PHARMACOLOGICAL TREATMENT FOR METHAMPHETAMINE DEPENDENCE

By

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Methamphetamine (MA) is a highly addictive drug whose abuse causes widespread global consequences. The negative impact of MA use on individuals and communities warrants its consideration as a public health concern. MA has a complicated pharmacological action, and chronic use results in neurological dysfunction, including deficits in dopamine. Changes in dopaminergic function make treatment of MA dependence especially challenging, and the mainstay treatment of psychotherapy is insufficient in addressing dopamine deficit. Pharmacological treatments are being explored, but no medication has attained Federal Drug Administration approval, as it requires proof of achieving abstinence. From a harm reduction standpoint, several medications show promise in treating MA dependence by reducing the amount and/or frequency of use. This paper examines the potential of eight medications in reducing MA use through their pharmacological actions. Recommendations for further research and prescribing practices are offered.
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Methamphetamine (MA) is a highly addictive illicit drug causing widespread consequences globally. It is the primary stimulant of abuse, and the prevalence of its abuse appears to be increasing around the world (United Nations Office on Drugs and Crime, 2013). MA is a major public health concern as use negatively impacts individuals and communities. MA use results in a multitude of health problems, including malnutrition, sleep deprivation, cardiac complications, seizures, increased exposure to communicable diseases, neurocognitive impairment, and psychiatric impairment to include psychosis. MA use decreases inhibitions, resulting in propensity for high risk and criminal behaviors. MA production poses individual and environmental hazards. Emergency services, public health, mental health, law enforcement, and criminal justice systems are inundated with consequences of MA use.

MA is an \( N \)-methyl analog of amphetamine. It is a stimulant and pseudosubstrate which enters neurons via monoamine transporters and synaptic vesicles via vesicular transporters for the monoamines (VMATs) (Brackins, Brahm, & Kissack, 2011; De La Garza, Zorick, London, & Newton, 2010; Newman et al., 2012; Stahl, 2008). The actions of MA associated with abuse appear to target reward circuits in the brain, primarily dopamine (DA) release from mesolimbic DA neurons in the nucleus accumbens (Brensilver, Heinzerling, & Shoptaw, 2013; De La Garza et al., 2010; Stahl, 2008), which is the central reward center for the brain, though other systems are also affected (Volz, Fleckenstein, & Hanson, 2007). DA is a monoamine responsible for pleasure, reward, motivation, and motor function, and has a role in associative learning.

In a DA neuron, MA enters via dopamine transmitter (DAT), competitively inhibiting DA at the VMAT, and is transported into the synaptic vesicles, displacing DA
This results in increased DA release and accumulation in the presynaptic neuron. DAT then reverses directions, releasing intracellular DA into the synapse while opening presynaptic channels for further DA release into the synapse. Therefore, both a decrease in reuptake, and an increase in vesicular release cause phasic flooding of DA into the synapse, resulting in euphoria. Repetitive use results in reward conditioning, and craving between doses. Consequently, phasic DA firing is replaced by tonic DA firing, and increased dosage is needed to attain euphoria. Repetitive high doses of MA have long term, and likely irreversible effects on DA neurons, including depletion of DA levels (Brackins et al., 2011; Brensilver et al., 2013; De La Garza et al., 2010; Shoptaw et al., 2008; Stahl, 2008; Volz et al., 2007), axonal degeneration (Stahl, 2008), and associated psychiatric and cognitive impairments (Brensilver et al., 2013; Dean et al., 2011; Galloway et al., 2011; Ghahremani et al., 2011; Kalechstein, De La Garza, & Newton, 2010; Longo et al., 2010; Stahl, 2008). DA deficit in the absence of MA makes abstinence especially difficult to maintain.

Psychotherapy has proven beneficial for MA dependence, and is currently the mainstay of treatment. It is, however, insufficient in addressing the complexities of MA dependence due to the lasting effects on DA systems (Colfax et al., 2013; Dean et al., 2011; Ghahremani et al., 2011; Heinzerling et al., 2010; Kalechstein et al., 2010) and other neurological dysfunctions, and comorbidity with other psychiatric disorders. Researchers are investigating pharmacological therapies as adjuncts to behavioral therapy. A number of medications have shown promise in clinical trials to reduce MA use. Thus far no medications have been Federal Drug Administration (FDA) approved for
treatment of MA dependence, which requires medications to achieve abstinence. Immunotherapies and pharmacokinetic strategies are being developed (Gentry, Rüedi-Bettschen, & Owens, 2010; Gentry, Rüedi-Bettschen, & Owens, 2009; Gorelick, 2012; Karila et al., 2010), but development of therapies and determination of safety and efficacy will take substantial resources and time.

