Pharmacological treatments for methamphetamine addiction: current status and future directions

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To cite this article: Javier Ballester, Gerald Valentine & Mehmet Sofuoglu (2017) Pharmacological treatments for methamphetamine addiction: current status and future directions, Expert Review of Clinical Pharmacology, 10:3, 305-314, DOI: 10.1080/17512433.2017.1268916

To link to this article:  https://doi.org/10.1080/17512433.2017.1268916

Accepted author version posted online: 07 Dec 2016.
Published online: 20 Dec 2016.

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Pharmacological treatments for methamphetamine addiction: current status and future directions

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\textbf{ABSTRACT}

\textbf{Introduction:} Methamphetamine (MA) abuse remains a global health challenge despite intense research interest in the development of pharmacological treatments. This review provides a summary of clinical trials and human studies on the pharmacotherapy of methamphetamine use disorder (MUD).

\textbf{Areas covered:} We summarize published clinical trials that tested candidate medications for MUD and also conducted PubMed and Google Scholar searches to identify recently completed clinical trials using the keywords ‘methamphetamine’ ‘addiction’ ‘pharmacotherapy’ and ‘clinical trial.’ To determine the status of ongoing clinical trials targeting MUD, we also searched the ClinicalTrials.gov online database. We conclude this review with a discussion of current research gaps and future directions.

\textbf{Expert commentary:} Clinical trials examining the potential for pharmacotherapies of MUD have largely been negative. Future studies need to address several limitations to reduce the possibility of Type II errors: small sample sizes, high dropout rates or multiple comorbidities. Additionally, new treatment targets, such as MA-induced disruptions in cognition and in the neuroimmune system, merit trials with agents that selectively modulate these processes.

\textbf{1. Introduction}

Methamphetamine (MA) and related stimulants have become the world’s second most widely abused drug class after cannabis, with an estimated 24 million users worldwide \cite{1}. About 60\% of the MA dependent individuals live in South East Asia, which has seen a steady increase in use over the past decade, and according to 2013 estimates, there are approximately 600,000 MA users in the United States \cite{1}. Although amphetamines and MA have similar pharmacodynamic effects, MA is more addictive due to greater CNS penetration and a longer duration of action. MA use is associated with an increased risk of medical problems such as HIV and hepatitis-C infection and many psychosocial problems including homelessness, unemployment, crime, and imprisonment. Other medical risks include cerebrovascular events, strokes \cite{2}, cardiomyopathy and other cardiovascular problems \cite{3}, dental and periodontal disease \cite{4}, and specific complications related to the route of administration including airway irritation and vascular infections. In addition, recent studies show that compared to other populations, people with a history of MA use are more likely to develop Parkinson’s disease later in life \cite{5}.

Currently available treatments for methamphetamine use disorder (MUD) are primarily behavioral and include contingency management, 12-step facilitation, cognitive behavioral therapy, and relapse prevention. Unfortunately, these treatments have variable efficacy and are not widely available \cite{6}. In addition, effective pharmacological agents for the treatment of MUD have not been developed despite ongoing preclinical and clinical research efforts \cite{7}. Given the significant medical and social burden resulting from MUD, the development of effective pharmacological treatments remains a global public health priority.

This review complements recent systematic reviews of clinical trials for MUD \cite{8-10} but extends the scope by highlighting emerging pharmacological trials that are using novel approaches such as cognitive-enhancement strategies and immunotherapies. We first briefly summarize the epidemiology and comorbidity of MUD followed by a review of the basic pharmacology and toxicology of MA. We then summarize completed double blind clinical trials for MUD (Table 1) and highlight ongoing studies in humans with innovative pharmacological targets (Table 2). We conclude with a discussion of current research gaps, future directions and an expert opinion.

