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SUBSTANCE USE AND RELATED DISORDERS (JR MCKAY, SECTION EDITOR)

Pharmacotherapy for Stimulant-Related Disorders

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Abstract Stimulant–related disorders (SRD) continue to be an important public health problem for which there are presently no approved pharmacotherapies. Although behavioral interventions provide some benefit response varies. The development of novel and effective pharmacotherapies continues to be a research priority. Understanding neural mechanisms critical to the action of stimulants has helped reveal several potential pharmacotherapies that have already shown promise in controlled clinical trials. Common to some of these medications is the ability to reverse neural deficits in individuals with SRD. Results from thoroughly conducted clinical trials continue to broaden our knowledge increasing the possibility of soon developing effective pharmacotherapies for SRD.

Keywords Pharmacotherapy · Cocaine · Methamphetamine · Amphetamine · Stimulants · Substance use disorders · Stimulant use disorder · Substance related disorders · Amphetamine type substance use disorder · Dependence · Addiction · Dopamine · Norepinephrine · Clinical trial

Introduction

Stimulant-related disorders (SRDs) (cocaine; methamphetamine, METH; and amphetamine, AMPH) remain a significant public health concern. For example, recent statistics indicate that cocaine was noted more often than any other illicit drug (METH/AMPH was 4th) among emergency department visits in the United States [1]. There are no FDA-approved medications for SRDs, thus the search for an efficacious pharmacotherapy continues to be a primary goal. Accumulating preclinical and clinical evidence has improved our knowledge of the underlying neurobiology, genetics and environmental factors associated with stimulant use and relapse. Neural deficits found across drug classes suggest SRD is a brain disease (Table 1). Understanding the nature of these neural deficits has helped clarify the rationale for developing medications that target and possibly reverse known neurochemical imbalances [2].

Numerous studies have documented cognitive deficits in chronic stimulant users for example, impaired executive functioning, working memory and response-inhibition. Of prime research interest presently is the idea that medications that enhance cognition by ameliorating deficits in stimulant users may be crucial to a medication's efficacy as a pharmacotherapy [3]. Evidence also suggests cognitive enhancers may augment the beneficial effects of behavioral therapies since either administered alone is not as effective as both treatments together [4].

The primary aim of this review is to first provide a brief description of neural deficits associated with SRDs (Table 1) and second, review recent clinical trials evaluating medications (Table 2) as possible treatments for cocaine and METH/AMPH use disorders. We focus on results from the most recent human laboratory, outpatient clinical trials and studies assessing medication combinations for SRDs.

Drug Effects and Neural Deficits Associated with Cocaine Use

Cocaine targets the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters blocking reuptake thereby increasing neurotransmitter levels within mesocorticolimbic circuits. These circuits include dopaminergic cells in the ventral

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Table 1 Neural abnormalities in humans associated with cocaine and METH/AMPH use

	Cocaine	METH/ AMPH	Selected reference
Baseline DA	↓	↓	[11, 35]
DA release	↓	↓	[17, 22]
DAT	↑	↓	[14, 32]
D1 receptors	ND	↑	[11, 33]
D2(D3) receptors	↓	↓	[18, 36]
D3(D2) receptors	↑	↑	[13, 37]
VMAT-2	↓	↓	[10, 29]
NET	↑	—	[7]
SERT	↑	↓	[8, 31]
Glutamate	↓	—	[9]

DA-dopamine, DAT-dopamine transporter, NET-norepinephrine transporter, SERT-serotonin transporter, VMAT-2-vasicular monoamine transporter, ND-no difference from controls, —unknown

tegmental area (VTA) that project to the nucleus accumbens (NAc) and prefrontal/orbitofrontal cortex (PFC). Both the VTA and NAc receive glutamaterigc inputs from the PFC. Neurons from the noradrenergic cell body region, locus coeruleus (LC), also project to the PFC and VTA significantly influencing cellular activity. The reinforcing effects of cocaine are generally attributed to increases in dopamine (DA) within limbic circuits. However, recent evidence indicates norepinephrine (NE) also plays an important role in the reinforcing effects of stimulants providing another possible therapeutic target [5].

