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Pharmacotherapy for Methamphetamine Dependence: A Review of the Pathophysiology of Methamphetamine Addiction and the Theoretical Basis and Efficacy of Pharmacotherapeutic Interventions

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Background. *Methamphetamine (METH) dependence is a significant public health, criminal justice, and social service concern, and although abuse of this drug spans the past 40 years in the U.S., effective treatments have only recently been developed and evaluated. Psychosocial therapies comprise the mainstay of treatment, yet many patients experience ongoing impairments in mood, cognition, emotional control, and motivation, suggesting a role for pharmacotherapy.*
Methods. *A search of the literature was performed to identify drug therapies utilized with METH dependent patients and the outcome of these trials.*
Results. *With the exception of bupropion, most trials employing direct monoamine agonists yielded negative or inclusive results, a counterintuitive finding. Positive results were produced by a trial of the mixed monoamine agonist/antagonist mirtazapine and by several studies employing indirect dopamine- and glutamate-modulating GABA agonists. Most trials were hampered by high rates of subject attrition, mirroring the difficulty in treating these patients in the outpatient setting.*
Conclusions. *Although considered preliminary, several therapeutic agents were identified that may prove beneficial in treating METH-dependent patients, including bupropion, mirtazapine, baclofen, and topiramate. Psychosocial therapy remains the cornerstone of treatment, and drug therapy should be regarded as an adjunct, rather than a replacement for psychosocial approaches.*

Keywords Methamphetamine dependence, Treatment, Pathophysiology, Neurotoxicity, Abstinence syndrome, Pharmacotherapy

BACKGROUND

The current epidemic of methamphetamine (METH) abuse in the U.S. began in the mid to late 1980s on the West coast and has spread across the Western states to the Midwest, Southern states, and the East Coast. A considerable body of evidence indicates that METH abuse can lead to serious and persistent cognitive, psychiatric, and neurological dysfunction in the user, and can negatively affect the development of children exposed to METH *in utero* and the well-being of children raised by METH-addicted parents. The epidemic has profoundly impacted the social service and criminal justice budgets of rural counties and less populated Western and

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Midwestern states, further strained by the resources needed to contain and clean up the highly toxic METH by-products at production sites. Patients with METH as their primary drug of choice are now the predominant patient population in the public-funded treatment systems of many states, and the need for effective treatment for METH-dependent patients has never been greater (1).

PHARMACOLOGY OF METHAMPHETAMINE

Methamphetamine (*N*-methyl-*O*-phenylisopropylamine) is a cationic molecule with potent sympathetic and CNS action (1) that is an analog of amphetamine (alpha-methyl-phenethyl-amine) (2). Although both molecules are very similar, METH is more highly lipophilic, crosses the blood-brain barrier more readily, and is therefore more potent than its parent compound (3). Currently, d-methamphetamine, which has greater CNS potency than the l-isomer or the racemic mixture, is the predominant isomer encountered in the illicit market (4).

Following oral administration, peak methamphetamine concentrations are seen in 2.6–3.6 hours and the mean elimination half-life is 10.1 hours (range 6.4–15 hours). The amphetamine metabolite peaks at 12 hours. Following intravenous injection, the mean elimination half-life is slightly longer (12.2 hours). Methamphetamine is metabolized to the active metabolite amphetamine and the inactive metabolites p-OH-amphetamine and norephedrine (4, 5). Methamphetamine is oxidized and metabolized in the liver through enzymatic degradation primarily involving cytochrome P450-2D6. Approximately 10% of Caucasians are deficient of this enzyme, making them ultrasensitive to the effects of METH since they lack the ability to efficiently metabolize and excrete the drug (6).

MECHANISM OF ACTION

The profoundly addictive properties of METH are directly related to its reinforcing effects, mediated by the rapid and sustained increases in monoamine (primarily dopamine) neurotransmission immediately following its ingestion. Broadly speaking, the mechanism by which METH stimulates monoamine release is initiated by its rapid passage through the blood-brain barrier followed by influx into monoaminergic terminals, interaction with vesicular monoamine transporters, entry into monoamine vesicles, displacement of both vesicular and intracellular monoamines into terminal cytoplasm, and culminating with monoamine release into the synaptic cleft (1, 7). Unlike cocaine and methylphenidate, which act through blockade of plasma membrane transporters that reuptake monoamines (8), specific METH-induced action includes redistributing catecholamines from synaptic vesicles to the cytosol, reversing the transport of neurotransmitters via plasma membrane transporters, blocking monoamine transporter activity, decreasing dopamine transporter expression on the cell surface, inhibiting monoamine oxidase, and stimulating tyrosine hydroxylase activity (2, 9).

PATHOPHYSIOLOGY OF METHAMPHETAMINE DEPENDENCE

Drug dependence, including methamphetamine dependence, is a chronic relapsing disorder characterized by neurobiological changes that lead to compulsive drug use, loss of control over intake, and impairment in social and occupational function (10). Evidence suggests that the acute reinforcing actions of drugs of abuse, including methamphetamine, are mediated by key elements of a basal forebrain macrostructure termed the extended amygdala and its connections (11), which contain parts of the nucleus accumbens and amgydala and involves key neurotransmitters such as dopamine, opioid peptides, 5-HT, gamma-aminobutyric acid (GABA), and glutamate (12).

