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The brain disease model of addiction: is it supported by the evidence and has it delivered on its promises?

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Since 1997 the US National Institute on Drug Abuse has advocated a brain disease model of addiction (BDMA). We assess the strength of evidence for the BDMA in animals, neuroimaging studies of people with addiction, and current research on the role of genetics in addiction. We critically assess claims about the medical and social benefits of use of the BDMA because the social implications are often implied as a reason to accept this model. Furthermore, we argue that the BDMA is not supported by animal and neuroimaging evidence to the extent its advocates suggest; it has not helped to deliver more effective treatments for addiction; and its effect on public policies toward drugs and people with addiction has been modest. The focus of the BDMA is on disordered neurobiology in a minority of severely addicted individuals, which undermines the implementation of effective and cost-effective policies at the population level to discourage people from smoking tobacco and drinking heavily. The pursuit of high technology direct brain interventions to cure addiction when most individuals with addiction do not have access to effective psychosocial and drug treatments is questionable.

Introduction

In 1997, Alan Leshner, then Director of the US National Institute on Drug Abuse (NIDA), published a report 1 in Science in which he argued that addiction was best conceptualised as a chronic, relapsing, brain disease. Although Leshner acknowledged that drug use was initially voluntary, he argued on the basis of animal models that chronic drug use flicked a neurochemical switch in the brain, making it very difficult for people addicted to drugs to stop using them, which would explain the high incidence of relapse in people treated for addiction. Researchers at NIDA have since done a substantial number of neuroimaging studies on people with drug addiction and they argue that the results explain how chronic drug use hijacks the brain's reward systems. 2

Proponents of the brain disease model of addiction (BDMA) have been very influential in setting the funding priorities of NIDA, and by extension the bulk of publically supported research on addiction. In 1998, Leshner testified that NIDA supports more than 85% of the world's research on drug abuse and addiction. 3 The American Society of Addiction Medicine has defined addiction as a "primary, chronic disease of brain reward, motivation, memory, and related circuitry". 4 In July, 2014, newly appointed Acting Director of US National Drug Control Policy, Michael Botticelli, launched a reformist strategy nationally, claiming decades of research have demonstrated that addiction is a brain disorder—one that can be prevented and treated. 5 The BDMA has also been widely discussed in leading scientific research journals 3,6 and most recently in a positive editorial in Nature. 7

In the USA, proponents of the BDMA have argued that it will help to deliver more effective medical treatments for addiction with the cost covered by health insurance, making treatment more accessible for people with addictions. 1,2,6 An increased acceptance of the BDMA is also predicted to reduce the stigma associated with drug

addiction by replacing the commonly held notion that people with drug addiction are weak or bad with a more scientific viewpoint that depicts them as having a brain disease that needs medical treatment.

In this Personal View, we critically assess the scientific evidence for the BDMA reported in leading general scientific journals and the extent of the social benefits that advocates of the BDMA claim it has produced, or is likely to produce, with its widespread acceptance among clinicians, policy makers, and the public. The BDMA is not co-extensive with neuroscience-based explanations of addiction. This review is not intended as a critique of all neuroscience research on addiction. We focus instead on the popular simplification of work in this specialty that has had a major influence on popular discourse on addiction in scientific journals and mainstream media.

Evidence for the BDMA

Studies of animal models have had a central role in the development of the BDMA by providing insights into the effects that chronic drug administration has on brain processes.8,9 These studies show that rats and other animals will self-administer psychoactive drugs at high frequencies (eg, by pressing a lever); 9,10 the drugs that animals self-administer are similarly addictive in humans; and self-administration of drugs is decreased by electrical stimulation of the so-called reward centres in the brain.9 The use of animal models has enabled researchers to identify the neural circuitry on which the most addictive drugs act, namely the mesolimbic brain reward system, including the ventral striatum, nucleus accumbens, amygdala, and frontal cortices. Dopamine signalling has a key role in this system. 11,12