Studies have revealed significant biochemical and structural neural abnormalities in cocaine users (Table 1). These presumed neuroadaptive changes may result from chronic drug use although many are not reversed by abstinence suggesting these changes may have been present before initiation of drug use [6]. For example, although a number of abnormalities have been identified [7–14], studies continually show individuals with cocaine use disorder (CUD) have low DA levels at baseline and blunted pre-synaptic DA release [15–18]. Blunted DA responsiveness is associated with increases in cocaine self-administration [17]. Low striatal D2/D3 receptor availability is a consistent finding in cocaine users [18, 19]. Cognitive deficits, impulse control and enhanced salience of drug-associated cues are linked to decreased D2/D3 receptor levels [20, 21]. Deficits in DA signaling are also associated with poor response to behavioral interventions and relapse to drug taking [17, 22]. In theory, medications that either directly or indirectly modulate DA to reverse deficits associated with chronic cocaine use may prove beneficial as treatments (Table 2).

Drug Effects and Neural Deficits Associated with METH/AMPH

The reinforcing effects of METH/AMPH are attributed to increases in central NE and DA neurotransmission through a variety of mechanisms. Generally, METH/AMPH acts as a substrate for the NET and DAT, and vesicular monoamine transporter (VMAT) reversing their action, in turn, increasing transmitter levels. METH/AMPH also induce presynaptic transmitter release independent of neuronal depolarization [23]. METH/AMPH are more potent at increasing NE than DA however increases in DA within mesolimbic circuits relate to METH/AMPH's positive subjective effects [24]. About 20 % of METH is metabolically converted into pharmacologically active AMPH and both are detected in urine [25]. METH's duration of action (plasma half-life approximately 11-12 hrs) allows exposure to continuously high levels of DA that are neurotoxic and associated with significant pathology [26, 27]. The neurotoxic effects of METH use is thought to contribute to overall neuropsychological impairment seen in chronic users [28–33].

Table 2 Medications assessed for cocaine and METH/AMPH use disorders

Substance	Medication	Target	Action
Cocaine	Disulfiram	Dopamine β-hydroxylase	↓NE, ↑DA
	Doxazosin	α1 receptors	↓ cocaine-induced DA
	Modafinil	DAT, α receptors	↑DA, Glutamate, Orexin,↓GABA
	Topiramate	AMPA/Kainate, GABA	↓ Glutamate, ↑GABA
	Methylphenidate	NET, DAT	↑NE,↑DA
	SR-METH/AMPH	NET, DAT	↑NE,↑DA
METH/AMPH	Bupropion	DAT, NET	↑DA, ↑NE
	Naltrexone	μ opioid receptors	↓ μ receptor activation
	Rivastigmine	Acetylcholinesterase	↑ acetylcholine
	Topiramate	AMPA/Kainate, GABA	↓ Glutamate, ↑GABA
	Perindopril	ACE	↑DA,↓NE
	Modafinil	DAT, α receptors	↑DA, Glutamate, Orexin,↓ GABA
	Methylphenidate	NET, DAT	↑NE↑DA

AMPA-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, ACE-angiotensin converting enzyme, DA-dopamine, NE-norepinephrine, GABA-γ aminobutyric acid, DAT-dopamine transporter, NET-norepinephrine transporter, SR-METH-sustained release methamphetamine, SR-AMPH-sustained release amphetamine

Chronic METH/AMPH users exhibit many of the same molecular and structural neural deficits as cocaine users (Table 1). Evidence suggests these neural deficits may contribute to unrelenting drug use and relapse in individuals with SRDs. For example, orbitofrontal cortex hypoactivity is associated with failure to adapt behavior based on prior experience [34]. Similar to cocaine, METH/AMPH users also exhibit low baseline DA levels [35] decreased D2/D3 receptor availability that is associated with impulsivity [36]. Finally, low D2/D3 levels in METH/AMPH users have been found to be associated with drug use severity [37] and individuals with low levels of striatal pre-synaptic DA release are more likely to relapse after a period of abstinence [22]. Overall, these findings provide further evidence some neurochemical and cognitive deficits found in chronic cocaine users are also present, in general, in chronic METH/AMPH users.

