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Pharmacotherapeutic agents in the treatment of methamphetamine dependence

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ABSTRACT

Introduction: Methamphetamine use is a serious public health concern in many countries and is second to cannabis as the most widely abused illicit drug in the world. Effective management for methamphetamine dependence remains elusive and the large majority of methamphetamine usersrelapse following treatment.

Areas covered: Progression in the understanding of the pharmacological basis of methamphetamine use has provided us with innovative opportunities to develop agents to treat dependence. The current review summarizes relevant literature on the neurobiological and clinical correlates associated with methamphetamine use. We then outline agents that have been explored for potential treatments in preclinical studies, human laboratory phase I and phase II trials over the last ten years.

Expert opinion: No agent has demonstrated a broad and strong effect in achieving MA abstinence in Phase II trials. Agents with novel therapeutic targets appear promising. Advancement in MA treatment, including translation into practice, faces several clinical challenges.

1. Introduction

Methamphetamine (MA) use is a serious public health concern in many countries and is second to cannabis as the most widely abused illicit drug in the world [1]. In recent years, MA use has become increasingly more prevalent throughout the Americas, Asia, and Australia [1,2] and psychostimulant-related hospital admissions and consultations have sharply increased [3]. Implications of use and dependence include societal costs and the burden on public health resources due to multiple medical and psychiatric comorbidities [3]. Unfortunately, however, effective management for MA dependence remains elusive. Psychological interventions represent an important approach in treating substance use but often need to be used in conjunction with other forms of treatment including pharmacotherapies. There are currently no approved pharmacotherapies for treating MA addiction.

Advances in the understanding of the neurobiological basis of MA use provide us with innovative opportunities to develop pharmacotherapies to treat dependence. The current review will first summarize relevant literature on the neurobiology of MA abuse and then outline the agents that have been explored for potential treatments over three sections: preclinical studies, phase I and II, and those currently under trial. For the first two sections, we identified articles for inclusion through extensive literature searchers conducted in June–July 2016 using the PubMed online medical database. We used the search terms ‘methamphetamine’ and (1) ‘rodent,’ ‘preclinical’ for preclinical trials and (2) ‘treatment,’ ‘pharmacotherapy’ for phase I and II clinical trials. We reviewed the search results and limited results to citations no older than 10 years. For the last section, the list of current agents being trialed was derived from the US National Institutes of Health clinical trials website (clinicaltrials.gov). We used the search term ‘methamphetamine’ under phase I open studies and ‘methamphetamine’ under phase II open studies, which yielded 6 phase I and II clinical trials after exclusion of non-pharmacotherapy studies or those with status unknown or withdrawn.

2. Neurobiology of MA use

2.1. Mechanism of action of MA

MA is a central nervous system stimulant resulting in increased euphoria and alertness lasting from 6 to 12 h depending on the route of administration and dose [4,5]. MA acts primarily to increase and sustain extracellular levels of the monoamines dopamine, serotonin, and norepinephrine [6]. The acute psychological effects include feelings of ‘high’ and ‘positivity,’ anxiety, insomnia, irritability, and psychosis while physiological indications include hypertension, tachycardia, and sweating [7]. Potent enhancement of dopaminergic neurotransmission within the mesocorticolimbic pathway is thought to mediate the reinforcing effects of MA [6]. The elevated level of dopamine in the extracellular synapse contributes to the severe neurotoxicity induced by large and extended doses (see below). Synaptic dopamine release is modulated by MA mainly acting at the vesicular monoamine transporter-2 (VMAT-2) and the bi-directional dopamine transporter (DAT). VMAT-2 is a membrane protein expressed on secretory vesicles that transport monoamines from the intracellular cytosol.
One trial demonstrated mirtazapine to be effective increasing rates of MA abstinence (primary outcome measure). Post-hoc analyses have shown some efficacy according to baseline MA use such as MPH-SR (heavy users), bupropion (light users) and topiramate (abstinent use at baseline). Compounds with novel therapeutic targets (eg anti-inflammatory) and modes of delivery (eg pharmacimunotherapy) are promising. Progression in the field requires strategies to improve compliance as well as more clinical research into novel strategies for efficacy.

Article Highlights

- Methamphetamine use is a serious public health concern in many countries.
- No single medication has demonstrated a broad and strong treatment effect in clinical trials.
- One trial demonstrated mirtazapine to be effective increasing rates of MA abstinence (primary outcome measure).
- Post-hoc analyses have shown some efficacy according to baseline MA use such as MPH-SR (heavy users), bupropion (light users) and topiramate (abstinent use at baseline).
- Compounds with novel therapeutic targets (eg anti-inflammatory) and modes of delivery (eg pharmacimunotherapy) are promising.
- Progression in the field requires strategies to improve compliance as well as more clinical research into novel strategies for efficacy.

This box summarizes key points contained in the article.

into the vesicles [8]. When MA acts at VMAT-2, a blockade or reversal of VMAT-2 transport occurs resulting in DA release from the intracellular secretory vesicles [9]. A rise in cytoplasmic DA concentration occurs which is followed by reverse transport of DA via the DAT into the synaptic cleft. At the extracellular DAT site, MA competes with the synaptic DA that has been reverse transported outside the neuron [10]. Furthermore, the DAT can also be removed from the plasma membrane by internalization into the endocytotic-recycling pathway which subsequently impedes the removal of extracellular levels of dopamine [11].

2.2. Consequences of MA use

2.2.1. Neurotoxicity

Clinical evidence using positron emission tomography (PET), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) provide support for prolonged neurotoxicity, including structural and metabolic changes, following extended use of moderate-to-large doses of MA.

PET studies have consistently observed reduced levels of DAT availability (from 11% to 28%) in abstinent MA users relative to nonusers in brain regions that include the dorsolateral prefrontal cortex, orbitofrontal cortex, amygdala, and striatum [12]. Chronic use of high doses can lead to downregulation of DAT that does not recover until many months of abstinence. One study has demonstrated a 38% DAT recovery within 2 weeks of abstinence [13], while another reported a 16–19% increase only after protracted abstinence (12–17 months) [14]. Downregulation in dopamine D2-type receptor availability has also been observed in the striatum of abstinent MA users [15,16]. Finally, reduced levels of the S-HT transporter (SERT) have been observed in cortical and subcortical brain regions in MA users abstinent for <12 months relative to controls [17] and reductions in VMAT-2 density of up to 10% have also been reported in chronic MA users following at least 3 months of abstinence [18].

Evidence from structural MRI studies has demonstrated cortical and striatal gray and white matter abnormalities in chronic MA users relative to controls. Reduced cortical gray matter volume has been observed following brief abstinence in the prefrontal cortex [19], anterior cingulate cortex, and limbic cortex [20] while larger striatal volumes have been reported following 3–4 months of abstinence, possibly due to a compensatory effect [21]. White matter abnormalities underlyning and interconnecting prefrontal cortex and the hippocampus have also been reported in chronic MA users [22].