\textbf{2. Methods}

We conducted PubMed and Google Scholar searches to identify different classes of medication that have been examined for the treatment of MUD. The keywords were ‘methamphetamine,’ ‘addiction,’ ‘pharmacotherapy’ and ‘clinical trial.’ Inclusion criteria included those studies that were written in English between 2000 and 2016, and studies using a double blind, placebo controlled study design (Table 1). To identify more recent unpublished and ongoing studies, we searched the ClinicalTrials.gov database using the same keywords (Table 2).
<table>
<thead>
<tr>
<th>Medication</th>
<th>Subjects</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Primary outcome</th>
<th>Results</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>100 bupropion</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>150 mg BID</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Anderson et al.[11]</td>
</tr>
<tr>
<td>Bupropion (DNRI)</td>
<td>104 placebo</td>
<td>12-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 mirtazapine</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>30 mg daily</td>
<td>MA use (urine)</td>
<td>Reduction in MA use.</td>
<td>Colfax et al.[12]</td>
</tr>
<tr>
<td>Mirtazapine (NASSA)</td>
<td>30 placebo</td>
<td>12-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 imipramine</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>150 mg daily</td>
<td>Retention</td>
<td>Higher retention with imipramine.</td>
<td>Galloway et al.[13]</td>
</tr>
<tr>
<td>Imipramine (TCA)</td>
<td>10 placebo</td>
<td>180 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline (SSRI)</td>
<td>120 sertraline</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>100 mg daily</td>
<td>MA use (urine and self-reported)</td>
<td>No differences.</td>
<td>Shoptaw et al.[14]</td>
</tr>
<tr>
<td></td>
<td>109 controls</td>
<td>12-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonist therapy</td>
<td>30 D-AMP</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>60 mg daily</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Galloway et al.[15]</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>30 placebo</td>
<td>8-weeks</td>
<td></td>
<td></td>
<td>Active group less craving and withdrawal.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55 MPH-SR</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>Final dose: 54 mg daily</td>
<td>MA use (self-reported)</td>
<td>No differences.</td>
<td>Ling et al.[16]</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>55 placebo</td>
<td>10-weeks</td>
<td></td>
<td></td>
<td>Active group less use and craving compared to baseline.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 MPH-SR</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>Final dose: 54 mg daily</td>
<td>Craving</td>
<td>Less craving and urine positive different in week 10.</td>
<td>Rezaei et al.[17]</td>
</tr>
<tr>
<td></td>
<td>28 placebo</td>
<td>10-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>142 modafinil</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>72–200 mg</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Anderson et al.[18]</td>
</tr>
<tr>
<td></td>
<td>68 placebo</td>
<td>12-weeks</td>
<td>70–400 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69 topiramate</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>Final dose: 200 mg daily</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Ma et al.[19]</td>
</tr>
<tr>
<td>Topiramate</td>
<td>71 placebo</td>
<td>13-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 baclofen</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>60 mg baclofen</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Heinzerling et al.[20]</td>
</tr>
<tr>
<td>Baclofen/Gabapentin</td>
<td>26 gabapentin</td>
<td>16-weeks</td>
<td>2400 mg gabapentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 placebo</td>
<td>16-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>45 aripiprazole</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>Final dose: 20 mg daily</td>
<td>MA use (urine)</td>
<td>No differences.</td>
<td>Coffin et al.[21]</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>45 placebo</td>
<td>12-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 NAC/Naltrexone</td>
<td>Double-blind placebo-controlled clinical trial.</td>
<td>Final doses: 2400 mg NAC/200 mg Naltrexone.</td>
<td>Craving</td>
<td>No differences.</td>
<td>Grant et al.[22]</td>
</tr>
<tr>
<td>Glutamate/Opiate modulators</td>
<td>17 Naltrexone</td>
<td>8-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Acetylcysteine plus Naltrexone</td>
<td>32 subjects initial cross over clinical trial.</td>
<td>NAC 1200 mg/day</td>
<td>Craving</td>
<td>Less craving</td>
<td>Mousavi SG et al.[23]</td>
<td></td>
</tr>
<tr>
<td>N-Acetylcysteine</td>
<td>23 subjects completed study</td>
<td>8-weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DNRI: dopamine and norepinephrine reuptake inhibitor; NASSA: noradrenergic and specific serotonergic antidepressant; TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor; MA: methamphetamine.
3. Epidemiology of MUD

Globally, the prevalence of MA use is relatively high in the United States (US), Mexico, China and Thailand, with South Asia and the Middle East representing the areas with highest increase over the past decade [24]. For example, in Iran, MA use has increased from a point prevalence of 6% in 2008 to 44% of drug abusers reporting a use history in 2012 [25]. In the United States, an estimated 569,000 people aged 12 or older are current MA users. This figure is similar to prevalence estimates made between 2002 and 2013. Although the prevalence of MA dependence in the US is similar among males and females, women seem to start using MA earlier than men [26]. In another survey of a clinical sample (n = 189) with a MUD, 57% had lifetime dependence on other substances (alcohol 33%, cocaine 27%, cannabis 15%, opioids 12%) [30]. Furthermore, in a recent study from a clinical sample (n = 100) diagnosed with MA dependence, the prevalence of comorbid psychiatric disorders was 36%, including mood disorders (16%), psychotic disorders (13%) and anxiety disorders (7%) [31]. It is important to highlight that longitudinal studies that might help tease apart the temporal relationship between these comorbidities have not yet been conducted.