Medications for Cocaine Use Disorder (CUD)

Disulfiram

Disulfiram (Antabuse®) is indicated for the treatment of alcohol use disorder however several randomized clinical trials have shown disulfiram decreases cocaine use [38]. Disulfiram and its metabolite diethyldithiocarbamate bind copper. Decreased copper levels inactivates copper-dependent enzymes such as dopamine-β hydroxylase (DβH) (Table 2), which converts DA to NE. DβH inhibition increases DA and decreases the synthesis of NE [39]. Disulfiram also inhibits carboxylesterase and cholinesterase enzymes that metabolize cocaine thereby increasing plasma levels of cocaine [40]. Inhibition of DβH by disulfiram and subsequent decrease in central NE levels is likely responsible for its ability to decrease cocaine use [38].

Interestingly, a large clinical trial suggested that low doses of disulfiram (62.5 mg and 124 mg/day) *increased* whereas a higher dose *decreased* (250 mg) cocaine use over time [41•]. Results from a recent study from our group may help explain the divergent effects of disulfiram found on cocaine use. In a double-blind, placebo-controlled, laboratory-based within-subjects study ($N=17$) using a choice procedure between cocaine (20 mg) and escalating amounts of money [42•], we found that low doses of disulfiram *increased*, whereas high doses *decreased*, choices for cocaine. In that study, disulfiram dose was calculated on a mg/kg basis which indicated that approximately 4 mg/kg or 280 mg/day for a 70 kg individual was needed to block the reinforcing effects of cocaine. Cardiovascular effects produced by cocaine were also increased by low doses of disulfiram [42•].

Pharmacogenetics is the field of study focused on how genetic variation affects responses to medications [43]. Gene variants may result in altered protein amounts and/or function. Identifying a particular sub-population in advance with gene variants that are associated with altered responses to a given medication has the potential to increase treatment efficacy. For example, the gene variant 1021C/T (rs1611115) (CT/TT) encoding DβH leads to reduced enzyme activity that may impact response to disulfiram for CUD. Recently, Kosten et al. conducted a pharmacogenetic study that included participants with both CUD and opioid use disorder treated with either disulfiram ($N=34$, 250 mg/day, 10 weeks) or placebo ($N=40$) [44••]. Results showed that disulfiram treatment was associated with a decrease in cocaine positive urines in participants with normal DβH genotype whereas disulfiram had no effect in participants with the genotype coding for low DβH activity [44••]. Taken together, evidence continues to support disulfiram as a potential pharmacotherapy for select individuals. Dose on a mg/kg basis and genotype should be considered to maximize the therapeutic efficacy of disulfiram for CUD.

Doxazosin

Studies testing medications that target specific NE receptor sub-types show promise as possible treatments for SRDs. Doxazosin is a selective α1-adrenergic receptor (α1R) antagonist indicated for the treatment of hypertension. Prazosin is also an α1R receptor antagonist but with a much shorter half-life (4-5 hrs) compared to doxazosin (11 hrs). α1R receptors are located within mesocorticolimbic structures such as the NAc where they modulate cocaine-induced increases in DA [45]. Centrally or peripherally administered prazosin and doxazosin block cocaine's behavioral effects in rodents [46, 47].