**Statement of Purpose**

The purpose of this paper is to evaluate current pharmacological treatment options for methamphetamine dependence amongst currently approved psychiatric medications in order to determine direction for further research efforts and prescribing practices.

**Conceptual Framework**

A Harm Reduction Framework is appropriate for evaluating pharmacological treatment for MA dependence. The impact of MA use is extensive, and any reduction in its use, reduces negative consequences. While abstinence from MA use is ideal, it is too early in research efforts for such a goal. Harm Reduction is widely accepted as beneficial in substance use disorders, and its applicability in pharmacological efforts is warranted.

**Search Strategies**

Searches were conducted on PsycINFO and PubMed to identify recent, peer-reviewed reports on clinical trials and sixty-nine results were screened by titles and/or abstracts for relevance. Search terms included: “methamphetamine addiction and/or dependence”, and “medications”. Limits included human trials, adult population, and quantitative studies, with a span of the last five years. Reviews were also screened for relevancy and to ensure absence of gaps in the search. Further searches were conducted on specific medications to ensure the most current studies were identified.
This search was not limited to randomized control trials due to the difficulty of conducting trials with this population, and the limitations it would impose on a thorough review. Studies evaluating polysubstance dependence were eliminated to hone in on MA dependence specifically. After initially intending to address all pharmacological options for MA treatment, the decision was made to focus specifically on medications already developed and in use for other psychiatric conditions, thereby minimizing safety concerns and cost of development of new therapies. One medication, minocycline, was discarded in order to limit medications to those a mental health prescriber would be readily familiar with, and have indication to use within the specialty. Reports on medications not showing adequate indications for further clinical trials were eliminated. During evaluation of research it became clear that the medication bupropion, while not having been trialed in the last five years, warranted inclusion, and two 2008 reports were included.

Twenty-one reports were chosen reflecting research into eight different medications currently used for psychiatric disorders with indication for further study in methamphetamine dependence. This is a limited literature review and does not incorporate all current knowledge and research into this area of interest. Further, it does not evaluate all secondary outcomes analyzed in individual reports.

**Reviewed Medications**

**Modafinil**

Modafinil is a wake-promoting agent with Federal Drug Administration (FDA) approval for narcolepsy, shift-work disorder, and obstructive sleep apnea. The onset of action of modafinil is rapid; it has been shown to immediately decrease daytime sleepiness, and to promote cognitive task performance within two hours of dosing. It has
a good side effect profile and little abuse or overdose potential (Stahl, 2011).

The exact mechanism of action of modafinil is unknown. It is likely to act through a slow, sustained rise in plasma level and incomplete occupancy of DAT (De La Garza et al., 2010; Stahl, 2008), which could enhance tonic DA activity, thereby encouraging wakefulness. Plasma levels remain stable for six to eight hours. Tonic, rather than phasic DA activity, is unlikely to promote reinforcement and abuse. DA activity innervates the cortex, leading to release of histamine in the tuberomammillary nucleus (TMN), part of the hypothalamic region that is responsible for initiating wakefulness, and orexin in the lateral hypothalamus (De La Garza et al., 2010; Stahl, 2008), which stabilizes wakefulness (Stahl, 2008).

**Dexamphetamine**

Dexamphetamine is a stimulant with FDA approval for Attention Deficit-Hyperactivity Disorder (ADHD) and narcolepsy. It is also commonly prescribed off-label for depression. It can cause adverse central nervous system (CNS) and cardiovascular (CV) effects. Therapeutic benefit occurs with first dose, and it is available in a sustained release formulation with up to eight hours of clinical action. Abuse potential is high, though less than with immediate release formulation (Stahl, 2011).

Dexamphetamine is a d isomer of amphetamine. Amphetamine is a pseudosubstrate and competitive inhibitor for DAT and norepinephrine transporter (NET), therefore it inhibits the reuptake of norepinephrine (NE) and DA in the synapses so it can self-transport. The action of d-AMP is higher for DAT than NET. By increasing DA and NE availability in the prefrontal cortex, executive function is improved. Sustained release formulations of amphetamine adjust the rate, amount, and duration of stimulant presence
at DAT and NET. This creates a tonic signaling of NE and DA signaling via alpha 2A and D1 receptors, respectively (Stahl, 2008).