4. Pharmacology and toxicity of MA

4.1. Basic pharmacology of MA

The reinforcing effects of MA are thought to be mediated by a drug-induced increase in synaptic dopamine (DA) levels within the mesocorticolimbic DA system that principally includes the ventral tegmental area DA projection neurons and their primary targets, the nucleus accumbens (NAC) and prefrontal cortex (PFC) [9]. MA also increases synaptic norepinephrine (NE) and serotonin levels. NE release mediates arousal and cardiovascular activation, as well as stress disorders was 51% and 39%, respectively [29].
response signaling that may drive stress-induced drug use/relapse [32]. Increased synaptic serotonin levels may enhance some of the behavioral effects of MA including the development of addiction [33].

In addition to monoamines, there are other less intensively studied neurotransmitters involved in mediating acute and chronic effects of MA including GABA, glutamate, acetylcholine (Ach), corticotropin releasing factor (CRF) and other stress hormones. GABA, the main inhibitory neurotransmitter in the brain, reduces the reinforcing effects of stimulants, presumably by modulating the DA release associated with stimulant drug activity and drug cues [34]. Glutamate, the main excitatory neurotransmitter in the brain, is one of the primary mediators driving sensitization and craving in response to stimulant drugs [35], and in preclinical models, glutamate plays an essential role in drug and cue-induced reinstatement [36] suggesting a role for glutamate in relapse to drug seeking. In addition, thorough its central role in drug-induced neuronal plasticity [37], alterations in glutamatergic signaling may explain other phenomena such as protracted abstinence [36]. Finally, Ach likely participates in mediating the cognitive-enhancing effects of MA, including sustained attention [38], and both acute exposure to MA, and abstinence from MA use, activate CRF and stress-hormone pathways [39].

In addition to neurotransmitters, there is growing evidence of neuroimmune involvement in the acute and chronic effects of MA [40]. In preclinical studies, MA exposure is associated with activation of microglia and astrocytes [41], and disruption of blood–brain barrier integrity [42]. For example, in a recent preclinical study of stimulants such as cocaine, the acute reinforcing action required activation of the Toll-like receptor 4 (TLR4) located on microglia [43]. TLR4 is involved in immune surveillance of pathogens, endogenous danger signals (substances released by cellular stress) and exogenous small molecules (xenobiotics). It is noteworthy that other substances such as alcohol, MA and opioids, may also share this mechanism [43]. These neuroimmune effects extend the current mechanistic paradigm of drugs of abuse by identifying the immune system as an important component of core neural mechanisms mediating reinforcement.

4.2. Primary behavioral effect of MA

MA is most frequently taken orally, intravenously or in smoked form. The route of administration influences the reinforcing effects of MA with some routes producing a more immediate onset of euphoria (e.g. intravenous or inhalation). After intravenous injection or inhalation of MA, euphoric effects are observed within 5 min and last up to 8–12 h, a much longer duration of action than cocaine (20–30 min) [8]. The majority of the participants in the clinical trials summarized in this review, used IV or smoked MA as their preferred route of administration.

4.3. Neurobiological and toxicological effects of chronic MA use

Chronic MA use is associated with many neuroadaptations in the CNS including hypofunction of DA activity in the reward circuitry that is believed to mediate dysphoria and drug craving [44]. Neuroadaptations also occur in other neurotransmitter systems including NE, 5-HT, glutamate, GABA, opioids, oxytocin, CRF as well as in the hypothalamic-pituitary-adrenal (HPA)-axis [45–47].

MA abuse also has direct neurotoxic effects on DA neurons including those in the nigrostriatal pathway. The underlying mechanism for this neurotoxicity is likely MA-induced elevations in DA levels in the cytosol of neurons rather than increased synaptic DA levels. Because DA can produce superoxide anion (O2·−) and other reactive oxygen species, lipid peroxidation and activation of proteases are considered to be important mediators of DA neurotoxicity. In addition, neuroimmune activation and release of inflammatory molecules in the CNS (cytokines, chemokines, adhesion molecules) are likely to be involved in the development and persistence of MA toxicity in different brain regions [48]. Finally, MA use is associated with an increased entry of HIV and HCV into the brain [49] through MA’s immunological [50] and blood–brain barrier effects and this may contribute to the development of HIV-related neurocognitive impairment [51].

