists remained silent about the relative harmfulness of licit and illicit substances; it was scientists from other disciplines who rashly stepped forward to make such comparisons (e.g. Hall, Room, & Bondy, 1999). In Britain, the psychopharmacologists have recently ventured into this contested territory, both by contributing to the scientific literature (Nutt, King, Saulsbury, & Blakemore, 2007) and by participating in the political process. This has led to an attempt to derive a single scale of harm caused by all drugs that is universally applicable across all cultures. This is somewhat problematic from a social science perspective, since harms associated with a given amount of use vary according to cultural circumstances (Room & Lubman, 2010). These intercultural variations need to be taken into account in considering the international drug conventions, the schedules of which share the psychopharmacologists’ assumption that there is a single universally applicable scale of harm for all drugs.

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V. PUBLIC POLICY AND LEGAL ISSUES
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INTRODUCTION

The law regulates addiction in two primary ways: by limiting access to controlled substances and by criminal and civil law doctrines that pertain to addicts. The general ability of the state to legally regulate
potentially harmful commodities and behaviors, including by criminal law prohibitions and punishment, is an unquestionably justifiable exercise of its police power authority to act for the benefit of public health, safety and welfare. The public policy issues are whether legal regulation is wise in a specific context and whether it may conflict with individual rights.

This chapter first addresses the basic definitional and conceptual issues concerning addiction that must be clarified to make progress. Then it turns to the justification of substance regulation in the USA and to the public policy issues themselves. The author suggests that the right to use substances recreationally, even at the risk of severe negative consequences such as addiction, is weighty and that regulation of substances and addiction-related behavior by the criminal law is problematic. Next, the chapter considers whether addiction should be a mitigating or excusing condition for crime and whether addicts can be involuntarily civilly committed. The current state of the law is described and it is proposed that, in most cases, addiction should not mitigate or excuse criminal offending and that addicts should not be civilly committed. A final section briefly considers sensible social and criminal justice policies that could alleviate the costs of addiction, even if society does not decriminalize drugs or excuse addicts.

**CLARIFICATIONS AND ASSUMPTIONS ABOUT DRUGS AND ADDICTION**

Virtually every statement that can be made about drugs and addiction, whether it is factual or normative, is contestable. In this section, the author will try to remain as neutral as possible.

Despite common belief to the contrary, there is no consensual definition either of a drug, which is the most common cause of an addiction, or of addiction, but clarity about both is necessary to discuss legal regulation sensibly. Let us start with the definition of a drug or a substance. Virtually all definitions are vague or overinclusive, permitting categorization as a drug of almost any substance that may be consumed. Some definitions are circularly dependent on legal regulations. If a law regulating “drugs” includes a particular substance within its ambit, it is a drug or a “controlled substance”, that is, a substance that cannot be consumed except under limited conditions such as a physician’s prescription (Drug Abuse Prevention and Control Act, 2010, Section 802(6)). If it is not so included, it is not a drug for legal purposes. Vague, overinclusive and circular definitions cannot sensibly guide public policy, especially when the state’s awesome power to blame and punish for illegitimate use is dependent on the definition.
Definitional problems concerning drugs and regulation cannot be entirely avoided by using allegedly scientific or value-neutral medical/therapeutic or nutritional concepts. Concepts such as disease and therapy are themselves value laden and inevitably problematic and controversial. Many substances that have unquestionably legitimate medical or nutritional uses can also be used for non-medical or non-nutritional purposes that may be of questionable legitimacy. Finally, definitions that define a substance as a drug in terms of its intended use rather than in terms of its inherent properties obscure important questions of legitimate use.

Despite the conceptual problems attending the definition of a drug, a loose but common-sense definition is possible for discussing addiction and regulation. This common-sense definition would be substances that can be consumed recreationally, that is, primarily to produce pleasure, whether or not those substances have other legitimate uses. For the purpose of understanding the current debate about addiction and regulation, recreational drugs can be defined as consumable substances that: (1) can affect mood, cognition and behavior in pleasurable ways; (2) can be used primarily for recreation, including relaxation, excitement and pleasurable states generally; and (3) can be used so as to endanger the user and others. Although admittedly loose, this definition covers both legal recreational substances, such as ethanol (alcohol), nicotine and caffeine, and substances that are illegal either per se or if they are not properly prescribed by physicians, such as marijuana, cocaine, opiates, e.g., heroin, barbiturates, amphetamines, phencyclidine (PCP), and the like. Let us defer the definition of an addictive drug until we have considered the nature of addiction.

The primary criteria of addiction commonly employed at present are behavioral, namely, persistent drug seeking and using, especially compulsively, in the face of negative consequences (Morse, 2009). The neural mechanisms of addiction are debatable, but are being intensively investigated and will probably be uncovered (Hyman, 2007), and environmental variables play an important role in explaining addictive behavior (Kalant, 2010).

The most important terms for legal purposes are “compulsive” and “negative consequences”. There is no gold-standard definition of or psychological or biological test for compulsivity, which also must be demonstrated behaviorally. There are extremely suggestive laboratory findings, especially with non-human animals (e.g. Everitt & Robbins, 2005), but none is yet diagnostic for humans. The usual behavioral criteria for compulsion are both subjective and objective. Addicts commonly report feelings of craving or that they have lost control or cannot help themselves. If the agent persists in seeking and using despite ruinous medical, social and legal consequences, and despite an alleged desire to stop, we infer
based on common sense that the person must be acting under compulsion. It seems that there is no other way to explain the behavior, but it is not based on rigorous tests of a well-validated concept. Negative consequences, both internalities and externalities, are not necessarily part of the definition of addiction because, depending on the circumstances, it is possible to be a highly functioning addict who does not suffer or impose substantial negative consequences. Contingent social norms and expectations play a role in explaining how negative the consequences must be, but addiction often has severely negative consequences (e.g. overdose, cancer, psychosis), independent of social norms and expectations.

There are many findings about the biology and psychology of addicts that differentiate this group from non-addicts, but none of these findings is independently diagnostic. Addiction must be demonstrated behaviorally. Although the characterization of addiction as a “chronic and relapsing brain disease” is widely used today, it is not justified by the data (Heyman, 2009). Brain causation and brain differences do not per se make associated behaviors the signs or symptoms of a disease. All behavior has brain causes and one would expect brain differences between any two groups exhibiting different behaviors. Moreover, the relapse data were not gathered on random samples of addicts, and characterizing a return to maladaptive behavior as a “relapse” begs the question of whether the behavior is the sign or a symptom of a disease. The latter must be proven independently (Fingarette & Hasse, 1979). Whether addiction should be considered a disease, a moral failure, or sometimes both, is still an open question. Even if addicts have difficulty controlling their behavior, they are not zombies or automatons; they act intentionally to satisfy their desire to seek and to use drugs (Hyman, 2007; Morse, 2000, 2007, 2009).

Using the definition just provided, an addictive drug would be one that has a substantial potential to cause users to persistently seek and use the substance, especially compulsively and with negative consequences. Most users of even the most allegedly addictive substances do not become addicts, but some substances increase the risk. And, as noted, whether one moves from casual recreational use or medical use to addiction is influenced by the agent’s set (psychological expectations) and by the setting (the environment and its cues) (Zinberg, 1986). The substance itself does not account for all the variance in explaining addiction. We would like to think, and it is probably true, that some substances are particularly addictive, holding the agent’s set and setting constant, but it is extremely difficult empirically to disentangle these causal variables.

A fascinating, fraught question is whether addiction should be limited to substances. After all, large numbers of people engage persistently and apparently compulsively in various activities, often at quite negative costs. Gambling is the most obvious example. If there are some activities
or non-drug substances that can produce the same “addictive behavior” and negative consequences as drugs, then legal regulation should perhaps be similar by analogy. The author believes for many reasons that the concept of addiction should be expanded beyond drugs, but the analysis in this chapter will be confined to drug-related addictions.

**THE JUSTIFICATION FOR LEGAL REGULATION: THE HARM PRINCIPLE AND ITS LIMITS**

The general justification for the legal regulation of addictive substances is best summed up in the preamble to the Federal Drug Abuse Prevention and Control Act:

*The Congress makes the following findings and declarations:*

1. Many of the drugs included within this subchapter have a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.
2. The illegal importation, manufacture, distribution, and possession and improper use of controlled substances have a substantial and detrimental effect on the health and general welfare of the American people. *(2010, Sections 801(1) & (2)).*

Just so. Who would deny that drugs can have beneficial effects, that some recreational (and medical) drug use leads to addiction, and that addicts often harm themselves and others? Even those recreational, “uncontrolled” addictive drugs that are legal to import, manufacture, distribute, possess, and use, such as nicotine and ethanol, are heavily regulated and violations of those regulations are often criminalized. Few people object to civil regulation of potentially dangerous substances, such as laws concerning safe manufacture, taxation and public use. The real debate among all but the most libertarian theorists is therefore about the use of criminal law to prevent people from having unauthorized access to controlled substances *(Husak, 2008)*. Therefore, this discussion will be limited to that topic, although it is clear that both nicotine and ethanol use create vast internalities and externalities.

The state’s police power to apprehend, prosecute, convict and punish citizens is the most awesome and affictive power it exercises. Infliction of such pain requires substantial justification in liberal democracies that seek to protect individual rights and liberty. Affictive and expensive criminal regulation should be avoided in favor of less intrusive means unless the harm is great, punishment would be deserved for causing it, and criminal prohibition seems necessary to reduce the level of harm and will not unduly impose on other important interests. Criminal law
Theorists term these limitations on the state’s power to criminalize the “harm principle” (Feinberg, 1984). For example, intentionally inflicting emotional cruelty on others is morally despicable, but such behavior is not criminalized because the harm is insufficient to justify criminal punishment. Socialization by families, religious organizations and schools is reasonably effective to limit such conduct, and regulating such behavior by criminal law might intrude on protected liberties, such as the right to free speech.

There is little debate about the state’s justification for prohibiting and punishing traditional crimes against the person, such as homicide and forcible rape, and against property, such as theft and arson, that cause grievous harm. Although individual liberties are precious, no citizen has a right to kill, rape, steal or burn the property of others for private advantage, and the criminal sanction seems morally appropriate and necessary to curb such behavior. Societies can disagree about the scope of appropriate criminalization. For example, there may be reasonable dispute about how much creation of homicidal risk should be necessary to warrant criminal penalties in addition to civil damages or how severely arson should be punished, but the state’s power to criminalize great harm to others is uncontroversial.

The harm principle suggests caution before criminalization, however, under the following conditions: when the harm is primarily inflicted on oneself; when the harm is primarily moral and not physical, psychological or economic; when using criminal law to prevent the harm appears to intrude on important rights; or when criminalization appears unnecessary to effectively reduce the harmful behavior. In liberal societies, the right of the state to criminally prohibit actions that harm primarily the actor (so-called legal paternalism or legal moralism) is more controversial than the right to prohibit harm to others. Respect for individual liberty and autonomy generally entails that citizens have greater liberty to harm themselves than to harm others (Feinberg, 1986, 1988). Such liberty is arguably most extensive and the state’s right to regulate criminally most questionable when the threatened harm to self is apparently solely moral and no other harm to self or to others can be discerned. Most liberal theorists reject the state’s power to use criminal law solely for the purpose of enhancing the moral perfection of its citizens. Such goals are arguably not the business of the state and should be achieved by other, less intrusive means.

