Withdrawal and Reward: Implications for Detoxification and Relapse Prevention

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What drives the addictive use of alcohol and other drugs—withdrawal or reward? How are the experiences of withdrawal and reward related to the prevention and treatment of addiction? The most intuitively satisfying laboratory model for the study of addiction is voluntary self-administration or lever pressing, first described by B.F. Skinner. A reinforcer is anything that maintains or strengthens a response. Although reward and reinforcement are usually used interchangeably, they can be distinguished: responses are reinforced while subjects are rewarded.

Drugs are chemicals that stimulate their own taking. Drugs are primary or unconditioned reinforcers. Addicts become attached to their drugs and also to their drug sources and the friends with whom they use drugs. These attachments continue down to the neighborhood, the rooms in which they use drugs, their paraphernalia, and even to the music and the behaviors they associate with drugs. Drugs are operant or instrumental reinforcers, meaning that drugs reinforce their own use based on trial-and-error learning. In addition to the rewarding aspects of the drugs of abuse, addicts establish conditioned attachments that potentiate the impact of drugs and other reinforcers.

These are incentive-motivational or priming effects, such as the association of salted peanuts and alcohol use or the smell of the cork before drinking wine.

In thinking about the mechanisms driving addictive behavior, it is useful to distinguish between positive reinforcement and negative reinforcement. Positive reinforcement involves euphoria and strong, difficult-to-describe good feelings associated with drug taking. Negative reinforcement involves the removal of distress and other negative effects. Most addicted people report that both positive and negative reinforcements play important roles in initiating and maintaining addictive use of alcohol and other drugs. Positive reinforcement is more likely to be mentioned earlier in the addict’s career.

It is remarkable that drug taking persists when addicts clearly describe that their drug does not make them high any more, even after they have lost their jobs, their homes, their health, and their loved ones. Because drug taking stimulates itself and establishes a strong new drive state, the absence of true euphoria may be another example of how, when it comes to addiction, behaviors speak louder than words. Addicts, reporting an absence of euphoria and persistent drug self-administration, tend to focus late in their addictive illnesses on the negative feelings associated with not only the distress of drug discontinuation, but with the absence of drug use from their lives, the way people in love talk about loss of the object of their love. Life simply loses its value without drugs.

Both positive and negative reinforcements are distinguished from aversive control or punishment, which is the experience of distress as a result of drug use. Drug tests linked to drug use in treatment, in the criminal justice system, and in the workplace are examples of pun-
ishment, not negative reinforcement. Disulfiram treatment of alcoholism is a pharmacological punishment because the alcoholic faces painful symptoms if alcohol is consumed. The use of electric shock and other aversive treatments paired to alcohol or other drug use are additional examples of punishment in the treatment of addictive behaviors.

TWO VIEWS OF ADDICTION: WITHDRAWAL AND REINFORCEMENT

Abstinence is recognized by addicts as unpleasant and reversible by the use of the drug on which they are dependent. Abstinence has both physical and motivational components. In the older view, the defining problem of addiction was physical dependence, implying that withdrawal symptoms following sharp dose reduction or acute abstinence was the primary engine driving addictive substance use.2 Detoxification was seen as the principal treatment for addiction. Free the addicted person from withdrawal and the grip of the addiction was broken because only then could the addict find release from pharmacological prison. For decades, the treatment of addiction focused on detoxification, with the “drying out” usually taking place in residential or hospital settings. Still today, the major emphasis of addiction treatment by primary care practitioners and many psychiatrists is acute abstinence. Cigarette smokers are treated with the nicotine patch. Alcoholics are treated with cloridiazepoxide (Librium) or, more recently, with loading doses of benzodiazepines. Opiate-dependent persons are treated with clonidine, clonidine plus naltrexone-accelerated detoxification, or buprenorphine.3 These treatments all focus on the problem of withdrawal, seeing it as central to the treatment of addiction.

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) treats withdrawal as a "substance-induced disorder."4 In making the diagnosis of substance-induced disorder, the presence of physiological dependence, characterized by tolerance and withdrawal, is limited to the dependence label because the lesser form of substance use disorder, “abuse,” cannot show evidence of physiological dependence. In other words, if withdrawal occurs, “dependence” is the correct diagnosis. The concepts of tolerance and physiological dependence are essential components of the hypothesis of neural adaptation to the drugs of abuse. The brain and the micro-neurotransmitter systems that drugs target are changed in an adaptive process that begins with the first dose and persists long after all drugs have been cleared from the brain.