Neuropharmacologic studies indicate that addictive behavior is driven by the negative motivational state stemming from dysregulated neurochemical mechanisms in specific brain reward circuits (opioid peptides, GABA, glutamate, and dopamine) and brain stress systems (corticotropin-releasing factor: CRF) that reside in the extended amygdala (11). Neurochemical elements mediating these neurobiological changes include decreased dopamine and serotonin neurotransmission in the nucleus accumbens and increased neurotransmission of CRF in the central nucleus of the amygdala (13).

Methamphetamine withdrawal is characterized by subjective symptoms of negative affect and dysregulated brain reward systems that involve many of the same neurochemical systems mediating the acute reinforcing effects of methamphetamine. The functional toxicity of acute withdrawal is also accompanied by recruitment of CRF. During post-acute withdrawal, which manifests during extended abstinence, continued dysregulation of the neural systems associated with drug reinforcement and stress represent a more subtle but persistent functional neurotoxic effect of chronic methamphetamine use and can be responsible for long-lasting vulnerability to relapse (14).

The development of addiction and vulnerability to relapse following withdrawal is proposed to be the result of neuroadaptive processes within the CNS that oppose the acute reinforcing actions of METH. These changes lead to impairment in the mechanisms that mediate positive reinforcement and the emergence of affective changes such as anxiety, dysphoria, and depression during withdrawal (15). It is this combination of decreases in function of neurotransmitters involved in the positive-reinforcing properties of drugs of abuse with recruitment of brain-stress systems within the extended amygdala that provide a powerful mechanism for allostatic changes in hedonic set point that can lead to the compulsive drug-seeking and drug-taking behavior characteristic of METH addiction (13).

SYMPTOMATOLOGY OF METHAMPHETAMINE DEPENDENCE

Signs and Symptoms of Acute Ingestion

The acute effects of METH are the result of a surge in newly synthesized catecholamines and serotonin, experienced as excitation and well-being, with increased alertness, highly focused attention, motivation, confidence, mood, energy, and decreased appetite (6). In METH-naïve subjects, acute doses can improve cognitive processing, including reduced reaction times during sleep-deprivation states (3). Dysphoric aspects of the hyper-excitation state may consist of anxiety, restlessness and insomnia. Other acute effects can include grandiosity, sexual arousal, paranoia, psychosis, hallucinations including delusions of parasitosis (a belief they are infested with parasites), depression, unprovoked aggressive/violent behavior, and irritability. Physiological signs corresponding to acute effects of the drug include increased heart rate, elevated body temperature, insomnia, increased blood pressure, increased respiration rate, and possibly profuse sweating, tremors, and neurological symptoms such as headaches and vision loss. Persons under the influence of acute ingestion of METH can appear excessively talkative, excited, agitated, aggressive, restless, and may be observed performing repetitive meaningless tasks (5, 16, 17).

Signs and Symptoms of Extended Use

Within days of steady use, biochemical alterations in the brain characteristics of the user begin to manifest, which include reduced dopamine transporter function and increased chemical markers indicative of dopaminergic nerve terminal degeneration (18). This state of catecholamine and serotonin depletion may manifest as profound exhaustion, depression, lethargy, and anhedonia. Psychological symptoms can include persistent anxiety, paranoia, insomnia, auditory hallucinations, delusions, psychotic or violent behavior, and homicidal or suicidal thinking. Behavioral signs may include unprovoked violent behavior, poor coping abilities, disorganized lifestyle, unemployment, and relationship estrangement. Physiological signs of chronic use include high blood pressure, pronounced fatigue, malnutrition, neglected hygiene, hair loss, involuntary movement disorders, sexual dysfunction, weight loss (possibly substantial), nosebleed from intranasal ingestion, and dental problems (16, 17, 18, 19).

COMPLICATIONS OF CHRONIC METHAMPHETAMINE USE

The effects of chronic METH abuse can include a variety of neurocognitive symptoms, as well as the development of psychiatric and behavioral comorbidity such as psychoses, protracted withdrawal syndrome, and aggressive and violent behavior. The cognitive, behavioral, and psychological dysfunction associated with chronic METH abuse is directly related to the neurotoxic effects of METH.

Neurotoxicity

Prolonged use of METH is associated with changes to the brain and CNS through several general mechanisms: depletion of pre-synaptic monoamine reserves; down-regulation of neurotransmitter transporters and receptors; neurotoxicity through reactive metabolic by-products of dopamine and serotonin; and excitotoxicity from the substantial and prolonged release of the excitatory neurotransmitter glutamate triggered by acute ingestion. Neurotoxicity can occur from as little as several days of METH exposure and may persist for months and even years (1, 18). Even a sub-neurotoxic reduction of dopamine activity can produce the lingering motivational difficulties often encountered by patients in early to intermediate recovery (1).