Clinical studies in humans assessing doxazosin as a treatment for CUD appear promising. In an inpatient laboratory study employing non-treatment seeking cocaine users, doxazosin (4 mg/day for 9 days) decreased cocaine's (20 and 40 mg) positive subjective effects, including "desire" for cocaine [48••]. A small pilot outpatient clinical trial showed that doxazosin (8 mg/day) treatment was associated with significantly fewer cocaine positive urines in treatment-seeking cocaine users compared to placebo [49••]. Doxazosin possesses a number of desirable pharmacological characteristics as a possible pharmacotherapy for CUD. For example, doxazosin is presently indicated for the treatment of hypertension, is cardioprotective and has few known drug interactions. Importantly, doxazosin blocks the hypertensive and positive subjective effects of cocaine in humans [48••]. Together, these preliminary studies suggest that α1 receptor antagonists may be beneficial for CUD. Larger outpatient clinical trials are needed to confirm these promising results.

Modafinil

Modafinil is indicated for narcolepsy but also used to treat shift work sleep disorder and attention deficit hyperactivity

disorder. Modafinil binds to the DAT inhibiting DA re-uptake but also acts on other neurotransmitter systems [50–53]. Imaging studies in humans confirmed that modafinil binds to the DAT within mesolimbic circuits [54]. Studies show modafinil administration decreases neural reactivity provoked by cocaine-associated cues, attenuates cocaine craving and improves cognitive function in individuals with CUD [55, 56•].

Although initial clinical trials appeared very positive for modafinil as a treatment for CUD, data from more recent studies have not been as promising [57, 58•]. The studies do suggest however that gender and alcohol consumption may influence the ability of modafinil to decrease cocaine use [57, 58•]. For example, although an 8 week randomized, double-blind, placebo-controlled clinical trial found no significant effect overall of modafinil (400 mg/day vs. placebo) combined with CBT (once/week) on cocaine abstinence (measured by urine drug screens), the study did show that males treated with modafinil tended to be more abstinent than females [58•]. A 12 week randomized, double-blind, placebo-controlled out-patient study compared the effects of modafinil (200 mg/day, $N=69$; and 400 mg/day, $N=69$) and placebo ($N=72$) on percentage of weekly non-use cocaine days (primary outcome) [57]. All participants received CBT (once/week) and drug screens were performed three-times per week. There were no significant differences overall between modafinil and placebo on the primary outcome yet subgroup analysis showed modafinil treatment was superior to placebo in individuals that were not comorbid for alcohol-use disorder. The number of consecutive cocaine non-use days was also greater in participants who received 200 mg/day modafinil [57]. A preliminary double-blind, placebo-controlled study tested the impact of modafinil ($N=20$, 400 mg) and d-AMPH ($N=22$, 60 mg) alone, and modafinil combined with d-AMPH ($N=15$, 60 mg) on cocaine use [59]. Results indicated that this drug combination *increased* cocaine positive urines over time whereas placebo combined with d-AMPH *decreased* cocaine positive urines [59]. Overall, it appears that modafinil may improve cognitive deficits associated with chronic cocaine and decrease use in a select population.

Methylphenidate

Methylphenidate is a potent NE and DA reuptake inhibitor primarily used to treat attention-deficit hyperactivity disorder (ADHD) [60]. Imaging studies indicate that methylphenidate reverses a number of neural deficits in mesocorticolimbic regions [61, 62] and decreases reactivity to cocaine-associated cues in cocaine users [63, 64].

In general, studies assessing the potential of methylphenidate as a treatment for CUD have been inconsistent. Initial positive laboratory interaction studies showed sustained-release (SR) methylphenidate attenuated cocaine's positive subjective effects and decreased choices for cocaine over money in participants with CUD [65] and in cocaine users comorbid for ADHD [66]. A recent 12 week randomized controlled trial compared placebo with ($N=17$) and without ($N=15$) cognitive behavioral group therapy (CBGT) to immediately releasable (IR) methylphenidate 30 mg twice daily with ($N=15$) and without CBGT ($N=15$). Participants were comorbid for cocaine and opioid use disorder [67]. Results revealed no difference between treatment groups as measured by cocaine positive urines over time. Further, the addition of CBGT with methylphenidate provided no added benefit over placebo [67]. These negative results may in part be due to low numbers of participants and the formulation of methylphenidate used [68, 69]. Well-designed studies employing larger numbers of participants are needed to better assess methylphenidate as a possible treatment for CUD.