Overcoming withdrawal or abstinence in medical treatment of addiction involves gradually diminishing doses of the drug of abuse itself or of a pharmacologically related cross-tolerant compound. More recently, medications like clonidine, which have the same net effect on the locus coeruleus neurons and norepinephrine-based autonomic nervous system in mediating alcohol and other drug withdrawal, have been successful in treating abstinence or the consequences of neuro-adaptation to alcohol and other abused drugs. While gratifying in their ability to reverse a variety of addiction-induced acute withdrawal states, once detoxified, withdrawal treatments lead to a return to drug self-administration.

These common clinical experiences of relapse after withdrawal have deepened the contemporary understanding of addiction and focused on reward rather than on withdrawal as the engine of addiction. Clearly, the positive aspects of the drug experience support drug self-administration. Animals and humans, whether bred for drug preference or not, whether dependent or drug-naive, whether reared in Milan or Miami, self-administer drugs of abuse. The reinforcing properties of drugs are powerful motivational forces that are preferred by the subject to natural reinforcers. Subjects in self-administration studies perform many difficult and time-consuming tasks to gain access to drugs. Drug users outside laboratories routinely choose their drugs over work, spouse, friends, and other reinforcers. Drugs that stimulate their own taking and are positively reinforcing in animals produce the same effects in humans. This relationship is so strong that drug self-administration in animals is predictive of human drug abuse.

Drug self-administration paradigms permit the study of the rewarding effects of various doses of drugs, of environments where drugs are used, and of the role of drug availability. Once an animal is trained to experience drug reward, the animal can be tested for an extended period. The investigator can study the release of dopamine in the nucleus accumbens and the ventral tegmental area that results from the use of the drug and from the anticipation of drug use, switching from active drug to placebo in double-blind studies. The information derived from animal and human self-administration of abused drugs supports the notion that drug reinforcement is the unifying feature of drug abuse and dependence. Drug abstinence is the behavioral and physical state released by the absence of the drug of abuse to which the chronic user has adapted. It is also reinforcing to reverse the negative hedonic state resulting from drug abstinence.

Of these two, the motivational rather than the physical aspect of the withdrawal syndrome has attracted the most recent study. Malaise, boredom, depression, anhedonia, decreased appetite, brain stimulation changes, increased behavioral responsiveness to stressors, and increased reward thresholds are all part of the withdrawal syndrome. Most of the work on the motivational effects associated with acute and protracted abstinence has been done with opiates, but disinhibition of stimulants, including cocaine, and discontinuation of alcohol are related to an aversive motivational state on cessation of drug taking.

Human addicts report that they need the drug to feel normal or simply to think straight.
after prolonged use. Musicians report a loss of creativity, authors report "writer's block," and others report a loss of color or brightness in their lives after the discontinuation of tobacco, alcohol, and other drugs. The withdrawal state sets up the profound negative reinforcing effects of drugs of abuse.

Withdrawal and reward mechanisms are associated with both positive and negative reinforcements in ways that are not easily separated clinically. The good feeling that is the goal of alcohol and other drug use usually involves both euphoria (positive reinforcement) and the reduction of distress (negative reinforcement). In the earlier view, which focused primarily on withdrawal as the major force behind addiction, relapse to using opiates, alcohol, or other drugs was seen primarily as a manifestation of untreated or poorly treated withdrawal. The failure of treatment as shown by relapse was attributed to inadequate medical treatment rather than to the positive drive of motivated behavior directed at the rewarding use of the alcohol or other drugs.

Physicians seemed miffed that their withdrawal treatments were unable to explain the high rate of relapse to alcohol and other drug use after detoxification. After all, if the addicted person's primary problem was the trap of withdrawal, it would be reasonable to expect that the newly freed prisoner would gratefully and steadfastly grasp onto the new drug-free status, never to return voluntarily to the torture of withdrawal, which is a predictable feature of addiction. Poor long-term efficacy did not stop physicians from detoxifying alcoholics and addicts without insisting that they attend 12-step fellowship meetings or be monitored for relapse for many years after detoxification. More recently, this same pattern of physician behavior is seen in nicotine addiction where physicians slap on patches, thumb the table, and state "You'd better quit."

