Future pharmacological treatments for substance use disorders

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Substance use disorders represent a serious public health and social issue worldwide. Recent advances in our understanding of the neurobiological basis of the addictive processes have led to the development of a growing number of pharmacological agents to treat addictions. Despite this progress, there are no approved pharmacological treatments for cocaine, methamphetamine and cannabis addiction. Moving treatment development to the next stage will require novel ways of approaching substance use disorders. One such novel approach is to target individual vulnerabilities, such as cognitive function, sex differences and psychiatric comorbidities. This review provides a summary of promising pharmacotherapies for alcohol, opiate, stimulant and nicotine addictions. Many medications that target positive and negative reinforcement of drugs, as well as individual vulnerabilities to addiction, are in different phases of development. Clinical trials testing the efficacy of these medications for substance use disorder are warranted.

Introduction

Worldwide psychoactive substance use is estimated at 2 billion alcohol users, 1.3 billion smokers and 185 million drug users [1]. Alcohol and illicit drug use account for 5.4% of the world's annual disease burden, with tobacco being responsible for 3.7% [2]. Furthermore, tobacco, alcohol and illicit drugs together account for 12.4% of all deaths worldwide [1]. In the USA, the economic costs related to substance use (e.g. health care, loss of productivity and criminal justice system costs) are over half a trillion dollars [3]. The cost in Europe has been estimated to be up to €18 000 per individual user per year [4].

Development of effective treatments for substance use disorders (SUDs) is essential to reduce the impact of substance use on both the individual and society. The role of pharmacological interventions to treat addictive disorders has solidified over the last decade. Despite the growing number of pharmacological agents to treat SUDs, they remain largely undertreated [5]. Furthermore, pharmacotherapies for some substances, such as cannabis, cocaine and methamphetamine, are lacking [6, 7]. For these reasons, there is a need to develop novel pharmacological interventions.

This review summarizes promising pharmacotherapies targeting positive and negative reinforcement, as well as

individual vulnerabilities (see Table 1). Traditional pharmacological approaches to substance abuse treatment are informed by the underlying neurotransmitters affected by substances of abuse [8–12] and are aimed at blocking or reducing drug reward (positive reinforcement) or alleviating withdrawal states (negative reinforcement). Some medications have an effect on both positive and negative reinforcement, and in this review these effects are described separately under the respective headings. More recent approaches have also focused on individual vulnerabilities as a treatment target for SUDs [13]. This review does not include medications that are marketed for the treatment of SUDs (for recent reviews, see [14, 15]). While we review potential treatments for alcohol, opioid, stimulant and nicotine addiction, the targets for stimulant dependence are emphasized. We conclude with future directions.

Promising medications for substance use disorders

Medications targeting positive reinforcement

Positive reinforcement is thought of as any stimulus that increases the probability of the preceding behaviour, and typically involves a hedonic reward. Self-administration is

Table 1

Summary of promising pharmacotherapies for the treatment of substance use disorders