In a simplified model of neurotoxicity from chronic use, repeated administration of METH stimulates release of the excitotoxic glutamate, which then stimulates dopamine release, leading to increased Ca^{2+} efflux and enhanced reactive oxygen and nitrogen species generation, resulting in apoptotic cascades mediated by apoptosis inducing factor, cytochrome C and caspase 9, culminating in neuron damage and destruction (1). The neurotoxic effects occur preferentially in the destruction of dopamine synaptic terminals rather than total cell loss (3).

In addition to the neurotoxic effects on dopamine (DA) neurons, repeated exposure to moderate- to high-dose METH can lead to substantial reductions in markers of serotonin (5HHT) axon terminals, likely the result of reductions in 5-HT concentration and 5-hydroxylindoleacetic acid (5-HIAA), decreased 5-HT transporter binding sites, and reductions in tryptophan hydroxylase activity, the rate-limiting enzyme in 5HHT synthesis (3, 7). Although METH exhibits a greater capacity to stimulate the release of norepinephrine than DA or 5-HT (20), little is known about METH-induced damage to these pathways (9).

Psychiatric Complications

Long-term use and cessation of METH use are associated with potentially serious psychiatric morbidity. Psychotic symptoms are associated with both METH use and METH withdrawal. Most METH users develop auditory hallucinations, persecutory delusions, and delusions of reference within one week of continuous use; continued use results in further loss of insight, increased psychoses, and possible violent behavior (21). The delusions, hallucinations, bizarre symptoms, negative symptoms, and anergia that comprise METH-induced psychoses make it indistinguishable from schizophrenia, and stress can precipitate spontaneous psychosis in formerly psychotic

methamphetamine abusers who are abstinent (22). A diagnosis of major depression, alcohol dependence, and antisocial personality disorder, and earlier and heavier use of METH, are associated with the development of psychoses (21) and neurological morbidity such as traumatic brain injury, birth trauma, learning disabilities, and soft neurological signs are associated with treatment-resistant METH-induced psychoses (3).

The acute effects of METH can include irritability, agitation, hypervigilance, and possibly violent outbursts, and chronic use of METH has a greater association with violent behavior than any other psychoactive drug. Alteration in brain monoamine levels is implicated as the causal factor. Violence is also associated with METH-induced psychoses, where the user can become delirious, confused, disoriented, anxious and fearful, delusional and paranoid (23). Violence can stem from domestic, drug-related, and gang-related assault, as well as random violence from road rage or stranger assault. However, violent behavior is not an inevitable outcome of even heavy long-term METH use (24). Among paroled inmates, METH use is associated with violent crime and recidivism, even after controlling for demographic variables, indicating the need for greater treatment engagement and parole supervision among parolees with a history of METH dependence (25).

Withdrawal from METH is characterized more by psychiatric symptoms than physical symptoms (3), and consists of hyperarousal, vegetative symptoms, anxiety-related symptoms, and severe dysphoria, mood volatility, irritability, and sleep pattern disruption (26, 27) that may persist for over 12 months (3). The intense and durable anhedonia, irritability, and poor concentration is better characterized as an apathy syndrome rather than a depression-mediated syndrome, and parallels the neuropsychiatric disorders associated with dysregulated brain dopamine systems such as Parkinson's disease, Huntington's disease, and progressive supranuclear palsy. The treatment implications are compelling, since pharmacotherapy for apathy syndromes involves dopaminergic agents that are generally distinct from antidepressant agents (28).

Neurocognitive Complications

The biochemical and structural changes induced by chronic METH use can lead to significant functional impairment in cognitive processes that can persist well into continuous abstinence from meth. During the first several weeks of abstinence, functional and structural changes to key brain regions associated with attention deficits (29), impaired visual pattern recognition, and decision-making speed and accuracy (30) have been observed. Abnormalities consistent with frontal lobe vascular damage related to the amount and duration of METH use have been noted, and may underlie the dysfunction in craving and compulsive behavior seen in METH addicts (31). Substantial impairment in attention/psychomotor speed, verbal learning and memory, and fluency-based measures of executive systems functioning have also been reported (32), and metabolic brain abnormalities in the limbic and paralimbic regions observed in METH addicts may underlie the affective dysregulation often experienced in early abstinence (33).

Deteriorating cognitive performance during the first three months of abstinence has been observed, with one study finding abstinent and abstinent patients with a recent lapse scoring worse on neuropsychological testing than patients with ongoing METH use, reflecting the difficulties in attention, understanding, and memory often encountered by METH addicts in treatment settings (34).

Functional and structural deficits associated with METH use have been observed 6–12 months into continuous abstinence and are characterized by a syndrome resembling subclinical Parkinson's disease, consisting of significant impairment in reaction time, working memory, and mental concentration; the similarity is relevant since both conditions are characterized by substantial dopamine transporter loss (35).

