

## **Methamphetamine Abuse and Dependence: An Update**

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### **Learning Objectives**

Clinicians will have a better understanding of the clinical issues associated with methamphetamine (MA) abuse and dependence and their impact on treatment response and outcomes, will comprehend the evolution and the scope of the MA epidemic and understand the basic epidemiology of MA-related drug disorders, will understand and recognize how MA affects the brain and the short- and long-term health effects associated with MA use, will learn about clinical assessments used for MA-related disorders, will appreciate the comorbidities and social ramifications associated with MA-related drug disorders, will gain awareness of the treatment challenges associated with MA-related drug disorders, and will identify existing treatment strategies for MA-related drug disorders.

## **Introduction**

The problems associated with methamphetamine (MA) abuse and dependence<sup>1</sup> in the United States (U.S.) have significantly expanded in the 2000s, as witnessed by the growing presence of MA-abusing populations within the treatment, medical, and legal systems. This paper provides an update on the current MA problem. The primary goals of the authors are to help clinicians improve their programs and services by providing them with the necessary information needed to increase their clinical knowledge and skills so that they can effectively treat individuals who abuse or are dependent on MA.

## **Evolution of the Methamphetamine Epidemic**

Methamphetamine, generally called “speed,” “crystal,” “crank,” “ice,” or “tina,” (“shabu” in the Philippines and “yaba” in Thailand) is a potent psycho-stimulant that can be swallowed in pill format orally or delivered via intranasal, injection, or smoking routes of administration. Immediately following World War II, MA was extensively used to reduce fatigue and suppress appetite. Following the war era, MA tablets, referred to as “work pills,” were widely used in Japan. In the late 1960s, MA became known as a dangerous drug that created substantial health threats to users, prompting the drug prevention slogan “speed kills.” Concerns about growing rates of MA use prompted the passage of the 1974 Drug Control Act, which drastically limited the medicinal usage of all amphetamines and virtually eliminated its large scale abuse.<sup>1</sup> During the late 1970s and through the early 1980s, the problem of MA use in the U.S. was, for the most part, limited to several California cities (e.g., San Francisco and San Diego), since the primary manufacturers and suppliers of MA at the time were members of Hells Angels and other motorcycle gangs headquartered in California. In the mid-1980s MA use escalated dramatically

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<sup>1</sup> Methamphetamine abuse and dependence are defined as substance use disorders by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). As such, this paper will use the term methamphetamine-related drug disorders to refer to methamphetamine abuse and dependence (American Psychiatric Association, 1994).

in Honolulu as “ice,” a smokable form of the drug that was imported onto the island of Oahu from the Philippines.<sup>2</sup>

MA is not difficult to produce. During the 1980s there was a rapid proliferation of large and small clandestine MA laboratories in the southern desert areas of California, including San Diego, Riverside, and San Bernardino counties. Primary precursor chemicals commonly used for manufacturing MA include: ephedrine or pseudoephedrine, hydrochloric or hydriotic acid, ether, and red phosphorus, which were readily available from numerous sources. Since there were few or no regulations on the purchase of these chemicals, the manufacture of MA was a rapidly growing “cottage industry.” However, federal restrictions on the purchase of ephedrine in bulk during the early 1990s resulted in two major consequences for MA production. First, there was a change in the “recipes” used to make MA in the U.S., such that pseudoephedrine replaced ephedrine as the main chemical used in production. As a result of the switch to pseudoephedrine as a precursor chemical for the manufacture of MA, pharmacies and convenience stores around the U.S. became unwitting suppliers of the MA production effort, since pseudoephedrine is the active ingredient in many over-the-counter cold and sinus medicines (e.g., Sudafed and Nyquil). Federal and state regulations, as well as voluntary actions by many of the manufacturers of pseudoephedrine-containing medications, led to packaging modifications, giving rise to blister packaging of all products with pseudoephedrine, which are now sold in limited numbers. Some states have passed legislation that requires that all pseudoephedrine products are moved behind the sales counters in pharmacies and stores, further restricting access, although these political efforts have been slow. These strategies are believed to have increased the difficulty for MA producers to acquire adequate supplies of

pseudoephedrine without drawing the attention of retailers and consequently law enforcement officials.