Target	Agent	Mechanism of action	Type of addiction	Efficacy
Dopamine	Amphetamines	Stimulate vesicle release and reverse dopamine transporter	Stimulants	Reduce drug use in short-term clinical trials in cocaine [33, 34] and methamphetamine users [35, 36]
	Modafinil, bupropion	Dopamine transporter inhibitors	Stimulants	Modafinil did not significantly reduce cocaine use compared with placebo [50–52]. Bupropion was only effective in light methamphetamine users [55–57]
	Disulfiram, nopicastat	Dopamine- β -hydroxylase inhibitors	Stimulants	Disulfiram is effective in decreasing cocaine use clinically [59–64]. Nopicastat blocks cocaine-induced reinstatement of cocaine seeking in rats [65], not tested clinically
	S33138, SB-277011A, NGB 2904, YQA14, BP-897, CJB-090	D ₃ receptor antagonists and partial agonists	Stimulants	Preclinically attenuated cocaine reinforcement [67], self-stimulation and reinstatement of cocaine and amphetamine [68–73]
Opioids	Nalmefene	μ - and δ -opioid receptor antagonists, partial κ -opioid receptor agonist	Alcohol	Reduced number of heavy drinking days and total alcohol consumed [77–80]
Immunotherapies	NicVAX	Nicotine vaccine		Vaccination failed to increase continuous abstinence rates over placebo [86, 87]
	TA-CD	Cocaine vaccine		Currently in phase IIB trial [88]
Neuropeptides	Antalarmin	Corticotrophin-releasing factor 1 receptor antagonist	Alcohol, opiates	Reduces ethanol consumption [117, 118] and attenuates stress-induced reinstatement of alcohol and heroin [115, 119]; reduces negative symptoms of opiate withdrawal [120–122] in preclinical studies
	SB-334867	Orexin-1 receptor antagonist	Alcohol, cocaine, nicotine, opiates	Reduces nicotine [127] and alcohol [128] self-administration; attenuates cue-induced cocaine reinstatement [129], cue- and stress-induced alcohol reinstatement [128, 130] and opiate withdrawal symptoms [126] in preclinical studies
Noradrenergic system	Lofexidine	α_2 -Adrenergic receptor agonist	Cocaine, opiates	May attenuate stress-induced relapse in cocaine and opioid users [133, 134]
	Carvedilol	α - and β -adrenergic receptor antagonist	Stimulants	Clinical trials underway; NCT00566969 and NCT01171183, clinicaltrials.gov
	Guanfacine	α_2 -Adrenergic receptor agonist	Stimulants	Clinical trial underway; preliminary results show attenuated cue-induced cocaine craving [135]
	Prazosin	α_1 -Adrenergic receptor agonist	Alcohol, cocaine, opiates	In humans, decreased drinking [140] and stress- and cue-induced alcohol craving [141]; reduced ethanol [136, 137] and heroin [138], and attenuated drug induced-reinstatement for cocaine [139] in preclinical studies
Glutamate	Memantine	Non-competitive <i>N</i> -methyl-D-aspartic acid antagonist	Alcohol, cocaine	Reduced cue-induced craving for alcohol [145], but did not reduce use of alcohol [146] or cocaine [147] compared with placebo
	<i>N</i> -Acetylcysteine	Cystine–glutamate antiporter stimulation	Cocaine, nicotine	Positive results in small clinical trials for cocaine [156] and nicotine addiction [158]
	LY379268	Group II metabotropic glutamate receptor agonist	Alcohol, cocaine, nicotine, opiates	In preclinical studies, reduces self-administration and reinstatement of drug-seeking behaviour for alcohol [159, 160], cocaine [161, 162], heroin [163] and nicotine [164]
	MPEP, MTEP	Metabotropic glutamate receptor 5 antagonists	Alcohol, nicotine, stimulants	Reduce rates of self-administration and cue-induced reinstatement for alcohol [160, 165, 166], stimulants [167–169] and nicotine [170, 171]
GABA	Vigabatrin	GABA transaminase irreversible inhibitor	Alcohol, cocaine	Compared with placebo, led to a higher percentage of subjects achieving and maintaining abstinence from cocaine and alcohol [174]
	Baclofen	GABA _B receptor agonist	Alcohol, opiates, stimulants	Shown efficacy and safety in promoting alcohol abstinence in alcohol-dependent patients [175–178], decreased opiate withdrawal symptoms [179], and mixed results with stimulant dependence [180–184]
	CGP7930, GS39783, BHF177	GABA _B receptor positive allosteric modulators	Alcohol, nicotine, stimulants	Attenuate the reinforcing and reward-enhancing effects of alcohol [188], nicotine [189, 190] and stimulants [191–194] in preclinical studies
Acetylcholine	Galantamine	Acetylcholinesterase inhibitor, allosteric potentiator of acetylcholine receptor	Cognitive enhancement: cocaine, nicotine	Improved sustained attention and working memory functions in abstinent cocaine users [223], and sustained attention and response inhibition [225] in smokers
Norepinephrine	Atomoxetine	Selective norepinephrine transporter inhibitor	Cognitive enhancement: cocaine	Improves attention and response inhibition functions in healthy control subjects and ADHD [231–233]; untested in cocaine users
Progesterone	Micronized progesterone	Exact mechanism unknown; possible GABA agonist effects	Cocaine	In cocaine-dependent women, progesterone attenuates cravings for [272] and subjective positive response to stimulants [273–276]

Abbreviations are as follows: ADHD, attention deficit hyperactivity disorder; GABA, γ -aminobutyric acid; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine.

the primary measure for drug reinforcement, and almost all reinforcing drugs induce subjective drug reward or 'liking' in humans. While the exact function of dopamine in addictive behaviour continues to be debated [16–18], dopamine is thought to mediate primarily incentive salience or 'wanting' [19], while drug pleasure or 'liking' is thought to be mediated by other neurotransmitters, including endogenous opioids, γ -aminobutyric acid (GABA) and endocannabinoids [20–22]. Identification of the neurotransmitter mechanisms that mediate drug 'wanting' and 'liking' responses may facilitate the development of new pharmacotherapy targets for SUDs.