Alterations in neuronal integrity and neuronal inflammation have also been observed in MA users relative to ‘never-used’ controls. MRS studies have found reduced concentration of N-acetyl-aspartate in basal ganglia and frontal white matter and reduced total creatine in the basal ganglia in chronic users [23]. PET studies have observed increased PK 11195 binding, a marker for neuroinflammation, in several brain regions of abstinent MA users including the striatum, thalamus, insular, and orbitofrontal cortex [24].

2.2.2. Neurocognitive and psychiatric consequences

Chronic MA use has been demonstrated to be associated with neuropsychological impairment [12]. Significant deficits in cognitive processes contingent upon fronto-striatal and limbic circuits such as executive function, episodic memory, processing speed, and psychomotor tasks have consistently been reported with medium effect sizes, with smaller effects observed for attention and language tasks [25–27]. These impairments are generally observed during the first 3 months of abstinence with some impairments improving following protracted sustained abstinence [25].

MA can lead to a range of psychiatric sequelae following acute use, withdrawal, and chronic extended use. Psychotic symptoms can be difficult to distinguish from schizophrenia and include persecutory delusions, auditory hallucinations, and loss of insight [28]. MA-induced acute withdrawal symptoms include negative affect, psychosis, anxiety, and fatigue [29]. Chronic MA users report higher rates of anxiety, depression, psychotic states, impulsivity, and aggression [30]. These symptoms can subside with protracted abstinence but some persist long term [31]. It has been reported that transient psychotic symptoms are related to earlier onset MA use while persistent psychotic symptoms are associated with a family history of psychosis and depression [32]. The prevalence of comorbidity between mental health disorders and substance use is well documented and results in poorer treatment course and outcomes.

Long term neuropsychiatric changes in MA users have been correlated with markers of long-term neurotoxicity. For example, low D2 receptor striatal availability has also been associated with greater impulsivity in MA users [15], memory deficits have been associated with reduced DAT site density [33], and reduced levels of SERT density in the orbitofrontal, temporal, and anterior cingulate cortices have been observed to be associated with higher levels of aggression [17]. Furthermore, reduced white matter integrity has been found to correlate with depression severity [22], reduced hippocampal volumes have been associated with poorer memory performance [20], and cognitive impairment has been found to be associated with several neuroinflammatory markers [34].

It has been questioned whether the degree to which the observed neurocognitive changes in MA users are clinically meaningful and also whether they are directly a result of MA-induced neurotoxicity or preexisting factors [35]. Given
the absence of prospective longitudinal studies, it is still possible that MA users have preexisting alterations in transporter densities and neurocognitive abnormalities. Nonetheless, systematic evaluations of the literature conclude that MA can induce clinically significant impairments but only in some users [36], whereby deficits may be moderated by individual factors such as age and genotypic variability in the metabolic clearance of MA via cytochrome p450-2D6 activity [37]. Finally, from a therapeutic perspective, it seems that markers of neurotoxicity are clinically important given that high striatal D₂ receptor availability in MA users at baseline predicts relapse [38] and DAT recovery with abstinence is correlated with recovery of executive function [13].

3. Potential pharmacotherapies for MA dependence

The complex mechanism of action of MA produced by repeated MA use opens several potential neuropathopharmacological angles regarding targets for management. Pharmacotherapies investigated for the management of MA have different underlying mechanisms that may (1) modulate the mesolimbic dopamine system either directly or indirectly to alter the experience of reward (e.g. GABA, glutamate, opioid, peptide hormones); (2) recover alterations in dopaminergic homeostasis through acting on the membrane protein (e.g. DAT, DA receptor partial agonists) to potentially improve neurocognitive deficits or psychiatric symptoms and attenuate negative reinforcing effects of withdrawal (and potentially promote treatment engagement); (3) reduce neurotoxicity using anti-inflammatory agents; and (4) modulate the pharmacokinetics of MA to reduce the amount of drug entering the brain (via immunotherapy).

3.1. Preclinical studies

Preclinical studies are an important step in the discovery of new pharmacotherapies. When investigating complex disorders, such as drug addiction, there are obvious limitations for the translation from rodent models to the human condition (species differences, simple models, greater homogeneity); however, they do provide the building blocks for understanding how chronic drug use affects brain function to suggest targets for drug development. Moreover, in comparison to other disorders, drug addiction has a known etiology, which can be more easily modeled in preclinical experiments through repeated drug administration.

It is important here to make the distinction between preclinical models that investigate drug reward or acute reinforcement and those that elucidate changes associated with repeated drug use and relapse. The former is problematic as therapies that are aimed at effective reduction of drug reinforcement are also likely to affect natural reinforcers, limiting their therapeutic potential. The latter have greater validity for promoting abstinence in users, particularly those that assess potential for relapse reduction. There are a number of models that investigate the enduring neurobiological changes associated with repeated MA abuse and addiction: the expression of behavioral sensitization [39], conditioned place preference (CPP) [39,40], and intravenous self-administration reinstatement models [39]. The following pharmacotherapies have shown some promise for alleviating MA addiction in preclinical models.

The atypical antipsychotic aripiprazole, which is a partial dopamine receptor agonist with serotonergic actions, has shown some efficacy for MA treatment in preclinical studies. Aripiprazole effectively attenuated MA self-administration in rats [41] and had greater efficacy in reducing the motivation to administer MA in rats exposed to long-access (6 h/day) compared to short-access (1 h/day) regimes [41]. Repeated aripiprazole treatment also reduced the expression of behavioral sensitization to repeated MA use when given daily for 5 days during the withdrawal period in mice [42]. Using an acute MA model, aripiprazole treatment also reduced MA-induced stereotypy in a dose-dependent manner in both pre- or posttreatment for MA use [43]. Together, these data indicate that aripiprazole may have therapeutic potential, not only to reduce drug intake and relapse but also to reverse MA overdose.

Reichel and See have demonstrated that chronic administration of the weak dopamine receptor, modafinil, reduces conditioned cue-induced and MA-primed reinstatement, an effect which remains 2 weeks following treatment cessation [44]. In addition to reducing MA relapse, this group has shown that modafinil may enable adaptive behaviors in MA-experienced rats by enhancing cognition, measured by restoration of spatial memory [45]. Similar effects have been measured for modafinil in MA-experienced mice for reversing deficits in object recognition [46]. Modafinil also works as a neuroprotectant and significantly reduced the neurotoxicity and inflammation induced by MA administration [47], providing a promising avenue for therapeutic investigation. New analogs of modafinil have recently been developed [48]. However, it should be noted that some studies [49], but not others [50], have indicated that modafinil may have reinforcing properties or enhance the effect of MA.