These neurotoxic effects of MA are consistent with observed neurocognitive deficits among individuals with MUD. However, the issue of causality remains controversial. In a 2007 meta-analysis MA users (n = 471), compared to healthy controls (n = 441), showed deficits in learning, executive function, memory, and speed of information processing [52, p.20]. Importantly, these neurocognitive deficits seemed to be correlated with reduced dopamine transporter (DAT) density in the striatum and were not reversible following 1 month of abstinence from MA use [53, p.2]. However, a recent critical review of neuropsychological and neuroimaging data questioned the clinical significance of previously shown changes in human cognition [54], while an even more recent comprehensive review of data from animal studies, twin studies, neuroimaging, cross sectional and longitudinal studies concluded that MA can cause cognitive decline, at least in some predisposed individuals [55]. Carefully conducted longitudinal studies are needed to more fully characterize the nature and extent of MA-induced changes on human neurocognition.

5. Pharmacological treatments for MUD

5.1. Dopamine agonist treatment

The primary therapeutic premise of agonist treatment for drug abuse is to replace a more addictive, unsafe drug with a less addictive and safer medication. Examples of established agonist treatment approaches include methadone and buprenorphine for opioid use disorder and nicotine replacement for tobacco use disorder (see [56] for a critical review of the agonist treatment). Agonist treatment approaches have also been examined for the treatment of MUD. Because preclinical and clinical studies have shown that chronic exposure to MA leads to a hypo-dopaminergic state in the ventral striatum, characterized by decreases in D2 DA receptor density and hypo-responsiveness to dopamine receptor agonist challenges
[57], treatment with a D2 agonist may counteract this hypo-
dopaminergic state by increasing synaptic DA activity.

To date, the agonist medications dextroamphetamine and methylphenidate have been systematically examined in three studies (Table 1). In an 8-week, double blind, randomized, placebo controlled clinical trial of individuals with MUD (n = 60), sustained release dextroamphetamine (60 mg/day) was no more effective than placebo in reducing MA use, as assessed by urine toxicology. However, the dextroamphet-
amine group did display less craving and withdrawal symptoms than the placebo group [15]. Similarly, in a placebo-controlled, double blind, randomized 10-week study of sustained release methylphenidate (54 mg) in 110 individuals with MUD, group differences were not observed for self-reported days of MA use during the last 30 days of the active phase. However, the active group, compared with the placebo group, did report fewer MA use days and lower cravings from baseline through the active phase [16]. Finally, in a recent placebo controlled, 10-week clinical trial, escalating doses of methylphenidate-SR produced less craving and MA positive urines in individuals with MUD than did placebo treatment [17].

An additional DA agonist medication currently under study is lisdexamphetamine, a prodrug that consists of dextroamphetamine chemically linked to the amino acid l-lysine. Once ingested, lisdexamphetamine is cleaved by enzymes within red blood cells resulting in the release of the active dextroamphetamine. A theoretical safety advantage of lisdexamphetamine is its long duration of effect and reduced abuse potential [58]. Lisdexamphetamine is currently the focus of an ongoing clinical trial for MUD (NCT02034201) (Table 2).

5.2. Antipsychotics

Antipsychotics may attenuate the reinforcing effects of MA by blocking D2-type DA receptors. An added partial agonist activity at D2 receptors in the ventral striatum and other brain regions could theoretically alleviate the hypo-dopaminergic state that is associated with long-term MA use. In a random-
ized, 12-week, placebo controlled study in 90 individuals with MUD, the group treated with aripiprazole, an antipsy-
chotic with D2 partial agonist activity, did not differ from the placebo group in the number of confirmed MA positive urine samples [21] (Table 1).