Agonist approaches Agonist medications act on the same types of neurotransmitter receptors as those stimulated by drugs of abuse. The main strategy of agonist treatments is to substitute a safer, more long-acting drug for the more risky, short-acting one. Traditional examples of agonist treatment include methadone for opioid dependence and nicotine replacement treatment for smoking cessation. The agonist treatment approach has also been examined for the treatment of stimulant dependence [23, 24] and has mainly focused on increasing extracellular dopamine. The dopamine system is a central target owing to its role in drug reinforcement [25, 26] and the dopamine function deficits that result from chronic drug use [27–29].

Amphetamines increase synaptic dopamine release by disrupting the storage of dopamine in intracellular vesicles and reversing the dopamine transporter [30–32]. Dextroamphetamine has reduced drug use in short-term clinical trials in cocaine [33, 34] and methamphetamine users [35, 36]. Methylphenidate, which like cocaine increases synaptic dopamine levels by inhibiting reuptake by monoamine transporters, has had limited success in cocaine-dependent individuals [37–40], and in one clinical trial reduced use among amphetamine-dependent individuals [41]. The long-term safety and abuse liability of amphetamines as a treatment for stimulant addiction remain to be determined.

Advances in drug delivery might prove beneficial in decreasing abuse liability and enhance the safety of amphetamines for the treatment of stimulant addictions. The prodrug lisdexamfetamine is one example. Lisdexamfetamine is converted to dextroamphetamine by enzymatic cleavage of lysine from the amphetamine [42], and this process results in a slow onset and long-lasting efficacy regardless of administration route [43]. Lisdexamfetamine attenuates the maximal response on measures of abuse liability compared with dextroamphetamine at equivalent doses of amphetamine base [44]. Clinical trials are currently underway to examine the use of LDX for cocaine dependence (NCT01490216, NCT01486810; clinicaltrials.gov).

Modafinil is another example of an agonist approach for psychostimulant dependence. It is a stimulant-like medication that acts as a weak dopamine transporter

inhibitor and increases synaptic dopamine levels [45]. Modafinil also stimulates hypothalamic orexin neurons, reduces GABA release and increases glutamate release [46]. Initial clinical trials with modafinil were promising for cocaine and methamphetamine addiction [47–49]; however, subsequent larger randomized clinical trials have been negative [50–52].

Other drugs that enhance dopamine have been evaluated as potential therapeutic interventions with mixed results. Bupropion, which acts as a dopamine and norepinephrine reuptake inhibitor [53] and enhances extracellular dopamine levels in the nucleus accumbens [54], has failed to show any significant effect for cocaine and heavy methamphetamine users, but does reduce use among light methamphetamine users [55–57]. Disulfiram, owing to its function as a dopamine- β -hydroxylase inhibitor, leads to increase levels of dopamine [58]. In clinical trials for cocaine dependence, it has been shown to decrease cocaine use [59–64]. A selective dopamine- β -hydroxylase inhibitor, nopicastat, has been found in preclinical trials to block cocaine-induced reinstatement of cocaine seeking in rats [65]. Clinical trials are still needed to determine the utility of nopicastat for cocaine use disorders, but its preclinical data and mechanistic similarity to disulfiram make it a promising therapy.

Antagonists Antagonists have their impact on the same neurotransmitter systems as abused drugs but block the effects of these drugs. Examples of established antagonist treatment include naltrexone or buprenorphine for opioid dependence, naltrexone for alcohol dependence and varenicline for nicotine dependence. Antagonists and partial agonist of the dopamine D_3 receptors are promising targets for the treatment of cocaine addiction [66]. While D_3 agonists enhance the rewarding effects of cocaine, D_3 antagonists or partial agonists, in animals attenuate cocaine reinforcement [67] and reduce self-stimulation and reinstatement of cocaine and amphetamine [68–73]. The efficacy of D_3 partial agonists and antagonists still needs to be examined in human studies.

Evidence suggests that μ - and δ -opioid receptors play a major role in ethanol reinforcement and dependence [74, 75]. Similar to naltrexone, nalmefene is a selective opioid receptor antagonist with activity at μ - and δ -opioid receptors and partial agonistic activity at the κ -opioid receptor [76]. Clinically, it has demonstrated efficacy in reducing the number of heavy drinking days and total alcohol consumed [77–80].