Evidence indicates that dopamine D₂ receptors may have a key role in mediating substance abuse. The administration of a novel D₂ receptor antagonist, YQA14, inhibited rat MA self-administration [51], facilitated extinction and decreased reinstatement to MA-induced MA-seeking behavior via CPP [52]. These results indicate some promise for D₂ selective antagonists as treatment for relapse to MA use. Gong et al. [53] observed that levo-tetrahydrodralmatine (L-THP), a mixed receptor antagonist, blocked self-administration and reinstatement of MA-seeking behavior. They concluded that L-THP may be useful for the treatment of MA addiction and has a better safety profile with fewer side effects than other DA receptor antagonists. Mi et al. [54] demonstrated that I-Scoulerine, which is a tetrahydroprotoberberine (THPB) alkaloid, blocked the expression of MA-induced CPP. THPBs represent a series of compounds extracted from the Chinese herb Corydalis ambigua and various species of Stephania and are a category of dopamine receptor ligands [55].

Mirtazapine is an atypical antidepressant that primarily acts on both norepinephrinergic and serotonergic systems, through the antagonism of their autoreceptors,α₂ adrenoreceptor and 5HT₂ receptor, respectively [56]. Activity at 5HT₁A receptors by mirtazapine also enhances dopamine
neurotransmission, notably in the prefrontal cortex [57], and it has been reported to have inverse agonist activity at 5HT2C receptors [58]. One research group has shown treatment with mirtazapine to be effective in reducing several preclinical indicators of MA addiction in rats – the expression of behavioral sensitization [59] and CPP [60] including a reversal of CPP when treatment occurred during withdrawal [61,62], and reinstatement of MA seeking triggered by cue reexposure [63]. Another study failed to see an effect of mirtazapine on MA sensitization in rats when used in combination with the dopamine and serotonin receptor agonist pergolide [64]. However, the treatment dose and period was almost half used in the mirtazapine treatment regime of McDaid et al. [59]. Together, these data suggest that mirtazapine or pharmacologically related compounds [65] are strong candidates for clinical investigation. Bupropion is also an atypical antidepressant and acts as a norepinephrine and dopamine reuptake inhibitor [66]. In preclinical models of MA self-administration, bupropion has reduced drug intake rats [67]; however, no research has been conducted in preclinical relapse models. It is proposed that bupropion would be used as ‘agonist’ or replacement therapy in MA users, and although it shows locomotor and sensitized behavior similar to MA administration [68], the effect was at 15-fold higher doses. This suggests, together with the reduction in MA self-administration behavior, that bupropion has low abuse potential at low–moderate doses [68].

Other potential ‘agonist therapies’ for stimulant dependence are treatment with methylphenidate or d-amphetamine, which work to either block or reverse DAT and NET, respectively [69], similar to MA. There have been a number of preclinical studies that have investigated the behavioral effects of either of these compounds; however, very few have investigated their effect on MA self-administration or relapse studies. In one study using rhesus monkeys, methylphenidate administration did not affect the intake of MA [70], and it has also shown significant reinforcing effects on its own to the point of dysfunctional intake in rats [71]. In contrast, d-amphetamine showed significantly less reinforcing effects when compared to MA administration in rhesus monkeys trained to self-administer cocaine [72], suggesting a realistic alternative for MA replacement therapy. Growing evidence supports a role for trace amine associated-receptor 1 (TAAR1) in the functional regulation of monoamine transporters and neuronal mechanisms that modulate dopaminergic activity, providing a potential avenue for drug development to treat psychostimulant addiction [73]. MA is a full agonist of the TAAR1 [74] and indeed, modulation of TAAR1 with the partial TAAR1 agonist RO5263397 has been reported to attenuate MA cue and drug-induced reinstatement and behavioral sensitization [75]. In addition, TAAR1 knockout mice displayed decreased acquisition of MA-induced CPP and increased retention compared with wild-type mice [76]. Taken together, these studies suggest that compounds aimed at TAAR1 regulation may be promising therapeutic targets for reducing MA addiction.

The administration of compounds targeting GABA and glutamatergic systems has also been suggested as important therapeutic directions for MA addiction. Treatment with the GABAβ1 receptor agonist, baclofen, facilitated the extinction of MA-induced CPP [77] and pretreatment with baclofen dose dependently inhibited the development and expression of MA-induced CPP [78]. Baclofen treatment also reduced the motivation to lever press for MA intake [79], suggesting that enhancing GABA neurotransmission may reduce MA addiction. The molecular structure of the anticonvulsant gabapentin was modeled off GABA; however, its mechanism of action is not yet fully understood. It is thought that gabapentin may act to antagonize voltage-gated calcium channels to inhibit neural activity. Through this mechanism, gabapentin treatment has prevented the development of sensitization or CPP to MA [80]; however, no preclinical data yet exist to suggest that gabapentin treatment can reduce relapse to MA addiction. Topiramate is another anticonvulsant drug and has mixed effects on calcium channels, sodium channels, GABA-A receptors, and AMPA/Kainate glutamate receptors; yet, no preclinical data exist on the therapeutic potential of this drug on MA addiction. Similarly, while it is known that glutamate systems are important mediators of MA relapse [39], there has been little preclinical studies on potential treatments in this domain. Pretreatment with CSB6B, a vesicular glutamate transporter inhibitor, has been reported to suppress the acquisition of MA-induced CPP [81]; however, the effect on MA relapse has not been conducted. The potential anti-addiction effects of N-acetylcysteine (NAC), which has multiple actions on glutamate neurotransmission [82], have been well described in models of preclinical cocaine addiction [39]; however, less has been shown in MA models. Treatment with NAC has shown potential to reverse neurotoxicity produced by MA abuse [83] and also reduced the expression of behavioral sensitization to MA [84]. NAC therapy had been suggested as a promising avenue for treating MA addiction [82].

The opioid antagonist, naltrexone, has been demonstrated to inhibit cue-induced MA-seeking behavior in rats that are previously trained to self-administer MA [85]. Some studies have reported that μ-opioid receptor knockout mice fail to demonstrate MA-induced behavioral sensitization [86] and have a shorter recovery duration to basal levels of extracellular dopamine metabolites induced by MA compared to wild-type mice [87]. There is also evidence regarding the potential role of endogenous hormones in MA treatment. Gou et al. [88] observed that cholecystokinin-8 (CCK-8) pretreatment significantly inhibited both the development and expression of MA-induced behavioral sensitization in a dose-dependent manner and attenuated the decrease of tyrosine hydroxylase and DAT in striatum. Peripheral administration of CCK-8 has been demonstrated to activate oxytocin-secreting neurons in the hypothalamus [89]. Interestingly, there are promising results from a few research groups who have consistently demonstrated that administration of oxytocin attenuates MA-related reward and MA-seeking behavior [90–92], possibly through mechanisms other than oxytocin receptor activation [93]. Varenicline is a partial agonist at α4β2 nAChRs and a full agonist at α7 nAChRs that has shown promise for reducing nicotine dependence; yet, little preclinical evidence exists for
its efficacy in MA models. Enhancement of acetylcholine neurotransmission will also be achieved through the use of anticholinesterase inhibitors, such as rivastigmine and perindopril that have been considered for use in the clinic for MA addiction. However, while activity at nicotine receptors (including varenicline) do not generally substitute for MA in discrimination tasks [94], two very recent studies have suggested that for MA-experienced animals, varenicline may actually enhance MA relapse in both male and female subjects [95,96].