**Bupropion**

Bupropion is a norepinephrine dopamine reuptake inhibitor with FDA approval for depression, seasonal affective disorder, and nicotine addiction. It is commonly used for ADHD. It is safe, though caution is needed in use with patients with seizure disorders, and has low overdose and abuse potential (Stahl, 2011).

Bupropion blocks DAT allosterically and inhibits reuptake of DA via DAT, thereby increasing DA concentration in the synaptic cleft. It occupies DAT at lower degrees and with a slower onset than stimulants, and is not transported by DAT or VMAT, so it is not transported into the neuron itself (Elkashef et al., 2012; Shoptaw et al., 2008; Stahl, 2008).

**Risperidone**

Risperidone is an atypical antipsychotic, specifically a serotonin-dopamine antagonist. It has FDA indications for schizophrenia, acute mania, mixed mania, autism-related irritability, and bipolar maintenance. It is used off-label for behavioral disturbances, bipolar depression, and impulse control disorders. It is available in a two-week injectable depot formulation, which requires oral titration to ensure tolerability. Risperidone has significant metabolic side effects, and potential for extrapyramidal symptoms. There is low overdose or abuse potential (Stahl, 2011), especially with depot.

Risperidone binds with D2, 5HT7, 5HT2A, alpha 1, and alpha 2 receptors. It causes a blockade of 5HT2A and D2 receptors, simultaneously causing opposite effects in different areas of the brain. D2 receptors are blocked in the mesolimbic pathway,
prefrontal cortex-limbic pathway, and the tuberoinfundibular pathway. Positive symptoms of psychosis and stabilization of affective symptoms result from blocked D2 receptors in the mesolimbic system. By blocking 5HT2A receptors, DA release is increased in the nigrostriatal and mesocortical pathways, reducing motor side effects and likely improving affective and cognitive symptoms. Risperidone has alpha 2 antagonist properties that may cause antidepressant effects.

**Mirtazapine**

Mirtazapine is an antidepressant also classified as an alpha 2 antagonist, and a norepinephrine and specific serotonergic agent. It has FDA approval for major depressive disorder, and is commonly prescribed for panic disorder, generalized anxiety disorder, and posttraumatic stress disorder. Action on insomnia and anxiety symptoms is rapid following titration, with antidepressive action delayed up to four weeks. It is safe with low overdose and abuse potential (Stahl, 2011).

Mirtazapine increases 5HT and NE levels by blocking alpha 2 receptors. The resulting increase of NE in the noradrenergic pathway to the raphe nucleus increases NE release there, in turn stimulating alpha 1 receptors to release more 5HT, improving depressive symptoms. 5HT1A agonist action results in release of DA, which is linked to improving depression and cognition. Mirtazapine also has 5HT2C antagonist properties, which increase NE and DA release in the prefrontal cortex. Mirtazapine also blocks histamine (HI) receptors, causing sedation (Stahl, 2008).

**Varenicline**

Varenicline is an alpha 4 beta 2 partial agonist at nicotinic acetylcholine receptors. It is a smoking cessation treatment with FDA approval for nicotine dependence. It is
indicated for twelve to twenty-four week treatments and requires titration to therapeutic dose. Overdose potential is unknown, and it is advised to use with caution in patients with a psychiatric history due to potential for psychiatric disturbance and suicidality (Stahl, 2011).

Varenicline acts on the cation channel associated with nicotinic cholinergic receptors by stabilizing receptors in an intermediate state, allowing the channel to be open intermediately. This allows for small, sustained release of DA, predominately on mesolimbic dopaminergic neurons in the ventral tegmental area, within the reward circuit. The low amount of DA reduces cravings, but is inadequate to provide euphoria (Stahl, 2008).

**Topiramate**

Topiramate is an anticonvulsant, specifically a voltage-sensitive sodium channel modulator, with FDA approval for seizures, and migraine prophylaxis. It is also prescribed as an adjunctive in bipolar disorder, and for eating disorders. Onset to action can be delayed for months in stabilizing mood. It is relatively safe, with low overdose and abuse potential (Stahl, 2011).

Topiramate appears to reduce glutamate function and increase gamma-aminobutyric acid (GABA) function through interference with sodium and calcium channels at an unknown binding site. Increasing GABA function decreases DA activity in the corticomesolimbic pathway. Topiramate also weakly inhibits carbonic anhydrase (Stahl, 2008).

**Buspirone**

Buspirone is an anxiolytic, serotonin 1A partial agonist, and serotonin stabilizer. It
has FDA indication for anxiety disorders, and is used off-label as an adjunctive for treatment-resistant depression. Efficacy takes up to six weeks to achieve and requires multiple daily dosing. Safety profile is good, with low overdose and abuse potential (Stahl, 2011).

