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REVIEW

Pharmacological Treatments for Methamphetamine Use Disorder: Current Status and Future Targets

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Abstract: The illicit use of the psychostimulant methamphetamine (METH) is a major concern, with overdose deaths increasing substantially since the mid-2010s. One challenge to treating METH use disorder (MUD), as with other psychostimulant use disorders, is that there are no available pharmacotherapies that can reduce cravings and help individuals achieve abstinence. The purpose of the current review is to discuss the molecular targets that have been tested in assays measuring the physiological, the cognitive, and the reinforcing effects of METH in both animals and humans. Several drugs show promise as potential pharmacotherapies for MUD when tested in animals, but fail to produce long-term changes in METH use in dependent individuals (eg, modafinil, antipsychotic medications, baclofen). However, these drugs, plus medications like atomoxetine and varenicline, may be better served as treatments to ameliorate the psychotomimetic effects of METH or to reverse METH-induced cognitive deficits. Preclinical studies show that vesicular monoamine transporter 2 inhibitors, metabotropic glutamate receptor ligands, and trace amine-associated receptor agonists are efficacious in attenuating the reinforcing effects of METH; however, clinical studies are needed to determine if these drugs effectively treat MUD. In addition to screening these compounds in individuals with MUD, potential future directions include increased emphasis on sex differences in preclinical studies and utilization of pharmacogenetic approaches to determine if genetic variances are predictive of treatment outcomes. These future directions can help lead to better interventions for treating MUD.

Keywords: methamphetamine use disorder, pharmacotherapy, clinical trial, animal models

Introduction

Methamphetamine (METH) is a synthetic and potent psychostimulant drug that increases attention and arousal, suppresses appetite, and produces euphoria.[1–3] Although these effects are often reinforcing, METH can cause life-threatening hyperthermia and heart arrythmias,[4,5] and it can produce symptoms that mimic schizophrenia.[6,7] Another major problem associated with METH is the development of tolerance with repeated administration and the emergence of aversive withdrawal symptoms such as depressed mood and lethargy upon cessation of use.[8–10] Long-term METH use can negatively impact one's health,[11] as individuals that use METH are at risk for dental problems ("meth mouth"), heart disease, stroke, and contraction of a sexually transmitted infection (STI).[12–15] Some of the adverse health effects of METH are compounded by its manufacturing process. METH can be synthesized from pseudoephedrine, a nasal decongestant, or from phenyl-2-propanone (P2P), a precursor to pseudoephedrine, using hazardous chemicals like lye and camping fuel.[16] Some clandestine labs now synthesize ephedrine and P2P using commercially available materials, which introduces additional impurities,[17] thus increasing the risk of adverse health effects.

There are several routes of administration associated with METH: oral, intravenous, intranasal, and inhalation. When ingested orally, peak subjective effects occur approximately 3 h after use; other routes of administration lead to rapid onset of subjective effects, occurring less than 15 min when injected or used intranasally and occurring within 20 min when smoked.[18] Because METH is lipophilic, it quickly crosses the blood-brain barrier, where it can exert its psychoactive effects.[19] METH also enters most organs, with high concentrations observed in lungs, liver, and kidneys.[20] METH is

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metabolized primary by the hepatic cytochrome P450 2D6 enzyme,[21] leading to 4-hydroxymethamphetamine and amphetamine (AMPH) as major metabolites,[22,23] before being eliminated from the body through urine.[24] Compared to other stimulants like cocaine, the half-life of METH is considerably longer, approximately 7–12 h depending on the dose and the route of administration.[18,25–27]

METH increases extracellular concentrations of the monoamine neurotransmitters dopamine, norepinephrine, and serotonin via several mechanisms. METH is a vesicular monoamine transporter 2 (VMAT-2) reverser, causing monoamine concentrations to increase in the presynaptic terminal button of neurons.[28] Depending on the dose used, METH can reverse the direction of monoamine transporters, inhibit dopamine transporters, and/or inhibit the enzyme monoamine oxidase (MAO).[29,30] Regardless, excess monoamine levels in the cytoplasm are released into the synapse, resulting in METH's wide-ranging physiological and subjective effects.[18] Increased dopaminergic activity in the mesocorticolimbic pathway underlies the reinforcing effects of METH,[31] although reduced dopamine release is observed in brain regions associated with reward (eg, nucleus accumbens) after chronic use, which may explain why tolerance develops to the reinforcing effects of METH.[32]

Since the 2010s, METH use has increased significantly throughout the world.[33–36] More problematic is the increase in methamphetamine use disorder (MUD) and corresponding increase in overdose deaths.[34] MUD, like other substance use disorders (SUDs), is characterized by several criteria according to agencies like the American Psychiatric Association[37] and the International Classification of Diseases.[38] Included in these criteria are using larger amounts of METH or using METH for longer periods of time than intended; persistent desire or unsuccessful efforts to control METH use; spending increasing amounts of time trying to obtain METH, use METH, and/or recover from METH's effects; craving to use METH; failing to fulfill other responsibilities due to METH use; continued use of METH despite negative consequences; developing tolerance to METH's effects; and experiencing withdrawal symptoms upon cessation of use.[37] Recurrence of substance use following abstinence ("relapse") is another prominent feature of SUDs.[39]

The socioeconomic costs of MUD are high as lost productivity, increased crime and incarceration rates, and premature mortality are consequences of the increasing popularity of this drug.[40–42] As MUD rates continue to increase, finding effective treatment strategies to help individuals reduce METH use is imperative, especially given that no pharmacological treatments currently exist for MUD. The purpose of the current review is to discuss the pharmacological treatments that have been screened in various assays related to METH dependence and MUD. The review is not limited to clinical studies using METH-dependent individuals. Instead, results of preclinical studies and human studies involving both dependent and nondependent individuals will be discussed to provide a comprehensive review of how certain treatments may be effective in (1) reducing METH intake in individuals, (2) decreasing the likelihood of resuming METH use following a treatment intervention, (3) ameliorating METH-induced cognitive impairments, and/or (4) serving as a complimentary treatment for other interventions (eg, cognitive-behavioral therapy).

Methods for Screening the Efficacy of Potential Pharmacotherapies for MUD

Animal research is valuable for screening potential pharmacotherapies to determine if they are (a) safe to administer and (b) efficacious at attenuating the behavioral effects of METH. Additionally, animal research allows one to isolate the neural mechanisms underlying treatment-induced alterations in METH's rewarding properties. To this end, numerous assays are used to study the neurobehavioral actions of potential pharmacotherapies.

Although tolerance develops to the rewarding properties of METH, individuals show behavioral sensitization following repeated METH use. Particularly problematic is the emergence of stereotypies.[43] In humans, common METH-induced stereotypies include excoriation, jaw clenching, and bruxism.[44,45] Repeated METH exposure increases behavioral sensitization and stereotypies in animals such as circling, biting, head bobbing, sniffing, and grooming.[46–50] Preclinical studies are primarily used to determine if a potential pharmacotherapy attenuates METH-induced locomotor sensitization and/or stereotypies. This research is valuable as behavioral sensitization is reported to be a risk factor for future drug taking in animals.[51–53]

Conditioned place preference (CPP) allows one to measure the conditioned rewarding effects of a stimulus such as METH.[54,55] Although CPP can be measured in humans,[56] no current studies exist in which METH was used. As such, discussion of METH CPP is limited to animal subjects in the current review. In CPP, the potential pharmacotherapy can be administered before each METH treatment to determine if acquisition of METH CPP can be blunted. Alternatively, the putative pharmacotherapy can be administered before the posttest; this measures the ability of the treatment to attenuate the expression of METH CPP. Detailed discussion of CPP as a tool for screening pharmacotherapies is detailed elsewhere.[57]

Self-administration uses operant conditioning principles to measure the direct reinforcing effects of a stimulus.[58] There are numerous self-administration paradigms that model distinct aspects of addictive-like behaviors, including short-access models (eg, < 3 h)[59–62] and extended access models (eg, 6+ h).[63–65] Extended access to drug often leads to escalation of drug intake, a defining trait of SUDs.[66] Progressive ratio schedules measure the reinforcing efficacy of METH by requiring the subject to emit more responses after each reinforcer delivery;[67,68] a break point is calculated, indicating the highest response ratio completed by the subject.[69] Self-administration can be assessed in humans that are not currently seeking treatment for their substance use.[70,71]

Individuals with a SUD have access to numerous reinforcers that compete with substances like METH. Choice procedures are useful for modeling preference for drug reinforcement over alternative reinforcers. In animal studies, subjects respond on one manipulandum to earn a drug infusion and respond on a separate manipulandum to earn an alternative reinforcer like food.[72,73] Several methods can be used with human participants. Individuals can choose between drug and placebo or drug and an alternative reinforcer such as money.[74,75] Choice procedures can also be used to compare preference for the same drug delivered via different routes of administration.[76]

In addition to using self-administration procedures, clinical pharmacology studies often have individuals rate their subjective experiences of a drug administered alone or in combination with a potential pharmacotherapy.[77] Subjective effects of METH include perceived physiological changes (eg, feeling stimulated), and pleasurable/aversive feelings. Clinical trials recruit individuals with a confirmed MUD, giving some of the participants the potential pharmacotherapy while giving other participants a placebo.[78] Variables such as drug-free urine samples and dropout rates are then compared between the drug treatment and placebo groups.