An emerging pharmacological intervention strategy is to target neurotoxicity using anti-inflammatory agents. The agent, ibudilast, a nonselective phosphodiesterase inhibitor and promoter of glial cell-derived neurotrophic factor, significantly reduced MA prime- and stress-induced reinstatement of MA seeking in rats [97]. Furthermore, Chahtikov et al. [98] reported that administration of ibudilast reversed the decrease in synaptic signaling protein produced by chronic MA intake by rats. Kim et al. [99] investigated sauchinone (a nitrous oxide inhibitor) and demonstrated that the agent blocked the acquisition of MA-induced CPP and pretreatment decreased MA-induced CPP. Sauchinone has been shown to significantly inhibit nitrite production and inflammatory mediators’ expression via heme oxygenase-1 upregulation [100]. Finally, Ren et al. [101] observed that 7,8-dihydroxyflavone (7,8-DHF), a TrkB agonist, treatment significantly protected against the reduction of DAT in the striatum after repeated MA dosing. Pretreatment with 7,8-DHF also significantly attenuated the development of behavioral sensitization. These data indicate that the agents listed above have several properties for effective management of MA use including improvement of dopaminergic and neuroinflammatory dysfunction and amelioration of behavioral changes.

New alternatives to the conventional pharmacotherapeutic strategies are anti-MA vaccines or immunotherapies. In contrast to the traditional pharmacodynamic approach, anti-MA vaccines are designed to generate antibodies that essentially act as pharmacokinetic antagonists that bind to MA and lessen brain concentration of MA. In line with this, a monoclonal antibody treatment for MA (mAB7F9) showed significant reduction in MA-induced locomotor activity over a 1-month period [102]. Interestingly, an earlier study reported an initial compensatory effect to pharmacokinetic antagonism with an increase in acquisition of MA self-administration following the monovalent vaccine METH-EP54 [103]. However, at this point, the most promising immunopharmacotherapies are keyhole limpet hemocyanin (KLH)-conjugated MA vaccines that produce significant MA antibody levels with high affinities for MA [104]. The KLH-conjugated MA-like hapten vaccine, MH6-KLH, has been shown to reduce MA-induced locomotor activity, thermoregulation [105] and acquisition of MA self-administration in rats [106]. The MA conjugate vaccine ICKLH-SM09 was also affective in reversing the anorectic effect of MA administration in rats over a 4-month period [107]. In mice, the vaccine succinyl MA (SMA–KLH) has been observed to decrease MA-induced locomotor activity and CPP in mice [108]. Similarly, an agent with a different carrier protein, succinyl MA tetanus toxoid, has been reported to reduce acquisition and reinstatement of MA-induced CPP in mice [109].

In order to produce continuing adequate levels of antidrug antibody, one research group has found that the administration of ICKLH-SM09 with the adjuvant glucopyranosyl lipid A in mice was more effective in elevating antibody levels over a 21-week period than using the adjuvant aluminium hydroxide [110]. Following on from this, the same research group has determined in rats that a combined monoclonal and polyclonal antibody approach produced effective reductions in brain MA for over 4 months [102]. While pharmacoinmunotherapy provides some promise for translation given that anti-MA antibodies do not cross the blood–brain barrier, therefore reducing the likelihood of psychiatric side effects from nonspecific actions, antibodies need to be maintained at an effective level with repeated administration, thus requiring greater cost and treatment engagement [111].

3.2. Human laboratory and clinical studies

Human laboratory studies should provide an efficient mechanism to provide an early indication of the potential efficacy of new drugs emerging from preclinical studies in addition to those currently approved for other clinical indications before proceeding to more costly and potentially risky clinical trials. Human laboratory studies include investigations of compounds altering MA-induced cardiovascular, subjective (high, craving, etc.), and reinforcing effects (self-administration) in controlled conditions with a small number of individuals (see Table 1). Phase II clinical trials measure MA abstinence as the primary outcome and craving, reduction of use and treatment adherence as secondary outcomes over an extended period.

The literature from other drugs of abuse (e.g. heroin, cocaine) indicates that a large number of false positives are yielded from medications altering subjective effects whereas human self-administration more accurately predicts whether a compound will be clinically efficacious [112]. Thus, altering the subjective effects of MA with a candidate compound in human laboratory studies may not necessarily have a correlation with clinical outcome in trials. For studies investigating treatments for MA use, there have been few studies that have both been tested in human laboratory paradigms and also been to clinical trial. It is thus currently difficult to determine which of these paradigms are robustly sensitive to new medications. With this in mind, the following therapeutic agents utilizing several different treatment strategies have been investigated.