5.3. Antidepressants

The similarity of MA withdrawal symptoms and depression [59], as well as the high comorbidity between major depressive disorder and MUD, has led researchers to hypothesize that antidepressants may be an effective treatment for MUD (Table 1). However, clinical trials with imipramine [13] and sertraline [14] have been negative and a recent 12 week randomized, double blind, placebo controlled study comparing 300 mg/day of bupropion (n = 100), an inhibitor of NE and DA reuptake, to placebo (n = 104) did not find group differences in abstinence from MA (defined as at least two negative urine samples on weeks 11 and 12) [11, p.201]. More recently, mirtazapine, an antidepressant that enhances NE and sero-
tnergic transmission by blocking both alpha2-adrenergic receptors and 5-HT2 and 5-HT3 receptors, was examined in a 12-week, double blind, randomized clinical trial in gay men with MUD. Treatment with 30 mg mirtazapine (n = 30) as compared to placebo (n = 30), reduced MA use measured as the proportion of positive urine test (RR of 0.57; CI 0.35–0.93; p = .02), and also reduced sexual risk behaviors [12]. It is important to note that participants in these studies were excluded if they had a diagnosis of major depressive disorder, and, as compared to placebo, none of the antidepressants improved depressive symptoms as measured with established scales. This raises the possibility, as already stated by Newton [60], that the depressive symptoms commonly reported in early MA withdrawal represent a distinct clinical syndrome.

5.4. GABA/glutamate modulators

Topiramate is an anticonvulsant with a complex mechanism of action that includes blockade of voltage-dependent sodium channels, increased GABA activity, antagonism of several glutamate receptors and inhibition of the enzyme carbonic anhy-
drase. Because topiramate has demonstrated promise for the treatment of alcohol and tobacco use disorders, it was exam-
ined in a recent 13-week multicenter, randomized, double blind, placebo controlled study in MUD comparing 200 mg/ day (n = 69) and placebo (n = 71). Although there were no group differences in MA weekly abstinence during weeks 6–12, 30 subjects were identified as ‘responders’ by either having reduced MA use over time or by achieving abstinence. This demonstrates that topiramate may have a favorable effect in a subset of individuals with MUD [19].

The pro-glutamatergic compound N-acetylcysteine (NAC) is thought to normalize extracellular glutamate levels in the nucleus accumbens by stimulating the cystine–glutamate antiporter [61] and is clinically used for the treatment of acetami-
nophen (Tylenol) overdose. NAC has been examined as a treatment for a wide range of psychiatric conditions, including addictions to nicotine, cocaine, cannabis and gambling [62]. NAC has also been examined in the treatment of MUD in a small randomized, placebo controlled, double blind trial of 14 subjects that used a combination of NAC and naltrexone (an opioid antagonist) with negative results [22]. However, a recent study demonstrated that NAC can reduce craving in MA dependent subjects [23] and NAC may therefore be useful as a pharmacological adjunct to behavioral interventions in patients with MUD.

The GABA-B receptor agonist baclofen and the anticonvul-
sant gabapentin, a drug with a complex mechanism of action including activity at a subunit of the voltage-gated calcium channel, have been examined in a 16-week randomized, pla-
cebo controlled study of baclofen (n = 25), gabapentin (n = 26) and placebo (n = 37). Although no group differences in primary or secondary outcomes were found, a post hoc analysis revealed a significant effect of increased medication compliance and reduction in MA use, especially in the baclo-
fen group [20].

Finally, vigabatrin (gamma-vinyl-GABA), an antiepileptic medication with potent GABA-enhancing properties through its inhibition of GABA transaminase, is being studied in a randomized, double blind, placebo controlled clinical trial of...
180 individuals with MUD. The results are currently pending (NCT00730522; www.clinicaltrials.gov; Table 2).

5.5. Medications targeting NE and DA

In many brain regions, NE and DA transmission are closely linked. There are neuroanatomical connections between the neurons projecting from the locus coeruleus (principal center of NE projections in the brainstem) and DA neurons of the ventral tegmental area. In addition, stimulation of NE neurons activates the dopaminergic system through the alpha-1 adrenergic receptors [63]. These preclinical data suggest that the modulation of NE systems is a viable therapeutic target with the alpha-1 adrenergic receptor antagonists prazosin and doxazosin currently being evaluated in clinical trials for MUD (NCT01371851 and NCT01178138; www.clinicaltrials.gov; Table 2).

Other pharmacological candidates that target NE systems include perindopril, an angiotensin-converting enzyme (ACE) inhibitor and candosartan, an angiotensin receptor blocker. Preclinical studies have shown an inhibitory effect of these medications on brain NE and DA neurotransmission although the exact effects have not been fully elucidated [64]. If effective, these medications could additionally reduce the elevated cardiovascular morbidity/mortality associated with MA use (NCT01062451; www.clinicaltrials.gov; Table 2).

Finally, entacapone, a drug that increases synaptic levels of DA and NE by inhibiting catechol-O-methyltransferase (COMT), an enzyme that degrades DA, NE and other catecholamines, is currently the focus of a Phase I study of MUD (Table 2).