Preclinical research often models recurrence of substance use with the reinstatement paradigm. Reinstatement can be assessed with both CPP and drug self-administration following extinction training in which drug is no longer paired with a specific environmental context (CPP) or delivered after completion of each response requirement (drug self-administration).[79–82] Incubation of craving is similar to the reinstatement paradigm, except that animals are not given extinction training; instead, they are given a single extinction session followed by a period of forced abstinence in which animals are kept in their home cage (eg, 30 days), followed by a second extinction session.[83]

Methodology for Literature Review

Between March and May 2024, multiple searches were conducted in PubMed, using combinations of terms, including those for the potential pharmacotherapies discussed in this review; "methamphetamine" and "methamphetamine use disorder" (including alterations to the word methamphetamine like "METH" and "methylamphetamine"); "withdrawal"; "subjective effects"; "self-administration"; "progressive ratio"; "conditioned place preference" or "CPP"; "reinstatement"; "incubation of craving"; "relapse"; "locomotor activity"; "stereotypy" or "stereotypies". Literature reviews and meta-analyses were excluded, and article titles and abstracts were screened for relevance. Additional articles were found by reviewing the reference sections of articles found during the literature search.

Potential Pharmacotherapies for MUD

Numerous drugs have been screened in assays measuring the physiological, the cognitive, and/or the reinforcing/rewarding effects of METH. Many of the drugs discussed below are already approved to treat other psychological and/or physical conditions while some have been tested in animals only. The treatments reviewed in the current paper are organized by their mechanism of action.

Pharmacotherapies for Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by increased hyperactivity/impulsivity and/or inattention and is linked to hypoactive catecholamine neurotransmission.[84] The primary treatment options are the psychostimulants *d*-AMPH and methylphenidate (MPH). Like METH, AMPH causes monoamines, specifically the catecholamines norepinephrine and dopamine, to be released into the synapse through their respective transporters, inhibits VMAT-2 functioning, and blocks activity of MAO; instead of reversing the flow of catecholamine transporters, MPH inhibits the reuptake of dopamine and norepinephrine, but there is evidence that MPH leads to a redistribution of VMAT-2.[85]

Giving METH-dependent individuals AMPH or MPH is a form of substitution treatment.[86] Substitution treatment is already used for other drugs (eg, tobacco)[87] and is an important component of harm reduction.[88] Ideally, providing METH-dependent individuals with a stimulant drug that can be taken in a safer manner than inhalation or injection can help minimize the health risks associated with these routes of administration (eg, contraction of an STI from sharing needles). However, caution is needed when providing individuals AMPH or MPH given that they have misuse potential and can be diverted (eg, dissolved and then snorted or injected).[89,90]

AMPH blunts some of the subjective effects of METH,[77] but results from animal studies are not as promising. Neither AMPH nor MPH affect METH self-administration in monkeys,[91,92] while self-administration of MPH potentiates the reinforcing effects of METH in rats.[93] These findings suggest that individuals maintained on AMPH or MPH may self-administer more METH to counteract the diminished subjective effects experienced during substitution treatment. Instead of targeting both dopamine and noradrenergic systems, an alternative approach is to use atomoxetine, a selective norepinephrine transporter inhibitor and non-stimulant treatment for ADHD. Although atomoxetine does not alter the subjective effects of METH,[94] it reduces METH craving and METH-positive urine samples in individuals receiving methadone maintenance therapy.[95] Preclinical studies assessing cocaine self-administration are encouraging as atomoxetine decreases relapse-like behavior in rodents.[96–98]

Modafinil

Modafinil is an anti-narcoleptic drug that acts as a weak dopamine transporter (DAT) inhibitor.[99] Modafinil decreases METH self-administration and attenuates drug-seeking behavior in rodents.[100–103] These effects may not be completely mediated by inhibition of DAT, as administration of the highly selective DAT inhibitor GBR 12909 potentiates METH-induced increases in locomotor activity and reinstatement of METH seeking.[104,105] Indeed, modafinil increases glutamate and histamine levels and decreases GABA levels.[106] Drugs targeting the glutamatergic and GABAergic systems will be discussed later in this review.

Modafinil somewhat blunts the positive subjective effects of METH and ameliorates METH-induced increases in systolic blood pressure,[107,108; but see109] but it does not significantly reduce choice for METH in a self-administration paradigm nor reduce METH use, craving, attentional bias toward METH-paired stimuli, or severity of dependence in METH-dependent individuals.[107–113] There is some evidence that modafinil can be used in conjunction with cognitive-behavioral therapy to reduce METH use.[114] At the cellular level, modafinil protects against METH-induced neuroinflammation, dopamine toxicity, and cell death in the striatum,[115] which is consistent with the inhibited dopamine release observed following selective blockade of DAT.[116,117] The neuroprotective effects of modafinil may account for its ability to reverse working and verbal memory deficits observed in both METH-dependent individuals and rodents.[112,118–120] Modafinil also improves learning in an associative learning task in METH-dependent individuals and improves inhibitory control in individuals with higher baseline rates of METH use.[121,122]

Antidepressant Drugs

The primary mechanism of action of antidepressants is to increase serotonin and norepinephrine levels. MAO inhibitors (MAOIs) prevent the metabolism of monoamines.[123] Tricyclics/tetracyclics prevent the reuptake of serotonin/norepinephrine, but they interact with multiple molecular targets (eg, histamine receptors, cholinergic receptors, adrenergic receptors). Commonly prescribed today, selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine

reuptake inhibitors (SNRIs) also prevent the reuptake of norepinephrine and/or serotonin, but they have fewer "off-site" targets.

Due to the side effect profile of MAOIs, with cardiovascular effects being particularly problematic, individuals treated with MAOIs need to maintain a restrictive diet to avoid a life-threatening hypertensive crisis.[124] As such, MAOIs are rarely tested in individuals with MUD. Selegiline (ie, deprenyl), a MAO-B inhibitor, fails to attenuate the positive subjective effects of METH, instead potentiating individuals' self-reported "bad effects" following METH administration.[125] This is somewhat concerning as aversive experiences, in conjunction with the dietary restrictions associated with MAOIs, may lead to lower compliance in METH-dependent individuals.

The tricyclic antidepressant imipramine increases treatment retention rates, but it does not significantly alter drug craving, self-reported use frequency, or drug-positive urine samples in stimulant-dependent individuals.[126] One important consideration is that most of the participants in this study were dependent on cocaine (151 out of 183 participants), with the rest (32/183) being dependent on METH. Similar results are obtained when a sample of METH-dependent individuals is used: increased treatment retention but no effects on drug craving or frequency of METH use.[127] Preclinical research demonstrates that desipramine increases dopamine release following METH administration while decreasing dopamine levels following administration of other amphetamines.[128] Additionally, imipramine, as well as clomipramine, potentiates METH-induced stereotypies in rats.[129,130] These preclinical findings may provide an account for the inability of imipramine to reduce the reinforcing effects of METH in dependent individuals.