Buspirone binds to 5HT1A receptors. As a partial agonist, it may diminish serotonergic activity postsynaptically, contributing to its anxiolytic effects. The agonist actions at presynaptic somatodendritic 5HT autoreceptors may contribute to its antidepressant actions by increasing serotonergic activity (Stahl, 2011). It also exhibits antagonistic properties at D3 and D4 receptors (Paterson, Vocci, Sevak, Wagreich, & London, 2014).

**Literature Review**

Clinical trials of these eight medications were reviewed in order to direct future research efforts and prescribing practices. Rational for medications based on mechanism of action and neurological impact were considered. Given the difficulties of conducting research with the population of MA users, the focus of this review is on the harm reduction potential of medications, with limited critique of the robustness of study designs. Additionally, there is limited discussion of medication adverse effects, as the assumption is that the adverse effects of MA outweigh them.

**Modafinil**

Modafinil is an analeptic, or non-amphetamine type stimulant with potential to decrease MA use by normalizing DA (De La Garza et al., 2010; Heinzerling et al., 2010; Mahoney et al., 2012) and to aid in repairing cognitive impairments of chronic MA use through unknown mechanisms (Dean et al., 2011; Ghahremani et al., 2011; Heinzerling
et al., 2010; Kalechstein et al., 2010). While the mechanism of action of modafinil is not fully understood, it appears to activate specific neurons in the lateral hypothalamus and weakly inhibit DA transporters through a relatively slow onset of action (De La Garza et al., 2010; Heinzerling et al., 2010; McGaugh et al., 2009). This results in a tonic DA level without the euphoria experienced with amphetamines (McElhiney, Rabkin, Rabkin, & Nunes, 2009). In addition to increasing DA, it increases extracellular NE, serotonin (5HT), glutamate, and histamine (HI) levels, while decreasing γ-aminobutyric acid levels (Dean et al., 2011; Ghahremani et al., 2011). The stimulating effects of modafinil can potentially decrease MA withdrawal symptoms, including fatigue, concentration difficulties, and disturbed sleep patterns (Anderson et al., 2012; Heinzerling et al., 2010; McElhiney et al., 2009) through similar action in the TMN and lateral hypothalamus as occurs with stimulant administration. It may also decrease MA-related subjective effects (De La Garza et al., 2010) by blocking D2 receptors, thus impacting the reward system. It can improve cognition, specifically memory, attention, executive functions, and inhibitory control, which are impaired with chronic MA use (Dean et al., 2011; Ghahremani et al., 2011; Heinzerling et al., 2010; Kalechstein et al., 2010; Shearer et al., 2009) and interfere with ability to benefit from psychotherapy.

The majority of research in this review was trials of modafinil. Twelve studies of modafinil were reviewed with primary aims to determine its safety (De La Garza et al., 2010; McGaugh et al., 2009; Shearer et al., 2009), evaluate reduction in MA use (Anderson et al., 2012; Heinzerling et al., 2010; McElhiney et al., 2009), improve study recruitment and/or retention (Heinzerling et al., 2010; Lee et al., 2013; McElhiney et al., 2009), reduce depressive symptoms (Heinzerling et al., 2010), and MA withdrawal
symptoms (De La Garza et al., 2010; Lee et al., 2013; Mahoney et al., 2012), to
determine its effect on cognitive functions (Dean et al., 2011; Ghahremani et al., 2011;
Hester, Lee, Pennay, Nielsen, & Ferris, 2010; Kalechstein et al., 2010), and for treatment
of HIV positive men who have sex with men (MSM) (McElhiney et al., 2009). Studies
had variable secondary aims that often overlapped with primary aims of other studies.

Modafinil use was found to be safe for current (Anderson et al., 2012; De La Garza et al., 2010; Dean et al., 2011; Ghahremani et al., 2011; Heinzerling et al., 2010;
Kalechstein et al., 2010; McElhiney et al., 2009; McGaugh et al., 2009; Shearer et al.,
2009) and recently abstinent MA users (Dean et al., 2011; Hester et al., 2010; Lee et al.,
2013; Mahoney et al., 2012), even at the maximum indicated dose for its FDA approved
conditions (Heinzerling et al., 2010; Kalechstein et al., 2010; McGaugh et al., 2009).
Decrease in MA use with modafinil was also found, though never to abstinence, and not
always at levels of statistical significance (De La Garza et al., 2010; Dean et al., 2011;
Heinzerling et al., 2010; Shearer et al., 2009) or by objective measures (McElhiney et al.,
2009; McGaugh et al., 2009). Depressive symptoms (McElhiney et al., 2009; McGaugh
et al., 2009) and daytime sleepiness (Mahoney et al., 2012) were decreased, which can be
protective factors in decreasing MA use. Withdrawal symptoms were reportedly
decreased (De La Garza et al., 2010; Lee et al., 2013; Mahoney et al., 2012; McElhiney et
al., 2009). Beneficial cognitive effects were also noted (Dean et al., 2011; Ghahremani et
al., 2011; Heinzerling et al., 2010; Hester et al., 2010; Kalechstein et al., 2010; Shearer et
al., 2009).