Even within liberal regimes, the permissible scope of paternalism and moralism may vary, although both require more substantial justification than criminalizing harm to others. Consideration of the state’s justifiable use of criminal law to regulate recreational drug use because it may lead to addiction, however, must attend to the appropriate limits of state power within a particular political regime. The remainder of this chapter
assumes that the regime considering its policies concerning drugs and addiction is liberal.

**DRUG USE AND RIGHTS**

It is often assumed that there is no right, no liberty interest to use drugs recreationally, and, consequently, that the state has appropriate authority to use criminal law to prevent such use. Such an assumption is seldom supported with cogent argument, however, and it is not easy to give compelling moral and political reasons for rejecting such a right, even if exercise of that right may sometimes lead to ruinous addiction (Husak, 1992).

Sensible discussion must begin with the recognition that people take drugs recreationally because they desire the pleasurable effects produced by consuming substances that alter mood and cognition. It seems clear, however, that the state has no justifiable interest in criminal prohibition simply because the primary or even sole goal of behavior is pleasure or because the behavior involves consumption of a substance that can alter mood or cognition. Many people might consider it wrong to engage in activities solely for pleasure, especially if alteration of mood and cognition were involved and there were some danger of dependence on the activity, but a liberal society does not interfere with a citizen’s right to make autonomous choices to engage in such potentially dangerous activities. Citizens surely have a prima facie right to seek pleasure for its own sake, and it is very difficult to imagine a secular, liberal argument suggesting that such a goal is immoral or harmful per se, even if some danger might sometimes be involved.

For example, suppose that a citizen engages in meditation solely for recreational purposes. No persuasive liberal moral or political theory would justify criminal prohibition of meditation, even if some citizens became dependent on meditating. Recreational drug use involves the consumption of a substance, but it is hard to imagine why the source of the recreation alone should make a difference. Currently illegal drugs produce pleasure by altering mood and cognition, but so do many legal activities, including meditation, mountain climbing, riding motorcycles, playing bridge, and the consumption of legal drugs such as caffeine, ethanol and nicotine. The state’s right to criminalize alterations of mood and cognition per se is questionable because such alterations are not per se immoral or harmful.

Citizens appear to have a prima facie right to engage in recreational alteration of mood and cognition by drug consumption and the state surely has the burden of justifying criminal prohibition of such recreation by powerful arguments. No right is absolute, however, and the possible
right to pursue recreational drug use must yield to a powerful state interest in preventing such use, especially the undoubted state interest in curtailing the threat that drugs will cause substantial harm by producing addiction, drug-related harms and their associated costs. Nonetheless, harm limitation counsels caution before using the criminal law.

Illegal drug use is often considered a “crime without a victim” because the person potentially most harmed—the user—in effect consents to the threat. Indeed, virtually no recreational user, including those who begin use in adolescence, is unaware of the risk of addiction. Of course, younger people often tend to be foolish risk takers who do not sufficiently appreciate potential dangers and anyone can be in denial about the risks to him or herself. However, everyone is at least intellectually aware of the risk that use may lead to addiction and that virtually no action affects only the agent. As a result of its effect on mental states and of its potential to produce addiction, recreational drug use sometimes threatens families and communities with economic, psychological and physical harms. Many of these harms may be paradoxically produced or enhanced by criminal prohibition itself, but many surely are not. Moreover, harms one consents to suffer are nonetheless harms. The question is whether the harms to others or to self that drugs produce are sufficient to trump the individual’s prima facie right to use drugs and thus to warrant criminalization of drug use.

The next section on cost–benefit analysis considers the harms drugs produce, but liberal societies often permit dangerous behavior in order to protect the right of citizens to pursue their own visions of how life should be led. Such dangerous behavior is regulated non-criminally, if at all. For example, consider the immense costs to many users and to society at large that flow from the consumption of ethanol and nicotine. Again, the state can appropriately regulate many aspects of such substance consumption to reduce the consequent harms, including the use of criminal law for egregiously harmful forms of misuse, such as drunk-driving. For many reasons, however, importantly including the right to make one’s own choices unencumbered by undue state interference, criminal prohibition of the consumption of ethanol and nicotine by the state is considered unwarranted and the attempt to prohibit the former in the USA was a failed social policy, although it admittedly produced some health benefits.

If drugs produce great harms and no one has a right to use drugs recreationally, or if that right is insubstantial at best, then the only question for analysis is whether criminal regulation is justified by the benefits it achieves. However, if there is a weighty liberty interest in making choices about how to live one’s life, including potentially unwise and dangerous choices about drugs, then the potential creation of harm is insufficient per se to warrant criminalization. Some dangerous behaviors
must be permitted to protect liberty and must be regulated primarily civ-
illy, including money damages and other impositions when addiction
produces externalities. Any adequate analysis of the regulation of drug
use by criminal law must therefore include consideration of the strength
of the liberty interest, and it appears that in liberal societies, the right is
substantial. Empirical analysis of the consequences of various behaviors
under various regulatory regimes is necessary to inform decisions about
the appropriate scope of criminalization and decriminalization of drugs,
but the question of rights cannot be avoided.

**COST–BENEFIT ANALYSIS OF CRIMINAL REGULATION OF DRUG USE**

This section of the article is a composite drawn from a number of lead-
ing commentators. For those who oppose decriminalization, see Falco
(1992), Jacobs (1990) and Wilson (1990). For those who propose decrimi-
nalization, see Nadelmann (1989), Husak (2002) and Global Commission
on Drug Policy (2011). For non-partisan analyses that reach different con-
clusions, see Husak (1992), Kleiman (1992), MacCoun and Reuter (2001),

The outcome of criminal justice regulation of drug use will be inde-
terminate because many of the data are unavailable or unreliable, or
fluctuate, and because the costs and benefits of an alternative regime
are speculative. Also, historical and cross-cultural comparisons are
of extremely limited value because social variables, which vary rad-
cially intertemporally within a society and across different societies,
immensely affect the consequences of drug use and regulation. The rest
of this section raises a number of issues, but readers should recognize
that this is an intensely complicated issue and that this chapter can only
touch on some of the considerations.

**Harms from Drugs and the Benefits of Criminalization**

Much debate about criminal regulation mistakes the probability and
extent of the risks drugs pose. For example, most people who use most
drugs recreationally do not become addicted and the moderate rec-
reational use of drugs is not per se dangerous if the drug is pure and
properly consumed. Nonetheless, the ease of access to drugs following
decriminalization would surely increase the prevalence of use, abuse
and addiction, and their further harmful consequences. The harms might
be especially great in poorer and minority communities, where the prev-
ance of drug use is no higher than in other communities, but where the
effects have been more devastating. Some responsible observers believe
that decriminalization may effectively destroy poorer and minority communities already ravaged by drug abuse and addiction.

The relation between drug addiction and other criminal activity and health harms is fraught because it is difficult to disentangle the effects of criminalization itself from the independent effects of drug use. Some drugs, especially if used heavily, can substantially impair judgment, facilitate impulsivity and have other effects that increase the risk of criminal offending and other dangerous behavior, such as careless driving, sharing needles for intravenous injection and unprotected sex. Increased drug use, especially heavy use and addiction, will raise the rates of such undesirable behavior.

Criminalization of drugs inhibits use generally and consequent addiction by making production, sale, possession and use more expensive and dangerous and by sending the clearest possible message that drug use is wrong. For example, there might have been both rights-based and consequential reasons to repeal Prohibition in the USA, but the data suggest that consumption and addiction-related diseases such as cirrhosis of the liver both decreased when most alcohol production and sale were illegal. Criminalization also helps to prevent drug use by minors. Although minors regrettabley have access to and consume drugs in a regime of criminalization, ease of access generally would also increase use, as would potential addiction among minors who are already developmentally predisposed to take unwarranted risks.

The use of criminal law to regulate drug use and addiction is obviously not fully successful by any standard and it is immensely expensive, but the proponents of continued criminalization argue that the current regime provides greater benefits than costs and that the unknown benefits, if any, of decriminalization would pale in comparison to the costs of inevitably increased use and abuse.

The Costs of Criminalization

Criminal law enforcement, including imprisonment, is an especially intrusive and expensive form of regulation of any behavior. The cost–benefit critique of criminalization argues that such costs are not outweighed by the benefits because criminal law makes only a small dent in the use of drugs and because criminalization itself creates avoidable harms. The attempt to eradicate drug use by criminal prohibition cannot fully succeed because large numbers of people want recreational drugs for the pleasure or relief they provide, and it is widely recognized that the dangers of drugs are sometimes exaggerated. Given the powerful factors that motivate the desire for drugs, the criminal sanction appears ineffective. The criminal justice system cannot prosecute and imprison more than a tiny fraction of the enormous numbers of people involved in the
illegal drug trade unless the justice system massively diverts resources from other, undisputed criminal law needs and abandons civil liberties protections. The criminal courts of the USA are already clogged with drug cases. It is hard to enforce laws that such large numbers of people wish to violate and that often have no immediate or complaining victim. Furthermore, public hypocrisy about drugs inevitably undermines law enforcement. Western society is not nearly as monolithically anti-drug as many claim, as public policy toward ethanol and nicotine indicates. Even spending vastly more money seemingly will provide only limited benefit. Fluctuations in drug usage appear far more related to major social, cultural and economic forces than to criminal law enforcement. Despite billions spent on drug enforcement each year, undoubted law enforcement successes and the huge numbers of people in prison for drug-related offenses, drugs are still freely available, and in many cases increasingly stronger and cheaper. Of course, the latter observations are open to the interpretation that criminalization is succeeding and forcing dealers to offer better product more cheaply.

Criminalization also threatens its own effectiveness and creates other problems. For example, criminal prohibitions raise the price on a good or service: the so-called “crime tariff”. This ensures that there will be an endless supply of producers and dealers who seek to realize their profits by any means necessary, including violence, and that many users, especially addicts, will be impoverished and driven to a life of further crime simply to support themselves and to obtain drugs. The immense profits facilitate the growth and power of domestic and international organized crime and can be used to corrupt law enforcement and politicians. Criminalization decreases the probability that drug consumption will occur under conditions safest to health. Finally, primary emphasis on criminal law virtually ensures that fewer resources will be devoted to investigating and implementing less intrusive and potentially more effective means to reduce the prevalence of addiction and the other harms it causes.

The Benefits of Decriminalization

Specific decriminalization proposals would produce different benefits, but the potential benefits of decriminalization are the opposites of the costs of criminalization. They include an increase in personal liberty; probable law enforcement cost savings; decrease in the crime, violence and corruption that criminalization produces; increased respect for law enforcement; and increased attention to possibly more effective means, such as education, treatment and civil regulation, to reduce use and consequent addiction and its related harms. However, the relation between drug use and criminal activity is extremely complicated. For example,
drug use has not abated in recent years in the USA, but crime rates, especially violent crime rates, have fallen substantially. Nevertheless, criminalization produces a significant amount of criminal activity by definition and as a consequence. In a regime of decriminalization, criminal law would be used only to prohibit particularly dangerous drug-related activities such as drugged-driving or selling to minors. Such traditional use of the criminal law would receive broad public support.