The atypical antipsychotic, aripiprazole, has been investigated by several research groups with the potential to act as an antagonist to reduce the reinforcing effects of MA. Newton et al. [113] reported that aripiprazole treatment (15 mg, for 2 weeks) did not reduce MA-cue-induced craving and actually increased rewarding and stimulatory effects of MA. Sevak et al. [114] observed aripiprazole (20 mg) to reduce the cardiovascular, subjective, and reinforcing effects of MA. Similarly, Stoops et al. [115] demonstrated that acute aripiprazole (15 mg) pretreatment yielded a significant reduction in self-administration for low (4 mg) and intermediate (8 mg) doses of MA. However, in a double-blind randomized-controlled trial (DBRCT), Coffin et al. [116] failed to demonstrate that 12 weeks
<table>
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<tr>
<td>De La Garza II et al. [113]</td>
<td>Rivastigmine 1.5 and 3 mg</td>
<td>DSM-IV TR MA abuse or dependence</td>
<td>DB between</td>
<td>Reinforcing effects: MA choice Subjective effects: VAS</td>
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<tr>
<td>De La Garza II et al. [124]</td>
<td>Rivastigmine 3 and 6 mg</td>
<td>DSM-IV TR MA dependence</td>
<td>DB within</td>
<td>Subjective effects: VAS Reinforcing effects: MA choice</td>
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<tr>
<td>Pike et al. [128]</td>
<td>d-amphetamine 40 mg</td>
<td>DSM-IV stimulant dependence</td>
<td>DB within</td>
<td>Subjective effects: ARS, DEQ, VAS Cardiovascular effects: HR, BP</td>
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<td>Non-treatment seeking</td>
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<tr>
<td>De La Garza II [126]</td>
<td>Modafinil 200 mg</td>
<td>DSM-IV TR MA dependence</td>
<td>DB within</td>
<td>Cardiovascular effects: BP, HR Subjective effects: VAS Reinforcing effects: MA choice, monetary value</td>
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<td>Non-treatment seeking</td>
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<td>Newton et al.</td>
<td>Perindopril</td>
<td>N = 30</td>
<td>Parallel</td>
<td>Cardiovascular effects: HR, BP</td>
<td>n.s. HR</td>
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<tr>
<td>[146]</td>
<td>2, 4, 8 mg</td>
<td>DSM-IV MA dependence</td>
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<td>Subjective effects: VAS</td>
<td>Attenuated MA effect on BP</td>
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<td>Non-treatment seeking</td>
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<td>Attenuated MA-induced 'any drug effect'</td>
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<tr>
<td>Verrico et al.</td>
<td>Perindopril</td>
<td>N = 60</td>
<td>IV</td>
<td>Cardiovascular effects</td>
<td>Reduced MA-induced 'anxious' and 'stimulated'</td>
</tr>
<tr>
<td>(2016) [127]</td>
<td>4, 8, 16 mg</td>
<td>DSM-IV-TR MA dependence</td>
<td>Parallel</td>
<td>Subjective effects: VAS</td>
<td>n.s. on peak cardiovascular or subjective effects</td>
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<tr>
<td>Ray et al. [143]</td>
<td>Naltrexone 50 mg</td>
<td>N = 30</td>
<td>Crossover</td>
<td>Cardiovascular response</td>
<td>n.s. dose-response effect</td>
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<td>DSM-IV MA abuse or dependence</td>
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<td>Subjective effects</td>
<td>n.s. effect on cue-induced cravings</td>
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<td>Non-treatment seeking</td>
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<td>Attenuated MA-induced HR, systolic and diastolic BP</td>
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<td>CR</td>
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<td>Attenuated MA ‘crave drug,’ ‘stimulated,’ ‘would like drug access,’ ‘feel drug effects,’ ‘drug high’</td>
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<td>DeYoung et al.</td>
<td>Ibudilast</td>
<td>N = 11</td>
<td>DB within</td>
<td>Cardiovascular effects</td>
<td>Increased MA ‘anxiety’ ‘bad drug effects’</td>
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<td>[147]</td>
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<td>DSM-IV MA dependence</td>
<td>Crossover</td>
<td>MA pharmacokinetics</td>
<td>n.s. cardiovascular effects</td>
</tr>
<tr>
<td>Worley et al.</td>
<td>Ibudilast</td>
<td>N = 11</td>
<td>DB within</td>
<td>Subjective drug effects: VAS</td>
<td>n.s. change in maximum concentration or half-life of MA</td>
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<tr>
<td>[148]</td>
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<td>MA dependence</td>
<td>Crossover</td>
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<td>n.s. mild to moderate AE</td>
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<td>Non-treatment seeking</td>
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<td>Attenuated MA ‘effect,’ ‘high,’ ‘good,’ ‘like,’ ‘stimulated,’ ‘use’</td>
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<td>Enhanced MA ‘nervous’ ‘bad’</td>
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<td>n.s. ibudilast × MA ‘want,’ ‘refuse’ or ‘crave’</td>
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</table>

DB: Double blind; VAS: Visual Analog Scale; MA: methamphetamine; IV: intravenous; n.s.: not significant; SA: self-administration; DD: Drug discrimination; CR: cue-reactivity; AE: adverse event; ARS: Adjective Rating Scale; DSST: Digit Symbol Substitution Test; ARCI: Addiction Research Center Inventory; BP: blood pressure; HR: heart rate; BPRS: Brief Psychiatric Rating Scale; BSCS: Brief Substance Craving Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; BSI: Brief Symptom Inventory; WSRS: Within Session Rating Scale; GCS: General Craving Scale; DEQ: drug-effect questionnaire.
Table 2. Phase II clinical trials of agents for the treatment of MA use.