The relationship to baseline MA use and effectiveness of modafinil emerged from
multiple studies’ data. A decrease in MA use amongst participants with low baseline use,
and with high baseline users after decreasing their MA use (McElhiney et al., 2009), while effectiveness in high baseline users, as opposed to low baseline users was suggested by double-blind, placebo-controlled trials of 200mg (De La Garza et al., 2010; Dean et al., 2011) and 400mg (Heinzerling et al., 2010) of modafinil. This could be attributed to the higher cognitive dysfunction of heavy MA users, and therefore greater benefit from modafinil (Ghahremani et al., 2011; Heinzerling et al., 2010; Hester et al., 2010; Kalechstein et al., 2010; Shearer et al., 2009).

Variables confounding results include sample sizes and attributes, whether or not participants were seeking treatment, dosing of modafinil, inclusion of behavioral therapies, and environmental controls. Secondary measures were inconsistent among studies, such as inclusion of baseline use or cognitive functioning. All studies were challenged by study retention. Specific outcome foci of modafinil treatment also varied, thus despite the number of studies, certain effects were not accounted for in every study. Statistical significance was not reached in all studies, but all findings favor further research into modafinil for MA dependence (De La Garza et al., 2010; Ghahremani et al., 2011; Heinzerling et al., 2010; Lee et al., 2013; Mahoney et al., 2012; McElhiney et al., 2009; McGaugh et al., 2009; Shearer et al., 2009), especially in repairing cognitive effects of chronic use (Dean et al., 2011; Ghahremani et al., 2011; Hester et al., 2010; Kalechstein et al., 2010). Findings were often found dependent on attributes of MA users, prompting evaluation of effectiveness amongst sub-groupings of users.

**Dexamphetamine**

Dexamphetamine is a CNS stimulant with properties similar to MA, but without the toxic additives present in the illicit substance. It presents an option for substitution
therapy, which is used successfully in opiate and nicotine addictions (Galloway et al., 2011; Longo et al., 2010), and is currently being used for MA users in England and Wales (Galloway et al., 2011). Similarly to MA, d-AMP increases synaptic DA levels through both increased vesicular release and inhibition of DA re-uptake, thus addressing the DA deficit caused by chronic MA use. D-AMP offers potential as treatment for MA dependence by addressing the DA deficit and deterring craving and withdrawal symptoms (Galloway et al., 2011; Longo et al., 2010).

Two randomized, placebo-controlled trials to determine safety and efficacy of sustained release d-AMP as substitution therapy were reviewed. Primary outcome measures included treatment retention, amount of MA use, and withdrawal severity (Galloway et al., 2011; Longo et al., 2010). While the earlier study showed promise for d-AMP treatment by a statistically significant increase in treatment retention and withdrawal severity, and a trend towards decreased MA use, (Longo et al., 2010), the follow-up study evaluated a lower daily dose (60mg vs. 110mg). While participants did report decreased withdrawal effects with d-AMP 60mg (Galloway et al., 2011), the lower dose may have attributed to the comparable levels of MA use and treatment retention with placebo. MA users likely have tolerance to amphetamines, which would indicate higher than average dosing would be required (Galloway et al., 2011).

These studies used strong objective measures, paired with standardized measures of subjective data, though determination of sufficient sample size was unknown. One report did not include the treatment-seeking status of participants (Longo et al., 2010). It is unfortunate the more recent study design used a lower maximum dose instead of building on the preliminary study establishing 110mg maintenance dosing as safe (Longo
et al., 2010). Further studies would benefit from increased sample size with doses up to 110mg per day.