Neuronal damage associated with metabolic abnormalities in frontal lobe regions has been found, possibly explaining the persistence of violence, paranoia, and personality changes well into intermediate-term abstinence (36). Ongoing dysfunction in executive control of verbal encoding and retrieval consistent with neurological damage to the prefrontal cortex was observed by Woods et al. (37). Significant correlations between aggression severity, extent of serotonin transporter density reduction, and duration of METH use have been observed well into abstinence (38), consistent with other studies linking decreased serotonin function with increased aggression and violence (39–42).

The persistence of dopamine transporter density reduction beyond one year of abstinence has been highly correlated with severity of METH use and residual psychiatric symptoms (paranoia, anxiety, irritability and depressed mood, auditory hallucinations and disordered thinking) but not with duration of abstinence (43). Degraded dopamine transporter activity has also been correlated with deficits in motor and memory performance, with duration of METH use strongly correlated with the degree of transporter reduction. No significant improvement beyond one year of abstinence was found (44). Reduced decision-making speed and impaired decision-making strategies are also associated with long-term changes in dopamine transporter density and duration of METH abuse (45). Together, these studies suggest that persisting dopamine transporter depletion underlies the pathophysiology of the ongoing psychiatric and neuropsychological disturbances in METH users well into abstinence (43).

Several studies, however, have documented improved functioning with abstinence from METH, and include observations of partial anterior cingulate cortex normalization (46), significant increases in striatum and putamen dopamine transporter density (44), and improved metabolic activity in the thalamus that was correlated with improved motor skill and verbal memory (47).

It should be noted that the absence of prospective longitudinal studies complicates the causal inference between duration and

amount of METH use, severity of neurocognitive and psychiatric dysfunction, and reduced dopamine and serotonin transporter density. In the absence of such data, it remains unknown if users selectively chose METH to counteract baseline anergia, depression, or impaired cognition, if a vulnerability to psychoses predates the METH use or if these symptoms and neuronal changes arise from METH use itself. Nevertheless, the number of studies, their design rigor, and the striking correlation between what is known about METH-induced neuronal damage and the functional and structural changes seen in METH abusers underscore the strength of the association between chronic METH use and persistent changes to the brain.

Medical Complications

The acute and chronic effects of METH can severely impact the cardiovascular system. The excessive level of monoamine-induced excitation elevates the heart rate and blood pressure, and can lead to palpitations, arrhythmias, cardiomyopathy, valvular disease, angina, myocardial infarctions, and cerebral vascular events. The chronic CNS hyperstimulation can lead to frequent headaches, hyperthermia, tremors, athetoid movements, and seizures. Smoking METH can cause respiratory symptoms and disorders such as pulmonary edema, bronchitis, pulmonary hypertension, hemoptysis, and granuloma. Extreme malnourishment and resultant decreased resistance to disease can stem from the powerful anorexic effects of METH (17, 48, 49).

"Meth mouth" is widespread among certain populations of METH users, particularly those incarcerated for METH-related offenses (17). "Meth Mouth" (dental deterioration) is a constellation of symptoms associated with chronic use of METH and is caused by METH-induced vasoconstriction and reduced salivary flow, METH-induced vomiting, frequent ingestion of sugary beverages, teeth-grinding, abandonment of oral hygiene, and accumulated chemical residue from smoking METH. This condition is characterized by widespread tooth decay and tooth loss, advanced tooth wear and fracture, and oral soft tissue inflammation and breakdown (17).

Other METH-related effects include muscle cramping from dehydration and depleted electrolytes; dermatitis around the mouth from smoking METH; dermatological conditions such as excoriated skin lesions; constipation from dehydration and lack of dietary fiber; nausea, headache, dizziness, and renal damage from the toxic fumes of METH production; burn injuries from lab accidents and explosions during production; and chemical burns from contact with precursors or by-products of production (17, 49). Fatalities associated with METH use stem from homicide, suicide, motor vehicle accidents, manufacturing, distribution and sales of the drug, and the direct toxic effects of the drug (19). Biologically based causes of METH-induced mortality include stroke and cerebral hemorrhage, cardiovascular collapse, pulmonary edema, myocardial infarction, hyperprexia, and renal failure (3, 16).

RATIONALE OF PHARMACOTHERAPY FOR METHAMPHETAMINE DEPENDENCE

Chronic METH abuse results in cognitive and psychological impairment stemming from the effects of METH on multiple interacting brain transmitter systems in the cortex, with collective degradation of function in dopamine and serotonin pathways resulting in deficits in attention, impulse control, and task performance (18). Treatment of METH dependence, typified by the Matrix Model, combines cognitive, behavioral, and psychological approaches, and is delivered to the patient immediately following acute withdrawal. Enhancing motivation for abstinence, improving strategies for avoiding use, and relapse prevention emphasized in this approach require the patient's attendance, comprehension, and effective memory storage and recall (50). METH users who are cognitively impaired or who have ongoing difficulties with paranoia, psychoses, or emotional lability will not be able to benefit from such treatment programming (34), and addiction researchers have begun to evaluate therapeutic agents that exhibit theoretical or preclinical evidence of efficacy in alleviating the negative impact of METH use on mood, reality testing, neuropsychological functioning, motivation and drive, and drug craving.