In contrast to tricyclics, tetracyclics block METH-induced increases in locomotor activity and locomotor sensitization in animals.[131,132] The tetracyclic antidepressant maprotiline reduces METH-induced stereotypies in rodents.[133] Mirtazapine, when administered after a conditioning session, prevents the expression of METH CPP,[134] and decreases cue-induced reinstatement in rats.[135] Mirtazapine also decreases METH use in individuals with MUD,[136,137] including cisgender men and transgender women who have sex with men,[136] although it is ineffective in facilitating retention in a METH withdrawal program.[138] This latter finding suggests that mirtazapine may not be beneficial for individuals actively going through withdrawal. Like MAOIs, using tetracyclic medications for long-term treatment of MUD is challenging given their side-effect profile. As tricyclic and tetracyclic antidepressants have multiple mechanisms of action, individuals can experience a wide range of side effects, including dry mouth, urinary difficulties, weight gain, drowsiness, and headaches.[139]

Similar to tetracyclics, SSRIs differentially alter locomotor responses to METH. Citalopram exacerbates locomotor activity following METH administration,[140] with this effect appearing to be influenced by increased dopamine, but not serotonin, depletion in the nigrostriatal pathway.[141] However, fluoxetine and paroxetine attenuate METH-induced locomotor sensitization,[142,143] and they decrease METH CPP.[143,144] Clinical trials with sertraline show that SSRIs can be contraindicated for individuals with MUD, as individuals treated with sertraline alone have lower treatment retention rates, experience more adverse events, and increase their METH use.[145,146]

Concerning SNRIs, duloxetine ameliorates METH-induced cognitive deficits,[147,148] and venlafaxine blocks reinstatement of METH CPP.[149] Clinical trials have not tested the efficacy of SNRIs for the treatment of METH dependence, although trials for cocaine dependence have largely been unsuccessful.[150–152; but see.[153,154]

Bupropion is a dual-purpose medication, prescribed to treat both depressive disorders and nicotine dependence; compared to other antidepressant drug classes, bupropion is unique in that it inhibits dopamine and norepinephrine transporters and upregulates VMAT-2 expression.[155] The ability of bupropion to inhibit reuptake of dopamine and to target VMAT-2 may make it a promising pharmacotherapy for MUD. To this end, bupropion blunts the positive subjective effects of METH,[156] and it decreases METH self-administration in monkeys.[91; but see[157] Unfortunately, bupropion also decreases self-administration of sucrose in rats,[158–160] suggesting that long-term bupropion treatment may lead to increased anhedonia in individuals. Indeed, anhedonia is observed in healthy individuals given bupropion.[161] Bupropion can also lead to significant adverse events, including tachycardia, seizures, and suicidal ideations.[162–164]

VMAT-2 Inhibitors

Studies examining the efficacy of VMAT-2-selective drugs have been limited to animals. The plant-derived lobeline decreases METH self-administration and METH-induced stereotypies in rodents.[165,166] Because lobeline is not entirely

selective for VMAT-2,[167] lobelane, an analog of lobeline, was next tested.[168,169] Like lobeline, lobelane decreases METH self-administration in rats, but tolerance develops following repeated lobelane treatment.[170] Lobelane analogs now show promise in reducing dependence-like behavior in rodents, as they decrease METH self-administration, reinstatement of METH seeking, METH CPP, and METH-induced hyperactivity, with no tolerance observed following repeated administration.[171–177]

Altering Tyrosine Levels

Tyrosine is a non-essential amino acid synthesized from phenylalanine that serves as a vital precursor to dopamine. Decreasing tyrosine levels or preventing the conversion of tyrosine to L-DOPA (l-3,4-dihydroxyphenylalanine; immediate precursor to dopamine) limits METH-induced increases in dopamine release,[178] thus diminishing the reinforcing effects of METH. Administration of the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine protects against METH's neurotoxic and hyperthermic effects,[179–182] and attenuates METH-induced dopamine depletion.[183,184] Only one study has examined the effects of tyrosine depletion on METH effects in humans, with subjective effects and METH-induced mania decreasing following tyrosine depletion.[185] There is evidence that tyrosine depletion decreases cue- and drug-induced craving for cocaine, but fails to affect cocaine self-administration in non-dependent cocaine users.[186] One major concern associated with tyrosine depletion is increased apathy and decreased contentment.[187]

Monoaminergic Receptor Ligands

By limiting tyrosine activity, dopamine is not the only neurotransmitter that is decreased; norepinephrine levels decrease following alpha-methyl-p-tyrosine administration,[188] most likely because dopamine is the direct precursor of norepinephrine.[189] Instead of targeting monoamine synthesis or metabolism, one approach is to use monoaminergic receptor ligands to block the effects of METH in individuals.

Each monoaminergic system has its own receptor types, with all but one coupled to a G protein (ie, metabotropic receptor).[190–192] Dopamine D_1-like (D_1 and D_5) receptors, all three noradrenergic beta receptor subtypes (1–3), and serotonin 5-HT_4, 5-HT_6, and 5-HT_7 receptors are G_s-coupled, leading to increased adenyl cyclase activity in the neuron, resulting in increased neuronal excitation.[190–192] Noradrenergic alpha-1 and serotonin 5-HT_2 receptors are also excitatory, but they are coupled to a G_q protein, which activates a different intracellular signaling pathway involving phospholipase C and protein kinases.[190,192] Dopamine D_2-like (D_2, D_3, and D_4), noradrenergic alpha-2, and serotonin 5-HT_1 and 5-HT_5 receptors are inhibitory. Stimulation of these receptors leads to decreased activity of adenyl cyclase.[190–192] Finally, the 5-HT_3 receptor is ionotropic, consisting of five subunits surrounding an ion channel. When a ligand binds to the receptor, the ion channel opens, allowing sodium ions to enter the neuron.[192]

Buspirone

Buspirone is an anxiolytic that acts as a partial agonist at serotonin 5-HT_{1A} receptors and as an antagonist at dopamine D_2-like receptors.[193] Buspirone decreases reinstatement of METH seeking in rats,[194] but it fails to alter choice of METH over food in monkeys and fails to affect the subjective or the reinforcing effects of intranasal METH in humans.[195,196] In fact, buspirone increases some positive subjective effects of oral METH.[197] These results raise concerns about the use of buspirone as a treatment for MUD.

Antipsychotic Medications

Historically used to treat psychiatric conditions like schizophrenia, antipsychotic medications exert their effects by acting as dopamine D_2 receptor antagonists, with atypical antipsychotics also acting as serotonin, specifically 5-HT_{2A}, and noradrenergic receptor antagonists.[198] Some antipsychotics, such as aripiprazole, act as partial agonists at dopamine D_2-like receptors and 5-HT_{1A} receptors in addition to antagonizing 5-HT_{2A} receptors.[199]

Antipsychotics decrease METH-induced hyperactivity and block locomotor sensitization following repeated METH administration;[200–211] but see.[212] The atypical antipsychotic risperidone increases METH self-administration in monkeys.[157] Aripiprazole produces biphasic effects when a fixed ratio schedule is used, decreasing self-administration when lower doses of METH are used, but increasing self-administration when a higher dose of METH is used.[213] The

increased self-administration observed in monkeys and in rats may not necessarily indicate that antipsychotics increases the reinforcing effects of METH; instead, animals may increase their responding to achieve a hedonic set point that is similar to when pretreated with vehicle. When a progressive ratio schedule is used, aripiprazole decreases the reinforcing efficacy of METH.[213]

Neither haloperidol nor risperidone blunt METH's stimulant effects in humans;[214] yet, individuals maintained on risperidone decrease their use of METH,[215,216] but these results are somewhat difficult to interpret due to the small number of individuals that completed treatment (eg, only 12 of 53 participants completed an 8-week treatment of risperidone injections).[216] Aripiprazole blunts some positive subjective effects of METH and decreases METH self-administration in non-dependent individuals,[217–219] but it fails to decrease METH use in dependent individuals.[220,221] As aripiprazole increases treatment retention,[221] it may be better served as a treatment given in addition to non-pharmacological-based interventions. However, evidence indicates that individuals given antipsychotics "off-label" may develop a hypersensitive dopaminergic system, which can increase drug cravings and worsen stimulant use disorder.[222]

One benefit of antipsychotics is they ameliorate the psychotomimetic-like effects of METH. Antipsychotics block behavioral disturbances in rodents that model schizophrenia-like behavior (eg, prepulse inhibition deficits) and abolish METH-induced self-injurious behavior in mice.[223–225] Clinically, antipsychotics reduce METH-induced psychosis and sedate individuals experiencing METH toxicity.[222,226–231] Related to METH toxicity, antipsychotics may be useful for reversing METH-induced hyperthermia.[232]

Dopamine Receptor Ligands

As dopaminergic dysfunction in the mesocorticolimbic pathway is heavily implicated in SUDs,[233] blocking dopamine receptors represents a potential mechanism for attenuating the physiological and/or the reinforcing effects of METH. The mixed dopamine receptor antagonist levo-tetrahydropalmatine decreases METH self-administration and METH-induced reinstatement.[234] The protective effects of levo-tetrahydropalmatine appear to be driven by blockade of D_1-like receptors, as D_1-like, but not D_2-like, receptor antagonists decrease METH self-administration and reinstatement of METH-seeking behavior.[105,235,236] However, both D_1-like and D_2-like antagonists block METH-induced hyperactivity and stereotypies, as well as the development of behavioral sensitization following repeated METH administration.[131,209,224,237–241] Likewise, blocking either dopamine D_1-like or D_2-like receptors attenuates the acquisition and the expression of METH CPP in rodents,[242–248] although some work shows that D_2-like receptors are uninvolved in the acquisition of METH CPP.[243,248] Another seemingly paradoxical finding is that while a dopamine D_2 receptor partial agonist decreases METH-induced hyperactivity,[209] D_2-like agonists increase METH seeking in a reinstatement model.[249]

Dopamine D_1-like and D_2-like receptors have complex interactions with one another in striatal pathways. Projections from striatal D_2-containing medium spiny neurons (MSNs) to D_1-containing MSNs are more common than projections from D_1-like MSNs to D_2-like MSNs, and synaptic connections formed by D_2-like MSNs are stronger than those formed by D_1-like MSNs.[250] Upregulation of D_2-like MSNs in nucleus accumbens also increases motivation for reinforcement via disinhibition of the ventral pallidum,[251] which mirrors increased motivation for reinforcement following direct stimulation of D_1-like receptors in nucleus accumbens.[252] Thus, D_2-like receptor antagonists can produce similar results as D_1-like receptor antagonists by preventing the inhibition of inhibitory neurons that typically regulate the release of dopamine.