**Bupropion**

Bupropion increases DA transmission in the nucleus accumbens and prefrontal cortex. Restoring DA levels in the nucleus accumbens may decrease withdrawal symptoms (Elkashef et al., 2008; Shoptaw et al., 2008), and increasing DA and NE in the prefrontal cortex may improve cognitive abilities such as concentration (Shoptaw et al., 2008; Stahl, 2008). It may be particularly effective for MA users with comorbid depression or ADHD, as they may be underlying causes for self-medication with MA. It can be protective against MA-induced decreases in DA uptake in striatal synapses, and against neurotoxic effects (Elkashef et al., 2008; Shoptaw et al., 2008).

Two studies trialed bupropion versus placebo in aims to show reduction in MA use (Elkashef et al., 2008; Shoptaw et al., 2008), increased treatment retention (Shoptaw et al., 2008), decreased depressive symptoms, and withdrawal symptoms (Elkashef et al., 2008; Shoptaw et al., 2008). Both studies showed a reduction in MA use among baseline light MA users to statistical (Shoptaw et al., 2008) or clinical significance (Elkashef et al., 2008). Decreased cravings for baseline light and heavy users was also noted (Shoptaw et al., 2008). Bupropion was found to be safe to administer on an outpatient basis to current MA users (Elkashef et al., 2008; Shoptaw et al., 2008).

**Risperidone**

Risperidone is an atypical antipsychotic with high affinity for the D2, 5HT2a, and alpha 1 and alpha 2 adrenergic receptors. Implications for using a medication with these affinities include decreasing the reward system by blocking the euphoric effects of MA at
D2 receptors, decreasing cognitive impairment by blocking 5HT2a receptors from MA exposure, and decreasing psychomotor effects at the alpha receptors (Meredith et al., 2009). It has been found to ameliorate cognitive deficits in schizophrenia, which are comparable to those found with chronic MA use. Risperidone is available in a long-acting intramuscular injection, which can increase medication adherence (Meredith et al., 2009).

One open trial of injectable risperidone was reviewed, and builds on previous studies of oral risperidone not included in this review due to search limits. While almost one quarter of the participants could not tolerate oral risperidone, and therefore were eliminated from the study, remaining participants tolerated injectable risperidone. There was a significant reduction in MA use with a trend towards abstinence, though the method of analysis was lacking. Findings support the likelihood of cognitive improvement with risperidone, specifically in verbal and visual memory, as well as reduction in psychiatric symptoms (Meredith et al., 2009).

While this study included significant limitations in design and lack of disclosure as to whether subjects were seeking treatment, the rationale for risperidone trials for MA dependence is strong. There are serious side effects associated with risperidone, which must be taken into consideration, but also weighed against the consequences of MA use.

**Mirtazapine**

Mirtazapine is an alpha 2 antagonist, and a NE and specific serotonergic agent that increases release of DA, NE, and 5HT. Increased release of monoamines occurs in the mesocorticolimbic system, allowing for hypothesis that it could decrease drug reward, craving, and reinstatement (Colfax et al., 2013). The unique action of mirtazapine blocks three serotonin receptors as well as histamine 1 (H1) receptors (Stahl, 2008). This results
in anxiolytic, antidepressant, and sedative properties that could benefit in withdrawal from MA.

A small (n=60) San Francisco based study of MA dependent men who have sex with men (MSM) found mirtazapine to be safe and well tolerated. Findings from this study suggest that even with poor to moderate adherence to treatment, mirtazapine may decrease use of MA. As MA users are unlikely to have high rates of adherence in a non-trial setting, these findings are particularly notable. Secondary outcomes were self-report versus medication event monitoring systems (MES) and impact on high-risk sexual behavior. Findings support lack of reliability in self-report, as they did not match MES data. There was indication that mirtazapine may aid in decreasing high-risk sexual behavior among MA addicts who are MSM through reduction of MA use (Colfax et al., 2011).

This study wisely tailored treatment to specific MA users for increased adherence by matching patient profile to side effect profile. By using a medication that has a low incidence of erectile dysfunction for a population of sexually active MSM, adherence was likely increased. Correlation of MA use to risky behaviors is valuable in promoting a harm reduction model.

**Varenicline**

Varenicline is a medication with FDA indication for smoking cessation. It is a full or partial agonist at certain nicotinic acetylcholine receptors (nAChRs). Increasing cholinergic activity at nAChRs has been suggested by animal studies to possibly reduce MA-related behaviors. Cholinesterase inhibitors may impact the reward system by reducing the subjective euphoric effects of MA (Zorick, 2009).
This study investigated the safety and tolerability of concurrent administration of varenicline and MA. It was a double-blind, placebo-controlled, crossover pilot study in an inpatient setting. Both varenicline and MA were administered to participants who had negative urine drug screens on admission, and self-report of abstinence for at least 4 days. Findings suggest varenicline is safe and tolerable, and indicated for further research as an aid in MA dependence. No serious adverse events were reported, and there was no statistically significant cardiovascular difference between varenicline and placebo. Depressive symptoms appeared unaffected by varenicline, and no suicidal thoughts were reported (Zorick, 2009).