Sustained-Release (SR) METH/AMPH

The NE/DA releasers SR-METH/AMPH are indicated for the treatment of ADHD, narcolepsy and obesity. METH/AMPH have been shown to decrease cocaine's reinforcing effects in rodents [70] and primates [71], attenuate the positive subjective effects of cocaine [72, 73] and decrease cocaine use in humans [74]. Case study reports also describe the ability of METH to abolish cocaine use [75]. Abuse liability is an obvious concern with using these medications; however, studies confirm SR formulations have reduced abuse liability compared to IR formulations and should be considered as possible treatments [76].

A recent 14 week, randomized, double-blind, parallel-group study compared the effects of SR-AMPH (60 mg/day) in combination with the antiepileptic topiramate ($N=39$, 150 mg/twice daily) to placebo ($N=42$) [77•]. The primary outcome was three consecutive weeks of abstinence as measured by urine toxicology. Results revealed a higher proportion treated with the combination achieved the primary outcome. Baseline cocaine use influenced treatment response suggesting that SR-AMPH/topiramate may be more effective in heavy users [77•]. Together, evidence to date supports the use of METH/AMPH SR-formulations for the treatment of CUD however abuse liability remains a concern.

Topiramate

Topiramate (TOPAMAX®) is an antiepileptic indicated for seizure disorder and migraine prophylaxis. Topiramate's therapeutic action for seizures appears to be through glutamate and GABA modulation (Table 2) yet it acts on multiple neurotransmitter systems [78, 79]. An initial clinical trial showed topiramate decreased heavy alcohol use and a pilot study indicated this effect extended to cocaine [80, 81]. Based on these positive results a current report tested the impact of

topiramate (N=83, 300 mg/day, 13 weeks) compared to placebo (N=87) on cocaine use in individuals with CUD and alcohol use disorder [82•]. All participants received CBT. Primary outcome measures were self-reported alcohol and cocaine use and urine drug screens three times per week. Secondary measures included cocaine and alcohol craving measures. Overall, treatment with topiramate was no better than placebo on any outcome. Yet study retention favored topiramate and individuals with more severe cocaine withdrawal symptoms on entering the study responded better to topiramate [82•]. A randomized, double-blind, within-subjects cross-over designed laboratory study by Johnson et al. assessed the effects of topiramate (100 mg twice daily for 5 days; N=24) compared to placebo in combination with low (0.325 mg/kg, iv) and high (0.65 mg/kg) doses of cocaine [83]. Interestingly, topiramate treatment reduced cocaine craving and monetary value of the high dose of cocaine but *increased* the subjective effects (e.g., euphoria) and monetary value of the low dose of cocaine [83]. Overall, evidence is not entirely convincing for the use of topiramate as a treatment for CUD. That topiramate increased the positive subjective effects of cocaine is concerning.

Medications for Amphetamine-Type Substance Use Disorder

Bupropion

Bupropion is a unique medication indicated for the treatment of major depressive disorder and smoking cessation. Bupropion binds to DAT and NET blocking reuptake and increasing synaptic levels of DA and NE (Table 2). In vitro experiments indicate bupropion prevents METH-induced DA release and self-administration studies in primates confirm the ability of bupropion to decrease the reinforcing effects of METH [84, 85]. Consistent with this finding, human laboratory studies have demonstrated bupropion treatment attenuates METH's positive subjective effects [86, 87]. Outpatient clinical trials comparing the impact of SR-bupropion (300 mg/day; N's=36-79) treatment to placebo (N's=37-72) on METH use however found no significant differences between treatments [88, 89]. Sub-group analysis did show however that SR-bupropion significantly reduced METH use in light or moderate METH users (defined as ≤17 days during the past month). Evidence that bupropion treatment did not robustly decrease METH use in two clinical trials after initial promising human laboratory studies prompted retrospective reanalysis of the outpatient clinical trial data. McCann et al. calculated the degree of success based on urine toxicologies and found a significant effect of bupropion to facilitate abstinence from METH [90•]. Brensilver et al. also found that individuals treated with bupropion unable to provide at least three negative urines for METH in the first two weeks had a greater than 90 % likelihood of treatment failure [91]. Available data suggests that bupropion may be useful as a treatment for METH use disorder in light to moderate users. Further, pharmacotherapy should be modified if METH use has not decreased within two week following bupropion treatment.

