The Persistent Challenge of Developing Addiction Pharmacotherapies

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There are currently effective Food and Drug Administration (FDA)-approved therapies for alcohol, nicotine, and opioid use disorders. This article will review the development of eight compounds used in the treatment of drug addiction with an emphasis on pharmacological mechanisms and the utility of preclinical animal models of addiction in therapeutic development. In contrast to these successes, animal research has identified a number of promising medications for the treatment of psychostimulant use disorder, none of which have proven to be clinically effective. A specific example of an apparently promising pharmacotherapeutic for cocaine that failed clinically will be examined to determine whether this truly represents a challenge to the predictive validity of current models of cocaine addiction. In addition, the development of promising cocaine use disorder therapeutics derived from animal research will be reviewed, with some discussion regarding how preclinical studies might be modified to better inform clinical outcomes.

There are currently effective U.S. Food and Drug Administration (FDA)-approved therapies for alcohol, nicotine, and opioid use disorders.[6] In some cases, these therapeutics were rationally designed and tested using a combination of various animal models of addiction. In many cases, however, effective drug therapies for substance use disorders were derived from the testing of compounds developed for other central nervous system (CNS) disorders (e.g., analgesics and antidepressants), which were tested clinically in the absence of prior animal research using addiction models. This article will review the development of eight compounds that are

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currently most effective in the treatment of alcohol, opioid, and nicotine use disorders with an emphasis on pharmacological mechanisms as well as the utility of animal models of addiction in the development of these therapeutics. In contrast to these successes, animal research has identified a number of promising medications for the treatment of psychostimulant use disorders, none of which have proven to be effective clinically. This raises questions about the validity of current animal models of psychostimulant addiction. A specific example of an apparently promising pharmacotherapeutic for cocaine use disorder (the D1 dopamine receptor antagonist ecopipam) that failed clinically will be examined to determine whether this truly represents a challenge to the predictive validity of current models of cocaine addiction. In addition, the development of promising cocaine use disorder therapeutics derived from animal research will be reviewed.

BUPRENORPHINE AND METHADONE FOR OPIOID USE DISORDER

The earliest references to animal models of addiction in the literature all referred to work on opioids, mainly morphine. Research using animal models prior to 1960 used the term addiction loosely given that the drug of abuse was experimenter delivered. For example, Plant and Pierce (1928) administered very high doses of morphine to dogs daily for 2–3 months. Indeed, the doses chosen were toxic in some cases as the authors reported that "two of our animals died in convulsions on doses of 190 and 220 mg per kg" (Plant and Pierce 1928). At that time, the severity of the withdrawal syndrome was thought to be the primary factor contributing to relapse among opioid-dependent humans. Therefore, Plant and Pierce sought to examine and characterize opioid withdrawal in animals. Following cessation of morphine treatment, they noted that "five of our dogs showed marked changes in temperament during the first week of withdrawal, in that they became very cross" and "one animal died in convulsions on the third day of withdrawal" (Plant and Pierce 1928). These authors summed up their observations as follows: "The period of addiction in dogs has given a picture that follows closely the description of addiction in man [including vomiting, constipation, hypersensitiveness, scratching, irritability, and decrease in narcotic action of the drug]." Note that Pierce and Plant defined addiction as opioid withdrawal and tolerance (Plant and Pierce 1928).

The first valid animal model of addiction was developed in the early 1960s. As a first step toward developing a model in which animals self-administer drugs of abuse, two water-deprived rhesus monkeys were trained to press a lever to receive intravenous infusions of saline (Clark et al. 1961). The authors also showed that saline self-administration could be extinguished and brought under stimulus control (i.e., the monkeys would lever press for light cues previously paired with the saline infusions) (Clark et al. 1961). Subsequently, it was demonstrated that rats (Weeks 1962) and monkeys (Thompson and Schuster 1964) would self-administer morphine intravenously.