Animal models reproduce some key features of human addiction.13 Animals provided with free access to drugs often increase the frequency and amount of drugs they self-administer and work harder to obtain drugs, mimicking the development of tolerance and dose escalation in humans. Furthermore, they will continue to self-administer drugs associated with aversive stimuli (eg, electrical foot shock). Animals will rapidly resume self-administration when they are given painful stimuli, are exposed to cues associated with the drug, or primed with a dose of the drug. 8,12,14

Results from animal studies are supported by the results of neuroimaging studies on the role of dopamine activation in the reward circuits in so-called normal and addicted human brains.6,15,16 Neuroimaging studies have shown dopamine-mediated changes in cortical areas correlate with impaired decision making and poor impulse control. 17,18 The persistence of many of these brain changes in people with addiction after long periods of abstinence is used to explain the high incidence of relapse in people treated for addiction. 19

Further support for the BDMA is provided by genetic research on addiction. Twin-studies indicate that genetic factors substantially contribute to the risk of development of alcohol, nicotine, and cannabis addiction .20,21 Estimates of the heritability of alcohol, nicotine, and cannabis dependence range from 40% to 60%.21 Large-scale genome- wide association studies show correlations between the presence of genetic markers and the risk of development of addiction. Risk alleles that affect drug metabolism and the effect that drugs have on the mesolimbic reward system have been identified, which suggests that addiction is the outcome of the effects of chronic drug use on the brains of genetically susceptible individuals. 20,21

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A critical examination of the evidence for BDMA

Is addiction a chronic disorder?

Critics of BDMA contest claims by its proponents that addiction is a chronic relapsing disorder and cite epidemiological evidence that most people with addiction recover without treatment. 22–24 Heyman 23 points out that most people with diagnosed drug dependence in epidemiological surveys are not drug dependent at the time of their interview, and have ceased recreational drug use years previously, usually in the absence of treatment. Similarly, a high incidence of recovery was shown in follow-up studies of heroin-addicted US veterans of the Vietnam war. 25

Critics also argue that it is difficult to reconcile a strong form of the BDMA with evidence that people addicted to recreational drugs respond to small changes in their personal situations. 22,23 For example, the receipt of small financial rewards or the avoidance of 24 h in jail by providing clean urine samples, substantially decreased drug use in people with drug addiction. 23,26 The responsiveness of drug users to these small incentives is hard to reconcile with the claim that drug use is a compulsive behaviour over which people who are addicted have little or no control. 22,23

The BDMA can be reconciled with the high incidence of recovery from addiction if we allow for the fact that addiction varies in severity, measured with common diagnostic criteria, and that less severe addictive disorders are the most common and people with this type of disorder the most likely to recover without treatment.27 Chronic addiction occurs in a minority of people with addiction, especially those who use drugs into their early 30s despite accumulated adverse health effects and social consequences. Chronic drug users seem a better fit to the picture of addiction as a relapsing brain disease because they are the group most likely to seek treatment after failure to control their drug use and to have changes in brain function that might have a role in their continued drug use.24

This modified BDMA applies to a few drug users who meet the diagnostic criteria for addiction in epidemiological studies. Advocates of the BDMA who accept this weaker form of the model cannot equate the lifetime prevalence of addictive disorders with the prevalence of the severe and chronic addictive disorders, which exemplify the BDMA. A critical analysis of research on the neurobiology of addiction, however, raises doubts about how compelling the BMDA is in terms of providing an explanation of the few people with severe, chronic addiction.