As D_2-like receptor antagonists have fewer extrapyramidal side effects compared to D_1-receptor antagonists,[198] there is growing interest in targeting these receptors for SUDs, particularly the dopamine D_3 receptor.[253] Selective dopamine D_3 receptor antagonists attenuate METH-induced behavioral sensitization,[254] ameliorate prepulse inhibition deficits following METH administration,[255] prevent METH-induced hyperthermia,[256] blunt METH CPP,[254] reduce intracranial self-stimulation following METH administration,[257,258] decrease the reinforcing efficacy of METH,[257,259–261] and block reinstatement of METH-seeking behavior.[257,259,260,262] While dopamine D_3 receptor partial agonists attenuate METH-induced intracranial self-stimulation and METH self-administration,[245,261] one selective D_3 receptor partial agonist has no effect on METH self-administration in monkeys in a choice procedure.[195] Despite this last finding, the results with dopamine D_3 receptor antagonists are promising and merit further testing.

Currently, there is little work examining the effects of selective dopamine D_4 receptor ligands on dependence-like behaviors despite evidence showing that this receptor may be an important target for preventing recurrence of stimulant use.[263] A selective dopamine D_4 receptor antagonist blocks METH-induced hyperactivity,[264] but has no effect on the development of behavioral sensitization.[265] There is recent evidence that D_4 receptor partial agonists decrease cocaine self-administration in rats;[266] thus, investigating how D_4 receptor ligands influence MUD-like behaviors is warranted.

Noradrenergic Receptor Ligands

Alpha-1 receptor agonists are used as decongestants and hypotension medications,[267,268] and beta receptor agonists are commonly prescribed for pulmonary-related conditions.[269] Alpha-1 and beta receptor antagonists are used to decrease hypertension.[270,271] Alpha-2 receptor agonists are used as sedatives in animal surgery,[272] with clonidine and guanfacine used as ADHD medications.[273] Alpha-2 receptor antagonists are often used to reverse the sedative effects of alpha-2 agonists,[274] with yohimbine being used to model stress-induced reinstatement of drug-seeking behavior, including for METH.[275,276] As METH increases norepinephrine levels, one approach to blunting the physiological/behavioral effects of METH is to block alpha-1/beta receptors and/or to stimulate alpha-2 receptors.

Research examining the efficacy of noradrenergic receptor ligands is limited to animals. Alpha-1 and beta receptor antagonists ameliorate METH-induced hyperthermia and conditioned hyperactivity.[179,277–279] Similarly, an alpha-1 receptor inverse agonist attenuates conditioned hyperactivity following repeated METH treatments.[280] Although the effects of alpha-1/beta receptor antagonists on the reinforcing effects of METH are unknown at this point, there is evidence that blocking alpha-1 receptors decreases cocaine self-administration;[281–283] but see.[284] Conversely, results with beta receptor antagonists are mixed, with some studies showing decreased cocaine self-administration,[285,286] no change in cocaine self-administration,[282] or increased cocaine self-administration.[283] While ineffective on their own, combination treatment of an alpha-1 receptor antagonist and a beta receptor antagonist attenuates cue-induced reinstatement of cocaine seeking.[287]

Alpha-2 receptor agonists attenuate METH-induced hyperactivity and stereotypies,[288] METH's hyperthermic effects,[289] and METH CPP,[290] although they do not show much efficacy in blunting the direct reinforcing effects of psychostimulants;[282,291] but see.[292,293] Alpha-2 receptor agonists reduce cue- and stress-induced cocaine seeking,[287,294–296] suggesting they may be an important treatment for individuals with MUD that are currently or have recently completed a treatment intervention.

Serotonin Receptor Ligands

Similar to dopamine receptor antagonists and noradrenergic alpha-2 receptor agonists, administration of 5-HT_{1A} agonists and antagonists, 5-HT_{2A} receptor antagonists, 5-HT_{2C} agonists, and 5-HT_{5A} antagonists reduces METH-induced hyperactivity.[131,209,297–299] METH-induced stereotypies are similarly blunted by 5-HT_{1A} agonists.[130] Conversely, 5-HT_{2C} antagonists potentiate METH-induced locomotor activity.[209] Concerning METH reward, a 5-HT_{1B} agonist attenuates the expression, but not acquisition, of METH CPP,[300] and 5-HT_3 antagonists block METH CPP.[301]

Psychedelic hallucinogens are receiving interest as potential pharmacotherapies for conditions like posttraumatic stress disorder and alcohol use disorder.[302,303] The major psychedelic hallucinogens are naturally derived and include lysergic acid diethylamide (LSD), psilocybin, mescaline, and *N,N*-dimethyltryptamine (DMT). Psychedelic hallucinogens are agonists at 5-HT_{2A} receptors, although they bind to multiple 5-HT receptor subtypes, with LSD also acting as an agonist at dopaminergic and noradrenergic receptors.[304] Results from the few studies examining the efficacy of psychedelic hallucinogens are mixed. LSD fails to alter intracranial self-stimulation following METH injection.[305] Psilocin, an active metabolite of psilocybin, decreases METH-induced hyperlocomotion and CPP but does not affect reinstatement of METH CPP.[306] Additional work further diminishes the idea of targeting the 5-HT_{2A} receptor as a pharmacotherapy for MUD as the 5-HT_{2A} inverse agonist/antagonist pimavanserin fails to reduce preference for METH over food in monkeys.[307]

Lorcaserin is a 5-HT_{2C} agonist that was previously used as a weight-loss drug.[308] Lorcaserin reduces stimulant use in METH-dependent individuals,[309] but the appeal of lorcaserin as a viable treatment for MUD is reduced by the finding that individuals choose cocaine *more* frequently compared to money when treated with lorcaserin despite reporting

decreased drug craving.[310] Additionally, results from a double-blind, placebo-controlled clinical trial show no benefits of lorcaserin for the treatment of cocaine use disorder.[311] Finally, lorcaserin is no longer on the market in the United States due to its potential carcinogenic effects.[312] Given that a 5-HT_{2C} inverse agonist, but not 5-HT_{2C} antagonists, attenuates METH-seeking in rodents,[313] this may provide a novel approach to treating METH dependence as opposed to stimulating these receptors.

Ondansetron is a serotonin 5-HT_3 receptor antagonist that is used as an antiemetic.[314] Ondansetron potentiates METH-induced locomotor activity,[131] which is interesting as a different 5-HT_3 antagonist reduces METH-induced hyperactivity.[315] Clinically, ondansetron is no more effective than placebo at reducing METH use, withdrawal symptoms, craving, or dependence severity.[316] Ondansetron does reverse the anorexic-like effects of METH,[317] which can be valuable for helping stimulate appetite in those with MUD.

Trace Amine-Associated Receptor Agonists

Trace amines are chemicals that are structurally related to monoamines and are derived from phenylalanine.[318] For example, phenylalanine is converted to phenethylamine by aromatic L-amino acid decarboxylase, the same enzyme that converts L-DOPA into dopamine. Other trace amines include tyramine, octopamine, and synephrine. Trace amines bind to the trace amine-associated receptor 1 (TAAR 1), which regulates monoaminergic neurons. Specifically, trace amines modulate monoamine transporter function.[319,320] Because METH acts as an agonist at TAAR 1,[319,321–323] there is interest in determining if TAAR 1 agonists can act as a form of substitution therapy for MUD. This research is limited to preclinical models so far, but results are promising. TAAR 1 agonists reduce METH-induced dopamine release in nucleus accumbens, attenuate METH-induced locomotor sensitization, decrease METH drug self-administration, blunt the reinforcing efficacy of METH, and block drug-induced reinstatement of METH seeking.[324–326] Another benefit of TAAR 1 agonists is that they can ameliorate motor impulsivity caused by acute METH administration and abrupt cessation of METH.[327]

Cholinergic Drugs

As numerous neurotransmitter systems are implicated in addiction,[328] testing the efficacy of non-monoaminergic drugs for METH dependence is needed. Acetylcholine is an important neurotransmitter that regulates muscle contractions and is implicated in learning and cognition.[329,330] Systemic administration of METH increase acetylcholine levels in ventral tegmental area and striatum of rodents,[331,332] regions of the brain involved in the addiction process.[333] Cholinergic receptors control dopamine release in nucleus accumbens when animals are presented with drug-paired cues,[334] suggesting that the cholinergic system may be an important target for preventing drug-seeking behavior.