In the past few decades, there has been a vigorous debate in the USA and Western Europe about criminal law regulation of drug use. Decriminalization has become a “respectable” position. For example, a prestigious international group, the Global Commission on Drug Policy, has issued a report calling for decriminalization (2011). Some countries and localities have engaged in decriminalization experiments or regimes. Nonetheless, criminalization is still the dominant form of regulation and most countries spend far more on law enforcement aimed at preventing all drug use than they do on prevention and treatment programs for drug abuse prevention and treatment.

CRIMINAL RESPONSIBILITY AND INVOLUNTARY CIVIL COMMITMENT

This section considers the criminal responsibility of addicts, diversion from the criminal justice system to specialized drug courts of addicts accused of non-violent crimes and involuntary civil commitment of addicts.

In *Robinson v. California* (1962), the US Supreme Court held that it was unconstitutional to convict and punish a person for being an addict. The rationale was that addiction is simply a status, and it is not fair to blame and punish people in the absence of a culpable act, a rationale that applies to attempted criminalization of any status. In *Powell v. Texas* (1968), the Supreme Court rejected a claim that, roughly, an alcoholic is constitutionally entitled to a “lack of control” defense to disorderly conduct in public as a result of alcoholism. In two later cases, the Court held that states may constitutionally bar defendants from introducing evidence of voluntary intoxication (*Montana v. Egelhoff*, 1996) and mental disorder (*Clark v. Arizona*, 2006) to negate the mental state criteria required by the definitions of crimes (mens rea), criteria that the Constitution requires the prosecution to prove beyond a reasonable doubt. The Supreme Court has never held that the defense of legal insanity is constitutionally required and it has upheld the constitutionality of the narrowest possible insanity defense (*Clark v. Arizona*, 2006). In sum, there are few constitutional limits on criminal responsibility and jurisdictions are free to adopt virtually any responsibility doctrines they wish,
including those that may be more permissive than those the Supreme Court has approved.

Although proponents have suggested that there ought to be an independent addiction defense to crime or that addiction should be a proper basis for an insanity defense, courts and legislatures faced with such claims have almost uniformly rejected them (e.g. *United States v. Moore, 1973*). Moreover, control tests for legal insanity, which are usually considered the most natural claim for excuse based on addiction, have been exceedingly disfavored for many decades on the grounds that they are poorly conceptualized and operationalized. In the USA, there is no generic doctrine of mitigation available at trial that an addict might employ. At most, sentencing judges with discretion to consider addiction for purposes of sentencing may do so, but addiction is a knife that cuts both ways. It may seem either to reduce or to enhance culpability depending on how addiction is viewed, and it may be a risk factor for dangerousness (*Monahan et al., 2001*).

The unforgiving response of US criminal law that denies or limits an excuse or mitigation for addiction may seem harsh, but there is justification for it. The criteria for crimes always require action and actions can always be morally evaluated, even if an action is allegedly the sign or symptom of a disorder. The generic excusing conditions in US criminal law are lack of rational capacity and lack of control capacity. The question is whether criminal behavior motivated in whole or in part by addiction meets either condition. No criminal behavior, other than possession or use itself, is a sign or symptom of the “disease” of addiction. Even if it were, a genuine excusing condition, such as lack of rational capacity or lack of control capacity, would have to be independently demonstrated. Also, there is substantial dispute about whether addicts have diminished culpability for their criminal conduct on rationality or control grounds, especially for property crimes or crimes of violence that may be committed either to support an addict’s habit or as part of a general criminal lifestyle associated with addiction. (For recent treatments, compare *Levy, 2011, Morse, 2011, and Yaffe, 2011.*) Moreover, addicts may be considered responsible for failing to take steps, such as entering treatment programs, that may prevent them from becoming less responsible. Finally, providing a defense to crime for addiction may establish perverse incentives that encourage drug use, and may increase addiction-related offending.

Given the disputes about the nature of addiction and the proper moral and legal response to it, limiting defenses based on addiction is not an irrational legislative or judicial judgment. The author’s view is that most addicts do not satisfy the excusing criteria and those who do may be held diachronously responsible based on an earlier failure to prevent their own condition of excuse. Nonetheless, even if addiction should not be a defense, sensible criminal justice reforms and other social
interventions involving drugs and addiction, to which the discussion will return in the next section, would be wise and just social policy.

Many US jurisdictions have established specialized drug courts to which addicts accused of non-violent crimes may be diverted in appropriate cases (see generally, Nolan, 2002). The details vary but, in essence, the diverted defendant must agree to treatment programs and to strict behavioral controls. If the addict successfully completes the program, the criminal charge is typically dropped. If the addict fails, then prosecution resumes. These courts are controversial on empirical and normative grounds. It is not clear whether they are cost-effective in reducing recidivism and other harms associated with addiction and there are questions about whether they are sufficiently well-theorized and just (see Wild et al., this volume, Chapter 8).

Some jurisdictions permit traditional involuntary civil commitment of addicts, but others have special forms of commitment for substance abusers (Parry, 2010). The criteria and procedures for these two types of commitment may differ, which the Supreme Court has ruled does not necessarily offend equal protection if the jurisdiction has a justifiable rationale for distinguishing addicts (Heller v. Doe, 1993). In many cases, the criteria are similar, however, and require a finding that the substance abuser is a danger to self or others or is gravely disabled. There are no good data about how many people are civilly committed because they are addicts, but the number is not likely to be large. On the other hand, temporary protective custody for those who are incapacitated as a result of addiction or substance abuse is apparently common.

The justification for these commitments is that the addict is not responsible for being dangerous or gravely disabled, a rationale in some tension with the criminal law’s refusal to recognize non-responsibility based on substance abuse or addiction. Responsibility standards in the criminal and civil justice systems need not be the same because the two systems do not have the same goals. Nonetheless, criminal blame and punishment is the most severe infliction the state can impose on citizens and one would think the state would be more forgiving about responsibility in such cases than in the case of a person who has committed no crime and would like to be at liberty. As argued in the next section, provision of adequate treatment in the community rather than involuntary civil commitment is the wiser course to deal with addiction.

**LEGAL REFORMS TO MINIMIZE COSTS ASSOCIATED WITH ADDICTION**

Even if the view is correct that most addicts most of the time can fairly be held responsible for the crimes they commit, including those such as buying and possessing controlled substances that are central criteria for
their disorder, it does not follow that the criminal justice policies our society pursues toward addicts and other users is wise. Indeed, the author firmly believes that society should decriminalize purchase and possession for personal use and use itself (Morse, 2009). Political liberalism and public health considerations suggest that criminal justice is not the optimum or even a sensible means to address these phenomena. Indeed, using criminal justice in such cases may be simply cruel. Moreover, doctrines of mitigation should be expanded to cover some cases when addicts commit other crimes that are not a part of personal use itself (Morse, 2003). Vastly more treatment ought to be available to those addicts who would benefit, including reducing their risk of criminal behavior. This would be cost-effective in itself and certainly more cost-effective and less liberty depriving than involuntary civil commitment. Further, it would not be unconstitutional or unwise to make entering a treatment program a condition for probation or parole or for more lenient conditions in prison. If these and similar policies were adopted, it is likely that the personal and social costs of addiction and substance abuse would decrease markedly and criminal justice would operate more fairly.

CONCLUSION

Whether and how potentially addictive substances should be legally regulated, especially by criminal law, are complicated, fraught questions that involve considerations of individual rights and issues of public health and welfare. Whether addiction should be a defense to crime and whether addicts should be subject to involuntary civil commitment are equally difficult issues. Many debatable and reasonable choices for public policy are possible, but some reforms would do much to ease the burdens on individuals and communities that current criminal and civil law regulation impose.

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Investment and Vested Interests in Neuroscience Research of Addiction: Ethical Research Requires More than Informed Consent

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INTRODUCTION

There are seven things that will destroy us: Wealth without work; Pleasure without conscience; Knowledge without character; Religion without sacrifice; Politics without principle; Science without humanity; Business without ethics.

Mahatma Gandhi

Most discussion about ethics in conducting neuroscience research of addiction understandably involves the protection of participants in this research; vulnerable individuals with an addiction or involved in the use of addictive drugs. The ethical principles pertaining to these discussions are: the respect for the rights or autonomy of potential subjects; the obligation to protect these individuals from harm as a result of participating in the study (non-maleficence), and if possible, the opportunity to do good (beneficence) (Beauchamp & Childress, 2001). The latter, in the case of addiction, might include providing addicted subjects with medical check-ups and information, access to health-care professionals and support in accessing addiction treatment (Adler, 1995; National Advisory Council on Alcohol Abuse and Alcoholism, 1989).

The essential condition of research ethics is the process of obtaining informed consent (Walker, Logan, Clark, & Leukefeld, 2005). This involves ensuring that the subject: (1) has the capacity to comprehend the risks and benefits of participating in the study; (2) is fully informed of these risks and benefits; and (3) is not forced or coerced to participate in research (Carter & Hall, 2008). These are important and often complex considerations in neuroscience research of addiction, particularly when it involves individuals suffering from a condition that can impair their decision making in some circumstances, is associated with comorbid psychiatric illness and other socio-economic deficits, and can involve participants who are often the subject of stigma and discrimination.
These and other important ethical issues in addiction research are discussed elsewhere (Carter & Hall, 2008; Miller, Carter, & Hall, 2010).

While the issue of informed consent is undoubtedly crucial when conducting and recruiting research with addicted participants, particularly when providing them with payments or addictive drugs, the ethical responsibility of those conducting this research does not stop there. An ethical analysis of neuroscientific research must also consider its clinical and policy impact. This chapter considers an issue seldom discussed in the research ethics literature: the role of vested interests and investment in influencing what is researched and how this research is portrayed. This involves asking questions such as: (1) who commissions and pays for research and why?; and (2) where should governments invest scarce societal resources in tackling addiction? These issues raise substantial ethical questions for those conducting neuroscientific research about whether they should accept funding from businesses involved in selling addictive commodities, and their role and responsibilities in disseminating the results of their research. They also raise important and difficult questions for policymakers in making decisions about research funding priorities. The chapter begins by discussing some powerful vested interests in neuroscience research of addiction, describing why and how they manipulate neuroscience research. It then considers the current government investment in addiction research, and examines the challenge of prioritizing investment of limited societal resources in such research.

VESTED INTERESTS

Every field of human endeavor has invested interests. These interests can take many forms. In science, this includes the simple self-interest of those conducting research with the aim of proving a hypothesis or furthering their professional standing within the scientific community. Vested interests may be more pervasive and powerful, representing multi-billion-dollar industries that seek policies that maximize profit (Oreskes & Conway, 2010). Within the addictions field, there have also been highly divergent ideological vested interests between advocates for harm reduction and those committed to zero tolerance policies (Kleinig, 2008). While any research is subject to a wide range of these biases, some are more intentional and targeted than others, and may have greater and broader impacts upon society.