Secondly, there was a shift in MA production-based markets from the U.S. to Mexico, where ephedrine was still available with few restrictions. The emergence of large-scale MA production just south of the border in Mexico has had an unforeseen consequence. Mexican drug trafficking organizations with established routes, smuggling strategies, and highly trained personnel for transporting marijuana and heroin into the U.S. have added MA to their “product line,” which introduced MA into medium-size cities in the western mountain region of the U.S. (e.g., Salt Lake City) and the Midwest (e.g., Des Moines). Expansion of MA in these geographic areas has not only impacted the rising and spreading rates of MA-related drug disorders in the U.S., but also increased the power and impact of Mexican trafficking organizations and their ability to subsequently further extend their commerce with MA into the Southeastern U.S..<sup>3,4</sup>

### **Scope of the Methamphetamine Problem in the New Millennium**

In the 2000s, MA has emerged as one of the most dangerous “homegrown” drugs in the U.S., and its clinical abuse and dependence poses significant public health challenges.<sup>5</sup> MA has not only been ranked as the most widely used illicit drug in the world after cannabis,<sup>6</sup> it has become the most dominant drug problem in many Western and Midwestern U.S. states, severely impacting rural and suburban areas, as well as small- and mid-sized cities. In some states, MA has emerged as the most significant drug problem within the treatment system: treatment admission rates for persons aged 12 years and older have drastically risen over the past decade from 10 per 100,000 in 1992 to 52 per 100,000 in 2002;<sup>7,8</sup> in 2002, 14 states cited that there were more admissions resulting from MA use than from heroin and cocaine use combined; and recent data reveal that MA admissions increased 10% between 2002 and 2003 (from 105, 754 to 116,

604). Similar trends have been documented in the health care and criminal justice system, as reports from emergency departments and medical examiners involving MA episodes more than doubled during the 1990s, and there was a steady increase in the percent of arrestees testing positive for MA across many geographical areas during this decade.<sup>9</sup>

### **Biological Mechanisms of Action**

Emerging scientific evidence from animal and human brain studies has led to remarkable changes in the way MA-related drug disorders are understood. Research efforts in these areas have provided an entirely new perspective on the impact of MA on basic neurophysiological systems and the conceptualization of MA abuse and dependence. Such research has led to the adoption of the perspective that addiction to MA constitutes a "brain disease." Although individuals initiate their use of MA for a variety of psychological and socio-cultural reasons, once MA has been administered, profound changes occur in the structure and chemistry of the brain. These changes influence the basic biological unit of brain functioning, namely the neuron creating alterations in the dopamine and other neurotransmitter systems. Neuroimaging studies have demonstrated that MA appears to damage the brain and neuronal functioning in ways that are different from, and in some ways more severe than, other drugs of abuse. Despite these detrimental effects to the brain, recent research has shown that such changes may be reversible.<sup>10</sup>

The mechanism of action for MA at the cellular level is similar, but not identical, to those of cocaine. Like cocaine, MA blocks the reuptake of dopamine, norepinephrine, and serotonin, resulting in increased levels of these neurotransmitters in the synapse of neurons in the nucleus accumbens and other areas in the mesolimbic region of the brain. In addition, and unlike cocaine, MA appears to also directly stimulate the release of dopamine at axon terminals in these brain regions, further increasing synaptic dopamine levels. MA causes the release of dopamine by a

two-stage process. First, it causes the release of dopamine from the storage vesicles into the cytoplasm within the neuron terminals. Second, MA promotes the release of this dopamine through the terminal wall increasing dopamine levels in the synapse. MA has been shown to be neurotoxic to dopamine terminals when administered to laboratory animals, including monkeys.<sup>11-13</sup> It appears that in addition to producing an increased release of dopamine in the synapse, the increased presence of dopamine in the extravesicular area of the terminal results in the formation of free radicals. It is believed that these free radicals are one of the primary causes of the destruction of the presynaptic dopamine terminals.<sup>14</sup>