Pharmacokinetic strategies Pharmacokinetic strategies, which target the drug molecule itself with the goal of reducing drug concentration via peripheral blocking with immunotherapies or increased drug metabolism, are attractive alternatives to conventional pharmacological treatments (for a comprehensive review, see Gorelick [81]). By developing antibodies that bind the drug of abuse

following its use, immunotherapies reduce the amount of drug that reaches the brain and attenuate its rewarding effects. Antidrug vaccines utilize active immunity and are the most developed type of immunotherapy. Initial clinical trials suggest some promise in this approach [82, 83]. However, the efficacy of vaccines to date has been undercut by a substantial induction period required to achieve clinically significant levels of circulating antibodies. Furthermore, even when antibody levels are maximized only partial blockade of drug effects are seen.

The nicotine vaccine, NicVAX [84], while initially promising [85], did not show greater abstinence in the vaccinated group compared with the placebo group in a phase III trial [86, 87]. A multisite phase IIB clinical trial for an anticocaine-addiction vaccine is currently underway [88], following the encouraging results from a placebo-controlled clinical trial of the vaccine [82]. Vaccines for methamphetamine and opiates are currently in preclinical development. High-affinity antimethamphetamine antibodies have been shown to reduce methamphetamine self-administration [89] and locomotor activity in rats [90, 91]. Polyclonal antibodies generated by morphine vaccines are able to bind to morphine with high affinity [92, 93], and efficacy studies have demonstrated a significant inhibition of the reinforcing effects of morphine in animals [88]. An important limitation of vaccines is that the antibodies produced are specific for a given drug of abuse, which will limit their clinical efficacy in polysubstance users. The most promising use of vaccines will be to prevent relapse in an individual whose drug use is limited to a single agent.

Another type of immunotherapy relies on antidrug antibodies generated via passive immunity, from monoclonal antibodies (mAbs) created outside the body. Currently, no antidrug mAbs have been studied in humans, but several are in preclinical development against cocaine, phencyclidine, methamphetamine and nicotine. Anticocaine mAbs, 2E2 and GNC92H2, reduce cocaine-primed reinstatement [94] and self-administration [95], respectively, while the antimethamphetamine mAbs, mAb4G9 and mAb6H4, decrease methamphetamine self-administration [91, 96]. The antiphencyclidine antibody, mAb6B5, decreases brain concentrations of phencyclidine and protects against the toxic and locomotor effects of phencyclidine [96]. While this preclinical evidence suggests that mAbs could be an effective treatment for acute cocaine, methamphetamine or phencyclidine intoxication or overdose, the clinical feasibility and utility of this approach remains to be determined. Further research is needed to address the lack of comprehensive animal toxicology studies, the lack of human trials, the short duration of action and the potential for evoking immune reactions.

The increased drug metabolism strategy has been studied only with cocaine, and utilizes drug-metabolizing enzymes and catalytic mAbs. Butyrylcholinesterase is a cocaine-metabolizing enzyme, which has been shown to increase cocaine metabolism substantially, to reduce

cocaine concentrations in the brain and to reduce the acute behavioural, cardiovascular and toxic effects of cocaine [97]. Bacterial cocaine esterase [98, 99] and anticocaine catalytic antibodies [100, 101] have also been studied and found to prevent the neurological and cardiovascular toxicity and to reduce self-administration in rodents. As with mAbs, drug-metabolizing enzymes and catalytic mAbs have the potential to become effective treatments for SUDs, but substantial further research is required to determine their clinical utility as described above.

Medications targeting negative reinforcement

Development of drug addiction is associated with neuroadaptive changes in multiple neurotransmitter systems in the brain, including dopamine, norepinephrine, corticotrophin-releasing factor (CRF), GABA and glutamate [102]. These neuroadaptive changes to the reward system are thought to underlie the negative reinforcing effects of abstinence from drug use that are clinically observed as withdrawal symptoms, craving for drug use and negative mood states, such as dysphoria, irritability and anxiety [103]. Increased CRF and norepinephrine activity is associated with the anxiety-like state seen during acute withdrawal [104]. Sensitization to drug-related cues, perceived as craving induced by drug cues, is likely to involve adaptive changes in the dopamine, GABA and glutamate systems [105]. Reduction of dopamine levels in the reward circuit is thought to mediate the anhedonia commonly observed following abstinence from drugs [106]. Examples of medications targeting negative reinforcement of drugs include methadone or buprenorphine, which relieve opioid withdrawal symptoms, and bupropion and varenicline, which relieve nicotine withdrawal symptoms and attenuate the negative mood states following smoking cessation [107, 108].