The following section presents a discussion on a prominent invested interest that was able to manipulate scientific research to change public policy to maximize profits while causing enormous social harm: the tobacco industry. It has become clear that tobacco companies are not
alone in their willingness to put profit over the lives and well-being of their customers; both the alcohol and gambling industries have increasingly engaged in similar tactics. For the sake of parsimony, the alcohol, gambling and tobacco industries are referred to here as the “dangerous consumptions” (DC) industries.

Governments also have substantial vested interests in the results of scientific research. Scientific research is often used in the formation of public policy, such as drug regulation, although scientific evidence is also often ignored if it does not sit well with political or ideological agendas, as seen in the 2010 sacking of Professor David Nutt, the UK’s chair of the Advisory Council on the Misuse of Drugs (ACMD) (http://www.webcitation.org/5yaogv01k) and the rejection of a scientific report to reduce alcohol harm in New Zealand (Kypri, Maclennan, Langley, & Connor, 2011). Economic and political imperatives can sometimes influence how this research is received. Different levels of government can also come into conflict. For example, in Australia, state governments, who are heavily dependent on revenue raised from gambling, are fighting federal government moves to introduce a scheme that would set limits on the amount of money that problem gamblers are able to lose; a policy recommended by a number of independent government inquiries (Productivity Commission, 1999, 2010).

**WHY SEEK TO INFLUENCE RESEARCH?**

Scientific research is a highly sought-after source of credibility and legitimacy. This is particularly so for the DC industries whose profits depend on the consumption of products that cause significant harm to some of their customers. Science is usually assumed to be independent and objective, and therefore holds a revered position within public policy debates. In such contexts, the ability to construct or construe evidence to advance a particular financial or political goal can be extremely influential. This has certainly proved to be the case in the DC area, where millions of preventable deaths have occurred while the industries that profit from these consumptions have manipulated evidence and contested facts that they knew to be correct in order to manufacture counterfeit controversies, corrupting the scientific process and many scientists in the process (Oreskes & Conway, 2010).

The goal of such activity remains the same for all of these industries: profit maximization. This is a legitimate goal for businesses, although there are ethical and, in some cases, legal rules (e.g. fraud) that regulate how companies may go about pursuing it. Profits can be maximized by: (1) increasing consumption in existing consumers, tapping into new consumer groups (e.g. youth), and developing new products and new
marketing strategies; (2) cutting costs, by moving factories to lower wage countries, for example; and (3) minimizing adverse environmental factors that reduce consumption, such as increased taxes or restrictions on the sale and promotion of the product. This text will focus primarily on the last of these, as this is where the DC industries have most actively sought to shape and influence scientific research in their interests.

WAYS TO INFLUENCE RESEARCH

Miller and colleagues (Miller, 2005; Miller, Moore, & Strang, 2006) identified five major avenues through which research can be influenced in an adverse way: (1) direct censorship (where material is edited or dissemination is interfered with); (2) limiting access to data (either influencing the interpretation of the evidence or ensuring a favorable interpretation); (3) ongoing funding insecurity (attaching conditions to subsequent funding, if previous findings have been unwelcome or detrimental to commercial interests); (4) using underqualified or easily influenced researchers such as those with little experience or researchers early in their career (which allows funders to control the quality

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<th>Five Ways in Which the Tobacco Industry in Germany Distorts Science, According to Gruning et al. (2006)</th>
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<td>Suppression</td>
<td>Closing the German Industry Research Institute, which it funded, when the head of the institute published results unfavorable to the industry, and having scientists it employed agree not to publish unfavorable results</td>
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<td>Dilution</td>
<td>Selective funding of research and the recruitment of scientists who had doubts about the adverse health effects of smoking or whose previous work had found no links and funding research projects designed to find no association between smoking and disease (e.g. Wander &amp; Malone, 2006)</td>
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<td>Distraction</td>
<td>Selecting and supporting a large number of confounder studies: studies aimed to distract attention from smoking by investigating other potential causes of smoking-related diseases. For example, pharmaceutical companies oversubscribe to studies that examine the efficacy of pharmacotherapeutic solutions to drug-related problems, which could make the evidence base appear to be overly favorable for such an intervention (Wagner &amp; Steinzor, 2007)</td>
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<tr>
<td>Concealment</td>
<td>Using third party scientists whose connection to the industry was hidden to increase the credibility and impact of the studies they published</td>
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<tr>
<td>Manipulation</td>
<td>Vetting of articles and presentations by the industry before publication or presentation (Gruning et al., 2006)</td>
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of investigation being carried out, even before the research has commenced); and (5) setting research agendas or dilution (financing research that suits the political, financial or ideological interests of the funder, i.e. research that contradicts or questions evidence against the company interests). Other authors (e.g. Gruning, Gilmore, & McKee, 2006; Kassirer, 2005) have provided similar, although slightly different, descriptions of the ways that interest groups have influenced health policy and scientific research (Table 15.1).

While all of these behaviors raise major ethical concerns, the tactics of most relevance to addiction neurosciences are dilution, as described by Miller (2006), and distraction, as described by Gruning et al. (2006). In particular, it is proposed that the DC industry funds addiction neuroscience to distract attention away from effective population-level strategies that will reduce consumption, by focusing on the characteristics of individual consumers to explain consumption-related harm.

TOBACCO INDUSTRY FUNDING OF GENETICS RESEARCH

The tobacco industry first recognized the potential policy and legal benefits of biological and genetic explanations of tobacco-related disease in the 1950s (Gundle, Dingel, & Koenig, 2010). These efforts were initially hampered by industry denial of the addictive qualities of tobacco. However, once scientific consensus rendered this position untenable, the tobacco industry redoubled its efforts to highlight the biomedical and genetic aspects of smoking and smoking-related harm. The aim of these studies was to demonstrate that tobacco-related harm could be explained by an individual’s constitution, shifting causal responsibility from the product to the individual smoker.

The tobacco industry funded researchers such as R. A. Fisher and others to develop and implement studies that would support genetic explanations of the carcinogenic properties of tobacco smoking. The Legacy Documents reveal that the tobacco industry undertook two separate lines of research to bolster the credibility of the constitutional hypothesis: the belief that one or more genes affect a person’s risk for lung cancer, and that at least some of the same genes influence whether people become smokers. Edwin Jacob, a tobacco industry lawyer who managed secret special projects that funded scientists to produce results that supported the industry’s positions, argued in a 1974 internal report that “it has become increasingly apparent that constitutional hypotheses merit massive investigation” (Gundle et al., 2010, p. 975). As Gundle et al. concluded, “the tobacco industry is poised to use genetic research to achieve its long-term goal: an alternative understanding of smoking
that will help the industry shed the aura of ‘death-peddling Big Tobacco’ and place the blame for smoking squarely on an individual’s genetic constitution” (Gundle et al., 2010, p. 980).

By the early 1980s, the idea that smoking behaviors may have a genetic component had begun to enter the scientific mainstream and tobacco-industry funded researchers led the field because of their generous funding. In fact, the research area was so successful that these researchers were able to obtain funding from the National Institute on Drug Abuse (NIDA). However, the tobacco industry, keen to maintain control of the research agenda, provided substantial funding of these research programs until the 1990s, when condemnation of tobacco industry funding of research led to guidelines against collaborating with tobacco companies, such as those published in the Journal of the American Medical Association (Todd et al., 1995).

**ALCOHOL INDUSTRY FUNDING OF GENETIC AND NEUROSCIENCE RESEARCH**

A recent analysis ranks alcohol as the most harmful drug overall (Nutt, King, & Phillips, 2010). As these public health concerns have become more prominent, the alcohol industry has also attempted to set a research agenda that steers policy attention away from what they call bad producers, bad retailers or bad products toward a small minority of bad consumers. The alcohol industry understood that if alcohol problems were increasingly seen as the responsibility of alcohol-dependent individuals, more attention would be focused on their identification and treatment, rather than on population-based strategies that attempt to reduce alcohol use more broadly in the population. Population-based strategies aim to affect the drinking of whole populations, including non-alcohol-dependent individuals who may also experience alcohol problems. These policies, which include limiting access and availability of alcohol through taxation and pricing of alcoholic beverages, can be an effective way of reducing alcohol-related problems (Midanik, 2006).

The absence of an equivalent to the Legacy Documents for the alcohol industry makes it difficult to undertake similar assessments of the motivation of the alcohol industry. However, tobacco industry involvement in the alcohol industry has shed some light on the alcohol industry tactics (Bond, Daube, & Chikritzhs, 2009, 2010). Philip Morris (PM), which controls one of the world’s largest tobacco companies, purchased the Miller Brewing Company (MBC) in 1970 (Bond et al., 2009), which subsequently merged with South African Breweries in 2002. Bond and colleagues used the PM 1996 CEO Issues Book from the tobacco document archives to systematically search for alcohol-related documents. This book provided
access to information on the policies of the company’s tobacco, food and alcohol divisions.

The Issues Books were prepared by PM for use by the company CEO at annual general meetings, where questions may be asked about any aspect of the company’s operations. It set out the company’s positions on key business and policy matters (Bond et al., 2009). These documents provide unique insights into the company’s views, policies, areas of concern, and responses to possible criticisms of alcohol and the alcohol industry. A major element of the alcohol industry’s research agenda was to focus on personal responsibility and biological explanations for alcohol-related harm. This has been more successful in some countries than others, although it is clear that this tactic has been exported to most countries where industry-friendly alcohol policies are under threat. This approach has been most successfully employed in the USA, where there has been a long acceptance of the disease model of addiction, coupled with strong liberal political beliefs in individual rights and responsibilities that are congenial to the acceptance of biological explanations of alcohol-related harms.

In addition to direct support of research, alcohol producers and alcohol industry-supported social aspects/public relations organizations (SAPROs) provided funds to university-based scientists engaged in alcohol research. This support has usually gone to biomedical researchers (Babor, 2009). The most notable examples in the USA include the Ernest Gallo Clinic and Research Center (established by the Gallo Winery at the University of California to study basic neuroscience and the effects of alcohol on the brain) and the Alcoholic Beverage Medical Research Foundation (ABMRF)—now rebranded the Foundation for Alcohol Research—which will be discussed in depth in the following section.

In Australia, the Lion-Nathan Alcohol and Health Research Grants scheme funds only biomedical research. It favors early career researchers; a tactic successfully used by the tobacco industry to develop life-long supporters (Adams, 2007; Babor & McGovern, 2007). Another alcohol industry body, Drinkwise, has recently broadened its focus from social marketing to support neuroscience research. The industry’s use of the results of this research has involved a subtle development of the theme of individual responsibility. Drinkwise now uses research that demonstrates harm to young brains from alcohol, to admonish parents not to allow their children to drink before the age of 18. While encouraging parents to prevent adolescent alcohol consumption is sensible policy, this advice completely ignores the biggest factors predicting youth drinking: low price, ready access and, especially, advertising directed at youth. Neuroscience research is used by the industry to make parents responsible for their children’s drinking problems, and shifts attention away from the biggest drivers of underage drinking. The industry can then say it
warned the public; an approach perfected by the tobacco industry many years before.