There are two major types of cholinergic receptors: nicotinic and muscarinic. Nicotinic receptors are ionotropic and consist of five subunits; stimulation of nicotinic receptors leads to sodium influx into the neuron. Muscarinic receptors are metabotropic and can be excitatory (M_1, M_3, and M_5) or inhibitory (M_2 and M_4).[335]

Nicotinic Receptor Ligands

Nicotine is an agonist at nicotinic receptors and is the primary psychoactive chemical in tobacco. One interesting finding is that as craving for nicotine increases, craving for and use of stimulants decrease.[336] Similarly, cue-induced drug seeking is enhanced in animals following antagonism of nicotinic receptors.[334] These results indicate that nicotine may be useful as a form of substitution treatment for MUD. Indeed, nicotine fully substitutes for METH in a drug-discrimination paradigm in animals while METH acts as a partial substitute for nicotine only.[337]

Repeated administration of nicotine during extinction training decreases reinstatement of METH seeking.[338] Yet, other research raises concerns about the viability of long-term nicotine administration as a treatment for MUD. First, repeated nicotine exposure fails to alter the acquisition, the extinction, and the reinstatement of METH CPP.[339] Chronic, but not acute, administration of nicotine augments locomotor activity following METH treatment.[340,341; but see342] While acute administration of nicotine transiently decreases METH self-administration, repeated nicotine administration fails to alter METH self-administration.[343] In fact, chronic nicotine treatment enhances METH self-administration in adult females.[344] Acute nicotine administration potentiates reinstatement of METH-seeking behavior,[343,345] although this

effect is not observed in rats treated with nicotine during adolescence.[346] Nicotine may be beneficial for ameliorating cognitive deficits resulting from METH use. Nicotine administration reverses METH-induced deficits in novel object recognition, memory, and prepulse inhibition and attenuates METH-induced increases in risky choice.[347–350]

Varenicline is a partial agonist at α4β2 and an agonist at α7 nicotinic receptors and is used to for tobacco dependence as a form of substitution treatment.[351] One concern is that varenicline decreases responding for both METH and saline/food,[174,352;] but see[353] suggesting that this treatment may increase anhedonia in individuals; furthermore, low doses of varenicline potentiate reinstatement of METH-seeking, although this effect may reflect an increase in general locomotor activity as responding increases on a manipulandum previously paired with saline,[352,353] There is evidence that varenicline blunts the positive subjective effects of METH,[354] but clinical research shows that varenicline is ineffective at decreasing METH use in dependent individuals.[355] Like nicotine, varenicline may be useful for reversing cognitive impairments resulting from METH use, as it reverses METH-induced increases in risky choice in rodents.[350] Instead of using an agonist or partial agonist at nicotinic receptors, one approach is to use a selective α4β2 nicotinic receptor desensitizing compound. To this end, an α4β2 nicotinic receptor desensitizing compound decreases METH self-administration in rats.[356]

Ibogaine is a naturally derived psychoactive substance found in certain plants that has high affinity for nicotinic acetylcholine receptors, adrenergic α_2 receptors, and the serotonin transporter.[357] Ibogaine blocks METH-induced hyperthermia,[358] but it increases METH-induced stereotypies.[359] The α3β4 nicotinic receptor antagonist 18-methoxycoronaridine (18-MC), a synthetic analog of ibogaine, decreases METH self-administration,[61,360,361] but it increases locomotor activity in rats chronically treated with METH and potentiates METH-induced stereotypies like ibogaine.[359] These results are concerning as they suggest that blocking nicotinic receptors can exacerbate problematic behaviors like skin picking in individuals with MUD.

Muscarinic Receptor Ligands

Benztropine is a non-selective muscarinic receptor antagonist used to treat tremors associated with Parkinson's disease.[362] More recent studies using benztropine analogs show that they decrease METH-induced locomotor activity, METH self-administration, and reinstatement of METH seeking.[363–365] One caveat to these findings is that one benztropine analog increases the reinforcing efficacy of METH as measured in a progressive ratio schedule.[364]

Scopolamine, another non-selective muscarinic receptor antagonist used to prevent motion sickness,[366] prevents the development of METH-induced behavioral sensitization and stereotypies.[367–369;] but see[370,371] While scopolamine does not affect METH CPP, the muscarinic M_1 receptor antagonist trihexyphenidyl (an antispasmodic) blocks METH CPP.[369] The selective muscarinic M_1 receptor antagonist dicyclomine (an antispasmodic used to treat irritable bowel disease) does not alter the acute effects of METH on locomotor activity, but it potentiates behavioral sensitization.[372]

The muscarinic receptor agonist oxotremorine reverses both METH-induced hyperactivity and prepulse inhibition deficits,[207] and the M1/M4 agonist xanomeline decreases METH-induced hyperactivity.[373] Administration of muscarinic receptor agonists is difficult as they increase tremors and are used to model Parkinson's disease.[374,375] A potential future direction is to use partial agonists at muscarinic receptors. *N*-desmethylclozapine, a major metabolite of clozapine which acts as a partial agonist as muscarinic M1 receptors,[376] prevents METH-induced psychotic-like effects.[377] Whether muscarinic receptor partial agonists are efficacious in attenuating METH dependence-like behavior is currently unknown.

Acetylcholinesterase Inhibitors

A different potential cholinergic target is the inhibition of acetylcholinesterase, which metabolizes acetylcholine.[378] Acetylcholinesterase inhibitors are currently used to treat Alzheimer's disease.[379] Despite blunting cocaine-induced behavioral sensitization and cocaine CPP, the acetylcholinesterase inhibitor donepezil fails to blunt these behaviors following METH administration.[380] Donepezil also fails to alter memory impairments resulting from METH administration, but the weak acetylcholinesterase inhibitor galantamine attenuates METH-induced memory deficits.[381] One positive findings is that both donepezil and galantamine decrease reinstatement of METH seeking.[382,383] Rivastigmine modestly reduces some subjective effects of METH but is ineffective at reducing the direct reinforcing effects of METH and METH-induced deficits in cognition.[384–387]

Opioid Receptor Antagonists

Consisting of endorphins, dynorphins, and enkephalins, endogenous opioids bind to G_i-coupled metabotropic receptors (mu, kappa, delta, respectively).[388] Given the influence of the endogenous opioid system to addiction,[389] opioid receptor antagonists may be a viable molecular target for MUD. Naltrexone is used to treat opioid use disorder and alcohol use disorder.[390] Naloxone is similar to naltrexone, but is most commonly used to reverse the effects of opioid overdose.[391] As such, there is little research examining naloxone's efficacy in METH dependence. The preclinical studies that have been conducted show that naloxone decreases stereotypical biting in mice but potentiates stereotypical sniffing and locomotor activity,[392] and exacerbates METH-induced stereotypies in rats.[393]

Research with naltrexone is more promising, as it attenuates METH-induced behavioral sensitization, METH CPP, and METH-seeking behavior.[392,394–398] The naltrexone analog nalmefene also decreases reinstatement of METH-seeking behavior.[399] In humans, naltrexone fails to diminish the subjective effects and the direct reinforcing effects of METH in a non-clinical sample;[400,401] but see.[71] but there is evidence that naltrexone reduces subjective cue-induced craving in individuals with MUD and reduces the number of METH-using days in individuals with MUD or in individuals that engage in higher METH use.[401–403] Naltrexone also decreases the ability of cue-induced craving to predict positive subjective effects.[404] Importantly, the ability of naltrexone to blunt the subjective effects of METH is enhanced in individuals with lower executive functioning,[405] indicating that neuropsychological tests should be performed in individuals to determine if naltrexone treatment will be effective.

The ability of naltrexone to selectively decrease the reinforcing effects of METH in dependent individuals may be related to a dysregulated dopaminergic system observed in these individuals. Individuals with MUD have increased resting state functional connectivity between brain regions like ventral striatum, amygdala, and hippocampus, which is blunted by naltrexone treatment.[402] Naltrexone also reduces functional connectivity of regions like dorsal striatum and VTA with sensory-processing and motor-control regions of the brain that are associated with cue reactivity.[406]

Like naltrexone administered alone, combining naltrexone with other pharmacotherapies is ineffective at altering the subjective or the reinforcing effects of METH in non-dependent individuals,[71,407] but it increases the percentage of drug-free urine samples in dependent individuals relative to placebo treatment, although the overall rate of success is moderately low.[78] Combination treatment of naltrexone and bupropion is significantly more effective in gay/bisexual men compared to heterosexual men,[408] an effect that is not observed when naltrexone is administered alone.[409] As METH use is higher in LGBTQ+ individuals,[410] naltrexone/bupropion provides a novel approach for treating individuals at increased risk for developing MUD.