Effective pharmacotherapy has the potential to substantially improve patient comprehension and engagement in treatment, as well as improving treatment retention and reducing relapse to METH use (3). The following is a review of the body of research employing drug therapies in the treatment of primary METH dependence, as well as conditions of clinical significance such as psychoses and depression that are secondary to the underlying addictive disorder. It is hoped that psychiatrists and primary care physicians will gain a practical understanding of the currently available drug options and the empirical basis supporting (or refuting) their use.

SPECIFIC PHARMACOTHERAPIES

Monoamine Agonists

Serotonergic Agonists

Sertraline. The observation that laboratory animals with neurotoxin or lesion-induced 5-HT signaling inhibition increased their self-administration of amphetamines (51), coupled with the observation that many METH withdrawal symptoms (fatigue, anhedonia, depressed mood, and hypersomnia) simulate a major depressive episode provided the rationale for the use of the selective serotonin reuptake inhibitor (SSRI) sertraline in METH patients. Shoptaw et al. (52) conducted a placebo-controlled trial where 229 METH-dependent outpatients were randomized to one of four conditions for 12 weeks: the SSRI sertraline (initially 50 mg/day, then 50 mg b.i.d. on study day 8) plus contingency management (CM), placebo

plus CM, sertraline only, and placebo only. Subjective measures included the Structured Clinical Inventory for the DSM-IV, the Beck Depression Inventory, and a visual analog scale to measure craving. Subjects receiving sertraline exhibited significantly worse outcomes than patients receiving CM or placebo on many measures, including number of METH-positive urine samples ($p < 0.05$), number of patients achieving three consecutive weeks of METH abstinence ($p < 0.035$), and outpatient group attendance ($p = 0.014$). Despite a very high percentage of medication protocol adherence (>80%), subjects receiving sertraline did not show improvement in depressive symptoms or cravings compared with non-sertraline-treated subjects.

Paroxetine. Another trial utilizing an SSRI (paroxetine) to treat METH dependence was reported by Piasecki et al. (53). Twenty subjects (6/20 male, mean age 34.2 years) were randomized to either placebo or paroxetine 20 mg/day for 8 weeks. Primary measures were cravings form METH, as measured by the modified Obsessive-Compulsive Drinking Scale (OCDS), and use of METH as measured by weekly urine screening. Attrition was substantial, with only 15% (3/20) completing the study protocol. Mean number of study days was 23 for placebo patients and 30 for active drug patients (ns). Of the 9 subjects who participated 5 or more weeks, 5/5 receiving placebo tested positive for MA, and 3/4 receiving paroxetine tested positive for MA, with only one subject remaining abstinent from METH during the 8-week study period. Mean changes in OCDS among these 9 subjects were not analyzed. The authors state that the weight gain, sexual side effects, and sedation often induced by paroxetine and other SSRIs are the opposite of the desired effects of METH that are sought after by users, possibly heightening difficulties with patient acceptance and compliance with this class of medications.

Fluoxetine. The feasibility and efficacy of fluoxetine treatment of METH dependence was evaluated by Batki et al. (54, 55). Sixty METH-dependent subjects (70% male, mean age 35, 50% gay/bisexual, 13.5% HIV+) were enrolled in an 8-week trial with a 1-week single-blind placebo lead-in followed by 7 weeks of double-blind randomization to either fluoxetine 40 mg/day or placebo. Craving was less in the active treatment group, with METH use declining in both groups, and no significant differences emerged between the two groups on measures of self-reported or urine toxicology screen detection of METH use (55).

Imipramine. The efficacy of the serotonergic/noradrenergic tricyclic antidepressant imipramine in improving treatment retention and drug use-related outcomes was tested in a randomized controlled trial of 32 METH-dependent outpatients (56). Participants received either 10 mg/day (inert) or 150 mg/day imipramine for 180 days, as well as counseling and medical and psychiatric care. Although patients receiving the 150-mg dose remained in treatment longer, there were no between-groups differences in craving, depression, percentage of METH-positive urine, days since last METH use, and study visit attendance.

Dopaminergic Agonists

Bupropion. Chronic METH use can result in neuroadaptation in presynaptic dopamine neurons, manifesting as dysphoria, depression, drug craving, and cognitive impairment in early abstinence, and suggesting the utility of the dopamine and norepinephrine reuptake blocker bupropion. Based on the theoretical mechanism of action of bupropion, as well as its demonstrated efficacy in an initial case report (57) of substantial reduction in craving over a 3-week period of treatment with 150 mg and then 150 mg b.i.d., the medication was further examined in a controlled fashion. In a randomized single-blind placebo-controlled trial, 26 non-treatment seeking subjects meeting the criteria for METH abuse or dependence received either 0 mg 2 × /day or 150 mg 2 × /day bupropion extended-release for 6 days, and were administered either 0 mg or 15 mg METH followed by 30 mg METH, both administered intravenously (58). Subjects were asked to assign a monetary value to each drug effect indicating what they would be willing to pay on the street. Compared with placebo, bupropion treatment was associated with reduced ratings of "drug effect" ($p < 0.02$), "high" ($p < 0.02$), and "desire to use" ($p < 0.05$), as well as reduced cue-elicited cravings ($p < 0.002$). Although the sample was small and the results need replication, these findings suggest that bupropion may play a role in reducing craving for METH in early abstinence and may diminish relapse severity by limiting the reinforcing effects of METH. However, other researchers have noted that the generalizability of these results to the outpatient setting may be limited, and the dose of METH used in this trial was modest, thereby casting doubt on any conclusions regarding efficacy (9).