Stress and the underlying mechanisms that regulate stress, including CRF, play an important role in the development of addiction and induction of relapse [109–113]. In rats, CRF type 1 (CRF1) receptor antagonists inhibit drug reinstatement of cocaine [114, 115] and methamphetamine [116]. Antalarmin, a selective, centrally acting CRF1 receptor antagonist, reduces established ethanol consumption [117, 118] and attenuates stress-induced reinstatement in animal models [119]. Furthermore, CRF1 receptor antagonists attenuate stress-induced reinstatement of heroin [115] and the negative symptoms of opiate withdrawal in preclinical studies [120–122]. While there have been no clinical trials of CRF1 antagonists for SUDs, in trials for depression and anxiety, CRF1 antagonists were safe and well tolerated, further supporting their promise for the treatment of SUDs.

Compounds that target orexin neurons, and orexin-1 receptor antagonists in particular, may provide novel treatments for addiction. Orexin A and B are neuropeptides deriving from the lateral hypothalamus [123], which contains neurons projecting to reward-associated brain

regions, including the nucleus accumbens and the ventral tegmental area [124]. Orexins are thought to play a role in drug craving, withdrawal and relapse [125], as well as the regulation of stress and negative affect. The orexin-1 receptor antagonist, SB-334867, attenuates opiate withdrawal symptoms [126], reduces nicotine [127] and alcohol self-administration [128] and attenuates cue-induced cocaine reinstatement [129], as well as both cue- and stress-induced alcohol reinstatement in animals [128, 130]. Clinically, orexins have been implicated in the affective dysregulation seen during withdrawal in alcohol-dependent patients [131, 132]. Future clinical studies are needed to evaluate the role of therapies involving the orexinergic system further.

Medications targeting the noradrenergic system have shown promising results for treatments aimed at withdrawal or relapse. Preclinical and human laboratory studies suggest that lofexidine, an α_2 -adrenergic agonist, may attenuate stress-induced relapse in cocaine and opioid users [133, 134]. Clinical trials are underway to test the efficacy of carvedilol (NCT00566969, NCT01171183; clinicaltrials.gov), an α - and β -adrenergic antagonist, and guanfacine (NCT00613015, NCT00585754; clinicaltrials.gov), an α_2 -adrenergic agonist, for psychostimulant addiction. Preliminary results from a guanfacine clinical study show attenuated cue-induced cocaine craving among cocaine-dependent individuals [135]. Prazosin, an α_1 -adrenergic receptor antagonist, decreased self-administration of ethanol [136, 137] and heroin [138] and attenuated drug-induced reinstatement for cocaine [139] in preclinical trials. In humans, prazosin led to decrease drinking [140] and decreased stress- and cue-induced alcohol craving [141].

There is growing interest in the role of the glutamate system in addiction [142, 143], and several agents targeting the glutamate system are under investigation as potential SUD treatments [144]. Memantine, a noncompetitive *N*-methyl-D-aspartic acid antagonist, has shown efficacy in reducing cue-induced craving for alcohol in alcohol-dependent patients [145]. However, clinical trials with memantine have not reduced use of alcohol [146] or cocaine [147] compared with placebo. Another medication that targets the glutamate system is *N*-acetylcysteine, a medication used for the treatment of paracetamol overdose. The proposed mechanism of action of *N*-acetylcysteine is the normalization of extracellular glutamate levels in the nucleus accumbens by stimulating the cystine–glutamate antiporter [148]. In preclinical studies, *N*-acetylcysteine reduces reinstatement of cocaine-seeking behaviour [149, 150], normalizes glutamatergic transmission in the nucleus accumbens altered by cocaine [151, 152] and decreases cue- and heroin-induced drug seeking [153]. In humans, *N*-acetylcysteine has shown some positive results in small clinical trials for cocaine [154–156], cannabis [157] and nicotine addiction [158]. Larger studies are underway to test its efficacy in these disorders.

Compounds targeting metabotropic glutamate receptors have also shown promise in the treatment of addiction. For example, the group II metabotropic glutamate receptor agonist, LY379268, in animal models reduces self-administration and reinstatement of drug-seeking behaviour for alcohol [159, 160], cocaine [161, 162], heroin [163] and nicotine [164]. The metabotropic glutamate type 5 receptor antagonists, 2-methyl-6-(phenylethynyl)-pyridine and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine, also reduce rates of self-administration and cue-induced reinstatement in animals for alcohol [160, 165, 166], stimulants [167–169] and nicotine [170, 171]. Several other metabotropic glutamate agonists are available for human use and need to be evaluated for the treatment of addictive disorders.