5.6. Medications targeting the opioid system

The opioid system is thought to mediate the euphoric and rewarding effects of different substances of abuse [65]. In fact, naltrexone, a mu opioid antagonist, is an FDA approved treatment for alcohol use disorder. However, several different clinical trials on MUD have not shown a clear benefit of naltrexone, including the already referenced study using a combination of NAC and naltrexone [21], and a pilot study examining sustained release intramuscular naltrexone in MA dependent subjects carrying the A118G polymorphism of the mu receptor [66]. However, in a recent laboratory study, cue-induced and subjective responses to MA were reduced in those subjects who received naltrexone over placebo [67]. In addition, there are ongoing clinical trials studying the effects of a combination of bupropion or oxazepam and naltrexone (Table 2).

An additional opioid drug with potential utility is buprenorphine, a partial mu opioid agonist and a kappa receptor antagonist that is primarily used for maintenance therapy in individuals with opioid use disorder. In a recent placebo controlled human study of 40 participants with MUD, buprenorphine reduced cravings for MA as compared to the placebo group [68]. However, a significant limitation of using opioids in the treatment of MUD is the unknown risks associated with exposing patients who do not have a history of abusing opiates to a class of drugs with clear abuse liability.

6. Novel treatment approaches

6.1. Neuroimmune modulators

Cumulating evidence suggests that the pharmacological reduction of neuroinflammation is a potential treatment for MUD [69]. In preclinical studies, amphetamine-type stimulants activate microglia, an important mediator of inflammation in the CNS, and the blockage of microglia activation prevents the reinforcing effects of MA and MA-induced neurotoxicity [70]. Although limited, human studies indicate that chronic MA use is associated with microglia activation and increased biomarkers of neuroinflammation suggesting that medications which modulate neuroimmune signaling, such as minocycline and ibudilast, may have potential utility in the treatment of MUD.

Minocycline, an antibiotic commonly used to treat acne, has anti-inflammatory and neuroprotective effects in the CNS that are thought to be mediated by the inhibition of microglia activation. Consequently, minocycline is under investigation for the treatment of a variety of neurodegenerative and neuropsychiatric disorders. In a clinical study of healthy controls, 5 days of minocycline (200 mg/day), compared to placebo, attenuated the subjective rewarding effects of oral dextroamphetamine (20 mg/70 kg) and improved response inhibition function as measured by the Go/No-Go task [71]. The effects of minocycline in individuals with MUD remain to be determined.

An additional candidate neuroimmune modulator is ibudilast, a phosphodiesterase-4 inhibitor that increases brain levels of glial derived neurotrophic factor and reduces microglial activation and pro-inflammatory cytokine production. In a clinical study of 7 days of 100 mg/day, ibudilast reduced the acute subjective effects of 30 mg of MA administered intravenously [72].

An additional feature of targeting activated glial cells is the reduction of secreted pro-inflammatory mediators that exacerbate the neurological dysfunction caused by MA. Consequently, the pharmacological targeting of activated microglia may also improve HIV-associated cognitive dysfunction that is often comorbid with MUD (NCT01860807; www.clinicaltrials.gov).

6.2. Cognitive enhancement

As stated above, the chronic use of stimulants, especially cocaine and MA, is associated with deficits in cognitive functioning, most notably decision-making, response inhibition, planning, working memory, and attention [73]. In clinical studies of individuals undergoing treatment, these cognitive deficits are associated with higher rates of attrition and poor treatment outcomes, possibly because these deficits interfere with the ability to engage in the treatment activities [74]. In addition, given that cognitive deficits may negatively affect treatment outcomes and general functioning, regardless of their cause, cognitive enhancement may serve as an important treatment target. Consequently, pharmacotherapies that ameliorate cognitive deficits represent a novel treatment strategy for MUD [75] and include the use of cholinesterase inhibitors (e.g. rivastigmine or galantamine), partial nicotinic acetylcholine receptor (nAChR) agonists (e.g. varenicline),...
norepinephrine transporter (NET) inhibitors (atomoxetine), DA and NE transporter inhibitors (modafinil) and a prodrug for choline (citicoline) [73].