<table>
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<tr>
<th>Reference</th>
<th>Drug</th>
<th>Drug Dose</th>
<th>Participants</th>
<th>Study design</th>
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<tr>
<td>Sulaiman et al. [117]</td>
<td>Aripiprazole 5-10 mg</td>
<td>daily</td>
<td>N = 37</td>
<td>DSM-IV MA dependence</td>
<td>DBRCT 8 weeks</td>
<td>Primary: abstinence from MA use</td>
<td>n.s. MA abstinence</td>
</tr>
<tr>
<td>Coffin et al. [116]</td>
<td>Aripiprazole 5-20 mg</td>
<td></td>
<td>N = 90</td>
<td>Treatment seeking DSM-IV-TR MA dependence</td>
<td>DBRCT 12 weeks Counseling</td>
<td>Primary: MA abstinence (urine) Secondary: medication adherence</td>
<td>n.s. abstinence</td>
</tr>
<tr>
<td>Anderson et al. [140]</td>
<td>Bupropion sustained-release 150 mg</td>
<td>twice daily</td>
<td>N = 204</td>
<td>User ≤29 days/month Treatment seeking DSM-IV MA dependence</td>
<td>DBRCT 12 weeks Counseling</td>
<td>Primary: MA abstinence last 2 weeks (urine) Secondary: treatment retention Subgroup analysis: low vs. high users</td>
<td>n.s. abstinence</td>
</tr>
<tr>
<td>Heinzelring et al. [141]</td>
<td>Bupropion sustained-release 150 mg</td>
<td>twice daily</td>
<td>N = 84</td>
<td>User ≤29 days/month Treatment seeking DSM-IV MA dependence Seeking treatment Excluded: current psychiatric illness, daily MA users</td>
<td>DBRCT 12 weeks CBT Stratified: gender, depression, smokers, adult ADHD symptoms</td>
<td>Primary: Abstinence from MA use (urine) Secondary: treatment retention</td>
<td>n.s. abstinence</td>
</tr>
<tr>
<td>Shoptaw et al. [123]</td>
<td>Bupropion sustained-release 150 mg</td>
<td>twice daily</td>
<td>N = 73</td>
<td>Treatment seeking DSM-IV-TR MA dependence Excluded: major psychiatric disorder</td>
<td>DBRCT 12 weeks CBT and CM</td>
<td>Primary: Reduction in MA use Secondary: treatment retention, depressive symptoms, cravings Post hoc: light vs. heavy users</td>
<td>n.s. MA use Post hoc analysis: light MA users greater abstinence n.s. retention, cravings, depressive symptoms</td>
</tr>
<tr>
<td>Elkashef et al. [139]</td>
<td>Bupropion sustained-release 150 mg</td>
<td>twice daily</td>
<td>N = 151</td>
<td>Treatment seeking DSM-IV MA dependence Exclusion: psychiatric disorder requiring medication</td>
<td>DBRCT 12 weeks CBT Stratified: gender, baseline depression severity, and self-report of MA use (≤18 vs. &gt;30 days)</td>
<td>Primary: weekly percentage abstinence (urine analysis) Secondary: quantitative MA in urine, self-report MA use, addiction severity, craving and depressive symptoms Subgroups analysis: adult ADHD</td>
<td>n.s. improvement MA-free urine n.s. treatment retention n.s. self-report MA use, severity, craving</td>
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<tr>
<td>Colfax et al. [142]</td>
<td>Mirtazapine 30 mg</td>
<td></td>
<td>N = 60</td>
<td>Treatment seeking DSM-IV MA dependence Exclusion: concurrent major depression</td>
<td>DBRCT 12 weeks Counseling</td>
<td>Primary: MA abstinence (urine) Secondary: medication adherence, sexual risk behavior</td>
<td>n.s. MA abstinence n.s. treatment retention Reduced sexual risk behaviors</td>
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<tr>
<td>Heinzelring et al. [118]</td>
<td>Baclofen 20 mg Gabapentin 800 mg</td>
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<td>N = 88</td>
<td>Treatment seeking DSM-IV MA dependent Exclusion: current psychiatric illness</td>
<td>DBRCT 16 weeks Counseling</td>
<td>Primary: MA abstinence (urine) Secondary: retention, depressive symptoms, craving, adverse events</td>
<td>n.s. MA abstinence Post hoc analysis: MA abstinence associated with higher counseling attendance, lower depressive symptoms, less severe MA use, medication compliance and drug group interaction n.s. retention, medication adherence n.s. craving, depression</td>
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<th>Reference</th>
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<th>Outcome measures</th>
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<tr>
<td>Elkashef et al.</td>
<td>Topiramate titrate up to 200 mg/day</td>
<td>N = 140, DSM-IV MA dependence, Exclusions: psychiatric disorder requiring medication</td>
<td>DBRCT 13 weeks</td>
<td>Primary: MA abstinence (urine), weeks 6–12, Secondary: use reduction, abstinence (21 days during treatment), relapse rates, GSD</td>
<td>n.s. MA abstinence weeks 6–12, n.s. trend craving, Attenuated quantity of MA use, self-reported use and GSD, Post hoc analysis: sustained treatment effect in users abstinent at baseline</td>
<td>Medication adherence: topiramate = 69.8%, placebo = 67.4%</td>
</tr>
<tr>
<td>Rezaei et al.</td>
<td>Topiramate titrate up to 200 mg/day</td>
<td>N = 62, DSM-IV MA dependence, Exclusions: psychiatric conditions requiring medication</td>
<td>DBRCT 10 weeks</td>
<td>Primary: ASI, Secondary: craving (BSCS), depression (BDI-II)</td>
<td>Attenuated drug use severity and drug need in ASI, n.s. craving or depression</td>
<td>Trial completion: overall = 81%</td>
</tr>
<tr>
<td>Galloway et al.</td>
<td>D-Amphetamine sustained-release 60 mg</td>
<td>N = 60, Treatment seeking, DSM-IV-TR MA dependence, Exclusions: current PTSD, lifetime schizophrenia</td>
<td>DBRCT 8 weeks, MET</td>
<td>Primary: cardiovascular safety, Secondary: MA use (urine, self-report), craving, acute withdrawal symptoms</td>
<td>n.s. HR, BP, attenuated withdrawal symptoms and craving, n.s. MA use, medication adherence, MET adherence</td>
<td>Medication adherence: d-AMP = 74.2%, placebo = 73.6%</td>
</tr>
<tr>
<td>Rezaei et al.</td>
<td>Methylphenidate 18–54 mg/day (sustained-release)</td>
<td>N = 56, DSM-IV-TR MA dependence, Exclusions: diagnosis of psychotic symptoms, requiring medication</td>
<td>DBRCT 10 weeks</td>
<td>Primary: cravings (ASI), Secondary: MA use (urine), BDI-II</td>
<td>Reduced craving, Reduced MA use, improved depressive symptoms</td>
<td>Trial completion: methylphenidate = 64.29%, placebo = 57.14% (self report), No figure given for medication adherence</td>
</tr>
<tr>
<td>Ling et al.</td>
<td>Methylphenidate 18 mg titrated up to 54 mg (sustained-release)</td>
<td>N = 110, DSM-IV MA dependence, Exclusions: psychiatric disorder affecting compliance</td>
<td>RCT 10 weeks active + 4 weeks single-blind placebo, CBT, MET</td>
<td>Primary: MA use last 30 days (urine, self-report), Secondary: VAS, medication adherence, treatment satisfaction, MA use week 1–10, MA use week 14</td>
<td>n.s. MA use last 30 days, Reduced MA use days week 1–10 and week 14, Reduced craving, n.s. medication adherence, treatment satisfaction, Post hoc analysis: medication effect in higher MA users</td>
<td>Trial completion: methylphenidate = 52.7%, placebo = 57.4%, Medication adherence: methylphenidate = 95.23%, placebo = 95.34%</td>
</tr>
<tr>
<td>Shearer et al.</td>
<td>Modafinil 200 mg</td>
<td>N = 80, DSM-IV MA dependence, Exclusions: active psychiatric illness</td>
<td>DBRCT 10 weeks, CBT sessions</td>
<td>Primary: MA use (urine, self-report), Secondary: Dependence severity (SDS), craving (VAS)</td>
<td>n.s. abstinence (urine, self-report), n.s. craving or dependence severity, n.s. treatment retention</td>
<td>Trial completion: modafinil = 29%, placebo = 36%, Medication adherence: modafinil = 78%, placebo = 77%</td>
</tr>
<tr>
<td>Heinzerling et al.</td>
<td>Modafinil 400 mg</td>
<td>N = 71, Treatment seeking DSM-IV-TR MA dependence, Exclusions: current psychiatric illness, Cognitive dysfunction, disorder</td>
<td>DBRCT 12 weeks, CBT and CM, Stratified: gender, cognitive dysfunction, MA use</td>
<td>Primary: MA use (urine), Secondary: dependence severity (AS1-Lite), depressive symptoms (BDI-II), cravings (VAS), medication adherence</td>
<td>n.s. MA use, n.s. depressive symptoms, medication adherence, tolerability or cravings</td>
<td>Trial completion: modafinil = 41%, placebo = 35%, Medication adherence: modafinil = 73%, placebo = 63% (self report pill count)</td>
</tr>
<tr>
<td>Grant et al.</td>
<td>Naltrexone titrate up to 200 mg/day, NAC titrate up to 2400 mg/day</td>
<td>N = 31, DSM-IV MA dependence, Exclusions: history of bipolar or psychotic disorder</td>
<td>DBRCT 8 weeks</td>
<td>Primary: craving (PACU), Secondary: MA use (urine), HAM-D, HAM-A</td>
<td>n.s. craving, n.s. MA use (urine), Improved treatment retention</td>
<td>Trial completion: active = 64.3%, placebo = 47.1%</td>
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<tr>
<td>Mousavi et al.</td>
<td>NAC 1200 mg</td>
<td>N = 32, Treatment seeking DSM-IV-TR MA dependence, Exclusions: psychiatric illness requiring medication</td>
<td>DBRCT, Crossover 8 weeks, Matrix model</td>
<td>Primary: Craving (CCQ-Brief), AE</td>
<td>Reduced craving</td>
<td>Medication adherence: overall = 72%</td>
</tr>
</tbody>
</table>

ADHD: Attention Deficit Hyperactivity Disorder; DBRCT: Double-blind randomized controlled trial; MA: methamphetamine; n.s.: not significant; AE: adverse event; CBT: cognitive behavioral therapy; MET: motivational enhancement therapy; CM: contingency management; VAS: Visual Analog Scale; HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety; ASI: Addiction Severity Index; BDI-II: Beck Depression Inventory II; GSD: global severity of dependence; SDS: Severity of Dependence Scale; PACS: Penn Craving Scale; CCQ-Brief: Cocaine Craving Questionnaire-Brief; BSCS: Brief Substance Craving Scale; NAC: N-acetylcysteine; MEMS: medication event monitoring systems.
of aripiprazole (5–20 mg) treatment significantly reduced MA use. Similarly, Sulaiman et al. [117] observed 8 weeks of aripiprazole (5–10 mg) to be safe but not effective in achieving abstinence from MA use.