Interventions targeting GABA activity have also been investigated for the treatment of various SUDs. Vigabatrin, or γ -vinyl-GABA, is an irreversible inhibitor of GABA transaminase [172] that has been shown to reduce cocaine-induced dopamine release in laboratory animals [173]. In a randomized control trial, vigabatrin led to a higher percentage of subjects achieving and maintaining abstinence from cocaine and alcohol [174]. Baclofen, a GABA_B receptor agonist, has shown potential clinical efficacy in the treatment of alcohol [175–178] and opiate dependence [179], as well as mixed results with stimulant dependence [180–184]. However, there are concerns over negative side-effects and tolerance associated with long-term use [185]. The use of allosteric modulators of the GABA_B receptor has been examined to address this issue. The GABA_B receptor positive allosteric modulators (PAMs) augment GABAergic signalling by increasing the efficacy of endogenous GABA instead of directly activating the receptor [186, 187]. In preclinical trials, PAMs attenuated the reinforcing and reward-enhancing effects of alcohol [188], nicotine [189, 190] and psychostimulants [191–194]. In addition, the co-administration of PAMs with baclofen enhances its potency [195] and could potentially minimize its deleterious effects. Thus, PAMs hold promise as potential pharmacotherapies for SUDs.

Preclinical studies have shown that while stimulation of nicotinic acetylcholine receptors (nAChRs) releases dopamine in the nucleus accumbens, the nAChR antagonist mecamylamine has the opposite effect [196, 197]. Varenicline, which is marketed for smoking cessation, is a partial agonist for the $\alpha 4 \beta 2$ nAChRs [198, 199] and it has been suggested as a candidate for the treatment of cocaine or alcohol dependence [200–202]. Varenicline decreased cocaine use and reward in one small clinical trial [200], but showed no effect on cocaine abstinence among methadone-maintained subjects [203]. Clinical trials are underway for testing the efficacy of varenicline for methamphetamine (NCT01365819; clinicaltrials.gov) or alcohol dependence (NCT01347112, NCT01071187 and many others; clinicaltrials.gov). The nAChR may also be a target

for the cognitive-enhancement approach (see '*Medications targeting cognitive deficits*' below).

Medications targeting individual vulnerability factors to addiction

Individuals vary in their vulnerability to addiction, and the individual factors contributing to this vulnerability are complex and have not yet been fully elucidated [204–213]. While the concept of individual vulnerabilities is not new, many of the individual vulnerability factors, such as cognitive deficits, sex differences and comorbid psychiatric conditions, can be targeted in novel ways by pharmacotherapies.

Medications targeting cognitive deficits A large body of evidence has demonstrated that chronic drug use, including cocaine, methamphetamine, alcohol and cannabis use, as well as cigarette smoking, is associated with deficits in cognitive functioning, including deficits in decision making, response inhibition, planning, working memory and attention [214–217]. Cognitive deficits are associated with higher rates of attrition and poor treatment outcomes [218, 219]. Cognitive-enhancement strategies may especially be important early in the treatment by improving the ability to learn, remember and implement new skills and coping strategies. The range of deficits that are found in addicted individuals are attributed to the prefrontal cortex. Cognitive functioning in the prefrontal cortex is modulated by many neurotransmitters, including glutamate, GABA, acetylcholine and monoamines (dopamine, serotonin and norepinephrine) [220]. Many cognitive enhancers targeting these neurotransmitters are in different stages of development, as will be summarized below.

Cholinesterase inhibitors have been used for the treatment of dementia and other disorders characterized by cognitive impairment [221]. Galantamine is an acetylcholinesterase inhibitor and an allosteric potentiator of the nAChR, especially $\alpha 7$ and $\alpha 4\beta 2$ subtypes [222]. In a series of studies, we examined the potential use of galantamine as a cognitive-enhancing treatment of drug addiction. In a recent double-blind, placebo-controlled study, galantamine treatment improved sustained attention and working memory functions in abstinent cocaine users [223]. In a separate, double-blind study in opioid- and cocaine-dependent individuals, those receiving galantamine submitted fewer cocaine-positive urine specimens and reported less cocaine use than those assigned to placebo [224]. Randomized clinical trials are underway to test the efficacy of galantamine for the treatment of cocaine addiction. In addition, in a recent placebo-controlled study in abstinent cigarette smokers, galantamine improved sustained attention and response inhibition [225]. Galantamine also attenuated the subjective effects of nicotine administered intravenously, consistent with the enhancement by galantamine of cholinergic transmission. These findings demonstrate the feasibility,

safety and promise of galantamine as a potential cognitive enhancer for the treatment of cocaine and nicotine addiction.