Chronic MA users have a significant loss of dopamine transporters (used as markers of the dopamine terminal) that are associated with slower motor function and decreased memory. Studies using positron emission tomography (PET) have found that MA-dependent users demonstrate a significantly lower level of dopamine D2 receptors compared to non-drug abusing controls,<sup>15</sup> which is associated with dependency (i.e., loss of control and compulsive drug intake) as well as major cognitive deficits impacting memory and attention.<sup>16</sup> Further, reduced levels of D2 dopamine receptors, associated with lower levels of glucose metabolism in orbitofrontal cortex, suggest that D2 receptor-mediated dysregulation of the orbitofrontal cortex may play a role in the development of some aspects of dependency (uncontrollability and compulsivity) and cognitive problems. The effect of abstinence, both short-term (6 months) and protracted (12-17 months) on the loss of dopamine transporters in the striatum has been studied in individuals with MA-related drug disorders using PET.<sup>17</sup> Results have shown that abstinence is related to significant recovery in the number of transporters accompanied by increase in thalamic, but not striatal, glucose metabolism. It appears therefore that dopamine terminals “recover” during MA

abstinence, but not enough for complete function recovery as indicated by lack of improvement on some cognitive tests.<sup>17</sup>

Additional brain imaging studies have reported neuronal damage in basal ganglia and frontal white matter with an increase in size and number of glial cells with MA users who have been abstinent for as long as 21 months.<sup>18</sup> The PET studies revealed glucose metabolism abnormalities in limbic and paralimbic regions of MA abstainers that correlate with self-reports of depression and anxiety.<sup>19</sup> EEG abnormalities consistent with generalized encephalopathy have been reported in MA-dependent users with 4 days of abstinence, which add evidence that MA-related drug disorders may be associated with a range of cognitive and psychiatric abnormalities.<sup>20</sup> A study with MA abstainers of 8 months showed persistent abnormalities in cerebral blood flow that was accompanied by reduced cognitive functioning, as tested by a battery of cognitive tests.<sup>21</sup> Overall, MA-related drug disorders are associated with persistent physiological changes in the brain that are accompanied by loss of control, compulsive drug use, increased cognitive impairment, and other psychopathology, supporting the “brain disease” conceptualization.

### **Acute and Chronic Effects and Withdrawal**

The euphoric feelings (i.e., “high” or “rush”) that accompany the use of MA, appear to be a result of dopamine release in the reward/pleasure centers of the brain. The timing and intensity of such stimulant effects are in large part dependent upon the route of administration. The powerful “rush” or “high” is almost instantaneous when smoked or injected. Conversely, it takes approximately 5 minutes after snorting or 20 minutes after ingestion for the onset of such drug effects to occur. The half-life of MA is approximately 8 to 12 hours and it is during this duration that the acute effects of MA occur. Immediate physiological changes associated with MA use

are similar to those produced by the fight-or-flight response, inducing increased blood pressure, body temperature, heart rate, and breathing. Even small doses can increase wakefulness, attention, and physical activity and decrease fatigue and appetite. Negative physical effects typically include hypertension, tachycardia, headaches, cardiac arrhythmia, and nausea; whereas the psychological impact is manifested by increased anxiety, insomnia, aggression and violent tendencies, paranoia, visual and auditory hallucinations. High doses can elevate body temperature to dangerous, sometimes lethal levels, causing convulsions, coma, stroke and vegetative states, and even death.

Prolonged use of MA frequently creates tolerance for the drug and escalating dosage levels creates dependence. As tolerance occurs, users typically increase the MA dose and increase the frequency of use. Long-term chronic MA abusers exhibit symptoms that can include violent behavior, anxiety, confusion, and insomnia. These symptoms are the combined result of direct drug effects plus the consequences associated with sleep deprivation, as abusers will often report days and even weeks of sleeplessness. Whether reports are accurate or exaggerated, it is clear that lack of quality sleep is profound. When in a state of prolonged MA use and sleep deprivation, users commonly experience a number of psychotic features, including paranoia, auditory hallucinations, mood disturbances, and delusions. One of the most regularly reported features is “formication,” the sensation of insects creeping on the skin. The paranoia can result in homicidal as well as suicidal thoughts.