Baclofen and gabapentin have also been investigated in a DBRCT to increase abstinence from MA in treatment-seeking outpatients. However, neither drug yielded significant beneficial effects on primary outcomes [118]. There has been some promise with the anticonvulsant, topiramate. In a phase II DBRCT, while not observing any significant difference on the primary outcome measures of MA abstinence, Elkashef et al. [119] demonstrated a reduction in median MA urine level and self-reported MA use in weeks 6–12 of the trial. Most recently, Rezaei et al. [120] completed a 10-week DBRCT of topiramate (escalating doses of 50–200 mg) and observed a significant reduction in MA use by topiramate-treated patients relative to placebo by week 6 and significant reductions in severity and craving.

There have been two human laboratory studies investigating a role for the nicotinic receptor agonist varenicline in reducing MA use. Verrico et al. [121] investigated the safety and efficacy of the varenicline, to reduce MA-induced positive subjective effects. They observed varenicline (1 and 2 mg) to significantly reduce some MA subjective effects such as ratings of ‘stimulated’ and attenuated ratings of ‘drug liking.’ No adverse events were reported. Given high rates of cognitive deficits in MA users and the potential impact of cognitive dysfunction on treatment, the role of investigational drugs in this domain is of therapeutic interest. In a study investigating the effect of varenicline on cognition in MA-dependent users, it was observed that varenicline (1 mg) improved information processing speed through a significant reduction on visual stimuli reaction time but had no impact on episodic or working memory [122]. There have been no phase II DBRCTs of varenicline in reducing MA use.

The cholinergic enhancer, rivastigmine, has been investigated to modulate MA-related subjective and reinforcing effects in several human laboratory studies. De La Garza II and colleagues demonstrated 3 mg rivastigmine to reduce significantly attenuated MA-induced diastolic blood pressure elevations and subjective effects such as ‘desire’ [123]. In a follow-up study investigating the effects of a higher dose, rivastigmine (6 mg) significantly reduced ratings of ‘likely to use’ but did not alter self-administration [124]. There have been no phase II DBRCTs investigating the efficacy of rivastigmine in treating MA use.

A novel class of medications, angiotensin converting enzyme (ACE) inhibitors, have been investigated as a pharmacotherapy for MA given evidence that they elevate striatal DA content [125]. Two human laboratory studies from the same group have investigated perindopril. Newton et al. [126] reported that perindopril was tolerated and did not significantly alter MA-induced changes in heart rate but did modify MA-induced changes in blood pressure. Perindopril did not alter MA-induced subjective effects except for ‘any drug effect.’ A follow-up study demonstrated that the moderate dose (8 mg) significantly reduced several subjective ratings including ‘anxious’ and ‘stimulated’ [127]. There have been no phase II DBRCTs evaluating perindopril in the treatment of MA use.

Agonist replacement therapy for MA use has thus far yielded mixed results. In a small, counterbalanced experimental study of dextroamphetamine (d-AMP), Pike et al. [128] showed that d-AMP produced no significant adverse events, reduced the MA-induced increases in systolic blood pressure and some subjective effects but no attenuation of MA self-administration. In a DBRCT over 8 weeks, Galloway et al. [129] demonstrated that sustained-release d-AMP (60 mg) did not have any beneficial treatment effect on abstinence from MA relative to placebo although significantly reduced craving and withdrawal scores. Rezaei et al. [130] conducted a DBRCT of sustained-release methylphenidate (MPH-SR) (escalating doses up to 54 mg/kg) in MA users finding that MPH-SR treatment led to a significant reduction in MA use, craving and depression scores relative to placebo with no significant differences in adverse events. Ling et al. [131] conducted a 10-week DBRCT of MPH-SR (54 mg/kg) with behavioral intervention. They reported that MPH-SR was safe and while a beneficial treatment effect of MPH-SR on some outcomes such as self-reported MA use and craving, they observed no effect on the primary outcome of MA use in the last 30 days of the trial. Moreover, Ling et al. [131] observed a significant effect of MPH-SR relative to placebo in patients with higher baseline MA use (>10 days of MA use at baseline) which is in line with the suggestion that stimulant replacement therapy should be targeted to moderate-to-high MA users [132]. It has also been argued that the doses utilized for substitution therapy in these studies may not be high enough to yield an effect on MA use [129,132].

Modafinil is a wakefulness-promoting agent with several monoaminergic stimulating effects (e.g. dopamine, norepinephrine, orexin, histamine). De La Garza II et al. [133] observed that modafinil (200 mg) attenuated MA-induced elevations in systolic blood pressure. One study investigated the effects of modafinil (200 mg) on cognition in MA users and found a facilitative effect of the agent on sustained attention but no improvement on other cognitive measures [134]. These authors reported as association of heavier frequency of baseline MA use and greater efficacy of modafinil on assessments relating to inhibition and processing speed. However, two DBRCTs have failed to demonstrate any beneficial treatment effect of modafinil on MA abstinence or cravings [135,136].

One of the most frequently investigated agents for the management of MA use is the antidepressant bupropion. Newton et al. [137] demonstrated a beneficial effect of bupropion to reduce subjective (e.g. ‘high’) effects of MA and also craving measures following MA cue exposure. In two 12-week DBRCTs, Shoptaw et al. [138] and Elkashef et al. [139] reported sustained-release bupropion (150 mg twice daily) to be effective in achieving a MA-free week relative to placebo in light but not heavy MA-dependent patients. However, in non-daily MA users, Anderson et al. [140] reported no significant effects of sustained-release bupropion (150 mg twice daily) on MA use or treatment retention. Similarly, Heinzler et al. [141] failed to observe any treatment effect on MA use in non-daily users in a 12-week DBRCT, although an effect on abstinence was found in participants compliant with medication and
concurrent cognitive-behavioral therapy (CBT) versus non-adherent participants (54% vs. 18%). The antidepressant mirtazapine has also been investigated in a 12-week DBRCT in men who have sex with men [142]. The agent was found to increase the rate of MA abstinence with a number needed to treat of 3.1, comparing favorably with the majority of MA trials.