Although results from the self-administration paradigm have contributed significantly to the development of more recent addiction pharmacotherapies, the first successes came from drugs that were developed for other purposes. For example, methadone, the first truly successful substance use disorder therapeutic, was originally developed at Hoechst in the 1930s as an analgesic. Methadone was tested for analgesic efficacy by scientists at Eli Lilly and Company and Burroughs Wellcome & Company in the 1940s (Scott and Chen 1947; Thorp et al. 1947). In early papers, methadone was sometimes spelled methadon and also was called dolophine. As an aside, it has been erroneously reported that methadone, which was developed in Germany, was originally named after Adolf Hitler (i.e., adolophine). Then, as now, a major goal of opioid research was to identify effective analgesics that lacked an addiction liability. Therefore, methadone was tested by a group of prominent behavioral pharmacologists whose findings were summed up as follows: "we believe that unless the manufacture and use of methadon are controlled addiction to it will become a serious public health problem" (Isbell et al.

1947). This conclusion was based in part on reports from their recovering opioid-dependent patients such as: "That is great stuff. I wouldn't have believed it possible for a synthetic drug to be so like morphine. Can you get it outside? Will it be put under the narcotic laws? I wish I could get it to kick my next habit." The authors also noted that "methadon prevented the appearance of signs of physical dependence in 12 men who had been proved to be addicted to morphine" (Isbell et al. 1947). These observations suggested that methadone might be used to treat opioid use disorder. This idea was not tested until the 1960s, with the publication of the landmark study by Dole and Nyswander (1965), which demonstrated that methadone relieved "narcotic hunger" and produced tolerance such that the euphoric effect of heroin was substantially blunted (Dole and Nyswander 1965).

Although methadone and morphine are both full μ-opioid receptor agonists with substantial addiction liabilities, methadone is a preferable opioid use disorder therapeutic because of a substantially longer half-life and higher oral bioavailability. Methadone distribution is restricted to clinics to ensure that the drug is taken orally, which obviates withdrawal and maintains tolerance in the absence of euphoria. Methadone is not prescribed for home use because of the legitimate fear that, in the absence of monitoring, the drug will be solubilized and administered intravenously, thereby producing a high roughly equivalent to morphine or heroin administered by the same route. In the case of methadone, the clinical trial came before animal studies. Over the years, a number of animal studies have confirmed that methadone prevents opioid withdrawal and blunts relapse in animal models of craving (Goode 1971; Jones and Prada 1977; Negus 2006).

Although there is no question that methadone has proven to be effective in the treatment of opioid use disorder, there are several problems with the methadone clinic model. Primarily, the distance to the closest clinic may render daily clinic visits unfeasible. For some patients living in close proximity to a clinic, the stigma associated with daily visits to a methadone clinic reduces compliance. A clever pharmacological strategy was developed to produce a therapeutic for opioid use disorder that could be taken at the convenience of the patient. It was noted that opioid receptor agonists have good oral bioavailability, whereas the opioid receptor antagonist naloxone does not. Thus, if a pill contains both compounds and is taken orally, the opioid receptor agonist effect predominates. In contrast, if the therapeutic is administered intravenously, the antagonist would block the agonist effect. This strategy led to the development of Suboxone, which is a combination of buprenorphine and naloxone. Buprenorphine, which was developed by Reckitt and Colman in the 1970s as an analgesic, was chosen over methadone because it is a partial μ-opioid receptor agonist, which, in contrast to methadone, has a low instance of death associated with overdose (Mendelson and Jones 2003). Suboxone was approved by the FDA for the treatment of opioid use disorder in 2002 following the passage of DATA 2000 by the U.S. Congress, which allowed individual physicians to be certified to prescribe opioid-based therapeutics for the treatment of opioid use disorder. Although Suboxone rapidly became the first-line prescription treatment for opioid use disorder (Department of Veterans Affairs and Department of Defense 2015), limits on the number of opioid-dependent patients each physician is allowed to treat have constrained the even wider use of this effective medication. Accessible and effective pharmacotherapeutic treatments for opioid use disorder, like Suboxone, are particularly important given the emergence of the opioid epidemic, declared a public health emergency by the U.S. Department of Health and Human Services in 2017.