### **MA Health Consequences**

MA can cause a variety of cardiovascular problems, including rapid and irregular heartbeat. Damage to small blood vessels in the brain can result in strokes. High doses of MA can produce potentially fatal hyperthermia. Chronic MA injection can result in endocarditis, severe

infections, and abscesses at injection sites. MA smokers appear to be at elevated risk for chronic obstructive pulmonary disease and other respiratory problems. High risk sexual behavior while under the effects of MA and injection use puts users, especially gay males at greater risk of contracting and transmitting infectious diseases, such as HIV, hepatitis B and C viruses, TB, and other sexually transmitted infections.<sup>22-25</sup> Within this particular group, effective treatment for MA-related drug disorders may be one of the most important strategies in reducing the spread of HIV and other associated communicable infections. Among heterosexual, injection MA users, hepatitis C rates of approximately 50-60% have been reported. MA use (especially injection use) has also been highly associated with participation in illegal behaviors, such as crime and violence, which has resulted in increased incarcerations and other problems within the legal system.<sup>26</sup> The production of MA is also associated with significant health risks, such as clandestine labs explosions, environmental fires, and accidental poisoning.<sup>27,28</sup>

### **MA Populations with Unique Clinical Concerns**

Recently, some states (e.g., South Dakota and Oregon) have reported elevated rates of MA injection. Smoking and, in particular, injecting MA appears to lead to a more difficult drug-related disorder. Injection users tend to report far more severe craving during their recovery and higher rates of depression and other psychological symptoms before, during, and after treatment. They also have higher drop-out rates and exhibit higher rates of MA use during treatment. In a recent sample of MA-dependent users who entered treatment in the Midwest, Hawaii, and California, the rate of hepatitis C (Hep C) infection was 22%. Of the MA injectors, over 70% were infected with Hep C. Clearly, preventive efforts that address behaviors that expose individuals to Hep C infection (blood-to-blood transfers or sharing drug paraphernalia) need to be incorporated into treatment protocols. MA abuse is also associated with very high risk sexual

practices, and, as noted above, has been shown to be a huge factor in HIV transmission among gay men. Research by Shoptaw, Reback, and colleagues in Los Angeles has shown that MA use is the biggest threat in the gay community to producing a renewed spread of HIV. They have developed treatment materials for this group and have shown that successful treatment of MA dependence is an extremely effective HIV prevention strategy.

Women use MA at rates equal to men. Use of other major illicit drugs is characterized by ratios of 3:1 for men to women (heroin) or 2:1 (cocaine). In contrast, in many large data sets, the ratio for MA users approaches 1:1. Surveys among women suggest that they are more likely than men to be attracted to MA for weight loss and to control symptoms of depression. Among women, MA-related drug disorders may present different challenges to their health, may progress differently, and may require different treatment approaches. Over 70% of MA-dependent women report histories of physical and sexual abuse, and are more likely than men to present for treatment with greater psychological distress. Many women with young children do not seek treatment or drop out early due to the pervasive fear of not being able to take care of or keep their children, as well as fear of punishment from authorities in the larger community. Consequently, women may require treatment that both identifies her specific needs and responds to them.

MA poses significant threats to the health of children in communities with high levels of availability and abuse.<sup>29</sup> The effects of MA on the unborn fetus are substantial: use by pregnant women can cause growth retardation, premature birth, and probable developmental disorders. Children are at high risk of negligence and abuse as a result of the drug preoccupation, erratic behavior, and psychiatric instability of their MA-abusing parents. Children who live in environments where MA is manufactured are at particular high risk for exposure to toxic

precursors of MA. In 2003, almost 10,000 seizures of MA labs were documented by the U.S. Drug Enforcement Agency, with reports estimating that children under the age of 15 are present in over one third of these lab busts. Children exposed to the vapor from MA cooking and residue has been shown to result in clinically detectable MA levels in over 50% of the children taken from these labs. Although patterns of adolescent MA use have been reported to be relatively low in national surveys (lifetime use of 3% by 10<sup>th</sup> graders and 3.4% by high school seniors) as measured by the Monitoring the Future study in 2004, in communities where MA use levels are high, adolescent MA users have been seen in treatment centers in significant numbers.<sup>30</sup> Little data is available on the extent of the dependence among these young individuals, but the impact of their MA use has been shown to be associated with high levels of emotional, psychiatric, and delinquent problems compared to adolescents with other drug abuse diagnoses.