Research also suggests that advertising campaigns against underage drinking reinforce adolescents’ perceptions of alcohol use as a marker of adult status, thereby increasing consumption. Similar campaigns against underage smoking by the tobacco industry have been shown to increase the uptake of smoking among youth (Wakefield et al., 2005, 2006). These campaigns also distract attention from the fact that the heaviest and most harmful drinking occurs among those over the minimum legal drinking age.

**Alcoholic Beverage Medical Research Foundation**

The ABMRF/The Foundation for Alcohol Research (from now on referred to as AMBRF in this text) describes itself as “the largest, independent, non-profit foundation in North America devoted solely to supporting research on the effects of alcohol on health and behavior and on the prevention of alcohol-related problems” (ABMRF, 2011a). It was established in 1982 and is supported by the following alcohol companies and organizations: The Brewers Association of Canada, MillerCoors LLC (joint venture of SABMiller and Molson Coors), National Beer Wholesalers Association, Sleeman Breweries Limited, The Beer Institute and Anheuser-Busch InBev. All of these companies are represented on the foundation’s trustee board, but according to ABMRF they do not participate in the grant selection process (ABMRF, 2011c). According to the website, two advisory boards evaluate the applications: the Medical Advisory Council (made up of biomedical experts in neurology, genetics, biochemistry and cardiology) looks at the scientific investigations in the biological, physiological and clinical sciences (ABMRF, 2011g); and the Behavioral and Social Advisory Council evaluates applications in the behavioral and social sciences.

The members of the latter are reported to be internationally recognized authorities in the fields of epidemiology, sociology, psychological sciences and public health (ABMRF, 2011b). With a group of experts like this, one would expect a high priority for studies of environmental approaches to reduce drug harm, for which there is strong evidence. However, the website states that “highest priority is given to young investigators, new to the field or trained in the field, to start a new line of independent research”. The next level of priority is given to investigators outside alcohol research who bring innovative ideas to the field. Lowest priority is given to established investigators in the alcohol research field unless the application offers “an extraordinary new idea”. The search for new and innovative ideas from young investigators could be seen to exclude research on environmental approaches for which there
is overwhelming evidence from long-standing experts in the field (Babor et al., 2010). This assumption is supported by an analysis of the types of research funded by the ABMRF between 2008 and 2010 (Box 15.1).

In the last 3 years (2008–2010), the ABMRF has given out around 30 grants per year, with a maximum of US $50,000 per annum for 2 years (ABMRF, 2011d, e, f). Just over half of all grants (58%) went to biomedical research (the Behavioral and Social Advisory Council assigned 17% of its grants to biomedical research) and 42% went to behavioral research. No funds went to environmental or public health research.
It would seem reasonable to conclude that the ABMRF’s research agenda excludes research on policies that may reduce population-level alcohol consumption. The board of trustees may not be directly involved in the grant selection process but, at the very least, they have clearly set priorities to select research projects that suggest that alcohol harm is the result of a few addicted individuals that can be treated medically, so that the rest of society can consume alcohol with impunity.

GAMBLING INDUSTRY FUNDING OF GENETIC AND NEUROSCIENCE RESEARCH

As the most recent of the DC industries to come under the scrutiny of public health and regulatory authorities, the gambling industry has learnt many lessons from the history of tobacco and alcohol industries. It is undoubtedly the most sophisticated in terms of distancing itself in the public mind from the bodies that seek to influence the research and policy debate. It creates multiple layers of funding where industry influence is only obvious to those who are determined to find out. The gambling industry funds innocuous-sounding centers [e.g. The National Center for Responsible Gaming (NCRG)], which in turn finance the Institute for Research on Gambling Disorders, which subsequently funds the Centers of Excellence at Yale University and the University of Minnesota. Declarations of competing interests from researchers at these institutions seldom make the source of their funding explicit.

As with tobacco and alcohol, there are serious concerns about the independence of gambling research, possibly to a greater extent than other fields (Livingstone & Adams, 2011). The vast majority of gambling researchers accept industry funding or are funded through government selected projects that adhere to an individual-focused model of gambling problems (Blaszczynski, Ladouceur, & Shaffer, 2004; Blaszczynski, Walker, & Sharpe, 2001; Griffiths, 2005; Jackson, Dowling, Thomas, & Holt, 2008; Potenza, 2007; Smeaton & Griffiths, 2004). The best example of how the gambling industry funds such research is discernable by analyzing its funding of the NCRG.

National Center for Responsible Gaming

The NCRG was established in 1996 by the American gaming industry. It was “the first organization devoted exclusively to funding independent peer-reviewed research on pathological and youth gambling and educating the public about problem gambling” (http://www.ncrg.org/about/ncrg-milestones.cfm). Before 2000, the NCRG reviewed the grant applications through peer-review panels and the NCRG’s
advisory board, which did not have any gaming industry representation. However, in 2000, the NCRG relocated the grant-making responsibilities to the Division on Addictions at Cambridge Health Alliance, a teaching affiliate of the Harvard Medical School that was established with a multi-million-dollar contract with NCRG. Part of the funding stayed at the Division on Addictions to support its in-house research program, while the remainder was distributed to other institutions and researchers through the competitive grant scheme, with review of applications undertaken by the Program Advisory Board. In total, the Division on Addictions (headed by Dr Howard Shaffer) received over US $7 million from the NCRG between 1996 and 2009.

In 2009, the NCRG replaced the Division on Addictions at the Harvard Medical School with the Institute for Research on Gambling Disorders as the NCRG’s grant-making body. The funding process is now overseen by the Scientific Advisory Board, while a peer-review panel evaluates the proposals and determines which proposals will receive funding. The NCRG website states that “project grants offer support for investigators from various disciplines and at all career levels, especially those new to the field” (http://www.ncrg.org/research/the-institute.cfm).

Despite the change in grant-making body, all members of the Scientific Advisory Board at the new Institute were members of the previous Program Advisory Board at the Division of Addiction. Both were also under the direction of the Executive Director Christine Reilly, who also was the first executive director of the NCRG (from 1997 to 2000). It would appear that these were largely superficial changes.

Like the alcohol and tobacco industries, the gambling industry funding of research is almost exclusively focused on the development of treatments of pathological gambling or the identification of the minority of individuals who develop serious gambling problems. In 2009, the NCRG created two NCRG Centers of Excellence in Gambling Research to support new research on gambling disorders. Each center received 3-year funding of US $402,500; the majority of the total funding provided. One of the centers (located at Yale University and led by Dr Mark N. Potenza) was funded to investigate pathological gambling treatments, including a placebo-controlled randomized clinical trial for drug treatment (naltrexone). The second center (located at the University of Minnesota and led by Dr Jon E. Grant) was funded to develop a susceptibility model of impulsivity that can identify young adults at risk of developing pathological gambling.

The NCRG website boasts that the NCRG has “supported more than 60 research investigations yielding the publication of more than 150 scholarly articles in peer-reviewed scientific journals” since 1996. To investigate what type of research the NCRG has funded, a thematic analysis was conducted of the projects listed on the NCRG website (Box 15.2)
(NCRG, 2011b): neuroscience received 32% of funding, behavioral sciences received 51% and mental health/comorbidity received 17%. Of the 45 projects listed, none focused on environmental influences on gambling or public health interventions. All of the research funded by NCRG, including the two Centers of Excellence (NCRG, 2011a), focused on the pathological gambler. The only research project the NCRG appears to have funded that investigated public health issues was done by Dr Shaffer and Dr David Korn, “where they created a framework for understanding gambling as a public health issue”. This was published in the Annual Review of Public Health in 2002 (Shaffer & Korn, 2002). This industry-funded review demonstrated a masterful reframing of the “public

<table>
<thead>
<tr>
<th>Research domain</th>
<th>N (%) grants</th>
<th>Total amount (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroscience</td>
<td>14 (31%)</td>
<td>US $1,686,615 (32%)</td>
</tr>
<tr>
<td>Behavioral sciences</td>
<td>25 (56%)</td>
<td>US $2,678,950 (51%)</td>
</tr>
<tr>
<td>Mental health/comorbidity</td>
<td>6 (13%)</td>
<td>US $881,927 (17%)</td>
</tr>
<tr>
<td>Environmental</td>
<td>0 (0%)</td>
<td>US $0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>US $5,247,492</td>
</tr>
</tbody>
</table>

BOX 15.2

A THEMATIC ANALYSIS OF NCRG-FUNDED RESEARCH

Because a trend was noted within the DC industries to pathologize the individual through biomedical and behavioral research, a thematic analysis was conducted on the projects that have been funded by the National Center for Responsible Gaming (NCRG). Information on these projects was accessed through the organization’s website (http://www.gamblingdisorders.org/project-grants/funded-project-grants).

The projects were assigned to the following research domains: biomedical, behavioral, mental health/comorbidity or environmental. The third domain (mental health/comorbidity) was included as there were a number of studies dedicated to either diagnosing “pathological” gambling as a mental health disorder or linking it to other mental health disorders, such as schizophrenia and depression.

The table includes the smaller project grants (below US $200,000) that were clearly assigned to one project.

Number (%) of Small Project Grants Awarded in Four Research Areas by NCRG Between 1996 and 2010

V. PUBLIC POLICY AND LEGAL ISSUES
health” agenda by promoting “harm reduction” and concluding that by “understanding the distribution and determinants of gambling problems in the general population and among subgroups, there is opportunity to develop effective strategies to protect vulnerable people, foster healthy gambling where appropriate, and improve the quality of community life” (Shaffer & Korn, 2002, p. 204). The article avoids any mention of the most effective public health measures employed in the most relevant comparative disorders (tobacco and alcohol use), that is: restricting access, availability and advertising (Babor et al., 2010). The link between “healthy gambling” and improved community health reads like an industry advertisement. The declaration of interest, identifying the NCRG, did not explain that this is an initiative funded by the gambling industry.

GOVERNMENT FUNDING OF NEUROSCIENCE RESEARCH

Governments also have interests in the funding of neuroscience research. NIDA, the US government institute dedicated to addiction research, claims that it is responsible for funding 85% of all addiction research worldwide (Vrecko, 2010). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) finances 90% of research on alcohol addiction (Midanik, 2006). Biomedical and neuroscience research makes up the largest percentage of NIAAA’s budget, which has been increasing exponentially (Fig. 15.1).

The main justification for government investment in neuroscience research on addiction is to reduce the significant economic and personal costs of drug use and gambling. Given the enormous governmental resources poured into neuroscience research, it is reasonable to ask whether there has been an appropriate return on the investment, particularly as other areas of addiction research and treatment have been underresourced despite evidence of the benefits of such investment (Babor et al., 2010; Room, 2007).