Animal models of addiction

Addictive behavioural patterns are not invariably the outcome of chronic self-administration of drugs in animals. Popular accounts of these studies underplay the extent to which the results depend on specifically bred strains of rats and the conditions in which the animals are housed.28 Rats taught to self-administer opiates under standard conditions for addiction behaviour do not display this behaviour when housed in more natural conditions (eg, with litter mates). 29 Rats housed in enriched environments might have different patterns of drug self-administration and reinstatement (a return or relapse to addictive patterns of drug self-administration following a stressful event or the consumption of a small quantity of the addictive drug). 28 Rats trained to self-administer drugs will abstain when given a choice of natural rewards such as food or pair bonding.28

Animal models of addiction reveal little about the incidence of recovery from addiction in the absence of specific interventions. 24 For example, Koob and LeMoal's analysis12 of the analogies

between animal models and the so-called stages of human addiction does not include recovery. Their implicit assumption is that once addicted an animal (or a person) will remain so unless treated, and if treated will be at high risk of relapse. This viewpoint might seem too pessimistic with respect to the epidemiological evidence reviewed above.

Genetics of addiction

Addiction is not a disorder confined to people who carry the small number of so-called addiction genes. A large number of alleles are involved in the genetic susceptibility to addiction and individually these alleles might very weakly predict a risk of addiction.20,21,30 Scores for the genetic risk of addiction based on different combinations of many risk alleles do predict the risk of addiction but do so no better than a simple family history (eg, number of parents who smoke).31 Generally, genetic prediction of the risk of disease (even with whole-genome sequencing data) is unlikely to be informative for most people who have a so-called average risk of developing an addiction disorder. 30,32

Human neuroimaging studies

Neuroimaging studies of addiction 33 show people with addiction differ significantly from people without addiction more than they should, in view of the studies' sample sizes and the sizes of the difference between groups. 33,34 The excess of significant results shows the effect of chance in large numbers of comparisons of activity between brain regions or structures, the selective publication of positive results, and delay in publication of failures to replicate the positive results.35 In studies that do robustly show people with addiction differ from controls, there are large overlaps in the size of brain structures and hypo-functionality or hyper-functionality of specific brain regions in people with addiction and in control groups.36 Researchers reporting results of neuroimaging studies on addiction37 acknowledge these limitations, but more popular accounts often do not.

Case-control studies do not show whether addiction is a cause or a consequence of differences in brain structure and function or some combination of the two. 38 Patterns of brain activity on MRI in people with addiction differ from people without addiction and do not show the use of drugs is a compulsion.39 The fact that decreased activity in frontal brain regions is modestly correlated with self- reported drug craving does not show that drug use is driven by irresistible impulses. 24

The increasing complexity of addiction neurobiology The postulated neurobiology underlying the BDMA has become progressively complicated since 1997. Chronic drug use once thought to hijack the reward centres in the brain is now acknowledged to affect brain structures involved in high-order cognitive control of impulses. 15,40 Volkow and colleagues17,41 acknowledge the neuro-pharmacological complexity of addiction in that many neurotransmitter systems are implicated in addiction (eg, γ-aminobutyric acid, N-methyl-D-aspartate, opioid, and serotonin). The researchers emphasise the importance of epigenetics (changes in gene expression that in brain systems might be produced by chronic drug use), which they identify as a new target for drug treatments. Despite acknowledgment of the complex neurobiology in addiction, the simplest form of the BDMA continues to dominate public education materials. 42

Promised policy payoffs from the BDMA

Improved drugs to treat addiction

Leshner predicted the BDMA would help to develop drugs and behavioural treatments to reverse or compensate for the brain changes underlying addiction,1 thereby delivering more effective treatment for addiction. New drugs to treat addiction include vaccines and implantable agonists and antagonists against neurotransmitters to decrease the risk of relapse; DNA tests to match patients to the most effective treatment; drugs to modulate the stress response; drugs to modify memories of drug- related cues; and most recently, drugs to reverse epigenetic changes in chronic drug use. 43–45