While a desirable outcome over a period of many years was virtually unheard of following decades of repeated detoxifications, it was remarkable how slow the medical profession was to recognize the implications of this observation. Rather than question the underlying assumption, which placed medical skills essential in the diagnosis and treatment of withdrawal at the center of the problem of addiction treatment, physicians seemed content to recycle addicted people through emergency rooms and detoxification experiences for what often proved to be an addiction-shortened lifetime.

**BRAIN BIOLOGY**

A new understanding of brain biology shows that withdrawal and reward use are entirely distinct brain mechanisms. Central opioid injection studies have demonstrated the power of ventral tegmental and nucleus accumbens injections to produce reward and motivate behavior. The classic opiate withdrawal symptoms are not seen in animals who are self-administering opiates into these dopamine-rich reward areas rather than injecting just a few millimeters away in the periaqueductal gray areas that mediate withdrawal. Drug-seeking behavior, these studies showed, was driven largely by reinforcement rather than by withdrawal. Interrupt the dopaminergic reward pathways, which are the neural substrate for most drugs of abuse and addictive behavior, and drug self-administration fails to reinforce drug use. Successfully lesioned animals cannot reliably differentiate cocaine from placebo once reward is blocked.

Interrupt surgically or chemically the noradrenergic locus coeruleus and the autonomic pathways of the withdrawal circuitry, and the addictive behavior and drug self-administration continue. Recent advances involving in vivo voltammetry and microdialysis make it possible to monitor the synaptic levels of brain dopamine in the nucleus accumbens of freely moving animals. These studies show that drugs of abuse are powerful in changing behavior and reprogramming the animal or human subject because they produce larger increases in dopamine than any natural rewards, even sex or food, the prototypical natural behaviors that trigger the release of dopamine in these brain areas.

The behavior-shaping actions of those fundamental motivational circuits of the brain evolved long before the first occurrence of addiction to alcohol and other drugs. The susceptibility of lower animals to drug dependence is a function of prior drug use, dose, and route of administration as well as of the drug itself. If the drug can get to the primitive meso-telencephalic dopamine reward system in the brain of an animal or a human being, it will cause the organism to pay attention and attribute species-specific survival to the drug self-administration event. Peer pressure and other environmental factors, while relevant to protective or risk factors and to initial drug use, have not been invoked successfully as causative of drug dependence. Rather, it is the drug's unique ability to stimulate its own taking as a result of specific brain activity that feeds addiction to nicotine, alcohol, and other drugs.

Addicts to marijuana and cocaine can be understood using the reward model of addiction, but they are incomprehensible using the earlier model of addiction based on the withdrawal model. Until it was understood that cocaine was one of the most powerfully rewarding drugs fostering intense pathological attachments between the users and the drug, to which even supra-normal incentives such as multi-million dollar sports contracts became powerless, cocaine was thought to be nonaddictive by virtue of the lack of a profound and reliable abstinence syndrome. The withdrawal model shaped both the professional and the public understanding of addiction for more than half a century, leading to the mistaken view that cocaine and marijuana were "nonaddictive" or "soft" drugs. This set
the stage for these two drugs to become the gateway drugs into the addiction syndrome.\textsuperscript{12}

Another complication of the older view that equated addiction with physical dependence was that it identified patients who are physiologically dependent on prescribed medicines as "addicted" to those medicines. This led to the mislabeling of many medical patients as addicted when they were using medicines to treat a variety of medical and psychiatric disorders, most often pain and anxiety. As a result, two generations of American patients have been underprescribed potentially beneficial medicines. In order to distinguish medical from nonmedical treatments, it is useful to have a clear picture of the common clinical presentations of the benign experience of physiological dependence and the entirely separate malignant experience of addiction.\textsuperscript{13,14}

Even with serious alcohol and heroin dependence it was observed that some addicted patients coming into treatment had few or no withdrawal symptoms despite the fact that their behaviors and histories showed high levels of addiction over long periods of time.\textsuperscript{15} Just as many nicotine-dependent patients do not need the nicotine patch, many alcoholics can be successfully detoxified without pharmacological interventions. These otherwise puzzling experiences are explained by the understanding that reward is primary in addiction. The reward mechanisms in the brain are stimulated by drug taking, by the thoughts of drug taking, and even by conditioned experiences related to drug taking. The addicted person is hooked on this reward experience that persists with or without withdrawal.