The allocation of scarce research dollars receives little attention in the biomedical research ethics literature. It is more often the domain of public health professionals than of research ethicists. In making decisions about where to allocate health resources, we often speak about the opportunity costs of investment. Opportunity costs refer to benefits forgone by investing in one area rather than in another. They highlight the relationship between scarcity and choice, and are a way of ensuring that scarce resources are used efficiently.
Neuroscience research on addiction has yielded valuable information about the molecular and neuronal changes that occur in the brain in response to the chronic use of addictive drugs and information about how these changes relate to addictive behaviors (see Chapters 1 and 2 in this volume) (Kalant, 2010b; Koob & Volkow, 2010). However, the therapeutic benefits of neuroscience research have so far largely been absent (Kalant, 2010b). This is generally true of biological research in psychiatry. According to a 2010 article in *Science*, “there have been no major breakthroughs in the treatment … [of mental illness] … in the past 20 years” (Akil et al., 2010, p. 1580), a period that has seen an exponential growth in neuroscience funding. With the exception of naltrexone, most of the currently used pharmacological treatments of addiction (e.g. methadone, buprenorphine and nicotine) did not emerge from neuroscientific addiction research. Such poor translation of basic science into clinical treatment has not matched the hype proffered by advocates of addiction.
neuroscience, such as NIDA and NIAAA. As the current head of the US National Institute of Mental Health (NIMH) said, “families need science to provide more than hope” (Insel & Wang, 2010, p. 1971).

Neuroscience addiction research may provide a strong after the fact justification for the use of pharmacotherapies, but it has had minimal impact in reducing moral objections to the use of these and other effective interventions so far (e.g. methadone maintenance, injecting centers, needle and syringe programs) (World Health Organization, 2004). Even if this were the case, this would represent a rather modest advance in the treatment of addiction, and not the radical innovations used to justify the large sums of money spent on neuroscience addiction research.

Neuroscience, by highlighting the neurochemical mechanisms for many features of addiction (e.g. withdrawal, tolerance, craving), encourages the view that addiction is best treated by developing pharmaceutical and neurological cures of addiction (Kalant, 2010b). These are often described as magic bullets that are mistakenly believed to quickly and simply ameliorate the symptoms of disease, requiring little effort from the patient or ongoing support from society.

However, as Harold Kalant, a leading addiction neuroscientist, has pointed out, such a reductionist approach is incapable of explaining what causes these neurobiological mechanisms to be brought into play in some people and not in others (Kalant, 2010b). There is abundant evidence that psychological, social, economic and specific situational factors play important roles in initiating addiction (Edwards, 2005). While there is certainly scope for the development of integrative approaches to the study of addiction, there seems debatable value in devoting a large proportion of resources to an ever-finer reductive approach that leads further away from the complex interaction of drug, user, environment and specific situations that characterize problem drug use and addictive behaviors in humans.

**MISSED OPPORTUNITIES AND EFFECTIVE, EXISTING INTERVENTIONS**

A focus on neurobiological treatments of addiction may also shift attention away from social and public health initiatives that we know are very effective in reducing the harm of gambling and drug use (Carter & Hall, 2010; Kalant, 2010a). Public health interventions that focus on reducing environmental enablers of such behavior (e.g. taxation, regulation) have consistently been found to be highly effective (Babor et al., 2010; National Preventative Health Taskforce, 2009; Productivity Commission, 2010). In contrast, interventions derived from biomedical or behavioral interventions generally have small effect sizes and only
on select populations, such as the extreme end of problem users that seek treatment. However, it is well known that episodes of intoxication in moderate alcohol consumers are collectively responsible for the largest share of alcohol’s burden on society because of their greater numbers (Babor et al., 2010). It would seem that when it comes to legally sanctioned DC, focusing on the individual, rather than their environment, best serves the industries’ purposes.

As is belatedly being recognized in genetic research, failure to evaluate the considerable promise of neuroscience research through a realistic lens may lead to exaggerated expectations that will undermine its legitimacy, “threaten its sustainability, and result in misallocation of resources. Fuelling unrealistic expectations … and uncritical translation of discoveries may also distract our gaze from other promising approaches to preventing disease and improving health” (Evans, Meslin, Marteau, & Caulfield, 2011, p. 861).

The history of medicine is strewn with ideas once thought promising that did not deliver when scrutinized through the lens of evidence-based medicine. Hormone replacement therapy, prostate-specific antigen screening, perimyocardial infarction lidocaine and many other seemingly good ideas, when prematurely implemented, created bubbles of expectation and investment, leaving sponsors disappointed and patients ill-served when reality did not live up to theoretical promise (Evans et al., 2011). Early recognition of this could have ensured that the money invested in these areas was directed toward more certain and beneficial needs.

While neuroscience has failed to realize its promise to revolutionize addiction treatment or provide simplistic cures, therapeutic utility is not the only benefit by which we judge investment in neuroscience research. Increasing our basic scientific understanding of psychiatric illnesses, such as addiction, is a worthwhile endeavor in itself. [Note that it is important to acknowledge that estimating the benefits of neuroscience research, as for many areas of science, is extremely difficult. Many of the benefits of scientific endeavors are difficult to predict and may not emerge for years and even decades. In addition, many of the costs also come down with time (like in genome sequencing).] Scientific research can also be viewed as an engine of economic growth (Carlsson, Acs, Audretsch, & Braunerhjelm, 2009). However, the significant investment in neuroscience research of addiction is rarely justified by these alternative social goods. They are nearly always sold on the promise that they will reduce the significant burden of disease attributable to addiction.

It is not the authors’ contention that neuroscience budgets should be dramatically reduced. However, justification of research investment should be based on a critical and transparent assessment of their likely or probable benefits. This question needs to be openly debated; it is currently absent from ethical debates about neuroscience research.

V. PUBLIC POLICY AND LEGAL ISSUES
WHY DO GOVERNMENTS INVEST SO HEAVILY IN NEUROSCIENCE RESEARCH?

Neuroscience research, and the imaging of brain activity in particular, is enormously seductive (Weisberg, Keil, Goodstein, Rawson, & Gray, 2008). So too is the allure of pharmaceutical fixes for complex social problems (Watkins, 2010). It is also cheaper and more easily defensible for governments to fund scientists to look for cures for a disease of addiction than to reform social structures to reduce poverty and the disparity between rich and poor; factors that have been often found to be a major predictor of dangerous consumptions and their associated harms (Babor et al., 2010).

Neuroscientists also stand to benefit from the promotion of addiction neuroscience. Despite the failure of neuroscience to produce significant advances in the treatment of addiction, proponents continue to express optimism about the ability of neuroscience research to transform addiction treatment: “Groundbreaking discoveries about the brain have revolutionized our understanding of drug addiction, enabling us to respond effectively to the problem.” (National Institute on Drug Abuse, 2008, p. 1).

As the historian David Courtwright explains, “The political subtext of Volkow’s statement is plain enough: keep funding our research. What may be less obvious is that virtually every historical claim in the statement is either factually incorrect or a form of wishful thinking” (Courtwright, 2010, p. 138).

Researchers gain funding, jobs and even fame, while pressure to commercialize their work or obtain addiction grant funding fuels the tendency to oversell their findings or the size of certain problems (Evans et al., 2011). Researchers are also unlikely to publicly challenge this view. Many alcohol and other addiction researchers are dependent on NIAAA and NIDA funding and there is therefore a major disincentive to publicly criticize the agency that supports their research.

AN ALIGNMENT OF INTERESTS?

This is not to argue that there is some grand plan or sinister motive behind funding of neuroscience research, as can be seen in the case of the tobacco industry funding of genetic research. Rather, a loose alignment of ideology and political interests may be seen between those who are interested in using biological explanations for addiction, those interested in constructing and maintaining a “war on drugs”, and those who are interested in reducing the stigma of addictive diseases.

Vreccko points out that “[w]hile constructionist analyses of addiction have usefully highlighted the sociopolitical aspects of addiction
medicine by demonstrating that addiction treatment may perform normalizing operations through the creation of pathological identities..., they have generally left unexamined the scientific and technical content of addiction science” (2010, p. 53). He goes on to propose that this seldom described trend seems to reflect a long-standing assumption (inspired by critical theory) that science is not more objective or robust, but only more dominant, than other types of knowledge. If one were to subscribe to a science-as-ideology view as typified by the work of Habermas (1970), then addiction science would be analyzed as a form of ideology that is political in nature (Vrecko, 2010).

The rise of addiction neuroscience has aligned seamlessly with an “addiction neuropolitics” and the professional domination of psychiatry in the USA (Vrecko, 2010). Volkow’s expression of gratitude toward science reflects the dominant accounts of the development of neuroscience models of, and treatments for, addiction, which assume that science has progressed more or less on its own (Courtwright, 2010). It is difficult to know whether addiction neuroscience would have been as generously funded if it were not for the influence of the war on drugs in the USA and the goal of some politicians to destigmatize addiction and alcoholism (Snyder, 1989).

**THE TASK AHEAD FOR NEUROSCIENTISTS**

The ethical concerns of research neuroscientists should not end with obtaining informed consent from research participants. Neuroscientists also have a moral responsibility to think about the ways in which their research is used and communicated in the public domain (Blakemore, 2002). Neuroscientists are best placed to prevent misuses or correct misrepresentations of their work by vested interests.

Neuroscientists should anticipate the predictable misuse of their research by vested industries, such as the DC, to maintain if not increase the consumption of their harmful products. To do so, they will need to ensure that accurate information is released to the media and that their publications include prominent disclaimers that correct predictable misinterpretations of their findings (ANCD, 2005; Australian Press Council, 2001). This includes identifying and correcting any misuses of the science in the media, and prompting policy makers to prevent the introduction of more harmful addiction commodities based on their research. Neuroscientists may want to consider carefully the motivations of DC industries and the likely consequences of accepting funding from DC industries. The authors would argue that researchers should refrain from accepting industry funding without some very significant justification or qualification.
Neuroscientists should also avoid overselling the benefits of their research in order to attract further funding. Exaggeration of the benefits of their research only enhances the ability of DC industries to exploit neuroscience, and misdirects resources from areas that will be of more benefit to addicted individuals. The nature of the grant review process and competition for research funding will be significant challenges to achieving this goal.

CONCLUSION

The ethical analysis of addiction neuroscience research needs to consider whose interests this research will best serve. Massive, multinational and multi-billion-dollar industries that profit from the promotion of harmful addictive commodities are investing heavily in this area while stridently attacking research into more effective population-level interventions that will adversely affect their bottom line. While it is certainly the role of industry to maximize profits, it may be argued that this creates a stronger impetus for governments to invest in these other areas, and a strong disincentive for scientists or institutes to accept industry money. There is clear evidence that research focusing on individual factors, rather than environmental ones, has been the preferred vehicle of industry funding. Tobacco industry documents make it clear that while the industry was fighting in the courts to deny the addictiveness of nicotine at the cost of millions of lives, the tobacco companies were investing millions of dollars in genetic research on nicotine dependence to protect future revenue. Worse still, governments around the world, but most particularly in the USA, have clearly failed to identify or act on this trend, choosing instead to join the search for miracle cures, rather than tackle the complex issue of improving the social circumstances that encourage drug use.

Governments need to consider what research will produce the greatest health benefits and not be seduced and bedazzled by the allure of addiction neuroscience. This is not an academic debate about the ethics of neuroscience; it is a very real debate about whether current funding priority to neuroscientific research results in greater harm to the addicted individuals that it purports to help.