The promised treatment benefits associated with the BDMA have not materialised.46 Few new drugs have been approved for the treatment of addiction in the past two decades.47 The most widely used drugs in addiction (eg, methadone and nicotine replacement therapy) preceded the BDMA by more than 30 years. A few drugs (eg, naltrexone and varenicline) derived from research into the neurobiology of addiction are only modestly superior to older drugs, such as disulfiram and substitution of cigarettes with non-smoked forms of nicotine, such as nicotine gum or patches.37,48–50 The investment of NIDA in research on vaccines against nicotine and cocaine dependence has produced disappointing results. 51–53

Substantial obstacles remain to the development of effective drugs to treat addiction. Many of these obstacles are shared with drug development in biomedicine more generally, 54 including very low success rates in replication of the findings of promising drug targets in basic research 55,56 and the low replicability of the results of small sample animal studies. 57 Few drugs showing promise in animal models progress to clinical trials due to unacceptable side effects, whereas others fail to show efficacy in phase 2 clinical trials.

Special challenges exist to the development of new drugs to treat addiction. Pharmaceutical companies might be reluctant to invest in drug development because they doubt new drugs to treat addiction will be profitable, in view of the limited capacity of people with addiction to pay for treatment, the absence or limited availability of health insurance coverage for addiction treatments in the USA, and regulations that prevent the clinical use of drugs with similar effects to recreational drugs. 47 Pharmaceutical companies might fear that the stigma associated with the treatment of addiction will discourage other potentially more profitable uses of these drugs (eg, to treat chronic pain).47

Direct brain interventions for addiction

Leshner's argument that attending to the brain needs to be a core part of treatment of addiction 1 has prompted proposals to directly intervene in the brains of people with addiction. In the early 2000s, Koob's work 58 was used to justify ablative neurosurgery as a treatment for heroin addiction in China and Russia. Deep brain stimulation (DBS) is now advocated as a more targeted and reversible alternative to neurosurgical ablation. 59,60

Advocates of DBS as a treatment for addiction cite animal studies in which lesions in the dopaminergic

reward pathway have decreased self-administration of drugs. 61 Case reports of patients who have been treated with DBS for indications other than addiction and who have reported that their addictive behaviour was decreased are also cited .62 Furthermore, case reports now exist of the apparently successful use of DBS to treat alcohol and heroin dependence.62

Advocates of DBS to treat addiction have argued that it will be an effective and cost effective way to reduce the economic and social costs of addiction. 60 However, the probable population-wide cost has been overstated to justify the high costs of the procedure (more than US$50 000 to implant a stimulator and $10 000 per year for maintenance). 63 If DBS is proven effective, only a few people with addiction who are wealthy enough to afford the treatment might receive it; patients with addiction who generate the social and economic costs that have been used to justify DBS trials are least likely to receive the treatment. 60

Overinvestment in high risk strategies for legal drugs

A major risk of the BDMA is that it will lead to the neglect of public health policies in favour of a search for biomedical treatments of people with severe addiction.64,65 This prioritisation is shown in the allocation of NIDA's 2014 $1065·24 million research budget: 23·8% to epidemiology, health services and prevention; 41·4% to basic and clinical neuroscience research; and 16·5% to pharmacotherapies and the rest spent on intramural research and research support.66

The imposition of high taxes on cigarettes, enactment of bans on advertising and restrictions on where people can smoke, have halved the incidence of cigarette smoking in Australia67 and the USA68 in the past three decades. These strategies are more efficient than drug vaccines, predictive genetic testing, or neurosurgical interventions aimed at smokers and people at risk of smoking.64 They are more cost-effective in the prevention of addiction than the screening of whole populations and intervention with a few people who are at high genetic risk of addiction if they smoke tobacco.69 Similarly, evidence exists to support the efficiency of population-based strategies in the reduction of the societal harms of alcohol misuse.70 The effectiveness of population-level approaches is not an argument against the provision of clinical treatment to people with addictive disorders. A real concern exists, however, that an overemphasis on the BDMA could undermine population level approaches when misused by the alcohol and tobacco industries in opposing public health policies. 71