Another promising medication for cognitive-enhancement strategy is atomoxetine, a selective norepinephrine transporter inhibitor used for the treatment of attention deficit hyperactivity disorder. In the prefrontal cortex, norepinephrine transporter is responsible for the reuptake of norepinephrine, as well as dopamine, into presynaptic nerve terminals [226], resulting in increased levels of both norepinephrine and dopamine. This increase in norepinephrine and dopamine may contribute to the cognitive-enhancing effects of atomoxetine [227, 228]. Consistent with preclinical studies [229, 230], atomoxetine improves attention and response inhibition functions in healthy control subjects and in patients with attention deficit hyperactivity disorder [231–233]. Attention and response inhibition functions are essential for the optimal cognitive control needed to prevent drug use behaviour. Both of these cognitive functions are impaired in cocaine users [234, 235]. Whether these cognitive functions can be improved with atomoxetine remains to be determined in clinical trials with cocaine users.

Minocycline, an antibiotic used to treat acne, is also under investigation for the treatment of neurodegenerative and neuropsychiatric disorders. It has anti-inflammatory and neuroprotective effects in the central nervous system that are thought to be mediated by the inhibition of microglial activation by minocycline [236]. Minocycline improved methamphetamine-induced recognition memory impairments [237] and neurotoxicity in mice [238]. In healthy control subjects, 4 days of minocycline (200 mg day⁻¹) improved response inhibition function as measured by the go/no-go task [239]. The effects of minocycline in addicted individuals remain to be determined.

There are many other potential cognitive enhancers (see Brady *et al.* [240]), including modafinil, guanfacine, amphetamines, partial nAChR agonists (such as varenicline) and metabotropic glutamate agonists [241, 242]. The safety and efficacy of these medications remain to be tested in clinical studies with addicted individuals. It is also worth noting that the comparison of individuals with SUDs and healthy control subjects on cognitive function requires careful consideration of potential confounders [242]. A recent review by Hart *et al.* noted that studies examining the neurocognitive effects of chronic methamphetamine use often do not control for differences between drug users and control subjects in education, IQ and other psychiatric comorbidities or length of abstinence within substance users [243]. In addition, some studies may employ suboptimal cognitive assessment tools and are often limited by small sample sizes [243]. Findings from these studies, therefore, need to be interpreted with such possible limitations in mind.

Sex differences: the role of estrogen and progesterone Accumulating evidence suggests that the female sex hormones, estradiol and progesterone, have wide-ranging effects on brain functioning, including modulation of the effects of drugs of abuse. A substantial amount of preclinical data supports a role for estrogen and progesterone in the acquisition, maintenance, sensitization to and reinstatement of stimulant drug use. Ovariectomized female rats [244–246] and monkeys [247] that are administered exogenous β -estradiol are more likely to self-administer [248–252] and express enhanced behavioural response to cocaine [253–255] compared with females that did not receive estrogen replacement. Progesterone has opposing effects and diminishes a number of cocaine-enhanced behavioural responses, including ambulation [256], rearing activity [256, 257] and conditioned placement preference [258, 259]. In addition, cocaine seeking [260], β -estradiol-enhanced cocaine self-administration [251, 252, 261] and reinstatement of cocaine self-administration [262, 263] are attenuated by progesterone.

The exact mechanisms for the effects of estrogen and progesterone on stimulant use are not well understood, but several potential mechanisms have been proposed (see Quinones-Jenab and Jenab [264]). β -Estradiol increases dopamine release in the striatum [265] and nucleus accumbens [266–269]. Cocaine-induced dopamine release in the striatum is enhanced by β -estradiol administration to ovariectomized rats [265], an effect that might be mediated by a decrease in GABA release from striatal neurons. An effect on GABAergic neurons would explain the opposing and therapeutic role of progesterone, which, along with its metabolites, has GABA agonist properties [270, 271].

Although data in humans are limited, they parallel findings in animals. Among cocaine-dependent women, progesterone attenuates cravings for [272] and subjective positive response to stimulants [273–276]. Our group compared the effects of smoked cocaine (0.4 mg kg^{-1}) in men and in women who were either in the luteal (high progesterone) or follicular (low progesterone) phase of the menstrual cycle, and found significantly attenuated responses to the subjective effects of cocaine in luteal phase women compared with women who were in the follicular phase and compared with men [277]. In a similar study, women's responses to cocaine were evaluated on three occasions: early in the follicular phase, again early in the follicular phase after administration of exogenous micronized progesterone and in the luteal phase. During conditions in which progesterone was elevated, the subjective effects of cocaine were attenuated [275]. This has also been replicated with amphetamine, where administration during the follicular phase led to greater euphoria than administration during the luteal phase [276]. We have also examined the interaction between exogenous progesterone and cocaine in female cocaine users, and demonstrated that either a single dose or two oral doses of 200 mg proges-

terone attenuated the subjective effects from repeated cocaine deliveries [273, 274].