In the face of decades of limited progress for treatment of mental disorders, and in the context of these fundamental difficulties in delivering care, spending nearly 90 million dollars in 2 years (for only 3 disorders) in a pursuit of molecular “magic bullets” … seems misguided and ethically unjustified on access-to-care comparisons alone (Sadler, 2011, p. 34).
Acknowledgment

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References


Private and Public Approaches to Addiction Treatment: Evidence and Beliefs

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INTRODUCTION

Addiction as Moral and Medical Challenge: The Ethical Perspective

Mental illness and addiction continue to be viewed by some as undesirable, antisocial forms of behavior, which are the consequences of a weak moral character or poor decision making. Intravenous drug users are a significant focus of this perception (Room, 2007; Sartorius, 2007), get for them and for others, there is no other medical condition that is stigmatized to the same degree in society, nor for which more resources are spent on control and enforcement than on treatment.

The harmful use of psychotropic substances is as old as humankind while symptoms of mental illness were described in ancient Greece. Individuals with such a variety of complex and concurrent conditions are generally seen as different, sometimes threatening, sometimes tolerated or even considered unworthy of life, as in Germany under Hitler. A common approach in dealing with mental illness was, and continues to be, ignorance, exclusion, incarceration and, sometimes, physical harm.

Despite the expansion of modern medicine and the development of psychiatry, the treatment of addiction remains detached from general medicine and treatment. Indeed, in the USA for example, only 17% of all investments in addiction are spent on treatment. Although, worldwide, a significant proportion of the mentally ill population also suffers from substance use disorders, individuals continue to be treated outside the traditional medical and hospital system, as the famous Swiss psychiatrist Eugen Bleuler remarked in the late twentieth century (Bleuler, 1975, 1982).

Similar experiences have been reported by those treated for physical illnesses arising from the effects of intravenous drug use. Patients who enter a hospital emergency room with a serious infection due to intravenous drug use will be treated with antibiotics for the infection, but do not routinely receive acute or long-term treatment for their drug dependence or trauma-related psychopathology (Room, 2007). An important reason for their non-compliance with medical treatment is a lack of attention to their specific needs; drug-addicted patients often leave the hospital with untreated, life-threatening diseases, because they do not receive drug substitution treatment or proper pain medication.

In most countries, funding for addiction care is limited. In the USA in 2008, Paul Wellstone and Pete Domenici signed the Mental Health Parity and Addiction Equity Act into law. This legislation introduced parity for mental health coverage for the first time in large groups of health insurance plans. The goal was to bring an end to a system in which could legally insurers limit care for mental health and substance abuse.
INTRODUCTION

conditions and require patients to pay more out-of-pocket costs than for other medical conditions (Burns, 2009). Allowing insurers to determine what condition they cover, however, makes access to care particularly complicated for most addicted patients.

What are the Possible Reasons for Neglect?

**Coincidence with a History of Trauma or Other Mental Challenges**

Substance use disorders are often not put into context. While the onset of most substance use disorders coincides with a history of trauma or other mental challenges, these are rarely assessed, often ignored and infrequently addressed in standard treatment programs (Krausz, Degkwitz, Kühne, & Verthein, 1998; Krausz & Müller-Thomsen, 1994; McLellan & Meyers, 2004). Although addiction is known to be critically important in treating human immunodeficiency virus (HIV) and hepatitis, cancer, chronic obstructive pulmonary disease and severe mental illness, it is often not included in patient care plans.

**Interaction of Relapse and Discrimination**

The long-standing structural discrimination and stigmatization of addicted people is reinforced by their high rates of relapse and the disturbing behaviors sometimes expressed by these patients. In the medical system, patients who do not do what their doctors and nurses recommend are considered to be non-compliant. This may reflect the inappropriateness of care or a lack of patient insight, but whatever the cause, the consequences will often be discharge and/or discontinuation of care. Without professional knowledge of addiction and with poor supervision, these factors contribute to personal distance from, and limited tolerance of these patients.

**Professional Pessimism**

Whether justified or not, many professionals doubt that addiction treatment can be successful. Lack of exposure to addiction treatment research and training in addiction creates a pessimistic, even nihilistic attitude toward addiction treatment that prevents addicted clients being engaged in care (O’Brien & McLellan, 1996). Symptoms of addiction may be misinterpreted as a chosen lifestyle, with the result that severely ill people do not receive proper medical attention and effective care.

**Needs Versus Resources**

Resources for health care are becoming increasingly limited. Healthcare providers must therefore curtail the number of programs that they can support. For example, cancer care and heart and lung programs are
financially aligned with the burden of disease that they cause, but this is not the case with mental illness. Psychiatric conditions account for 25% of the burden of disease, but only 5% of available resources are devoted to treating them. The consequence is that programs for mental illness and addiction are not receiving the attention and support that are needed.

**SYSTEM VULNERABILITY**

Medicine and health care are highly vulnerable to inequality, and within the system, ethnicity, age, social status or diagnosis can all differences in gender impede an individual’s access to proper health care. Medical ethics and value-based approaches to a legal and regulatory framework are important in reducing such social inequalities (UNODOC, 2008). This framework is defined by the principles of consequentialism, human rights and medical ethics (Burns, 2009; Uchtenhagen, 2010a).

The Universal Declaration of Human Rights (United Nations, 1948) contains a number of articles important for addiction and mental health care, such as:

- No discrimination (Article 2)
- No degrading or inhuman treatment (Article 5)
- Right of equal access to medical care and social services (Article 25/1)
- Limitations of right and freedom admissible on the basis of the requirement of morality, public order and the general welfare (Article 29/2)

The European Convention on Human Rights (Council of Europe, 1950) further stipulates that a person with alcoholism or drug addiction may only be deprived of liberty after a legal process (Article 5/I1e) with a right to appeal to a court (Article 5/4).

Many of these rights were created to protect the most vulnerable in society because of an international history of intolerance and misuse, as has occurred in Germany, South Africa, Russia and the USA. They are also referenced in other constitutions and in legislation, such as the Canada Health Act (Government of Canada, 1984), that aims to establish a balance between protecting individual rights and respecting the needs of society for public order and general welfare. Compulsory measures against people with a substance dependence may be admissible on the basis of national laws (e.g. narcotics laws), but are highly controversial from a human rights perspective. The inclusion of this discourse, given the high level of stigma and violence against addicted individuals, would be an important addition. It is surprising, however, that this suggestion is rarely raised (Burns, 2009). The United Nations declaration on
the rights of persons with disabilities from 2006 is a recent example of a specific human rights instrument that responded to ongoing discrimination (United Nations, 2006):

It marks a paradigm shift in attitudes and approaches ... from viewing persons with disabilities as “objects” of charity, medical treatment and social protection towards viewing [them] as “subjects” with rights, who are capable of claiming those rights and making decisions for their lives based on their free and informed consent as well as being active members of society (Burns, 2009; United Nations, 2006).

Medical ethics only applies to substance dependence if it is understood as a medical condition. This has been the official position of leading professional organizations for decades (Leshner, 2001).

Two kinds of initiative are key to the current efforts in medicine: (1) a long tradition of self-regulatory codes of conduct for physicians; and (2) non-medical regulations and guidelines. Several international and national bodies have started to work on the best practice development in addiction and concurrent disorders (Rush, 2002) in keeping with these initiatives. Recent examples of the conduct code are the Standards of Conduct of the American Medical Association (American Medical Association, 2001) and the Good Medical Practice of the English General Medical Council (General Medical Council, 2010). Some of the main issues are: the patient’s autonomy of decision making; informed consent; dignity and confidentiality; non-discriminatory beneficence and non-maleficence. Another issue is the necessity to maintain professional standards in providing the best possible care by continuing education and networking with other services and colleagues.

In the USA, professional organization codes include a responsibility to seek a change in official or legal requirements that are contrary to the best interests of the patient. These codes acknowledge the occurrence of ethical conflicts and provide links for support. Examples of non-medical regulations include specific laws on research, preventive measures, promotion of medicinal products, birth control and palliative care. Other examples are guidelines issued by faith-based groups, advocates or consumer protection organizations. A distinction must be made between the legal impact of binding regulations or laws and non-binding recommendations. In each instance, the relevant national rules are the binding framework.

In the absence of specific rules for the treatment of substance dependence, general ethical rules for good medical practice should be applied. The four major principles are:

- Do no harm or non-maleficence
- Improve the well-being of the patient or beneficence
- Respect patient autonomy
- Apply justice
It is obvious that even these few principles cannot be followed without generating conflict (Rust, 2000). The debate on harm reduction principles in addiction care, therefore, needs to be reframed on the background of basic medical principles. The substantial controversy in the USA over harm reduction approaches (e.g., needle and syringe programs, supervised injecting centers, heroin prescribing), and agonist substitution treatment in Russia highlight the unique position that addicted individuals, especially intravenous drug users, still hold in public policy. For example, what is considered standard practice in the European Union is forbidden in Ukraine, Russia, and other countries and subject to major political controversies. Treating all patients equally, in principle, is impossible when resources are so limited. Confidentiality and data protection are often in conflict with administrative and law enforcement interests in the case of illicit drug use. If the patient’s interests collide with those of families, partner or other third parties, a compromise needs to be negotiated.

The autonomy of the patient as an ethical principle should remain a priority that is very carefully considered and not be overruled in the name of abstract societal values. Involuntary interventions to prevent harm conflict with the autonomy of unwilling patients. Ethical guidance and best practice guidelines need to be developed to deal with coercive treatment, violence against a patient, or the symptoms of addictive illnesses (UNODOC, 2008).

Society’s interests have always played a special role in the use of psychotropic substances. Because many controversies are political in nature, they cannot be understood solely on the basis of scientific or medical considerations. Uchtenhagen (2010a, b) names three aspects that need to be considered: the individual citizen’s obligations, public safety, and the sociocultural acceptability of behavior. Another dimension involves economic implications, which have been extremely important historically. For example, during the Opium Wars in the late nineteenth century, the British Empire battled China to guarantee free opium trade and access to Chinese markets.

The relationship between individual and society is fundamental for the functioning of any society. The individual obligation to live a socially responsible life may be limited by illness, disability or, for example, cognitive impairment. When a symptomatic behavior is illegal, such as illicit drug use, public order, as defined by law, is challenged. All kinds of behavior under intoxication, such as driving under the influence and drug-related public nuisance, create a tension between the individual and common social interests. In Western societies, the individual right to self-fulfillment also adds a crucial component. Who decides what is good for an individual and what is in the domain of self-responsibility and the freedom of choice when it comes to drug use? Does the individual...
in the twenty-first century have the freedom of intoxication? Where does society want to draw the line in terms of regulation of individual behaviors? Should those who are obese, smoke tobacco or engage in dangerous sports be punished? Should those individuals pay more health insurance or receive less treatment?

In order to make these decisions, it is critical that we interpret addictive behavior as a consequence of pleasure seeking or as a way of coping with mental challenges. Considering the high prevalence rates of traumatic experience or mood disorder, especially among intravenous drug users (Krausz et al., 1998), the self-medication hypothesis is particularly poignant. Individuals in a critical situation do what they learned from their families and respond to the crisis with their available tools. This model (Khantzian, 1985) interprets substance use as a way to cope with mental challenges and symptoms such as anxiety, mood swings, pain or sleep disturbances, which avoids the interaction with psychiatry or the medical system in general.