MA self-administration likely exceeds the 30mg per day dose used in this study, leaving uncertainty as to the safety of varenicline in a less-structured setting. Given the propensity for co-morbid psychiatric illness including psychosis in MA users, it is unclear how widely accepted this treatment could be for MA dependence. It could certainly complicate larger, outpatient trials due to the publicity regarding varenicline and suicidality.

**Topiramate**

Topiramate is an anticonvulsant that promotes GABA function, which decreases DA activity in the cortico-mesolimbic pathway, thus potentially reducing craving for MA. It also antagonizes glutaminergic activity through kainate receptors, which could decrease reinstatement of drug use. Anticonvulsants have shown benefit in decreasing cravings for other substances and addictions (Elkashef et al., 2012).

This study set the goal of MA abstinence, with secondary outcomes of reduction in use and psychosocial variables. Concurrent alcohol dependence and severity of MA use
were considered. Findings suggest this medication may decrease MA use over time, especially in individuals who are abstinent at outset, or light users, and may potentially deter reinstatement in abstinent individuals (Elkashef et al., 2012).

No implication of subjects’ desire for treatment was reported. Subjects were permitted to take a decreased dose of medication, which may have been subtherapeutic, in addition to complicating data analysis.

**Buspirone**

While the anxiolytic effects of buspirone are attributed to its partial agonist action at 5HT1A receptors, it has equally strong antagonistic affinity for D3 and D4 receptors (Newman et al., 2012; Paterson et al., 2014). D3 receptors are upregulated in MA users, and normalization of their function is hypothesized to reduce relapse potential (Newman et al., 2012; Paterson et al., 2014). D3 receptors regulate phasic activity of dopaminergic neurons, and their distribution is limited primarily to subregions of the brain reward circuitry. Targeting D3 receptors may have potential in addressing multiple conditions including addictions, therefore buspirone is being investigated for MA dependence (Paterson et al., 2014).

A small pilot study was performed to evaluate safety and initial efficacy of buspirone in MA dependent subjects. Only five non-treatment seeking subjects were included, and the study was limited to nine days duration. Data suggest safety and tolerability of buspirone taken concurrently with MA (Paterson et al., 2014). Implications from this study are greatly limited by study design. Nonetheless, the pharmacological basis for buspirone as a potential agent for MA dependence is compelling, and study findings do not deter further research into its potential.
Strengths

These studies, which are predominantly double-blind, placebo controlled, build on promising therapies through human trials. Ethical and safety considerations were sound, and participant screening was thorough, though sometimes lacking in disclosure of treatment-seeking status (Elkashef et al., 2012; Longo et al., 2010; Meredith et al., 2009). All studies utilized a combination of biophysical measures, standardized screenings, and self-report, with the exception of two inpatient studies that did not include biophysical measures (Dean et al., 2011; Hester et al., 2010). Results underwent strong statistical analysis, with the exception of a pilot study which candidly disclosed its analysis to be primarily descriptive (McElhiney et al., 2009). The majority of studies provided psychotherapy concurrently with the treatment regimens (Anderson et al., 2012; Colfax et al., 2013; Elkashef et al., 2008; Elkashef et al., 2012; Heinzerling et al., 2010; Longo et al., 2010; McElhiney et al., 2009; McGaugh et al., 2009; Meredith et al., 2009; Shoptaw et al., 2008). Multiple studies suggested that the research treatment positively affected quantity of MA consumed (De La Garza et al., 2010; Dean et al., 2011; Heinzerling et al., 2010; Longo et al., 2010; Meredith et al., 2009; Shearer et al., 2009), primarily within certain sub-groupings of MA users (Colfax et al., 2011; Elkashef et al., 2008; Elkashef et al., 2012; Heinzerling et al., 2010; Shoptaw et al., 2008). Potential for addressing cognitive deficits caused by MA use is also suggested (Dean et al., 2011; Ghahremani et al., 2011; Hester et al., 2010; Kalechstein et al., 2010; Meredith et al., 2009). All medications were found to be safe to use with the sample populations.