### **MA Psychosis**

MA-related drug disorders can include a psychotic state that appears virtually indistinguishable from paranoid schizophrenia.<sup>31-33</sup> Evidence from a study of cocaine-induced psychosis shows that as many as two thirds of chronic stimulant users suffer from delusional psychoses.<sup>34</sup> Paranoid delusions and transient auditory and visual hallucinations are frequent with this diagnosis. The delusions may be brief; however, clinicians are increasingly reporting longer episodes, lasting several days to months.<sup>35</sup> Among the documented cases are psychotic behaviors that likely resulted from perceptual-cognitive disturbances, and enduring disorders resembling the symptoms of schizophrenia. Sekine and others (2001) found that the severity of psychiatric symptoms was significantly correlated with the duration of MA use,<sup>36</sup> although psychotic symptoms have been documented in users who have used MA for as little as 3 months<sup>37</sup> and in users as young as 17.<sup>33</sup> Murray (1998) reports that even casual MA use can

precipitate psychotic reactions, and research has documented the dangers for even first-time users.<sup>38</sup> Although most symptoms improve with the use of neuroleptics, chronic MA users may be resistant to treatment and show continued psychotic symptoms despite extended abstinence.<sup>32</sup> In a study of MA psychosis among 104 Japanese patients, symptoms disappeared in 54 patients within a week after MA abstinence and antipsychotic medication, but persisted for more than 3 months in 17 patients.<sup>33</sup> Spontaneous recurrences of MA-induced paranoid-hallucinatory states have also been noted in response to stress.<sup>39-41</sup> In a study of 86 MA users, 52 had previous or persistent episodes of MA psychosis,<sup>42</sup> although no other psychiatric disorder was diagnosed in the absence of MA use.

In those circumstances when individuals with MA-induced psychosis present in emergency rooms or other health facilities, a common clinical practice is for physicians to use a combination of atypical antipsychotics and benzodiazepines to help calm the individual and prevent them from injuring themselves or others until the psychosis-inducing effects of MA have dissipated. In many cases, the psychotic symptoms will remit within 12-24 hours. Without medical intervention, such patients should be provided with a low stimulation environment for safety monitoring.

### **MA Withdrawal**

Effects associated with MA withdrawal include fatigue, insomnia or restless hypersomnia, unpleasant dreams, hyperphagia, psychomotor agitation/retardation, dysphoria, anhedonia, and fragmented attention span. These symptoms can be intense and may be protracted because of the long duration of action of MA. Withdrawal from MA has aversive psychological qualities as well, but it is not accompanied by the same degree of physical pain and discomfort as the withdrawal from opiates. Withdrawal anhedonia and fatigue may contribute to an urge to use MA after recent

cessation. For individuals who used MA to maintain long working hours and/or high energy, the withdrawal syndrome may be viewed as intolerable, as the lethargy and anergia can be quite severe and can last for several weeks or more. At present, there are no pharmacologic agents with demonstrated efficacy for relieving the severity of the withdrawal syndrome. Rest, exercise, and a healthy diet are probably the best recommendations for addressing this syndrome.

### **MA Assessment**

As with other drugs, the crux of the MA assessment quandary is to identify what we need to know about the phenomena of MA-related drug disorders and MA users in order to develop the most effective treatment strategies. Since research has not provided definitive answers, assessment is predicated on a common sense approach--collecting as much information as possible across multiple domains. Typical areas of assessment include demographic characteristics, drug use history and substance use diagnosis, treatment history, and other functioning problems, such as medical and legal. Because MA use does not occur in isolation from other behaviors, assessment for treatment purposes should include consideration of other drug and alcohol use, socio-cultural and economic setting, family history, personal history, pre-morbid personality, medical conditions, and psychological and psychiatric symptoms.

The clinical tool most often used to diagnose MA-related drug disorders is the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).<sup>43</sup> This clinical tool is particularly designed to determine whether the client meets the criteria for substance abuse or dependence. MA-related disorders of abuse and dependence are included in the section addressing amphetamine-related disorders. The DSM-IV diagnostic criteria for amphetamine dependence are the same generic criteria applied to other substances. Amphetamine and MA use disorders are divided into two categories on the basis of symptomatology and severity of symptoms.