**TREATMENT OF ADDICTION AND CONCURRENT DISORDERS: INTERVENTIONAL APPROACHES AND PRINCIPLES**

The key to any system of care or interventional approach is to have a good model of addictive behavior and related concurrent disorders (Khantzian, 1985; Krausz & Müller-Thomsen, 1994; Marsh & Fair, 2006; West, 2006). With its high burden of disease, addiction is treated in nearly all parts of the health-care system (Marsh & Fair, 2006). However, only approximately 10% of all clients who fulfill the criteria of a substance use disorder are seen by a specialist (Wienberg, 2008). This process may take as long as 10 years, from first symptoms to first professional response, to assessment or treatment. To improve the system of care for addiction and concurrent disorders it is important to understand the different models for these disorders and define the upcoming challenges.

Addiction, and its different variations, is defined in the current diagnostic systems [i.e. ICD-10 (WHO, 1993) and DSM-IV (American Psychiatric Association, 1994)] by the principles of descriptive psychopathology. Diagnostic principles, particularly for addiction, have been discussed and modified for a long time. From a research perspective, current definitions need to be seen as historical compromises (Rounsaville, 2002).

The current diagnostic criteria for addiction include biological symptoms, such as tolerance and withdrawal, and psychological symptoms of craving or desire to reduce consumption, loss of control over consumption,
and neglect of other activities and interests. The diagnostic algorithm is fulfilled when at least three key symptoms are present in a 1-year period.

A different model exists for the etiology of substance use disorders (West, 2006). This approach stems from biological psychiatry and basic neuroscience; it focuses on biological changes in brain function and morphology (Volkow, Fowler, & Wang, 2003). Another perspective connects addictive behaviors to other experiences or mental health issues, especially to the coping of mental challenges related to traumatic experience, mood disorders and other syndromes (Krausz & Schäfer, 2004). Social learning theory has described addiction as learned excessive behaviors (Marlatt & Gordon, 1985); an approach that integrates pathological gambling and other non-substance based behaviors into the addiction field. It is most likely that the learning process and possible biological adaptations are intertwined and connected with an attempt at self-medication.

If the substance is seen as the major reason for developing dependence, then abstinence ought to be the most common treatment approach (Rush, 2002). The more multidimensional the process becomes, the more differentiated approaches are needed.

The biological consequences of substance use are strongly related to the specific substance, the patterns of its use and contextual factors. Nearly all addicts experience withdrawal symptoms. However, many problems related to withdrawal are experienced before professional help is sought, when the need for coping techniques is greatest and would be most helpful. Different treatment strategies need to address different treatment goals and individual needs of the client.

The World Health Organization (WHO) identified different levels of treatment that are necessary for a long-term recovery process. The ethical challenge is to provide the addicted patient with the most appropriate level of support while understanding that addictive behaviors span a wide range of behaviors, from single harmful use to dependence. Different patients may have different needs. As addictive behaviors cover a range of syndromes and are related to a spectrum of medical problems, treatment goals need to become more specific and adapted to the patient’s current stage (Prochaska & DiClemente, 1982). To achieve this goal, a hierarchy of objectives has been developed (UNODOC, 2008).

The support of survival and management of any physical crisis became the accepted priority in international conventions (UNODOC, 2008). Possible interventions have the main goal of stabilizing physical functions. From there, the next steps, with the patient’s agreement must be determined, and may include detoxification, stabilization, substitution, psychiatric or psychological crisis intervention and rehabilitation.
ETHICAL CONSIDERATIONS AND BEYOND: THE FUTURE OF CARE

Stigma

Regardless of the different theoretical schools or therapeutic approaches, structural discrimination and stigma continue to be the major obstacles to developing an appropriate system of care. It is often found in the history of medicine, and especially in the history of psychiatry, that a lack of client focus, intolerance and inappropriate beliefs have caused major harm to patients in desperate need (Room, 2007).

Besides the extreme examples, common-day behaviors in the system of care all over the world need to be addressed. Clients with severe addictions, who are most likely suffering from the consequences of substance use, chronic physical illness and concurrent mental disorders, require access to emergency care as well as the treatment system overall. They need the same professional attention as other multi-morbid and high-need clients. The practice of care for these patients needs to be reframed according to the mentioned standards of care, human rights and medical ethics.

The successful response to the HIV epidemic would not have been possible without a paradigm shift in the social and medical approach to this epidemic. The fight against the stigma of HIV-positive clients, intravenous drug users or gay men was a crucial component in shifting attitudes and changing the health-care system. This paradigm shift brought the important aspect of prevention into focus. The HIV and AIDS epidemic exemplifies the complexity of major medical challenges and an appropriate response to them. It may be a blueprint for necessary changes in the efforts needed to address addiction and concurrent disorders. An intravenous drug user is at an increased risk for premature death, reducing lifespan by 20 years on average. This impact is larger than that on an HIV client in a functioning and caring environment today.

Access

Access to care based on needs is a core principle that is not realized for patients suffering from an addiction. With extremely limited capacities and restricted access to care, the system is contributing to relapse and poor outcomes. The low level of integration also contributes to ineffective care. Physical health, mental health and addiction are addressed in different domains of the health-care system and only a few professionals are trained to deal with complex concurrent disorders and understand the continuum of care required.
The first lines of treatment in primary care and emergency departments receive limited support and usually function separately. Different illness models, values and treatment philosophies are making it difficult for professionals, patients and families to navigate the system.

**Political Framework**

The care of patients suffering from mental illness and addiction is the most underfunded area in medicine. As mentioned earlier, compared to a burden of disease of about 25%, only 5% of resources are spent on their treatment. Addiction research also receives only a small amount of funding.

Effective treatments such as substitution medications (e.g. Polamidon in Germany, slow-release morphine in Austria) and other types of treatment, such as injectable slow-release naltrexone in the USA, are not regulated or funded for use in addiction in Canada, and so are not available.

Patients with addiction and concurrent disorders are often marginalized, without a job or homeless. Therefore, the support required for recovery needs to include not only effective treatment, but also social integration and housing. A comprehensive strategy to reintegrate vulnerable urban populations on the regional level is the key, supported by provincial and federal capacities. To address the situation in critical neighborhoods, the different providers in the system of care need to be well connected. The community must respond at a system level.

As documented in numerous police reports and surveys, enforcement agencies have to deal with all kinds of medical emergencies (Wilson-Bates, 2008) without being appropriately equipped and trained.

A significant proportion of inmates in prisons in North America have substance use disorders and drug-related offenses are a major reason for incarceration. In prisons, the risk of acquiring a life-threatening disease, such as hepatitis C, is high and the chance of receiving proper treatment for addiction and concurrent disorders is small. Individuals end up in the prison system because of an illness, and are more exposed to life-threatening infections without any appropriate care afterwards.

On a regional and provincial level, police authorities and criminal justice experts are supportive of more mental health and addiction services and the development of specialized courts for individuals suffering from addiction and related psychopathology. A reconsideration of the political framework in Western countries based on a health approach with the inclusion of harm reduction principles would address high-risk behaviors and reduce the risk of relapse.

**Evidence-Based Treatment**

The driving force behind the implementation of new treatment programs in the development of the system of care is evidence for improved
health. The effectiveness of addiction treatment does not differ from that of many other chronic diseases (e.g. diabetes) (McLellan & Meyers, 2004; O’Brien & McLellan, 1996). To improve the quality of care, a system of clinical research and clinical innovation needs to be in place. The continuum of care needs to be supported by ongoing evaluation and clinical research. These strategies should be implemented and adopted by professional organizations such as the College for Physicians and Surgeons. In the end, professional certification, qualification and training should benefit from this approach. Only high standards of care can achieve positive outcomes and sustainable recovery. This would be the appropriate interpretation of ethical standards of care for the high-needs population with addiction disorders.

FURTHER CONSIDERATIONS AND CONCLUSION

The current situation for individuals with addiction and concurrent disorders in our system of care is unsatisfactory. Political paradigms, stigma and discrimination, limited access to quality care and a lack of funding all contribute to an unacceptable state. Cultural and political values, such as the declaration of human rights, and substantial social values documented in constitutions should be a strong starting point to change this current state. Professional ethics, health care and beyond should guide the necessary process of change.

In response to the fact that addictive behaviors cover a range of syndromes and are related to a spectrum of medical problems, treatment goals become more specific and adapted to the stage a patient is in (Prochaska & DiClemente, 1982). A hierarchy of objectives is then developed over the course of the patient’s treatment. Appropriate treatment goals need to reflect both concurrent physical and mental disorders that directly interfere with recovery. The delivery of treatment is in competition with natural coping styles. The treatment needs to have advantages in order for the patient to choose it.

A theoretical discussion, which reflects this dynamic discourse, focuses on the self-medication hypothesis (Krausz, 1999a, b)—the use of a substance to cope with the symptoms of mental illness. A rough description of possible levels of treatment under this hypothesis is provided in a related report by the Ministry of Health in the UK in 2002. The report describes:

- Reduction of psychological, social and other problems directly related to drug use
- Reduction of harmful or risky behaviors associated with the use of drugs (sharing equipment)
- Attainment of controlled, non-dependent or non-problematic drug use
Abstinence from key problem drugs
Abstinence

The WHO sets slightly different accents and includes the importance of help for survival and risk reduction before anything else. The dramatic experiences from the overdose epidemic in the twentieth century and other life-threatening experiences contributed to this systematic paradigm shift.

Another aspect of these principal considerations is the expectation one has of any therapeutic intervention. Treatment is often identified with seeking a cure. However, most chronic conditions in medicine are not curable. Treatment is designed to address suffering and pain, to improve the quality of life or prevent complications. As such, treatment simply means a reduction of risk and harm; as stated in the Hippocratic Oath, a core responsibility for any physician.

The very emotional and fundamental controversy over the role of harm reduction in North America tends to ignore this core principle of medical ethics. Harm reduction is an integrated medical principle and a core component of most treatments, not an alternative to a possible cure. As studied in the evaluations of safe injection sites, needle exchange programs or other harm reduction programs, the participation of drug users in these programs not only prevents the spread of infectious disease but very often also provides a point of contact to the system of care (Wood et al., 2004, 2006).

Research demonstrates how effective a needs-based, individualized approach to treatment planning can be. The US National Treatment Improvement Evaluation Study (Gerstein et al., 1997) documented significant correlations between drug-free urine after 1 year and the different needs included in the treatment plan: “The combination of treatment components and services to be employed must be tailored to meet each of the needs of the individual, including where he or she is in the recovery process” (NIDA, 1999).

The differential approach also responds to the needs of society. In the treatment of drug addiction, abstinence-based treatment programs are only successful in reaching out to a minority of patients. Intravenous drug users are a high-risk population for life-threatening epidemics such as HIV/AIDS or hepatitis C; and open drug scenes in vulnerable inner city neighborhoods, such as the downtown eastside of Vancouver, Canada, are becoming a significant economic and social problem area for all cities. An integrated approach to addiction disorders that brings together medicine, policy, ethics, and individual and society wellness is clearly the imperative at hand.

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