Modafinil

The wake-promoting medication modafinil improves cognitive deficits and withdrawal symptoms associated with chronic METH/AMPH use [92–94]. Initial pilot studies appeared positive for modafinil as a possible treatment for METH use disorder [95, 96]. Based on these findings, the possibility that modafinil may decrease the reinforcing effects of METH was assessed in a randomized, placebo-controlled within-subjects (N=13) laboratory-based interaction study [97]. Results revealed that modafinil (200 mg/day) tended to attenuate METH's subjective effects and decrease choices to self-administer METH but the effects were not robust [97]. Further, a double-blind, placebo-controlled, trial described by Shearer et al. assessed whether modafinil (200 mg/day; 10 weeks, follow-up at 22 weeks) treatment would decrease METH use [98]. Approximately half of all participants received some sort of self-selected counseling. Overall, modafinil was no different from placebo as indicated by urinalysis. Results may have been influenced by less than optimal study retention (placebo: 15/42, 36 %; modafinil: 11/38, 29 %) and medication compliance (intention to treat basis, placebo: 49 %; modafinil: 44 %). Medication compliant participants however tended (p=0.07) to provide clean urines and those who received any form of counseling had better outcomes [98].

Anderson et al. conducted a 12-week, randomized, double-blind, placebo-controlled (N=68) study with a 4-week follow-up period testing the impact of two doses of modafinil (N=72, 200 mg; N=70, 400 mg) on METH use in treatment-seeking participants with METH use disorder [99]. Results revealed no differences between placebo and either dose of modafinil on primary or secondary outcomes likely because of medication non-compliance [99]. The top quartile of participants (compared to the bottom three quartiles) that did take modafinil however significantly decreased their METH use as confirmed by urinalysis. Results from the Anderson et al. study in general, parallel Shearer et al. indicating non-compliance for modafinil may have compromised any likely positive outcomes. Evidence to date appears to provide tentative support for the further development of modafinil as a possible treatment for METH-use disorder.

Naltrexone

The μ-opioid receptor antagonist naltrexone (ReVia®) is approved for the treatment of opioid and alcohol use disorders.

An intramuscular depot injection formulation was made available in 2006 (Vivitrol®). There is an implantable naltrexone formulation surgically placed subcutaneously for consistent medication delivery but is not presently approved in the United States [100]. Experiments in rodents implicate the μ-opioid receptor in the behavioral effects of METH/AMPH [101, 102]. Accordingly, pretreatment with naltrexone blocks the development of METH locomotor sensitization, cue-induced METH-seeking in rodents and AMPH self-administration in primates [103–105].

Results from human studies appear to be generally consistent with preclinical data regarding the effectiveness of naltrexone to attenuate METH/AMPH's reinforcing effects. For example, human laboratory experiments have shown that pretreatment with naltrexone (50 mg) attenuates the subjective effects of oral d-AMPH (30 mg, PO) in healthy volunteers and in participants with AMPH use disorder [106, 107]. A 12 week, open label, clinical trial (N=20) tested medication compliance for naltrexone (50 mg) treatment and whether naltrexone with relapse prevention therapy (RPT) would reduce AMPH use [108]. Results showed that naltrexone was well tolerated with acceptable rates of compliance as indicated by the presence of naltrexone's metabolite (6-β naltrexol) in urine. Naltrexone plus RPT was also associated with significant decreases in frequency and amount of AMPH consumed compared to baseline [108]. This study was followed by a 12 week, randomized, placebo-controlled out-patient clinical trial comparing naltrexone (50 mg/day; N=29) to placebo (N=26). Results revealed that participants treated with naltrexone presented significantly lower numbers of AMPH-positive urines and reported less craving for AMPH compared to placebo [109].