*Amphetamine abuse* describes a pattern of maladaptive use of the drug leading to clinically significant impairment or distress and occurring within a 12-month period in which the symptoms have never met the criteria for amphetamine dependence. *Amphetamine dependence*, as the more severe diagnosis, is defined as a cluster of physiological, behavioral, and cognitive symptoms, taken together, that indicate that the person continues to use amphetamine-like drugs despite significant problems related to such use. Dependence is distinguished from abuse by the presence of physical factors such as tolerance and withdrawal, and by increasing loss of control over drug use.

The Addiction Severity Index (ASI)<sup>44</sup> is another clinical tool of assessment that has been widely utilized in the treatment field. The ASI is a standardized, multidimensional measure for assessing problem severity in areas commonly affected by alcohol and drug misuse. It has been used with diverse populations, treatment modalities, and drug classes, and has been found reliable and valid in numerous settings since its construction.<sup>44</sup>

MA use, abuse, and dependence are also diagnosed with other non-clinical assessment methods, including biological tests and self-report. Biological tests of urinalysis offer the ability to objectively ascertain use in the recent past given identified cut-off levels. MA can be detected for varying lengths of time in urine—usually several days, depending on frequency of use, amount of dose, and sensitivity of the testing method; however, no information about pattern, progression, and severity of use and related behaviors is possible. MA metabolites can also be detected in other biological tests of blood, saliva, and hair. Blood and saliva furnish a better index of current levels, whereas urine provides a longer window of opportunity for detecting use over the previous few days. Conversely, self-reported use allows subjective assessment of an unlimited amount of information about the user and his/her drug use history, but is limited by the unknown reliability

and validity of the self-reported information. The assessment of past and present drug use is vital to treatment planning.

### **MA Treatments**

Research collected over the past decade has demonstrated, to a large extent, that treatment for MA-related drug disorders is effective. That is, treatment produces measurable and desirable changes in drug use and other social behaviors compared to no treatment. Two recent outcome evaluations conducted from multi-county longitudinal data, examined treatment patterns and outcomes among a large group of primary-dependent MA abusers (n=1,073) in California receiving standard-based treatment models of differing modalities.<sup>45,46</sup> Results revealed that treatment participation, in general, was associated with positive retention, reductions in MA use, and substantial improvements in overall psychosocial functioning after treatment. Findings from another large sample of primary MA-dependent users (n=2,337) who entered public outpatient treatment programs between 1994 and 1997<sup>47</sup> found positive rates of improvement and treatment completion among MA users relative to users of other drugs. A similar pattern was observed in another study conducted in Iowa that examined the relative effectiveness of conventional drug treatment among a group of MA abusers, with increased sobriety, employment, and reductions in psychiatric symptoms and fewer arrests following treatment.<sup>26</sup>

*Cocaine vs Methamphetamine Outcomes:* Despite the growing body of treatment outcome studies specific to MA-related drug disorders, the majority of studies investigating the effectiveness of treatment for stimulant addiction have focused on cocaine abuse and dependence, with fewer studies on MA. Despite differences between the two stimulants in individual health, psychological, and cognitive effects, both groups tend to show comparable responses to psychosocial behavioral treatments.<sup>48-50</sup> In a large study using the Matrix Model,

500 MA-dependent individuals were treated alongside 250 cocaine-dependent individuals at the same clinic, by the same staff, over the same time period, using the same approach.<sup>51</sup> Treatment outcomes were identical both during treatment and at follow-up. Similar findings have been reported from treatment studies in San Francisco and from data collected in Los Angeles County and throughout California. There is absolutely no evidence that MA clients respond differently than cocaine clients to psychosocial treatments, as large-scale treatment outcome studies suggest that treatment outcomes for MA and cocaine users is comparable. It is likely therefore that the array of treatments with demonstrated efficacy for cocaine dependence can be applied to MA-dependent users with an expectation of comparable outcomes. For a review of stimulant-based treatments, see CSAT TIP #33.<sup>52</sup>

*Medications:* Currently there are no medications with evidence to support their efficacy in treating MA intoxication, psychosis, withdrawal, or dependence. The discovery of a pharmacotherapy for the treatment of MA dependence is currently a major priority, as clinical observations suggest that the neurobiology of some MA-dependent individuals is so disrupted and their functioning so severely impaired, that without effective medication, successful treatment with psychological/behavioral approaches is unlikely. The National Institute on Drug Abuse (NIDA) has a very active program of research underway to test the safety of potential medications and examine their efficacy for treating MA-induced clinical conditions. Specific medication targets are compounds that can reverse and/or reduce MA overdose symptoms, symptoms of psychosis, withdrawal symptomatology, MA craving, MA relapse, or such protracted symptoms as cognitive deficits or anhedonia.