In addition to naltrexone, future research may want to consider using drugs that are highly selective for one opioid receptor to better determine how endogenous opioids mediate the effects of METH in individuals. The mu opioid receptor antagonist β-funaltrexamine attenuates METH-induced increases in self-biting in mice, an effect that is not observed following selective blockade of kappa or delta receptors.[392] The kappa receptor antagonist norbinaltorphimine dihydrochloride (nor-BNI) decreases escalation of METH intake in rats,[411] while the non-selective delta opioid receptor antagonist naltrindole and the delta-2 opioid receptor antagonist naltriben reduce METH CPP.[412]

GABAergic Receptor Ligands

GABA is the major inhibitory neurotransmitter in the nervous system and binds to two receptor types: $GABA_A$ and $GABA_B$.[413] $GABA_A$ receptors are ionotropic, consisting of five subunits, and allow chloride to enter the neuron when activated. $GABA_B$ receptors are metabotropic, coupled to a G_i protein. Dysregulation of the GABA system is implicated in addiction.[414] Furthermore, METH impairs signaling of $GABA_B$ receptors,[415] and decreases immunoreactivity of inhibitory neurons in nucleus accumbens.[416] The inhibition of GABAergic neurons, in turn, leads to further increases in dopamine release in the mesocorticolimbic pathway. Increasing GABAergic neurotransmission may be an effective treatment option for those with a MUD.

Many anxiolytics potentiate activity of $GABA_A$ receptors by binding to the benzodiazepine site of the receptor.[417] Clonazepam prevents the acquisition, but not the expression, of METH-induced locomotor sensitization in rats, an effect that is blocked by co-administration of the $GABA_A$ receptor antagonist flumazenil.[418,419] Oxazepam attenuates METH

CPP,[420] and decreases METH-seeking behavior when combined with the steroidogenesis inhibitor metyrapone.[421] Anxiolytics can differentially affect METH self-administration, with oxazepam decreasing METH self-administration across various doses and alprazolam potentiating self-administration at low unit doses and decreasing self-administration at higher doses.[422] One potential future direction is to use $GABA_A$ negative allosteric modulators. One such modulator reduces intracranial self-stimulation and nucleus accumbens dopamine release following METH administration in mice.[423]

Baclofen is a $GABA_B$ receptor agonist prescribed to treat muscle spasms. GABA inhibits dopamine release in striatal regions.[424] Baclofen exacerbates METH-induced stereotypies in mice,[425] but it attenuates the acquisition and the expression of METH CPP,[426] facilitates extinction of METH CPP,[427] and decreases METH self-administration.[67] Baclofen also reverses METH-induced impairments in prepulse inhibition and recognition memory.[428–430] Overall, baclofen does not significantly alter METH use in individuals that are dependent on METH; however, there is some evidence that individuals that show better medication adherence decrease their use to a greater extent than placebo-treated individuals.[431]

Glutamatergic Targets

Glutamate is the major excitatory neurotransmitter in the mammalian brain. Like the GABAergic system, the glutamatergic system is composed of both ionotropic and metabotropic receptors.[432] Kainate, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and NMDA (N-methyl-D-aspartate) receptors consist of four subunits and allow sodium (and calcium in the case of NMDA receptors) into the neuron when activated. Metabotropic glutamate receptors (mGluRs) are divided into three groups: Group I (excitatory $mGluR_1$ and $mGluR_5$), Group II (inhibitory $mGluR_2$, $mGluR_3$, and $mGluR_4$), and Group III (inhibitory $mGluR_6$, $mGluR_7$, and $mGluR_8$).

Ionotropic Glutamate Receptor Ligands

The effects of selective kainate receptor ligands on METH-related behaviors are unknown in both animals and humans. However, riluzole, which non-selectively inhibits ionotropic glutamate receptors,[433] prevents increased locomotor activity following acute METH administration and blocks METH-induced locomotor sensitization.[434] The effects of riluzole do not appear to be influenced by antagonism of AMPA receptors, as an AMPA receptor antagonist fails to alter METH-induced behavioral sensitization or METH-induced stereotypies.[46] Additionally, AMPA receptor antagonists do not alter METH self-administration or METH-seeking behavior.[435,436]

Memantine is an NMDA receptor uncompetitive antagonist (ie, channel blocker) that is used clinically to treat Alzheimer's disease.[437] Not surprisingly, memantine is efficacious in reversing memory impairments resulting from METH administration.[438,439] However, memantine administration produces stereotypic sniffing and increases locomotor activity.[440] While memantine decreases self-administration of higher doses of METH, it potentiates self-administration of a low unit dose of METH.[441] Memantine also fails to alter the subjective effects of METH in non-dependent individuals,[442] although the effects of memantine have not been tested in dependent individuals.

Like memantine, ketamine is an NMDA receptor channel blocker, but it is used as an anesthetic in animals and is now used as a rapidly acting antidepressant in humans.[443,444] Specific to METH-dependence-like behavior, ketamine decreases self-administration in animals.[445] Ketamine also decreases cocaine-induced hyperactivity in animals,[446] and decreases cocaine self-administration in humans.[447] One caveat to this latter finding is that preclinical research shows that ketamine attenuates the reinforcing effects of both cocaine and food,[448] suggesting increased anhedonia. There is some evidence that ketamine blocks reinstatement of cocaine seeking in monkeys,[449] but this study tested three subjects only. A recent clinical trial shows that combining a single ketamine infusion with mindfulness-based therapy helps improve abstinence.[450]

Beyond NMDA receptor channel blockers, drugs that selectively target NMDA receptors that contain a specific subunit provide a potential avenue for treating SUDs. NMDA receptors are composed of two GluN1 subunits and combinations of GluN2A, GluN2B, GluN2C, and GluN2D subunits. Glutamate binds to the GluN2 subunits while the co-agonist glycine binds to the GluN1 subunits.[432] Rats prenatally exposed to METH have increased expression of GluN1 and GluN2B subunit, an effect that emerges during adulthood.[451] METH treatment leads to differential GluN

subunit expression in regions of the dorsal striatum, with upregulated GluN1 and GluN2A expression observed in dorsolateral striatum, and downregulated GluN2A and GluN2B expression observed in dorsomedial striatum.[452] METH CPP also upregulates GluN2B-containing NMDA receptors in hippocampus,[453] and METH self-administration increases GluN2B expression in medial prefrontal cortex.[454]

The GluN2B subunit has received increased attention as GluN2B-selective antagonists prevent reinstatement of nicotine and heroin seeking in animals.[455,456] While the contribution of GluN2B-containing NMDA receptors to METH relapse-like behavior has not been elucidated, antagonism of GluN2B-containing NMDA receptors fails to alter the rate of extinction of METH self-administration.[457] However, GluN2B-selective antagonists attenuate METH-induced locomotor activity and the acquisition and the expression of METH-induced behavioral sensitization.[458,459] Additionally, one GluN2B-selective antagonist blocks the acquisition, but not the expression of METH CPP in rats.[460]

Metabotropic Glutamate Receptor Ligands

Similar to ionotropic glutamate receptors, METH alters the expression of mGluRs. Specifically, extended access to METH leads to decreased expression of $mGluR_{2/3}$ in nucleus accumbens and striatum.[461] As these receptors are inhibitory, $mGluR_{2/3}$ agonists should be efficacious in blunting the effects of METH. Direct stimulation of $mGluR_2$ or administration of $mGluR_2$ positive allosteric modulators decrease METH-induced hyperactivity.[462,463] An $mGluR_2$ agonist selectively decreases the reinforcing efficacy of METH without altering food-maintained responding.[464] However, while an $mGluR_{2/3}$ agonist blunts reinstatement of METH-seeking, it also decreases reinstatement of food-seeking behavior.[465] In contrast to $mGluR_2$ agonists, an $mGluR_2$ antagonist ameliorates depressive-like behavior resulting from METH withdrawal.[466]

Although there is no evidence for $mGluR_1$ involvement in the incubation of METH craving,[467] selective $mGluR_1$ antagonists block METH-induced increases in locomotor activity and disruptions in prepulse inhibition,[468,469] and decrease METH self-administration and choice for METH over food.[470] Likewise, blocking $mGluR_5$ selectively decreases METH self-administration.[471] A positive allosteric modulator of $mGluR_5$ reverses METH-induced deficits in recognition memory.[472] However, negative allosteric modulators of $mGluR_5$, but not $mGluR_1$, attenuate the expression of METH CPP.[473]