A recent randomized controlled trial in opioid and AMPH users assessing the impact of implantable naltrexone compared to placebo showed that naltrexone significantly increased study retention rate (naltrexone: 58 %; placebo: 28 %) and proportion of drug free urine samples (naltrexone: 38 %; placebo: 16 %) [110•]. Equally impressive results have come from a study of implantable naltrexone for the treatment of AMPH use disorder indicating blood levels of naltrexone above 2-5 ng/ml were associated with high rates of self-reported periods of abstinence (90.9-100 %) [111]. Although positive, the study may have been biased since blood and urine samples were not systematically collected from all participants and there was no comparison group. Overall, evidence supports naltrexone for the treatment of AMPH use disorder. Whether naltrexone may benefit METH users remains to be determined by properly controlled clinical trials.

Methylphenidate

Preliminary case reports and one pilot study suggested treatment with methylphenidate may reduce AMPH use [112, 113]. A larger parallel-groups, double-blind, randomized, placebo-controlled, follow up study assessed the impact of SR-methylphenidate (titrated over 2 weeks, maximum dose 54 mg/day for 20 weeks) on METH/AMPH use. Results showed that although participant retention was significantly higher in the methylphenidate treatment arm, methylphenidate did not significantly reduce METH/AMPH use [114]. At present, in contrast to CUD, evidence does not appear to support methylphenidate as a treatment for METH use disorder.

Topiramate

Promising results from clinical trials showing topiramate decreased alcohol and cocaine use prompted a series of studies that evaluated topiramate as a possible treatment for METH use disorder. Contrary to what was generally expected, initial human laboratory studies found acute administration of topiramate (200 mg) enhanced the positive subjective effects of METH (15 mg and 30 mg)[115]. A follow up pharmacokinetic study suggested that topiramate (N=10, 200 mg/day, 9 days) tended to increase plasma METH levels which may have contributed to enhancement of METH's subjective effects [116]. Interestingly, in that same cohort, topiramate (100 mg and 200 mg) treatment was associated with improvement in certain cognitive domains when administered alone, and in combination with METH (15 mg and 30 mg) [117]. A recent 13 week, double-blind, placebo-controlled, outpatient (N=140) multi-center trial determined whether topiramate 200 mg/day or maximum tolerated dose would facilitate abstinence as measured by urine toxicology [118•]. Although groups did not significantly differ on abstinence, topiramate treatment was associated with reduced weekly median urine METH levels and dependency severity scores (quantified by the Clinical Global Impression Scale-Observer). A key finding in this study was that participants before randomization that were negative for METH achieved greater levels of abstinence while treated with topiramate compared to placebo [118•]. A number of factors could have contributed to the negative outcome for topiramate in this study: retention rate was poor for both groups (55 % by week 12), not all participants reached the target dose of 200 mg/day of topiramate, and medication compliance (<70 %) was not optimal [119]. Generally, although more studies are needed, the data presently do not fully support topiramate as a treatment for METH use disorder.

Rivastigmine

The cognitive enhancer rivastigmine is an acetylcholinesterase/butyrylcholinesterase inhibitor indicated for the treatment of Alzheimer and Parkinson-associated dementia. Human clinical trials have shown rivastigmine may attenuate METH's subjective effects. For example, an initial double-blind within-subjects placebo-controlled study (N=23) found that treatment with rivastigmine (3 mg/day) blocked METH's (30 mg, IV)

effects on diastolic blood pressure and decreased subjective ratings for "desire" for METH in non-treatment seeking METH users [120]. The effects of rivastigmine in combination with METH were further assessed using a laboratory-based, double-blind, placebo-controlled paradigm (N's=6-9) evaluating three different doses of rivastigmine (0 mg, 1.5 mg, 3.0 mg/day). Results showed that treatment with the highest dose of rivastigmine (3 mg) attenuated the positive subjective effects (e.g., "any drug effect", "high", "desire", "stimulated") of self-administered METH [121]. Consistent with previous results, a recent follow-up study also found a higher dose of rivastigmine (6 mg, PO for 6 days) attenuated the subjective effects of METH dose (15 mg, IV) but did not alter the number of choices to self-administer METH [122•]. Neurocognitive assessments in this same participant cohort however found no effects of rivastigmine (0 mg, 3 mg, 6 mg/day for 6 days) on a wide range of measures [123]. Outpatient clinical trials assessing rivastigmine as a possible treatment for METH use disorder are warranted.