Methylphenidate. An approach consistent with the harm reduction model has been proposed by Shearer et al. (16) and involves prescribing dextroamphetamine to patients addicted to METH. The basis of this treatment is the success seen with agonist replacement therapy such as methadone treatment of heroin and other opiate addiction and nicotine replacement therapy for smoking cessation. However, ideological and regulatory obstacles exist in the U.S. to the implementation of such a treatment regimen.

Preliminary data ($N = 4$) from an investigation utilizing methylphenidate to treat withdrawal symptoms in non-ADHD, non-METH-using long-term prescription amphetamine abusers appears promising (59). Specifically, severe and protracted depression following amphetamine cessation was resolved with ongoing methylphenidate treatment at long-term (2–4 year) follow-up assessment.

Mixed Monoamine Agonist/Antagonist

Mirtazepine. Through the exertion of presynaptic alpha2-adrenergic antagonist, serotonin 5-HT-1 agonist, serotonin 5-HT2 and 5-HT-3 antagonist, and histamine H1 antagonist properties, mirtazapine facilitates the co-release of norepinephrine and dopamine from noradrenergic terminals in the cerebral

cortex through alpha-2-adrenoceptor inhibition, providing the theoretical basis for its use in the treatment of METH detoxification and withdrawal. A randomized placebo-controlled trial of mirtazapine was performed to assess its impact on amphetamine withdrawal (60). Twenty amphetamine-dependent subjects detained in a short-term correctional facility received either the study drug (15–60 mg/day) or placebo for 14 days and were evaluated on days 3 and 14. Active treatment subjects exhibited significantly lower scores on the Hyperarousal subscale, Anxiety subscale, and total score of the Amphetamine Withdrawal Questionnaire compared with subjects receiving placebo, with no significant between-groups differences measured by the Montgomery-Asberg Depression Rating Scale. The authors speculate the result may indicate a specificity for amphetamine withdrawal symptom reduction with mirtazapine that cannot be attributed to amelioration of depressive symptoms.

Monoamine Antagonists

Dopamine Antagonists

Haloperidol and Risperidone. Mesolimbic dopamine pathways are believed to play a large role in the reinforcing properties of stimulant drugs, including METH, and serotonin (5-HT) may also contribute to the subjective effects of amphetamines. Based on the observation that dopamine-blocking agents attenuate the reinforcing properties of stimulant drugs in laboratory animals, the dopamine D2 blocker haloperidol (3 mg) and the D2 and 5-HT2 receptor antagonist risperidone (0.75 mg) were given to 17 and 18 non-addicted normal human subjects, respectively, in a placebo-controlled trial to examine their possible efficacy in blocking the rewarding effects of METH (20 mg) (61). Both drugs failed to block the euphoric effects of METH, suggesting that the pleasurable and rewarding properties of METH are not mediated through dopamine D2 or 5-HT2 activation.

Quetiapine. A similar theoretical basis that drugs of abuse share a final common pathway of mesocorticolimbic dopamine circuit activation led to a study of the atypical neuroleptic D2 antagonist quetiapine in the treatment of a mixed inpatient population (62). In this retrospective chart review of nine patients who received quetiapine (50 mg–300 mg/day) for nonpsychotic anxiety, all were diagnosed with alcohol dependence and 2/9 with METH dependence. Although the authors state that HAM-D scores and self-reported craving severity significantly decreased in study drug responders over the course of treatment, the very small sample size, lack of subject blinding, retrospective nature of the study design, and sample heterogeneity with regard to diagnosis preclude any conclusions being drawn from this study.

Despite the potential for METH to produce symptoms consistent with paranoia and psychoses that persist following cessation of use, there is very little data and no controlled trials on the management of post-METH psychoses.

GABA Receptor Agonists

Baclofen and Gabapentin. Gamma-amino butyric acid (GABA) neurons decrease dopamine transmission in the nucleus accumbens and ventral tegmental mesolimbic regions in preclinical models, possibly decreasing the reinforcing effects of psychostimulants and providing the theoretical basis for trials of GABA agonists with METH-abusing patients. Baclofen and gabapentin increase GABA transmission through selective activation of $GABA_B$ receptors and inhibition of GABA transaminase, respectively, and Heinzerling et al. (63) reported the results of baclofen (20 mg 3×/day) and gabapentin (800 mg 3 × /day) in a double-blind, randomized placebo-controlled trial of 16 weeks duration. A total of 88 METH-dependent outpatients were randomized to either baclofen, gabapentin, or placebo, and all subjects attended clinic three times a week for assessment, counseling, and urine drug testing. Protocol completion rates among the treatment groups were baclofen 60%, gabapentin 34.6%, and placebo 40.5%. There were no statistically significant between-groups differences at completion of the 16-week trial,with no reduction in depressive symptoms, craving for METH, or reduction in METH-positive urine samples. However, when patients with high protocol adherence were compared, baclofen recipients exhibited greater numbers of METH-negative urine samples relative to gabapentin and placebo subjects, suggesting a small but positive effect of baclofen in reducing METH use. Greater attendance of psychosocial therapy groups was also associated with decreased METH use across all three groups, underscoring the importance of psychosocial therapy augmentation of pharmacotherapy for METH dependence.