If withdrawal were the primary force driving addiction, as many clinicians and researchers continue to believe, once an addicted person was free of physical dependence, the addiction should be terminated. It is a common experience for seriously addicted smokers to go through physical illnesses that temporarily force them to stop smoking. They seldom, if ever, require nicotine patches for these involuntary experiences, and they rarely complain about withdrawal. Even after long periods with no use of any tobacco products, once the physical illness that makes smoking unpleasant is gone, most addicted smokers quickly relapse to nicotine dependence. It is hard to imagine that physical dependence is driving this common example of addictive behavior. Similar patterns are seen in persons who are addicted to other drugs including alcohol, cocaine, and heroin; many of them have repeated episodes of nontherapeutic abstinence that do not require treatment and do not lead to prolonged abstinence or "recov-"

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This, of course, is not to deny that withdrawal is an important component of addiction. Withdrawal remains one of the most distinctive features of addiction to alcohol and other drugs. Successful treatment of withdrawal symptoms can foster the physician-patient relationship and improve long-term compliance if the physician remains consistent and focused on the long-term treatment of the addictive disease that retains its power over the addicted patient long after withdrawal is past. Successful treatment of withdrawal, however, is not related to drug-free outcomes at 1 month, 6 months, or 1 year. Reflecting this newer view of addiction, the DSM-IV diagnostic criteria for substance dependence lists withdrawal as a major, but not a necessary, condition for the diagnosis of substance dependence.\textsuperscript{4}

**PREVENTION IMPLICATIONS**

The view of addiction, based on the recognition of the primary role of reward and the enduring brain changes that drugs induce, has implications for the prevention of addiction. This view supports the zero tolerance goal of primary prevention so that the drug-induced brain changes caused by addictive substance use do not occur. This view of addiction does not support the harm reduction goal of prevention of addiction that accepts the use of an addicting substance while working to reduce the negative consequences of that use.\textsuperscript{16}

**TREATMENT IMPLICATIONS**

The first goal of the modern treatment of addiction to alcohol and other drugs is to help addicted patients become and stay alcohol and drug free.\textsuperscript{17} Once that goal is achieved, long-term work is needed to help patients avoid relapse and improve the quality of their lives, including dealing with their medical and psychiatric disorders.\textsuperscript{18} Helping addicted patients overcome their character defects is part of the process of becoming and staying clean and sober.\textsuperscript{19}

There are three general phases to the treatment of addiction. The first is getting started, the process of developing the willingness to enter treatment, or what Alcoholics Anonymous calls "the desire" to stop drinking and using drugs. There are many important components in this first phase of the addiction treatment experience, including decreasing social tolerance for the use of alcohol and other drugs, as evidenced by drug testing in the workplace and rehabilitation programs for DWI offenders (driving while impaired). The modern structured intervention is an organized approach to overcoming the most basic stages of denial in order to get addicted people into treatment.\textsuperscript{19}

The second phase of addiction treatment is stopping use, which can be done either in an inpatient or an outpatient basis. It is in this stage that medical treatment of abstinence may be important. This is the phase of the treatment experience in which medically managed detoxification takes place.

The third phase of addiction treatment is staying clean and sober. This is the stage in which relapse prevention and relapse prevention programs, Alcoholics Anonymous, Narcotics Anonymous, Al-Anon, and other programs built on the original foundations of AA, play their biggest roles.\textsuperscript{20} Relapse-preventing psychopharmacology is an important new addition to this
phase. Medications that deny brain access to the reward rather than punish the addict for using alcohol and other drugs are in the early phases of what may become a dramatic change in the field of addiction treatment. Treatment with the opiate antagonist naltrexone has made some relapsing, and even chronic relapsing, alcoholics more amenable to 12-step fellowships and to positive behavior change. Treatment of concurrent psychiatric illness, such as major depression, manic depression, eating disorders, or panic and anxiety disorders, helps to cope with the double trouble of comorbidity. Comorbid patients need hope that the treatment of their mental disorder, their risk will be reduced for depression-related and anxiety-related relapses to addictive drug use and to related suicides. Twelve-step programs are important in the treatment of dual-disordered patients.\textsuperscript{22} The DSM-IV criteria focus on the specific substance to which patients are addicted so that dependence, or abuse, is diagnosed to specific substances.\textsuperscript{5} This substance specificity fits well with the unique pharmacologically induced problems of intoxication and withdrawal faced medically as a result of the use of specific addictive substances. However, modern brain biology has identified the final common pathways for both reward and withdrawal, leading to a unitary biological perspective on addiction. This unitary approach offers the hope that both pharmacological and nonpharmacological treatments will be developed that span a wide range of substances and focus instead on the specific brain mechanisms that underlie both reward and withdrawal. 