N-Acetylcysteine

Instead of targeting a specific receptor, some research has focused on restoring glutamate homeostasis with *N*-acetylcysteine, a medication used to reverse acetaminophen overdose.[474,475] Loss of glutamate homeostasis is proposed to be a major driving force of addiction.[476] In animals, *N*-acetylcysteine blocks the development of behavioral sensitization induced by METH, which corresponds to the ability of *N*-acetylcysteine to prevent METH-induced depletion of dopamine in striatum.[477] However, *N*-acetylcysteine fails to alter METH self-administration and drug-induced reinstatement of METH seeking in rats.[158] Also, *N*-acetylcysteine, whether administered alone or in conjunction with naltrexone, is ineffective at reducing METH craving, METH use, or severity of dependence in those that are dependent on METH;[478,479] but see.[480]

Anticonvulsant Drugs

Anticonvulsant drugs (ie, antiepileptics) decrease excitatory neurotransmission through several mechanisms: blocking sodium or calcium channels, blocking glutamatergic receptors, and/or stimulating GABAergic receptors.[481] One commonly prescribed anticonvulsant is gabapentin, which is also used as a nerve pain medication.[482] Gabapentin prevents membrane trafficking of the α2δ subunit of voltage-gated calcium channels as opposed to blocking these channels directly.[483] Gabapentin attenuates locomotor activity, locomotor sensitization, and CPP following METH administration.[245,434,484] However, this drug fails to reduce METH use in dependent individuals.[431] An early study reported that combination treatment of oral gabapentin and intravenous infusion of flumazenil, a GABA receptor antagonist, decreases drug cravings and METH use,[485] but a later study did not replicate this initial finding.[486]

Topiramate has multiple mechanisms of action, blocking voltage-gated sodium channels and glutamate AMPA receptors, potentiating GABA transmission, and modulating L-type calcium channels.[487] Topiramate has shown some

promise in treating individuals with cocaine dependence.[488,489] Specific to METH, topiramate decreases the desire to use METH,[490] and increases drug-free urine samples in METH-dependent individuals.[491,492; but see[490,493] Inconsistencies are reported concerning topiramate's effects on cognition. Topiramate increases concentration but impairs perceptual-motor in a digit symbol substitution test.[494] This finding is consistent with cognitive deficits observed in cocaine-dependent individuals receiving combination topiramate/methadone therapy.[495]

Gamma-vinyl GABA (vigabatrin) increases inhibition in the nervous system by inhibiting GABA transaminase, the enzyme that converts GABA into glutamate.[496] As vigabatrin decreases METH-induced increases in dopamine,[497] this drug has received some attention. Vigabatrin blocks reinstatement of METH CPP in rats.[498] Although vigabatrin does not alter subjective effects of METH,[499] it increases the rate of methamphetamine-negative urine samples in individuals that use stimulants, including METH.[500,501] These results are promising and indicate that increasing GABAergic transmission is a viable target for treating MUD.

Calcium Channel Blockers

As discussed above, some anticonvulsants work by blocking voltage-gated calcium channels or by preventing membrane trafficking of these channels (eg, gabapentin). Calcium channel blockers are also used to treat hypertension.[502] Acute METH administration inhibits L-type calcium channels, but chronic administration leads to an upregulation of such channels.[503] Relatedly, L-type calcium channels are upregulated in regions such as frontal cortex and limbic forebrain following CPP of various drugs, including METH,[504] with upregulation being dependent on activation of dopamine receptors.[245] Voltage-gated calcium channel blockers reduce METH-induced neuronal damage,[505] and they delay the onset of and reduce the severity of METH-induced stereotypies and self-injurious behavior.[506–508] Voltage-gated calcium channel blockers also decrease METH CPP and attenuate cue-induced reinstatement.[509–512]

In humans, isradipine decreases positive subjective effects of METH and decreases craving for METH;[513] however, isradipine's effects are dependent on when it is administered. Specifically, isradipine alters the subjective effects of METH when it is administered after placebo, but not when it is administered first.[514] Given the promising results obtained with animals, future studies examining other calcium channel blockers on the direct reinforcing effects of METH in dependent individuals are warranted.

Sigma Receptor Ligands

Sigma receptors were once proposed to be a type of opioid receptor, but are now known to be a type of chaperone protein located in the endoplasmic reticulum of cells.[515] One important mechanism of sigma receptors is regulating calcium homeostasis.[516] As calcium channel blockers show some efficacy in decreasing the reinforcing effects of METH (see above), some have investigated the role of sigma receptor ligands on METH-related behaviors. Sigma 1 receptor antagonists attenuate the locomotor stimulant, neurotoxic, and hyperthermic effects METH.[517–519] A similar effect is observed with the sigma receptor ligand CM156.[520] Low doses of sigma receptor agonists potentiate METH-induced hyperactivity, whereas higher doses blunt locomotor activity.[521,522] More recent work shows that the sigma 1 receptor ligand PD144418 and the sigma 2 receptor ligand YUN-252 dose dependently decrease METH-induced hyperactivity.[523] Work is needed to determine if sigma receptors regulate the direct reinforcing effects of METH.

Cannabinoid Receptor Ligands

The endocannabinoid system has two receptor subtypes: CB_1 and CB_2, which are both coupled to G_i proteins; the most well-known exogenous cannabinoids are delta-9-tetrahydrocannibinol (THC) and cannabidiol (CBD), found in cannabis plants.[524] Similar to psychedelic hallucinogens, there is increased interest in testing the efficacy of cannabinoids for multiple conditions, including fibromyalgia and chronic pain,[525,526] mental disorders,[527] and SUDs.[528]

While THC prevents METH-induced neurotoxicity,[529] pretreatment with THC significantly potentiates locomotor activity in mice and ataxia and stereotypies in rabbits.[530–532] THC attenuates drug-induced reinstatement but potentiates cue-induced reinstatement; however, when THC is administered repeatedly during extinction or 24 hours before the reinstatement test, reinstatement is blunted.[533] Similarly, a CB_1 positive allosteric modulator decreases reinstatement of METH seeking.[534] Like THC, the full CB_1 agonist WIN55, 212–2 prevents METH-induced neurotoxicity, but it also

blunts METH-induced hyperactivity.[535; but see536] One concerning finding is that a CB_1 agonist potentiates METH CPP.[537]

As CBD is non-intoxicating,[538] there is growing interest in studying its efficacy in multiple conditions.[539] CBD decreases METH-induced behavioral sensitization,[540] the reinforcing efficacy of METH and reinstatement of METH-seeking behavior,[541] and METH CPP.[542,543] Currently, there are no published clinical trials testing CBD in METH-dependent individuals. However, CBD does not appear to be an effective treatment for cocaine use disorder.[544,545]

Cannabinoid receptor antagonists decrease METH-induced behavioral sensitization, METH self-administration, and reinstatement of METH seeking.[533,534,546–548; but see549] Additionally, the CB_1 antagonist rimonabant administered after each conditioning session prevents acquisition of METH CPP, and rimonabant prevents the expression and the reinstatement of METH CPP.[550,551] Rimonabant also improves METH-induced deficits in novel object recognition memory.[552] Unfortunately, CB_1 antagonists like rimonabant are associated with increased suicidal ideation,[553] which greatly limits their therapeutic use.

Endocannabinoids are metabolized by fatty acid amide hydrolase and monoacylglycerol lipase.[554] The fatty acid amide hydrolase inhibitor URB597 blunts the anxiogenic and the depressive effects of METH withdrawal.[555] Preventing the hydrolysis of the endocannabinoid 2-arachidonoylglycerol (2-AG) inhibits cue- and stress-induced reinstatement of METH seeking, an effect not observed following administration of URB597.[556] As such, monoacylglycerol lipase inhibitors merit further examination as a treatment for MUD.