A number of medications have been evaluated in placebo-controlled trials and have been found to produce outcomes not different than placebo. These include: tyrosine, amitryptlin,

desipramine, isradipine, amlodipine, sertraline, and ondansetron. At present, there are placebo-controlled trials underway to assess bupropion, topiramate, baclofen, and modafinil. Promising candidates include: lobeline, a vesicular monoamine transporter medication; aripiprazole, a dopamine stabilizer; and vigabatrin, a GABA enhancer. Other possible pharmacotherapy candidates include disulfiram, selegiline, and naltrexone. Another approach to management of MA overdose and psychosis is the administration of monoclonal antibodies to MA and amphetamine. NIDA is currently funding research to develop this technology.

*Psychosocial/Behavioral Treatments:* Presently, two approaches that have evidence to support their efficacy for the treatment of MA abuse users are the Matrix Model and contingency management. During the 1980s, the Matrix Institute on Addictions group in Southern California (which included the present author, Rawson), created a multi-element treatment manual with funding support from NIDA, designed for application with stimulant users on an outpatient basis. The Matrix approach evolved over time, incorporating treatment elements with support from scientific evidence, encompassing cognitive behavioral therapies (i.e., relapse prevention techniques), a positively reinforcing treatment context, components of motivational interviewing, family involvement, accurate psycho-educational information, 12-step facilitation efforts, and regular urine testing. The Matrix Model is delivered using a combination of group and individual counseling sessions delivered three times per week over a 16-week period followed by a 36-week continuing care support group with 12-step program participation recommendations. Over 7,000 MA users have been treated with this approach during the past 20 years. The manual and related materials have been published by Hazelden and SAMHSA (for more details see [www.Hazelden.org](http://www.Hazelden.org) and [www.SAMHSA.gov](http://www.SAMHSA.gov)).

In 1999, the Center for Substance Abuse Treatment (CSAT) funded a large-scale evaluation of the Matrix Model for the treatment of MA-related drug disorders coordinated by the University of California Los Angeles (UCLA). A large sample of MA-dependent individuals (N=978) were admitted into eight different treatment study sites.<sup>53</sup> In each of the sites, 50% of the participants were assigned to either receive treatment using the Matrix Model or to a “treatment as usual” (TAU) condition, which comprised a variety of counseling techniques idiosyncratic to each community-based treatment site. Results showed that individuals assigned to treatment in the Matrix approach received substantially more treatment services, were retained in treatment longer, gave more MA-negative urine samples during treatment, and completed treatment at a higher rate than those in the TAU condition. These in-treatment data suggested a superior response to the Matrix approach. When data at discharge and follow-up were examined, it appeared that both treatment conditions produced comparable posttreatment outcomes. Participants in both conditions showed very significant reductions in MA use, significant improvements in psychosocial functioning, and substantial reductions in psychological symptoms, including depression. Follow-up data indicated that over 60% of both treatment groups reported no MA use and gave urine samples that tested negative for MA (and cocaine) use. Use of other drugs, such as alcohol and marijuana were also significantly reduced.<sup>40</sup> A particularly interesting finding was that across the eight treatment sites, the “drug court site,” (e.g., the one that enrolled individuals who were participating under a drug court program), produced superior results compared to the other seven sites, suggesting a substantial beneficial influence of drug court involvement. Overall, this evaluation is the largest controlled study of MA treatment that has been conducted.