The use of medicines in treating addictive disease is limited in comparison to treatment of many other mental disorders, including the affective and anxiety disorders. Addiction, affective and anxiety disorders share the distinction of being the most prevalent classes of mental disorders. While cognitive-behavioral approaches have been effective in the treatment of both affective and anxiety disorders, pharmacotherapy dominates the clinical management of these diseases. In substance use disorders, pharmacotherapy plays a relatively minor role, and the 12-step programs, the most potent cognitive-behavioral approach, are ascendant. 

With respect to treatment of the reward dimension of addiction, there are several medicines that play a role today. Naltrexone has been effective in the treatment of both opiate dependence and alcoholism.\textsuperscript{23} Disulfiram has been used to decrease reward by the threat of painful symptoms if alcohol is consumed. Withdrawal from alcohol or other drugs has been treated with clonidine. Unlike treatments targeting reward, clonidine treatment is useful for all addictions that involve the norepinephrine withdrawal pathways based in the locus coeruleus, the brain's novelty and danger detector. Reward plays a central role in all three phases of addiction treatment, while withdrawal is primarily a problem in the second phase, stopping use. 

The nicotine patch for nicotine dependence or methadone and buprenorphine treatment of opiate addiction involve both reward and withdrawal systems, because these drugs reduce craving as agonists and reduce withdrawal by virtue of being cross-tolerant with other opiates. The dream of modern pharmacological research is to find more specific and effective treatments that block the drug-induced effects of both the reward and the withdrawal pathways, without producing agonist effects or other potentially harmful effects. Antagonists that reverse the effects of cocaine and marijuana, as naloxone reverses the effects of opiates, are essential for emergency rooms and pharmacotherapies for relapse prevention. 

The 12-step programs use a unitary approach to addictive disease by largely disregarding the specific substances being used. Alcoholics Anonymous appears to be an exception because AA, from its earliest days, has adopted the principle of singleness of purpose, focusing only on the use of alcohol. Nevertheless, AA takes a unitary view of addiction by making clear that staying sober means not only not drinking alcohol, but also not using other brain-rewarding drugs. Beyond not using alcohol or other drugs, AA and other 12-step programs work to change the lifestyles of alcoholics and addicts so that they live better, more honest, and less self-centered lives.\textsuperscript{24} 

Naltrexone and other relapse-preventing pharmacological treatments that do not produce brain reward can be viewed as adjuncts of this approach to lifelong recovery. To the extent that clonidine or other treatments for withdrawal are available, they are useful adjuncts to the acute treatment of patients suffering from physiological dependence as these patients make the transition from physiological dependence to the alcohol- and drug-free state. 

Just as the early preoccupation with withdrawal as the central focus of addictive disease was excessive, so perhaps today's dismissal of withdrawal as a major factor in addiction is an overreaction. If generally effective ways were found to treat the withdrawal symptoms resulting from the physiological dependence on any substance, whether taken medically or nonmedically, such treatments might have broad application both in addiction treatment and in medical practice. 

**SUMMARY**

New brain research has demonstrated the separation of the reward and withdrawal pathways. Reward is mediated by dopamine and focused in the nucleus accumbens and the ventral tegmental area of the brain. Withdrawal is mediated by norepinephrine and is focused in the locus coeruleus. Novel medicines have been developed that have been used successfully to eliminate withdrawal, and others have been
found to reduce the drive to addictive drug use resulting from drug reward.

Addiction primarily is a reward-driven behavior caused by repeated drug stimulation that produces lifelong changes in the addicted brain. The most striking manifestation of these enduring changes is the propensity to relapse even after prolonged abstinence. Relapse most commonly occurs when drug-free addicts believe that they are cured and stop attending 12-step meetings. They come to believe that they can return to occasional and controlled use of brain-rewarding drugs. They often complain of boredom or anhedonia off drugs. Relapse often occurs spontaneously without warning or premonition that the individual is about to restart drug use.25 The 12-step programs, focusing on the unitary and lifelong aspects of addictive disease, offer a uniquely effective program for dealing with the cognitive and the behavioral manifestations of addiction and for the prevention of relapse.

REFERENCES