NALTREXONE FOR OPIOID USE DISORDER AND ALCOHOL USE DISORDER

In the early 1970s, receptor-binding assays were used to show that "narcotic antagonists" such as naloxone bind to specific receptors in the brain. Opioid receptor antagonists including naltrexone and naloxone were subsequently tested as pharmacotherapies for opioid addiction (Martin et al. 1973). The discovery of endogenous opioids and their receptors prompted research

into the potential role of opioid peptides in the effects of many drugs including alcohol. Initial reports suggested that naltrexone and naloxone reduced alcohol preference in hamsters and rats (Ross et al. 1976) and attenuated alcohol reinforcement in rhesus monkeys (Altshuler et al. 1980). Based on these and similar findings, a placebo-controlled, double-blind clinical trial examining the effect of naltrexone on alcohol relapse was performed. Results indicated that naloxone cut the relapse rate approximately in half compared to controls (Volpicelli et al. 1992). These results were rapidly replicated, with the highest rates of abstinence observed in patients who received both naltrexone and supportive therapy (O'Malley et al. 1992). Numerous trials subsequently showed that naltrexone is effective in the treatment of alcohol use disorder.

A single-nucleotide polymorphism at A118G (Asn40Asp) in exon I of the μ-opioid receptor was identified and shown to triple the potency of β-endorphin at these receptors (Bond et al. 1998). This polymorphism was shown to be associated with alcohol addiction (Bart et al. 2005) and individuals with one or two copies of the Asp40 allele treated with naltrexone had significantly lower rates of relapse than patients homozygous for the Asn40 allele (Oslin et al. 2006). Thus, naltrexone treatment of alcohol use disorder is one of the few examples of a pharmacogenomic therapeutic. Naltrexone, which is marketed as ReVia and Depade, has been used in the treatment of opioid use disorder since 1984 and alcohol use disorder since 1995. In 2006, an extended-release injectable formulation of naltrexone (Vivitrol) was approved by the U.S. FDA for the treatment of alcohol and opioid use disorders. Naltrexone and acamprosate are each currently first-line pharmacotherapies for alcohol use disorder in the United States.

ACAMPROSATE FOR ALCOHOL USE DISORDER

Acamprosate, a homotaurine derivative, was developed in France in the 1980s. The rationale was that since alcohol activates $GABA_A$ receptors and homotaurine is a GABA receptor agonist, perhaps homotaurine derivatives might serve as alcohol replacement therapies (Boismare et al. 1984). Indeed, calcium bis acetylhomotaurine (acamprosate) significantly reduced the voluntary intake of alcohol by rats (Boismare et al. 1984). Based on this result, acamprosate was tested in a double-blind placebo-controlled clinical trial with the success criterion defined as alcohol abstinence following 3 months of outpatient treatment. Results indicated that 20 of 33 patients receiving acamprosate remained alcohol-free compared to 12 of 37 subjects receiving placebo (Lhuintre et al. 1985). The efficacy of acamprosate as an effective therapeutic for alcohol use disorder has been repeatedly replicated (Mason and Heyser 2010). Acamprosate has been used for the treatment of alcohol use disorder in Europe since 1989. Surprisingly, the precise mechanism of action of acamprosate remains unclear. Because of the ambiguity of the drug's mechanism of action, the U.S. FDA delayed approval of acamprosate (marketed as Campral) until 2004.

Although acamprosate was targeted for the treatment of alcohol use disorder because of presumed effects on GABA and taurine transmission, the therapeutic effects of this drug appear to be due primarily to effects on glutamate systems. Although initial reports suggested that acamprosate is an NMDA receptor antagonist, subsequent work indicated that acamprosate acts as a partial agonist at spermidine sites on NMDA receptors (Dahchour and De Witte 2000) and also is an mGluR5 receptor antagonist (De Witte et al. 2005). Alcohol withdrawal is associated with a number of changes in neurotransmission including, notably, increased glutamate transmission in regions of the CNS (Mason and Heyser 2010). A growing body of evidence is consistent with the notion that acamprosate blunts alcohol craving and withdrawal by normalizing glutamate transmission (Heilig and Egli 2006).