Cholinesterase inhibitors have been used for the treatment of dementia and other disorders characterized by cognitive impairment [38]. Rivastigmine is an inhibitor of the enzyme acetylcholinesterase that degrades acetylcholine and has been used in a completed clinical trial that has not yet been published (NCT01073319; www.clinicaltrials.gov). Varenicline is a partial nicotinic agonist that acts on neuronal α4β2 receptors and in a human laboratory study of 22 volunteers with MUD, pretreatment with varenicline at 2 mg was associated with a reduction in the positive subjective effects of 30 mg of smoked MA [76]. In addition, a clinical trial has examined the efficacy of varenicline for MUD but the results have not yet been published (NCT01365819; www.clinicaltrials.gov).

Atomoxetine, a selective NET inhibitor used for the treatment of attention deficit hyperactivity disorder (ADHD), is another promising medication targeting cognitive enhancement. In the prefrontal cortex, the NET is responsible for the reuptake of NE, as well as DA, into presynaptic nerve terminals [77] and the blockage of both of these actions may contribute to the cognitive-enhancing effects of atomoxetine [78,79]. A recently completed clinical trial that examined the efficacy of atomoxetine in individuals with MUD awaits publication (NCT01557569; www.clinicaltrials.gov).

Modafinil is a cognitive enhancer with weak stimulant-like properties (and hence less potential for abuse and diversion) and is approved by the FDA for the treatment of sleep apnea, narcolepsy and shift work-induced sleep disorder. It is a weak inhibitor of DA and NE transporters and has additional actions on brain GABA, glutamate and orexin [80]. In a 12-week multicenter, randomized, double blind study comparing 200 mg of modafinil (n = 72), 400 mg of modafinil (n = 70) and placebo (n = 68) group differences were found in the primary outcome of 1 week of MA negative urine. However, the study was confounded by a medication adherence rate of only 50% as determined by urine modafinil concentrations [18]. In addition, the study did not assess cognitive performance of the study participants and it remains to be examined if modafinil would be more effective in MA users with cognitive deficits, but as noted above, the interpretation of neurocognitive performance in the context of MA use is a complex issue requiring further study.

Finally, citicoline an intermediate in the generation of phosphatidylcholine, a major phospholipid in biological membranes, also facilitates synthesis of DA and acetylcholine. In preclinical and clinical studies, citciline has cognitive enhancing and neuroprotective properties [81] and a recently completed, but yet unpublished, clinical trial has tested the efficacy of citicoline for MUD (NCT00950352).

6.3. Vaccine immunotherapies

Despite previous inconsistent results, there is a renewed interest in the use of immunotherapies, especially vaccines, for the treatment of different drugs of abuse including nicotine, cocaine and MA [82]. Immunotherapies reduce the amount of drug that reaches the brain by stimulating the production of antibodies that bind to the drug molecule after it has been systemically absorbed during drug use. The limitations of a vaccine include the prolonged time it takes to develop sufficient circulating antibodies, the large variation in the antibody titer and incomplete blockage of drug effects. Furthermore, the antibodies developed are specific for a given drug molecule and this limits effectiveness in individuals using multiple drugs [82]. For MUD, vaccines could be most effective in preventing relapse in individuals who use MA sporadically. While there are several ongoing MA vaccine studies, there is also a completed clinical trial using Ch-mAb7F9, a human–mouse monoclonal antibody that binds to methylphenidate (NCT01603147; www.clinicaltrials.gov).

6.4. Oxytocin

There is cumulating evidence of a potential benefit in the use of the ‘pro-social’ hormone oxytocin for treating substance use disorders [83]. So far, results are inconclusive with both positive and negative effects in humans that may depend on the type of substance used. Although the exact mechanisms remain elusive, some authors have proposed an inhibitory effect of oxytocin in the reward circuit, particularly in the nucleus accumbens and subthalamic nucleus projections [84]. A recent clinical trial will examine the potential utility of oxytocin combined with motivational enhancement group therapy in HIV positive gay men with MUD (NCT02881177; www.clinicaltrials.gov).

7. Conclusions

Despite the significant advances made over the past several decades in the understanding of the basic neurobiology of stimulant addiction, these advances have not been translated into effective pharmacological treatments for MUD. Clinical trials testing potential medications for MUD have largely been negative, and currently there are no consistently effective pharmacological treatments for MUD. Novel treatment targets include cognitive-enhancement strategies, the modulation of the neuroimmune system and immunotherapy through vaccine development. These and other promising treatment approaches need to be tested in well designed and adequately powered clinical trials while the results of recent studies with novel therapeutic targets await publication.