Illicit drug policy

Striking differences exist in policies based on research into the neurobiology of addiction. In the USA, proponents of the BDMA have been mostly silent about its implications for US drug policy, arguably allowing the BDMA to become part of an overinvestment in law enforcement efforts to decrease drug supply .72

NIDA has expended substantial resources to replace the view of addiction as morally wrong with one of addiction as a treatable medical disorder.1,2,6 Until now there have arguably been meagre returns on this investment. The most positive development was the inclusion of addiction treatment in the Patient Protection and Affordable Care Act and provision of health-care through Obamacare. 5

By contrast, in the UK leading addiction neuroscientists have used their research to question whether cannabis, 3,4-methylenedioxy-N-methylamphetamine (MDMA), and LSD should remain illegal. David Nutt, formerly the government's chief drug advisor, has argued that the harms caused by alcohol, cannabis, cocaine, heroin, MDMA, and tobacco do not justify the different legal status of these drugs.73

The results of research into the neuroscience of addiction cannot be, and ought not to be, the decisive factor in setting drug policy. In democratic societies, government drug policy should come from the trade-off between goods and harms, such as the pleasurable effects of drugs enjoyed by adults, the harms that drug use can cause, and the social and economic costs and benefits of the different ways to allow or restrict the sale and use of drugs. Ideally, these tradeoffs should be made by political representatives who are well informed about epidemiological, sociological, economic, and neuro- biological research on drug use and addiction.

Conclusions

Considerable scientific value exists in the research into the neurobiology and genetics of addiction, but this research does not justify the simplified BDMA that dominates discourse about addiction in the USA and, increasingly, elsewhere. Editors of Nature were mistaken in their assumption that the BDMA represents the consensus view in the addictions specialty,7 as shown by a letter signed by 94 addiction researchers and clinicians (including one of the authors of this Personal View).74 Understanding of addiction, and the policies adopted to treat and prevent problem drug use, should give biology its due, but no more than it is due. Chronic drug use can affect brain systems in ways that might make cessation more difficult for some people. Economic, epidemiological, and social scientific evidence shows that the neurobiology of addiction should not be the over-riding factor when formulating policies toward drug use and addiction.

The BDMA has not helped to deliver the effective treatments for addiction that were originally promised by Leshner and its effect on public health policies toward drug addiction has been modest. Arguably, the advocacy of the BDMA led to overinvestment by US research agencies in biological interventions to cure addiction that will have little effect on drug addiction as a public health issue. Increased access to more effective treatment for addiction is a worthy aim that we support but this aim should not be pursued at the expense of simple, cost effective, and efficient population-based policies to discourage the whole population from smoking tobacco and drinking heavily. Nor should the pursuit of high technology cures distract from the task of increasing access to available psychosocial and drug treatments for addiction, which most people with addictive disorder are still unable to access.

Our rejection of the BDMA is not intended as a defence of the moral model of addiction.6 5 We share many of the aspirations of those who advocate the BDMA, especially the delivery of more effective treatment and less punitive responses to people with addiction issues. Addiction is a complex biological, psychological, and social disorder that needs to be addressed by various clinical and public health approaches.65 Research into the neuroscience of addiction has provided insights into the neurobiology of decision-making, motivation, and behavioural control in addiction. Chronic use of addictive drugs can impair cognitive and motivational processes and might partly explain why some people are more susceptible than others to developing an addiction. The challenge for all addiction researchers—including neurobiologists—is to integrate emerging insights from

neuroscience research with those from economics, epidemiology, sociology, psychology, and political science to decrease the harms caused by drug misuse and all forms of addiction. 46

Contributors

The study and drafting of the paper was done by WH. WH and AC designed the study and did an initial search of the literature. All authors were involved in devising the final search strategy, retrieving and critically reviewing the articles. WH prepared the initial draft of the paper. All authors were involved in the subsequent writing and editing of the manuscript.

Declaration of interests

We declare no competing interests.

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