Disulfiram also is used in the treatment of alcohol use disorder. However, this drug does not specifically target aspects of addiction or withdrawal. Rather, disulfiram blocks aldehyde dehydrogenase resulting in the accumulation of

acetaladehyde after alcohol ingestion, which produces an array of aversive symptoms. Thus, disulfiram acts as a punishing agent in the event of relapse rather than a therapeutic. Although disulfiram continues to be used in the treatment of alcohol use disorder, there are concerns related both to the safety and effectiveness of this compound (Heilig and Egli 2006).

NICOTINE, VARENICLINE, AND BUPROPION FOR NICOTINE USE DISORDER

The history of nicotine replacement therapies dates to a letter Dr. Claes Lundgren, a physiology professor at Lund University, sent to his friend Ove Fernö at Aktiebolaget Leo pharmaceutical company in 1967. Lundgren and his colleague, Stephan Lichtneckert, suggested oral nicotine as a substitute for tobacco based on the observation that sailors sometimes switched from smoking to chewing tobacco without difficultly when assigned to submarine duty. Fernö immediately recognized the promise and commercial potential of nicotine replacement and embarked on a research program to design a means to orally administer nicotine with delayed absorption. The result was nicotine gum. Years later, Fernö reflected on his work as follows: "Putting nicotine into chewing gum is not an invention. Fixing the nicotine to an ion exchange resin and putting that into a chewing gum to enable the chewer to control the rate of release—that is an invention" (Ferno 1994). Initial clinical trials performed in Sweden (Ferno et al. 1973) and London (Russell et al. 1976) in the 1970s indicated that nicotine gum was effective in reducing nicotine withdrawal and maintaining smoking abstinence. A landmark randomized double-blind, placebo-controlled clinical trial published in 1982 indicated that smoking abstinence was 47% in the nicotine gum group compared to a 21% success rate among controls (Jarvis et al. 1982). These results led to the approval of nicotine gum, which Aktiebolaget Leo (acquired as McNeil by Johnson & Johnson) named Nicorette, by the U.S. FDA in 1984. Nicotine gum, nicotine lozenges, patches, nasal sprays, and inhalers are all popular forms of nicotine replacement therapy and are effective in maintaining abstinence from tobacco use (Polosa and Benowitz 2011). The combination of slow-release forms like transdermal patches and acute nicotine replacement via lozenges or gum have been shown to be particularly effective at maintaining abstinence and reducing craving in meta-analyses of clinical trials (Shah et al. 2008; Lindson et al. 2019). Electronic cigarettes (or e-cigarettes) were initially considered as another form of nicotine replacement therapy. However, concerns about lack of consistent regulations, unknown long-term health consequences, and the possibility of their use as a "gateway" to smoking cigarettes or cannabis, particularly among the youth, all contribute to the failure of any e-cigarettes or similar vaping products to be approved by the FDA as nicotine use disorder therapeutics (Sharpless 2019).

Animal studies are notably absent in the history of Nicorette. More recently, a rational strategy led to the development of the partial nicotinic receptor agonist varenicline for smoking cessation. Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ions channels composed of combinations of at least 17 different subunits (Pierce and Kumaresan 2006). A number of studies indicate that α4β2 nAChRs, which are the most widely expressed subtypes in the brain, play a critical role in nicotine-induced dopamine release and reinforcement (Mineur and Picciotto 2008). The α4β2 nAChR partial agonist varenicline was developed by Pfizer for smoking cessation. The rationale was that varenicline might serve the dual purpose of moderately increasing mesolimbic dopamine levels, which are reduced during nicotine withdrawal, and also blunting nicotine-induced dopamine release in the event of relapse (Coe et al. 2005). Animal studies revealed that varenicline reduced nicotine-induced dopamine release in the nucleus accumbens (Coe et al. 2005) and inhibited nicotine self-administration as well as the reinstatement of nicotine seeking (O'Connor et al. 2010). A randomized double-blind clinical trial demonstrated that the smoking abstinence rate with varenicline was 44% compared with nearly 18% for placebo (Gonzales et al. 2006; Jorenby et al. 2006). Notably, measures of nicotine withdrawal and craving also were reduced by

varenicline (Gonzales et al. 2006). Based on these results, the U.S. FDA fast-tracked approval for varenicline (Chantix) as a smoking cessation drug, which was granted in 2006.