Angiotensin Receptor Antagonists and Angiotensin-Converting Enzyme (ACE) Inhibitors

Angiotensin is a hormone that primarily regulates blood pressure and promotes sodium retention in the kidneys; angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE).[557] Angiotensin receptor antagonists and ACE inhibitors, like some calcium channel blockers, are used to treat hypertension.[557] In the brain, there is evidence that the renin-angiotensin system influences dopamine release. Specifically, angiotensin II induces dopamine release while dopamine depletion leads to an upregulation of angiotensin receptors.[558] Therefore, there is recent interest in using angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors to blunt the effects of METH, and early reports are promising thus far. The angiotensin-converting enzyme inhibitor perindopril attenuates METH-induced hyperlocomotion in animals, with a similar effect observed following selective blockade of angiotensin II type 1 receptors.[559,560] Blocking angiotensin II receptors also reverses METH-induced increases in body temperature, rescues METH-induced deficits in memory and cognition, and decreases METH self-administration and reinstatement in rats.[560–562] Perindopril also decreases subjective effects of METH, but interestingly, these effects disappear at a higher dose of perindopril.[563,564] As argued previously, the inability of a higher dose of perindopril to alter subjective effects of METH may be due to inhibition of ACE in more brain regions compared to lower doses of perindopril.[564]

Oxytocin

Oxytocin is a hormone involved in various physiological processes (eg, milk let-down reflex) and maternal/social behaviors.[565] METH is known to affect oxytocin levels, as repeated METH administration increases blood plasma oxytocin levels,[566] and causes upregulation of oxytocin receptors in amygdala and hypothalamus, but not in nucleus accumbens or dorsal striatum.[567] However, compulsive METH seeking leads to upregulated oxytocin gene expression in nucleus accumbens.[568] Oxytocin inhibits METH-induced hyperactivity, METH self-administration, and reinstatement of METH seeking.[569] Adolescent treatment of oxytocin attenuates the reinforcing efficacy of METH and reduces drug-induced reinstatement of METH seeking during adulthood.[570] Repeated administration of oxytocin during extinction blunts reinstatement of METH CPP.[571] The ability of oxytocin to decrease the addictive-like properties of METH may be related to attenuated glutamate release in medial prefrontal cortex and potentiated glutamate release in hippocampus following co-administration of METH and oxytocin.[572] While oxytocin decreases reinstatement of METH seeking and incubation of craving in a self-administration paradigm,[275,573–576] decreased reinstatement of sucrose seeking is also observed.[564]

In a clinical setting, oxytocin increases group therapy attendance without significantly altering METH craving or METH use.[577] However, there is evidence of decreased craving and anxiety in METH-dependent individuals receiving 4 weeks of oxytocin treatment.[578]

Phosphodiesterase (PDE) Inhibitors

Phosphodiesterase (PDE) inhibitors are used to treat several health conditions, such as chronic obstructive pulmonary disease, pulmonary arterial hypertension, psoriasis, and erectile dysfunction.[579] PDE is an enzyme that degrades cyclic nucleotides, including cyclic adenosine monophosphate (cAMP), an important second messenger involved in intracellular signal transduction. Drugs are known to increase cAMP levels in brain regions associated with reinforcement,[580,581] but the degradation of cAMP by PDE is important mediator of the addiction process. Upregulation of cAMP is proposed to lead to tolerance to a drug's reinforcing effects whereas the breakdown of cAMP promotes increased drug seeking.[580] As such, PDE inhibitors may be an effective treatment for reducing the reinforcing effects of METH and recurrence of METH use.

In rodents, PDE inhibitors attenuate METH-induced hyperactivity, stereotypies, and cognitive deficits;[581–587] but see.[588] The non-selective PDE inhibitor ibudilast attenuates METH self-administration and drug- and stress-induced reinstatement of METH seeking,[589,590] and the PDE 4 inhibitor roflumilast reduces incubation of METH craving following forced abstinence.[591] While the PDE 4B inhibitor A33 decreases METH self-administration, it fails to block relapse-like behavior.[592] This result suggest that PDE 4A inhibitors may be more efficacious in preventing recurrence of substance use. So far, only ibudilast has been tested in dependent individuals. Ibudilast does not facilitate METH abstinence,[593] but it decreases peripheral markers of inflammation associated with METH use.[594] This latter finding may partially account for the cognitive improvements observed in animals following administration of PDE inhibitors. More work is needed to determine if selective PDE inhibitors are a viable treatment for ameliorating cognitive deficits associated with long-term METH use.

Discussion

Summary of Findings

As covered in the current review, numerous molecular targets have been examined as putative treatments for MUD. Multiple treatments that blunt dopaminergic/noradrenergic neurotransmission reduce hyperactivity stemming from METH use (eg, antagonists at dopamine, muscarinic, and sigma receptors; agonists at GABA receptors; calcium channel blockers). Numerous pharmacological manipulations reduce the rewarding/reinforcing effects of METH in animals, but have little efficacy in treating MUD (eg, modafinil, antipsychotic medications, baclofen). However, there is potential that these treatments, plus medications like atomoxetine and varenicline, can be used to ameliorate the psychotomimetic effects of METH and/or reverse METH-induced cognitive deficits. Promising pharmacotherapies that have been tested in animals only include VMAT-2 inhibitors, mGluR ligands, and trace amine-associated receptor agonists.

Future Directions

In addition to continuing research with promising pharmacotherapies described above, there are important considerations that need to be taken into account when screening potential treatments for SUDs. These future directions will be discussed first.

Preclinical Screening Considerations

One major limitation to many of the drug self-administration studies highlighted in this review is the use of a fixed ratio (FR) schedules to measure the reinforcing effects of METH. Dissociating a drug's locomotor effects from its reinforcing effects is difficult when FR schedules, as well as progressive ratio schedules, are used because animals may show increased responding for a drug like METH as they become more hyperactive. Similarly, if a potential pharmacotherapy decreases responding for METH, this effect becomes more difficult to interpret if the pharmacological manipulation suppresses METH-induced hyperactivity. This caveat may account for why some interventions decrease the reinforcing effects of METH in animals but fail to improve treatment outcomes in METH-dependent individuals (eg, gabapentin). To

avoid this limitation, schedules that control the rate of reinforcement, such as variable interval or second-order schedules, can be used.[470,595]

Another major weakness of preclinical models assessing METH-dependence-like behavior is the near exclusive use of male subjects as sex/gender are shown to modulate the effects of METH in an individual and modulate treatment responses for MUD.[596] For example, adolescent male, but not female, rats exposed to repeated nicotine treatments self-administer more METH,[344,346] and preadolescent exposure to nicotine enhances oral METH self-administration in female, but not male, adolescent rats.[597] Also, oxytocin is more effective at reducing the reinforcing efficacy of METH and cue-induced reinstatement in females relative to males.[573]

Given the increased prevalence of METH use in pregnant women,[598] increased work is needed to determine if pharmacotherapies are safe for these individuals and do not cause serious, long-term side effects in children. For example, mice prenatally exposed to modafinil display increased anxiety-like behavior and show greater METH-induced behavioral sensitization.[599] These results suggest that in utero exposure to modafinil may put individuals at risk for future addictive-like behaviors. In addition, nicotine treatment may be problematic for pregnant women as rats exposed to nicotine in utero respond more for METH in both fixed ratio and progressive ratio schedules.[600,601]

Pharmacogenetic Approaches

Pharmacogenetics incorporates one's genome when prescribing a medication. For example, some individuals prescribed amitriptyline may not respond well to treatment if they have specific alleles for cytochrome P450 enzymes.[602] Additionally, individuals that have a cytochrome P450-2D6 phenotype characterized by more efficient METH metabolism show increased METH-induced neurocognitive impairment;[603] conversely, individuals classified as low cytochrome P450-2D6 metabolizers are less likely to develop METH-related heart failure or to develop METH dependence.[604,605] Specific to treatments for psychostimulant use disorders, individuals with cocaine use disorder that have a single nucleotide polymorphism of the serotonin 5-HT_3 receptor show a greater percentage of cocaine-free urine samples during ondansetron treatment.[606] Additionally, individuals with genetically higher levels of DAT respond better to disulfiram (Antabuse) for cocaine dependence,[607] and individuals with genetically lower levels of the dopamine metabolizing enzyme dopamine beta-hydroxylase are less likely to use cocaine during levodopa treatment.[608]

Currently, the only study examining pharmacogenetic approaches to treating MUD found that a single nucleotide polymorphism of the mu opioid receptor (A118G) does not predict response to naltrexone.[609] A recent meta-analysis reported that two genes that are strongly related to MUD are those that encode fatty acid amide hydrolase and brain derived neurotrophic factor, a protein that is critical for neuron growth and plasticity.[610] Considering one's genetic makeup can allow for more tailored treatment options that can help an individual better manage cravings and enable them to maintain abstinence long term.

Conclusion

Currently, there is no single pharmacotherapy that prevents continuation of METH use or recurrence of METH use following abstinence. Given the numerous factors that influence the addiction process,[328] such medication may not exist, but there appears to be pharmacological options that can be utilized in conjunction with other therapeutic approaches, leading to positive outcomes for the individual (eg, oxytocin to increase group therapy attendance). With increasing MUD rates, continued research is necessary to find treatment options that can (a) reduce METH use, (b) ameliorate adverse events associated with METH use (eg, psychotomimetic-like effects, cognitive disturbances), and/or (c) reduce the likelihood of recurrence of METH use following therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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