Gamma-Vinyl GABA. The safety and efficacy of another GABA agonist, the GABA-transaminase inhibitor gamma-vinyl GABA (GVG) was evaluated in a 9-week open-label pilot study involving 10 METH-dependent, 17 METH- and cocaine-dependent, and 3 cocaine-dependent subjects (64). Eighteen patients continued participation beyond the initial dose-escalation phase (500 mg b.i.d. initial dose, buildup to 3000 mg/day on day 15 for the next 28 days, then tapered off over next 21 days) and were the subject of the evaluation. All patients were encouraged to attend weekly group therapy sessions. Primary measures included substance use assessment by twice-weekly urine drug screen. Since GVG has not received FDA clearance in the U.S. due to documentation of concentric visual field defects associated with its use, the study was carried out in Mexico. A total of 18/30 subjects completed the trial; 16/18 subjects tested negative for METH and cocaine during the last 6 weeks, with a median of 42 days drug free for this group during the 63-day study period. Although unblended and lacking a control group, these results are promising, especially in light of the absence of effective pharmacotherapy for METH addiction. However, these results need to be replicated in randomized placebo-controlled trials before any conclusions regarding efficacy can be drawn. A separately published paper on the safety outcomes (65) stated that the 18 subjects who completed

the protocol received examinations by two glaucoma specialists, who failed to detect changes in visual field, abnormalities in visual acuity, or ocular adverse effects.

Topiramate. The reinforcing effect of METH involves activation of mesocorticolimbic dopamine projections, and topiramate, a sulphamate-substituted fructopyranose derivative, inhibits dopamine action in this circuitry, possibly indicating efficacy in the treatment of METH dependence. The putative therapeutic benefit of topiramate in METH dependence is also believed to stem from its inhibition of kainate and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid-type glutamate pathways (66). Johnson et al. (67) tested this hypothesis with a randomized, placebo-controlled cross-over factorial-designed pilot study employing 10 METH-dependent patients. Subjects received low- or high-dose (15 or 30 mg IV) methamphetamine and low- or high-dose (100 or 200 mg oral) topiramate, and parameters of drug reinforcement such as stimulation, euphoria, craving, and reinforcement were subjectively measured. Topiramate alone showed a trend towards reductions in positive mood and reinforcement, but when combined with METH actually resulted in enhancement in the positive METH effects of stimulation and euphoria but not craving or reinforcement, indicating that acute dosing with up to 200 mg topiramate accentuates rather than attenuates some of the positive subjective effects of methamphetamine. This interactive effect was not due to increased plasma methamphetamine levels (68).

Many patients presenting for treatment of METH dependence experience significant and ongoing cognitive dysfunction. The enhancement of cognitive performance is a frequent reason for using METH, and patients may be reluctant to take a medication that is perceived as worsening cognitive functioning that may already be tenuous. Johnson et al. (68) examined the effects of topiramate on attention span and concentration in a sample of 10 METH-dependent inpatients. Subjects were pretreated with 0 mg, 100 mg, or 200 mg oral topiramate given in divided doses the evening before and the morning of cognitive testing, and then received 0 mg, 15 mg, or 30 mg IV METH. There was no evidence of worsening cognitive function with topiramate; the overall effect was varied and unexpected, with a tendency to improve attention and concentration when given alone and with METH, with a worsening of psychomotor performance. The authors conclude the effects of topiramate on cognitive performance do not present an obstacle in patient adherence and compliance, and may improve cognitive functioning on some dimensions.

DISCUSSION

Until very recently, pharmacotherapy for METH dependence mirrored the general approach used to identify and evaluate effective drug therapies first for opiate dependence, then with cocaine dependence, where the focus was on testing agonist agents with a similar pharmacological profile used to alleviate symptoms emergent during cessation of use and withdrawal, and antagonist agents used to block the desired or reinforcing effects (69). Advances in the understanding of brain reward circuitry, especially as it applies to drugs with a high liability of abuse and dependence, have broadened the focus on potential therapeutic agents to include drugs with indirect modulatory properties, and the results of this review seem to indicate that GABA agonists with indirect dopaminergic modulation are a particularly promising class of agents. Contrary to predictions from theoretical and preclinical evidence, results from studies utilizing direct agonists to counter monoamine depletion and adaptive down-regulation have yielded negative or inconclusive results, with little effect in aggregate on treatment utilization and drug-use parameters. The exception was bupropion, which may have a useful role in craving reduction.