The initial varenicline smoking cessation clinical trials used bupropion as a positive control. The abstinence rate for bupropion was nearly 30%, which is significantly greater than placebo but substantially lower than varenicline (Gonzales et al. 2006; Jorenby et al. 2006). Bupropion, which was developed by Burroughs Wellcome & Company (now GlaxoSmithKline), was approved for the treatment of depression by the U.S. FDA in 1985. A sustained release formulation of bupropion, marketed as Wellbutrin SR, remains a highly successful antidepressant. Antidepressants were tested as smoking cessation agents because cigarette smokers have higher rates of depression that may be exacerbated by nicotine withdrawal (Glassman et al. 1990). Double-blind placebo-controlled clinical trials revealed that a sustained-release formulation of bupropion significantly increased the rate of smoking cessation (Hurt et al. 1997). Bupropion was approved for the treatment of nicotine addiction in 1997 and is marketed as Zyban. Similar to other antidepressants, bupropion is a dopamine and norepinephrine reuptake inhibitor. Interestingly, bupropion also is an nAChR antagonist at various subtypes including $\alpha4\beta2$ (Slemmer et al. 2000), which may account for the effectiveness of bupropion as a smoking cessation agent relative to other antidepressants.

PSYCHOSTIMULANTS

Despite decades of focused research efforts, there are no effective pharmacotherapies for psychostimulant use disorders. Indeed, a broad range of drugs targeting multiple CNS transmitter systems have been tested as treatments for psychostimulant dependence without success (Kampman et al. 2005). Drugs that modulate dopaminergic transmission were among the first assessed for the treatment of psychostimulant addiction both in animal studies and clinical trials. Dopamine receptors are classified as either D1-like or D2-like. There was substantial interest in D1-like dopamine receptor antagonists as psychostimulant use disorders therapeutics as they lack the sometimes serious extrapyramidal side effects associated with D2-like dopamine receptor antagonists (Haney and Spealman 2008). Animal and human laboratory studies revealed that acute administration of D1-like dopamine receptor antagonists attenuated the reinforcing effects of cocaine (Romach et al. 1999; Platt et al. 2002). However, clinical use of a D1-like dopamine receptor antagonist requires repeated administrations. Unfortunately, when humans were maintained on the D1-like dopamine receptor antagonist, ecopipam, cocaine self-administration actually increased (Haney et al. 2001). This finding is consistent with results from rhesus monkeys utilizing continuous drug administration (Kleven and Woolverton 1990) and is likely due to antagonist-induced increases in D1 dopamine receptor density in the brain (Haney and Spealman 2008). It is important to emphasize that in the case of ecopipam, the animal and human data paralleled one another both when the drug was administered acutely and repeatedly.

Fortunately, there are other examples of rationally developed therapeutics for psychostimulant use disorders that appear promising. *N*-acetylcysteine (NAC), which is used to treat acetaminophen overdose, has been shown to normalize decreased nucleus accumbens glutamate levels following cocaine self-administration as well as the reinstatement of cocaine-seeking behavior in rats (Baker et al. 2002, 2003). Clinical trials demonstrate that NAC attenuated cocaine use and decreased desire to use cocaine (LaRowe et al. 2007; Mardikian et al. 2007). Recent clinical trials also support the ability of NAC to reduce incentive salience for cocaine cues (Levi et al. 2017) and delay relapse in cocaine-abstinent subjects (LaRowe et al. 2013), suggesting that NAC may be therapeutically beneficial in maintaining abstinence and/or preventing relapse. Another interesting strategy is the development of cocaine vaccines. Active immunization with a cocaine vaccine attenuated cocaine self-administration as well as the reinstatement of cocaine seeking in rats (Kantak et al. 2000). Clinical data indicate that the cocaine vaccine, TA-CD, produced selective anti-