*Contingency Management (CM)*: Positive reinforcement is a powerful tool in increasing desired behaviors. School teachers who have given "special prizes" for superior performance, companies who give employee incentive bonuses for meeting production goals, AA meetings that give "chips" and cakes to acknowledge successful progress in achieving sobriety are all examples of the effective use of positive reinforcement. Many existing treatment programs informally use positive reinforcement as part of their treatment milieu. Frequently, the reinforcement takes the form of verbal praise, or earning program privileges, or graduating to a higher level of status in the program or some other practice to acknowledge and reward progress in treatment. CM is simply the systematic application of these same behavioral reinforcement principles. In many studies investigating CM approaches, treatment participants can earn vouchers that are exchangeable for non-monetary desired items associated with promoting drug-free lifestyles (e.g., free movie tickets, restaurant dinners, grocery certificates, gasoline coupons, etc.). Typically the individual can earn larger valued rewards for longer periods of continuous abstinence from drugs and alcohol.

Over the past 30 years, a number of research groups at Johns Hopkins (Stitzer, Silverman) and UCLA (Roll and colleagues) and researchers from Vermont (Higgins and colleagues) and Connecticut (Petry and colleagues) have demonstrated the powerful effect of CM techniques to reduce heroin, benzodiazepine, cocaine and nicotine use. Recently CM techniques have been implemented with MA-dependent users in Southern California by the group at UCLA and by researchers in the NIDA Clinical Trials Network. Results from these investigations have provided powerful support to the effectiveness of this behavioral strategy as treatment for MA-related drug disorders. Individuals who have been assigned to CM conditions have shown better retention in treatment, lower rates of MA use, and longer periods of sustained

abstinence over the course of their treatment experience.<sup>54</sup> Without question, CM is a powerful technique that can play an extremely valuable role in improving the treatment response of MA-dependent individuals.

### **Summary and Lessons Learned**

This paper delivers information to treatment providers and clinicians for understanding the evolution and scope of the MA epidemic and its epidemiology; the medical, psychological, and social effects associated with MA-related conditions, including psychosis, withdrawal and dependence; and assessment of MA-related drug disorders. As with many other drug use disorders, a complex array of bio-psycho-social factors are involved with MA abuse and dependence, and these may impact the course of treatment. MA-dependent populations typically present for treatment with clinically challenging demographic and health profiles, including engaging in many risky health behaviors, such as daily drug use, injecting and sharing needles, hazardous sexual activity, and violent tendencies. In particular, recent reports of increased MA abuse in conjunction with high risk sexual practices within subsets of the gay male community, have created considerable concern among leaders in public health and HIV-prevention communities.

The unique clinical symptoms commonly experienced among MA clients seeking treatment suggest that effective treatment of MA-related disorders should be comprehensive, including an emphasis on infectious disease transmission, psychiatric-related conditions, and other psychosocial issues. Numerous clinical trials have been conducted to test the efficacy of various pharmacological agents for MA treatment, although to date, there are no effective pharmacological therapies available. Treatment for MA has been grounded on existing treatments that have been empirically tested as effective for stimulant use disorders, mostly

cocaine. Cognitive behavioral approaches, including the Matrix Model and contingency management are among the most effective for MA treatment. Findings from the few studies that document MA-related outcomes provide promise to the field in terms of psychosocial models being able to adequately treat the problems associated with MA-related drug disorders of abuse and dependence. Treatment efforts should continue to focus on enhancing existing treatment regimens with supplemental services that address the underlying individual differences among MA patients. Most important, efforts aimed at increasing risk-related perceptions associated with risky practices among this group are needed in treatment models.

### **Future Clinical and Research Directions**

This paper offers information and opportunities for clinicians and treatment providers to effectively treat the various populations with MA-related drug disorders. Future outcome-based studies on the long-term clinical aspects of MA abuse and dependence are needed to provide a comprehensive overview of the unique challenges associated with such clinical disorders after treatment. Currently, a 3-year follow-up study on treatment outcomes among a subsample of MA-dependent users who participated in the large Matrix Model clinical trial is underway. This study will not address treatment outcomes, but will examine the clinical issues present among MA clients over time. Certainly, further research is needed on many topics concerning MA-related drug disorders, including development of combined pharmacotherapies and behavioral approaches, information on treatments for MA-using adolescents, and children removed from MA labs, among many other clinical and basic research questions. This paper demonstrates the pivotal role clinical research plays in understanding the issues involved with MA-related drug disorders and treatment effectiveness.

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