Pregnancy, which is characterized by high circulating progesterone levels [278], is associated with decreased substance use [279]. Unfortunately, drug use increases again after delivery [280, 281]. The incremental decrease in drug use over the course of pregnancy as progesterone levels increase and the escalation in drug use after delivery when progesterone levels drop, suggest the possibility that progesterone influences drug use during this period. We are currently conducting a double-blind, randomized, placebo-controlled study evaluating the efficacy of oral micronized progesterone in reducing cocaine use among postpartum women with a history of cocaine use (NCT01249274; clinicaltrials.gov).

Treatments targeting comorbid psychiatric conditions

While beyond the scope of this review, it is worth noting the comorbidity that exists between drug addiction and primary psychiatric disorders, including schizophrenia, mood and anxiety disorders and attention deficit hyperactivity disorder [282–285]. Individuals with comorbid SUDs and psychiatric disorders usually have poorer outcomes than those without comorbidity [286–291]. One of the possible mechanisms underlying this high comorbidity is self-medication, in which individuals with primary psychiatric disorders use drugs or alcohol to relieve specific symptoms, such as negative affect, or side-effects of their treatment medications, such as sedation. Alternatively, common underlying factors may lead to high comorbidity between primary psychiatric disorders and drug addiction [292–294]. Common vulnerability factors may include impulsivity, increased reward sensitivity and cognitive deficits, including attention, working memory or response inhibition. From a treatment perspective, one implication of the comorbidity is that effective treatment of psychiatric disorders may also reduce the substance use, although existing clinical trials point to mixed results in this regard [295].

Future directions

As reviewed above, pharmacological approaches to addiction have focused on the specific roles of neurotransmitters, including dopamine, opioids and the adrenergic system. To develop medications for cocaine addiction, for example, most of the research has focused on identifying medications that attenuate drug reward [296], which is mediated by the dopaminergic system in the reward pathway. While neurochemical mechanisms of addictions remain important for pharmacotherapy development, approaches to understanding brain function related to addiction are increasingly focusing on neurobiological mechanisms that underlie development and maintenance of SUDs [297]. As described above, focusing on individual

vulnerability factors may broaden our ability to develop novel medications for SUDs. Preliminary work on the cognitive deficits, sex differences and psychiatric comorbidities shows promising results in the treatment of addictions. Identification of other vulnerability factors for SUDs may further broaden our ability to develop novel medications.

Pharmacogenetics is another area of research that may enhance the benefits from pharmacotherapies for SUDs in the future. The ability to predict response to treatment and side-effects based on genetic make-up can lead to optimal treatment matching. For example, the presence of the A118G polymorphism of the μ -opioid receptor and polymorphisms of the *CYP2A6* gene predict clinical response to naltrexone in alcohol dependence [298–300] and nicotine replacement therapy in smoking [301–303], respectively. Other polymorphisms that predict response to therapeutics have been identified for cocaine, tobacco, opiates and alcohol (see Sturges *et al.* [304]). However, while promising, many of these findings require replication and further evaluation to determine their clinical utility. The challenges in replication are in part due to heterogeneity in study design, sample size, outcome measures and participant characteristics across studies [305]. To determine the clinical utility of pharmacogenetic approaches for SUD, systematic studies addressing these potential limitations are needed.

Unfortunately, despite the many promising novel targets and therapeutics described above, very few reach clinical use. There are several factors that may contribute to this mismatch, as follows: the high cost of bringing a medication to market [306]; the lack of pre-clinical and clinical models that have demonstrable predictive validity for the clinical efficacy of SUD therapeutics; and the regulatory requirements of abstinence being the clinical outcome in efficacy trials [307]. Investment in medications for the treatment of SUDs by the pharmaceutical industry, which has traditionally assumed the research and development costs associated with drug development, has been modest. For more effective development of medications for SUD, these methodological, regulatory and financial issues need to be addressed [307].

In summary, while significant advances have been made over the past several decades in the development of effective treatments for SUDs, they remain a substantial public health problem. Advances in our understanding of the neurobiological mechanism for SUDs provide an exciting opportunity for applying these advances to develop novel treatments. Novel treatment targets for SUDs include cognitive function, modulation of stress and synaptic plasticity. Efforts should also focus on identifying clinically relevant individual differences that may be used to guide the selection of therapies, including pharmacogenetics.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that MS had support from the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC), and National Institute on Drug Abuse grant K02-DA-021304; A.F. had support from National Institute on Drug Abuse grants K12-DA-000167-20 for the submitted work; A.F. has no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years. M.S. serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline; there are no other relationships or activities that could appear to have influenced the submitted work.

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