8. Expert commentary

Similar to MUD, there are no effective pharmacological treatments for addiction to cocaine, a similarly acting stimulant for which a much larger number of clinical trials using various medications has been conducted. This failure in progress for development of pharmacological treatment for MUD could be influenced by multiple factors including small sample sizes in the majority of studies compounded by high dropout rates, in the range of 40–50 %. Therefore, the majority of clinical pharmacological trials for MUD are simply underpowered. In addition, there is also an ongoing debate about which clinically significant outcome measures should be used in clinical trials.
of stimulant use disorders. Future work should address these methodological limitations.

As noted earlier, individuals with addiction, including those with MUD, have many comorbid disorders including other addictions, anxiety, psychosis and mood disorders. These disorders have overlapping symptom clusters across different diagnostic categories and therefore, new treatment approaches that use trans-diagnostic treatment targets, rather than trying to develop specific treatments for individual addictions and other psychiatric disorders, may be constructive. Consistent with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health (NIMH), using such an approach is responsive to what some have called a ‘therapeutic stagnation’ for mental health disorders. The proposed RDoC approach, by identifying trans-diagnostic treatment targets, may be especially fruitful in developing pharmacotherapies for highly comorbid conditions like stimulant addiction where neuroimmune mechanisms, especially microglia activation and cognitive deficits, are relevant targets across a range of psychiatric disorders. Although not novel for other addictions, immunotherapies for MUD have already demonstrated some promising findings.

Finally, pharmacogenetics is another area of research that may enhance the benefits from pharmacotherapies for SUDs. The ability to predict treatment response and adverse effects based upon genetic markers can lead to an optimal treatment matching. While promising, the effect of pharmacogenetic testing on treatment outcomes in clinical settings requires further study.

9. Five-year view

An important issue that has not yet been addressed is the development of a consensus on the main outcome measures to be used across clinical trials for MUD. Currently, clinical trials use a wide range of outcome measures focusing on MA use during the clinical trial. However, the clinical significance of these measurements is not always clear. The standard outcomes that are widely used for clinical trials in tobacco and alcohol use disorder are noteworthy predicates to consider in this regard. In addition, given the historically low retention rates in MA studies, sample sizes need to be increased to ensure that future clinical trials have adequate power to test the efficacy of promising treatments. Conducting multisite studies can help with addressing this sample size issue, while interventions like contingency management are effective in improving retention. With the implementation of improved clinical trial methodology, the field will be better positioned to effectively test the potential for novel treatments of MUD.

Key issues

- On a global basis, methamphetamine (MA) and related stimulants continue to be the second most widely abused drug class after cannabis. Currently available treatments for methamphetamine use disorder (MUD) are primarily behavioral and have limited efficacy.
- Despite considerable effort, no medications have been approved for the treatment of MUD. Numerous clinical trials have been conducted utilizing medications that act on a variety of different targets including DA agonist treatments (dextroamphetamine, methylphenidate), antipsychotics (aripiprazole), antidepressants (imipramine, sertraline, mirtazapine, bupropion), GABA/glutamate modulators (topiramate, N-acetylcysteine, baclofen and gabapentin). Other pharmacological systems are currently under study and include medications targeting NE and DA (prazosin, doxazosin, candosartan, entacapone), and the opioid system (naltrexone, buprenorphine).
- Novel and exciting approaches for the treatment of MUD include neuroimmune modulators (minocycline, ibudilast), cognitive enhancers (rivastigmine, galantamine, varenicline, atomoxetine, modafinil, citicoline), vaccines, and oxytocin.
- The future of the field will likely depend on overcoming methodological limitations (high drop-out rates, small samples, agreement on outcome measures), and might benefit from the development of trans-diagnostic criteria.

Funding

This research was supported by the Veterans Administration Mental Illness Research, Education and Clinical Center (MIRECC).

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.


This review provides a nice perspective and classification of different agents and systems that perhaps will be used in the future for the treatment of substance use disorders.
This very recent article provides a comprehensive and well integrated view of the proposed neuronal circuits affected in individuals with substance use disorders.

- Müller CP, Homberg JR. The role of serotonin in drug use and addiction. Behav Brain Res. 2015;277:146–192.

This is a comprehensive review that gives a good perspective of the complexity of this controversial topic.
- This article introduces the topic of cognitive enhancement as a potential treatment for drug addictions, combining certain pharmacological agents (cognitive enhancers) with behavioral and psychological treatments (cognitive remediation).
- **This article offers a good update of an area that is not very well-known but that it is becoming increasingly important.**