Perhaps more so than abusers of most other substances, patients who become addicted to METH are in need of inpatient or at least residential outpatient treatment due to the immediate need for adequate sleep and nutrition, and the high likelihood of ongoing and protracted difficulties with drug craving, the ubiquity of environmental triggers, neurocognitive impairment, and the overwhelming desire for relief from the continuous dysphoria and anhedonia. Unfortunately, such patients are also among the least likely to have access to the resources necessary for such cost-intensive healthcare services. Accurate appraisal of the efficacy of many of the drugs evaluated in this review was hampered by the very high rate of subject attrition, which reflects a major problem encountered by treatment professionals in the engagement and retention of these patients in the outpatient setting.

Our understanding of efficacious and well-tolerated pharmacotherapies for METH dependence lags significantly behind those for other substance use disorders. Emerging data, however, suggest that METH users frequently respond to both pharmacological and psychosocial interventions. Although both pharmacological and psychosocial treatment interventions have shown early promise for METH dependence, no comparative studies have been performed. Should an individual with METH dependence start with medication or therapy or both? Also, are there differences in individuals with METH dependence that may indicate a preferential response to a particular intervention? Research addressing these issues is lacking. Due to the limitations of current research, it is still unclear which treatment approach may be most beneficial for a particular individual with METH dependence.

An assessment of clinical presentation and comorbidity, however, may provide useful clues to treatment interventions. Is the patient experiencing severe depression after METH use that may lead to relapse? If so, bupropion may be an appropriate medication option. If the person is having intense cravings to use METH, then topiramate, bupropion, or baclofen may be beneficial. Does the person have attentional problems that predate METH use and make METH particularly attractive? Then bupropion may be a reasonable choice.

Of the agents that showed the most promise, positive outcome was often associated with attendance of clinic appointments and psychosocial therapy, underscoring two points: that positive drug effect may be partially related to a dose-dependent synergistic psychosocial therapy effect, and that psychosocial therapy remains a crucial component of treatment for METH dependence. Psychosocial therapy can be directed at improving and optimizing patient compliance with pharmacotherapy, whether in the context of a trial or outpatient treatment, and the Matrix Model has been effectively used as a psychosocial platform for medication trials for METH dependence (52).

Although methamphetamine (METH) has been a drug of abuse for over 60 years, .effective treatment approaches have only recently emerged and are in the early stages of development and evaluation. Most have been borrowed from approaches effective in treating cocaine dependence and include cognitive-behavioral therapy (CBT), contingency management (CM), and the Matrix Model. Despite the substantial association of METH use with profound and lasting changes in mood, reality testing, cognition, and motivation and drive, effective pharmacotherapies are lacking, and psychosocial therapies emphasizing the application of operant and cognitive-behavioral techniques predominates the treatment domain (52).

Effective treatment of patients with METH dependence pose many challenges; for instance, poor treatment engagement and high treatment dropout rates, severe or ongoing paranoia or psychotic symptoms, high relapse rates, intense protracted cravings, and dysphoria and anhedonia are among the commonly cited obstacles to success in this population (70). Current government-funded pharmacotherapy efficacy studies underway for the treatment of METH dependence include N-acetyl cysteine plus naltrexone, long-acting injectable risperidone, buproprion combined with behavioral therapy, as well as topiramate, rivastigmine, perindopril, mirtazapine, aripiprazole, and reserpine. Particular interest has been generated in the possible efficacy of modafinil in the treatment of METH withdrawal, and a National Institute on Drug Abuse (NIDA)-sponsored trial employing this agent is currently being conducted at UCLA (71).

Determining the most effective treatment components for METH addiction is complicated by the special needs of METH-using subgroups. Each special population has unique needs that should be addressed to optimize therapeutic outcome (72), and this is illustrated by the culturally sensitive approach tailored for gay and bisexual men (GBM), termed gay cognitive-behavioral therapy (GCBT) (73).

In conclusion, there are no FDA-approved medications for the treatment of METH dependence, and although the body of evidence from studies with rigorous experimental design is preliminary, bupropion and mirtazapine appear useful in managing some of the symptoms associated with METH abstinence syndrome, with several GABA agonist agents, including topiramate and baclofen, showing promise in improving treatment engagement and drug use outcomes. Psychosocial therapy remains the backbone of treatment for these patients. Recently published studies have found that contingency management is associated with rapid reduction in METH use (73), significantly greater treatment retention, increased outpatient attendance, more frequent alcohol and drug-free urine tests, and longer periods of abstinence (74, 75); that the Matrix Model is associated with decreased substance use, increased treatment retention, and improved psychosocial functioning (70, 76); and that cognitive behavioral therapy is associated with improved psychological functioning (77) and rapid reduction in high-risk sexual behavior among gay men (73). Medication trials that are in the pipeline will hopefully prove useful in identifying agents of therapeutic utility in alleviating the ongoing psychological distress, cognitive impairment, and overpowering urge to use METH that many of these patients struggle with in early abstinence.

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