Limitations

Small sample size, convenience sampling, low medication adherence, and low
treatment retention are limitations anticipated with this population, and presented in these studies. Study lengths were three days to sixteen weeks duration, which considering the time to onset of action for most of the medications, is limited. As the medications studied are all indicated for other conditions, the effective dosages for MA dependence are unknown, as acknowledged in multiple reports (Elkashef et al., 2012; Galloway et al., 2011; Heinzerling et al., 2010). All but one of the studies (McElhiney et al., 2009) had exclusions for participants with polysubstance use and/or major mental illness. While these are reasonable exclusions at this stage of research, it limits the generalizability of the findings as the subjects likely represent a minority of MA users. Further limitation is presented by lack of knowledge as to subjects treatment-seeking status in a number of studies evaluating medication effect on MA use (Elkashef et al., 2012; Longo et al., 2010; Meredith et al., 2009), as motivation for treatment can effect results.

**Discussion**

The primary significance of these findings is that pharmacological intervention shows promise in reducing MA use in clinical trials. Medications are able to decrease reward, deter reinstatement, and repair deficits caused by previous and/or current use of MA. The impact of medications appears to be dependent on baseline level of use, which can be explained through an understanding of the pharmacological action of the medications in relation to the action of MA.

As high baseline MA users experience chronically depleted DA levels and decreased cognitive function, this subgroup will likely have the most favorable outcomes with medications that increase DA availability and repair cognitive deficits, such as d-AMP and modafinil, and may require long-term substitution therapy. While some benefit
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may occur from blocking the reward system, they are unlikely to settle for treatment that does not supplement their DA deficit. Cognitive deficits are high amongst this group, and impair their ability to benefit from cognitive-type therapies. Modafinil and risperidone are both promising in addressing this aspect of treatment.

Lower baseline users are likely to heed more benefit from blocked reward as they have less damage to their monoamine systems. Decreasing DA activity to deter craving could possibly aid in maintaining abstinence, although it seems unlikely that even past MA users would be adherent with a treatment that further decreased available DA. More promise lies in agents such as bupropion, which increases DA levels and may preventively protect against long-term damage from continued MA use.

Decrease of withdrawal symptoms is imperative in reducing use in all subgroups of MA users. Agents such as mirtazapine show indication for withdrawal by blocking multiple 5HT receptors and H1 receptors. This increases DA, NE, and 5HT levels, decreasing anxiety and depressive symptoms, while blocking H1, and therefore modulating disturbed sleep cycles. Substitution therapies will also decrease withdrawal symptoms by mimicking the monoamine activity of MA.

**Indications for Practice**

MA users have varying levels of neurological dysfunction dependent on baseline use. Different medications will be more beneficial for different subgroupings of MA users. Medications are needed to decrease reward, deter reinstatement, and repair deficits caused by previous and/or current use. This will likely require multiple mechanisms of action, and therefore polypharmacy is clearly indicated. Polypharmacy is the norm for
psychiatric treatment, and a disorder as complicated as MA addiction, is unlikely to be an exception.

The population of MA users is difficult to capture in the clinical trial setting. This will complicate studies and make for questionable findings. Different patient profiles likely result in different treatment effects. Medication efficacy may be dependent on use patterns, gender, or cognitive functioning. Given the prevalence of preexisting or MA-induced comorbidities, treatments can be chosen to fit FDA indications for comorbid diagnoses, with a secondary benefit of reducing MA use. When treating depression, trial bupropion or mirtazapine; with psychotic symptoms, risperidone; for mood stabilization, topiramate.

FDA approval for medication requires an outcome of abstinence in clinical trials. This requirement does not take into consideration the benefit of decreasing MA use from a harm reduction perspective. Reduction of MA use results in a reduction of adverse effects, therefore treatment of MA dependence should not wait for FDA approval. Off-label prescribing is a mainstay in mental health. There is always risk and liability involved in prescribing off label. The severity and impact of MA dependence warrants this practice extends to its treatment; the consequences of MA use far outweigh the risks.

**Future Research**

Larger, multi-site clinical trials of medications are indicated. Trials should build on the existing implications and match specific medications with subgroupings of MA users. Treatment protocols involving multiple medications are also indicated. Studies will need to eventually include other psychiatric diagnoses, as well as polysubstance users, in order to fully capture the population intended to treat.
Conclusion

While studies thus far have failed to identify medications that highly support abstinence from MA, some have shown promise in reducing amount of use. Reduction of amount or frequency of MA use results in reduction of adverse events from MA, and is valuable in addressing this global problem. Research efforts and prescribing practices can be driven by research attained thus far.
References