The role of the opioid system in the reinforcing effects of MA and the potential naltrexone in treating MA use has gained some recent attention. Ray et al. [143] found a significant effect of naltrexone in attenuating MA-induced craving and subjective responses to MA such as ‘drug high,’ ‘would like drug,’ and ‘stimulated.’ The endogenous opioid system may underlie some of the reinforcing characteristics of MA given that opioid receptors are highly expressed in regions of the mesolimbic reward pathway [144]. However, in an 8-week DBRCT, no significant treatment effects of naltrexone (in combination with NAC) relative to placebo were observed, although this result may be due to a lack of power ($N = 31$) [145].

NAC has been noted to be a potential candidate for MA dependence [82]. Studies thus far have been mixed. While Grant et al. [145] failed to find a beneficial effect of up to 2400 mg/day on craving and MA use, more recently Mousavi et al. [146] demonstrated NAC 1200 mg to be safe and to significantly reduce craving for MA in a crossover DBRCT ($N = 32$). This inconsistency could be due to increased power by utilizing a cross over design and/or a potentiation effect from concurrent psychological intervention.

The anti-inflammatory agent, ibudilast, has been investigated in preliminary phase I trials. No significant interactions between ibudilast and MA on cardiovascular measures or pharmacokinetics have been reported, apart from a lower MA area under the curve to last time point [147]. In a within-subjects human laboratory study, Worley et al. [148] reported ibudilast to significantly attenuate MA-induced subjective effects such as ‘high,’ ‘like,’ and ‘stimulated.’ To date, there have been no phase II DBRCTs investigating the role of ibudilast in treating MA dependence.

4. Conclusion

There are several agents based on rational neurobiological targets that have been demonstrated to successfully reduce markers of MA dependence in animal models. In human laboratory studies and phase II trials over the last decade, many medications have been investigated including aripiprazole, bupropion, mirtazapine, baclofen, gabapentin, topiramate, rivastigmine, d-AMP, and MPH-SR, modafinil, naltrexone, ibudilast, and NAC. There is mixed consistency across these studies and, while there have been some signals of efficacy at various points, no single medication has demonstrated a broad and strong effect in the MA-dependent population.

5. Expert opinion

Currently, there are no approved medications for the treatment of MA dependence and no medication is emerging with consistency from the scientific literature to yield a sound beneficial treatment effect. From the small number of DBRCTs, mirtazapine has shown some beneficial effect, while bupropion, MPH-SR, and topiramate have shown some efficacy depending on the level of MA use at baseline via post-hoc analyses.

Advancement in MA treatment, including clinical research and translation into practice, faces several challenges. Regarding the utilization of stimulant agonist substitution therapy such as MPH-SR, there is potential for exacerbation of cardiovascular and psychiatric problems from dopaminergic toxicity. However, Levin et al. [132] outline that there have been few adverse events in studies thus far and the harm reduction benefits outweigh these risks. Some authors have indicated that the doses utilized for stimulant substitution therapy may not be high enough to yield an effect on MA use given that Ling et al. [131] found an effect of MPH-SR in patients only with higher baseline MA use [129,132]. Several trials are currently underway, including a dose-escalating study in Australia, that will provide further information with regards to dose, safety, and efficacy of this approach [149].

Promising avenues for treatment include drugs with novel therapeutic targets such as NAC, oxytocin, and ibudilast. Novel TAAR1-targeted compounds may also hold new opportunities for development. Agents with novel modes of delivery such as MA vaccines, which modulate the pharmacokinetics of MA and thus reduce the amount of drug entering the brain, may also have potential. However, antibodies need to be maintained at an effective level with repeated administration, which may prove difficult with MA blood levels and limit effective translation into practice. Regulatory approval is a rate-limiting factor for timely progression of novel agents from preclinical studies to human laboratory and phase II clinical studies [150].

A key component for drug discovery to treat MA dependence is to enable early stages of investigation to predict efficacy in larger scale phase II clinical trials. Medications with clinical efficacy should have robust effects in human laboratory paradigms yet those that are not should have negative or inconsistent outcomes. Compounds that perform well in the laboratory for MA have thus far not yielded positive signals in clinical trials (aripiprazole and to an extent, naltrexone), and there are several medications (some with signals of clinical efficacy such as mirtazapine and topiramate) that have not been tested in human laboratory designs. This can be contrasted with the extensive pharmacotherapy literature for the treatment of alcohol dependence, whereby there is concurrence across preclinical models, human laboratory, and clinical trials for naltrexone. There are only a small number of agents investigated in human laboratory MA studies that have progressed to larger RCTs such that it is difficult to outline which markers are predictive of efficacy at this point.

Validated preclinical and human laboratory models should be an efficient mechanism for translation by providing an early indication of the potential efficacy of medications in one or more stages of the addiction cycle. The cocaine and heroin translational research literature indicates that self-administration outcomes from human laboratory studies can have good predictive validity for effective pharmacotherapies [112], with effects associated
with subjective outcomes leading to numerous false positives. In preclinical studies, the intravenous self-administration/relapse models are arguably the most valid as these allow the ‘choice’ of drug use by the animal, instead of contingent on administration by the experimenter. These models continue to grow in sophistication, allowing extended drug access paradigms, identification of genetic vulnerability for addictive phenotypes, and different experimental conditions during abstinence (extinction of operant responding or incubation) prior to relapse produced by known triggers (drug reexposure, cues associated with drug use, stress).

One particular challenge in clinical trials is low adherence to medication in MA users. Poor compliance is a common problem in the drug and alcohol field and limits the effectiveness of treatment in practice [151]. Several of the phase II clinical trials have yielded low adherence and in some cases lower than 40% (see Table 2). Objective biomarkers of compliance are not often provided. Indeed, one study observed that the difference between compliance as recorded on medication event monitoring systems versus self-report was 26%. Further, one pooled event-level analysis of two RCTs (mirtazapine and buproprion) demonstrated that MA use is negatively associated with adherence to medication [152]. Therapeutic agents should be integrated with interventions that include specific strategies to enhance medication adherence (e.g. compliance therapy [153]) and/or interventions to improve neurocognitive impairments.

Finally, the diverse range of clinical contexts arising from MA abuse may require different pharmacotherapeutic strategies. These may include dependent treatment seekers with varying severity of use, those with neurocognitive damage and/or poor treatment compliance, those with psychiatric comorbidity, and those presenting with medical or psychiatric symptoms associated with acute MA intoxication or also withdrawal. Research designs aimed at developing effective treatments may need to encompass these diverse clinical needs. Testing potential medications across a range of preclinical and human laboratory models is recommended. More clinical research will be required before we can ascertain whether MA human laboratory paradigms are robustly responsive to medications with proven signals of clinical efficacy. As the literature matures and greater efficacy in clinical research is reported, a clearer examination of preclinical and human laboratory data that is predictive of this efficacy will emerge such that these markers can then be used for ongoing drug discovery.

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


• Stimulation substitution approach (DBRCT)


• A DBRCT of the tetracyclic antidepressant, mirtazapine, which demonstrated a beneficial treatment effect on primary outcomes


- Anti-inflammatory approach (within-subjects human laboratory study)