cocaine antibodies, which blunted the intoxicating effects of cocaine (Haney et al. 2010). In these studies, insufficient immune responses to vaccines is a persistent issue, which has led to the development of novel vaccines designed to generate consistently high antibody titers (Wee et al. 2012). An adenovirus-based cocaine vaccine reduced motivation for cocaine and reinstatement of cocaine seeking in rats (Wee et al. 2012) and delayed reacquisition of cocaine self-administration in nonhuman primates (Evans et al. 2016); this cocaine vaccine dAd5GNE is currently under investigation in a phase I clinical trial. An obvious issue with vaccines is their specificity. That is, a cocaine vaccine will not be effective against amphetamine or its derivatives, which might be substituted for cocaine during a bout of drug craving. Cocaine antibodies also could be whelmed with a sufficiently high dose of the drug.

In terms of the validity of animal models of psychostimulant addiction, we note that the preclinical and clinical data are consistent when the animal model is drug self-administration (Haney and Spealman 2008). Moreover, two of the more promising cocaine use disorder therapeutics (NAC and cocaine vaccines) were tested primarily with self-administration models of addiction and relapse.

SUMMARY AND CONCLUSIONS

We have reviewed the development of the eight main compounds currently used in the treatment of substance use disorders. As outlined in Table 1, two of these drugs are antagonists, one is a transporter inhibitor, two are full agonists, and three are partial agonists. Clearly, the most successful treatments for addiction involve receptor stimulation, with the primary goal of obviating drug withdrawal. Agonist therapeutics also reproduce some of the positive aspects of the drug of abuse (e.g., mood elevation), which enhances compliance. Partial agonists are particularly appealing as they blunt the psychoactive effects of the drug of abuse in the event of relapse. Moreover, the risk of overdose is substantially diminished with partial relative to full agonists.

Table 1 Therapeutics used in the treatment of substance use disorders and their mechanism of action

Therapeutic	Drug of abuse	Mechanism of action
Acamprosate	Alcohol	Partial agonist
Buprenorphine	Opioids	Partial agonist
Bupropion	Nicotine	Indirect agonist
Methadone	Opioids	Agonist
Naloxone	Opioids	Antagonist
Naltrexone	Alcohol, opioids	Antagonist
Nicotine	Nicotine	Agonist
Varenicline	Nicotine	Partial agonist

The fact that partial agonists are particularly effective addiction therapeutics raises the question of partial dopamine agonist treatments for psychostimulant use disorders (Platt et al. 2002; Keck et al. 2015). Surprisingly, there is very little clinical research in this area. Indeed, the only compound tested clinically is the D2-like dopamine receptor partial agonist aripiprazole, which is approved for the treatment of schizophrenia, depression, and bipolar disorder. Aripiprazole reduced cocaine reinstatement in rats (Feltenstein et al. 2007) and decreased the discriminative stimulus properties of amphetamine in a human laboratory study (Lile et al. 2005). Initial clinical trial results have been mixed with one study reporting that aripiprazole reduced cocaine craving and use (Meini et al. 2011). In contrast, another clinical trial showed that aripiprazole increased the self-administration of smoked cocaine, apparently to compensate for decreased subjective effects of cocaine (Haney et al. 2011). These experiments highlight both the promise of partial agonists in the treatment of psychostimulant use disorders and the persistent frustration in developing clearly effective therapeutics for stimulant craving and addiction.

Overall, it is clear that a disconnect exists between even well-designed preclinical studies that identify potential addiction pharmacotherapies and clinical outcomes in patients with substance use disorders. One important factor may be sex differences in the responsiveness to any given treatment. In 2016, the National Institutes

of Health instituted a requirement that all research studies account for sex as a biological variable. Increased preclinical focus on sex may clarify whether the effects of potential pharmacotherapies are dependent on sex, expanding upon previous studies that may have been predominantly performed in males. Personalized medicine strategies could also unlock new treatments for substance use disorders. Pharmacogenomic approaches that tailor treatment to individuals based on single-nucleotide polymorphisms, illustrated above by improved outcomes of naltrexone treatment for alcohol use disorder in patients with the Asp40 allele (Oslin et al. 2006), are excellent examples of how individual differences can be leveraged for better pharmacotherapeutic development and implementation.

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