Perindopril

Perindopril is an angiontensin-converting enzyme (ACE) inhibitor indicated for the treatment of hypertension. Inhibiting ACE prevents the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Preclinical evidence suggests that ACE inhibitors enhance learning and memory, increase striatal DA levels and are neuroprotective in animal models of Parkinson disease [124]. In a preliminary clinical trial, treatment with perindopril augmented L-dopa's effects in Parkinson patients consistent with the notion that ACE inhibition may increase central DA levels [125]. ACE inhibitors also decrease NE levels an effect consistent with their indication as treatments for hypertension [126]. Whether ACE inhibition blocks METH-induced increases in NE is unknown.

Administration of ACE inhibitors decreases alcohol reinforcement in rodents suggesting these medications may decrease use of other substances [127]. Indeed, using a double-blind, placebo-controlled study design, Newton et al. found perindopril (4 mg/day) decreased subjective ratings for "any drug effect" following METH (30 mg, IV) in non-treatment seeking METH users [128•]. Follow-up studies are needed to further assess the possibility of using ACE inhibitors to treat METH use disorder.

Conclusions

Despite decades of research there are currently no FDA-approved medications for SRDs. Recent advances in understanding of the neurobiology involved in the etiology and development of SRDs have helped guide investigators toward identifying potential pharmacotherapies (Table 1). Indeed, individuals with SRD have low baseline DA levels and decreased tone that relates to cognitive deficits, drug craving and relapse. Based on this, some of the medications reviewed here in particular, those that target both DA and NE in combination with counseling appear promising as possible treatments (disulfiram, modafinil, bupropion) (Table 2). Preliminary human clinical trials seem positive for using cardiovascular medications (doxazosin, perindopril) and cognitive enhancers (rivastigmine). Studies also indicate that some medications may be more efficacious in subgroups of individuals with SRD. For example, bupropion may be useful for light to moderate METH users whereas SR-AMPH in combination with topiramate may be better for heavy METH users and topiramate alone for maintaining abstinence once achieved. Modafinil might prove beneficial in reducing METH use for males that are not comorbid for alcohol use disorder. Dose (4 mg/kg) and genotype (DβH) appear critical to the efficacy of disulfiram as a treatment for CUD. Evidence supports naltrexone as a treatment for AMPH use disorder. Whether naltrexone will prove an effective treatment for METH use disorder remains to be determined through testing in well-controlled outpatient clinical trials. Although not entirely consistent, many studies reveal benefits of some form of counseling either alone or in combination with the study medication. Medication noncompliance (modafinil, topiramate) continues to adversely affect any likelihood of achieving positive study outcomes. Positive preliminary human studies support assessing doxazosin for CUD and rivastigmine and perindopril for METH/AMPH use disorder in large outpatient clinical trials. In contrast to some of the medications reviewed here, these medications (doxazosin, rivastigmine, perindopril) are historically well tolerated, have no known abuse liability and may provide other benefits in addition to being treatments for SRD. D2 receptors are decreased whereas D3 receptors are increased in individuals with CUD and METH/AMPH use disorder. Whether medications that increase D2 receptor levels and block upregulated D3 receptors may be beneficial treatments remains to be ascertained. Future studies should also continue to explore neural substrates that mediate the reinforcing effects of stimulants. Knowledge gained may provide insight into developing better treatment strategies.

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Compliance with Ethics Guidelines

Conflict of Interest Colin N. Haile and Thomas R. Kosten declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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