REVIEW

Implications of Chronic Methamphetamine Use: A Literature Review

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Methamphetamine (MA) abuse is increasing to epidemic proportions, both nationally and globally. Chronic MA use has been linked to significant impairments in different arenas of neuropsychological function. To better understand this issue, a computerized literature search (PubMed, 1964–2004) was used to collect research studies examining the neurobiological and neuropsychiatric consequences of chronic MA use. Availability of MA has markedly increased in the United States due to recent technological improvements in both mass production and clandestine synthesis, leading to significant public health, legal, and environmental problems. MA intoxication has been associated with significant psychiatric and medical comorbidity. Research in animal models and human subjects reveals complicated mechanisms of neurotoxicity by which chronic MA use affects catecholamine neurotransmission. This pathology may underlie the characteristic cognitive deficits that plague chronic MA users, who experience impairments in memory and learning, psychomotor speed, and information processing. These impairments have the potential to compromise, in turn, the ability of MA abusers to engage in, and benefit from, psychosocially based chemical-dependency treatment. Development of pharmacological interventions to improve these cognitive impairments in this population may significantly improve the degree to which they may be able to participate in treatment. Atypical antipsychotics may have some promise in this regard. (HARV REV PSYCHIATRY 2005;13:141–154.)

Keywords: **amphetamine, catecholamine, cognition, dopamine, methamphetamine, neurobiology, neuropsychology, neurotoxicity syndromes**

The United States is currently experiencing an epidemic of methamphetamine (MA) use, in part due to recent technological advances in its synthesis and administration. This epidemic has had substantial effects in regard to public health, psychiatric comorbidity, and economic costs. As scientific evidence accumulates on the long-term psychiatric comorbidities secondary to MA abuse, and as recreational use of this compound escalates, there is a pressing need for further research in the areas of prevention and treatment. This review will present a brief historical introduction to the current MA epidemic, an overview of the pharmacologic and neurotoxic effects of MA administration, a summary of MA's pathological effects on general physical health and on cognition, and a description of its contribution to psychiatric comorbidity. We will finish with a review of treatment and a discussion of arenas in which future research is urgently needed. In order to address these issues, a computerized literature search (PubMed, 1964–2004) was used to collect research studies examining the neurobiological and neuropsychiatric consequences of chronic MA use. Various combinations of the following keywords were used: cognition, methamphetamine, neuroimaging, neuropsychology,

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neurotoxicity, and treatment. We also considered sources cited in the reports identified by our original search. Given the limited number of available studies in certain areas, particularly treatment, we did not exclude them based on standards of quality or rigor.

THE MA EPIDEMIC

History

A derivative of the stimulant amphetamine, MA was first synthesized from ephedrine by the Japanese pharmacologist Nagayoshi Nagai in 1893.[1] It did not become widely used until the 1940s, when it was utilized by Japanese, American, and German military personal to combat fatigue and increase performance, as well as by Japanese factory workers, during World War II. Following the end of the war, surplus military stocks flooded the Japanese market, culminating in an epidemic of abuse in which 5% of the population is estimated to have abused MA, one-tenth of whom are thought to have experienced MA-induced psychotic symptoms. Abuse in Japan temporarily decreased in response to passage of the stimulant control act in 1951, but there have been several epidemics since then.

In the United States, in response to various pharmaceutical companies' withdrawal of several formulations of MA from the domestic market, underground MA labs emerged in California's Bay Area in the early 1960s.[2] Motorcycle gangs such as the Hells Angels quickly took control of this newly developing illicit market, and MA abuse spread up and down the West Coast.[3] Law enforcement efforts targeting motorcycle gangs, coupled with the development of simpler methods for MA synthesis, had the effect of shifting control of the United States' illicit MA market to Mexican-based traffickers in the early 1990s.[4]

Bay Area biker groups had utilized the "P2P method" of MA synthesis, with the principal chemicals phenyl-2-propanone (P2P), aluminum, methylamine, and mercuric acid.[5] Passage of the Federal Chemical Diversion and Trafficking Act of 1988, however, led to the development of strict federal controls on P2P, making reliance on the P2P method less profitable.[6,7] Subsequently, the P2P method has been essentially replaced by the ephedrine/pseudoephedrine reduction method, which often utilizes a phosphorous-based precursor such as red phosphorous or hypophosphorous acid.

Epidemiology

The ephedrine/pseudoephedrine reduction method is cheaper, simpler, and more efficient than its predecessor, resulting in much purer yields of the extremely potent and addictive D-isomer of MA. With the advent of this method of synthesis, "superlabs" that have the capacity to produce ten or more pounds of MA in one production cycle have recently spread extensively throughout Mexico and the American Southwest. Precursor compounds can be easily diverted from legitimate use and smuggled across international borders (from both Canada and Mexico), to be used for clandestine MA production in both the Southwest and Northwest.[5] Isolated from rechargeable camera batteries, elemental lithium can also be used as a catalyst in the ammonia/alkali method of reduction of ephedrine into MA.[8,9] Sometimes referred to as the "Nazi method," this chemical reduction has become popular in some western regions of the United States, resulting in the production of "crank." The name "crank" is said to derive from bikers' using the crank cases of their motorcycles to transport the substance.

In high-production regions such as the Southwest and Northwest, local and state legislators have tried to fight independent producers in home-based labs by passing legislation limiting the quantities of over-the-counter pharmaceuticals available for purchase that contain possible MA precursors.[10] Congress has passed the Comprehensive Methamphetamine Control Act, which limited access to precursor chemicals and increased penalties for manufacturing MA or trafficking in it.[11,12] The 2001 SAMSHA National Household Survey on Drug Abuse Data reported that 4% of the U.S. population had some use of MA in their lifetime; 1.1% had used MA in the past year; and 0.5% had used in the past month.[13] Data from 2002 suggested that 5.3% of Americans have used MA in their lifetimes, with 0.7% in the last year.[11] Out of 180,455 male arrestees surveyed from 39 sites across the United States in 2003, 12.9% reported using MA annually, and 8.7% reported use within the past week.[14] Data from arrestees, emergency room (ER) presentations, and treatment admissions have consistently suggested a higher prevalence of use in the U.S. Southwest, West Coast, and Midwest, with lower rates of use in the Southeast and Mid-Atlantic states.[13–15] Studies have shown that in some populations, up to 50% of individuals who have used amphetamines several times develop dependence.[16] It is estimated that over 35 million people internationally abuse MA or amphetamines, compared to 15 million abusers of cocaine and less than 10 million regular abusers of opiates.[17] Historically, higher-use regions have included Asia, Australia, Scandinavia, and the United States.

Legal efforts to combat the growing MA epidemic have led nationally to significant increases in lab seizures—from 1,918 in 1999 to 13,092 in 2001, with 8,129 through October 2002.[18] While the total number of seizures has begun to decrease in high-risk regions, the proportion of "superlabs" making up these seizures has increased. Nevertheless, total illicit MA production is thought to be further increasing. ER visits with mention of MA or amphetamine increased 54%, from 25,254 to 38,961, from 1995 to 2002, with most visits centered around the major cities of the West Coast

and Southwest.[19] In that same time span, among patients aged 6 to 17 years, ER visits related to MA or amphetamine increased by 88%.

Public Health Consequences

In addition to the specific impact on users, as discussed above, the increase in MA use has had other significant public health effects in the United States. The use of phosphorous-based solvents has led to the pollution of water supplies, agricultural land, and even housing. The impact of MA on the environment cost California $5.5 million to clean up in 2001.[5] That same year, 1,231 children found at in-home labs during drug seizures in California, Missouri, Oregon, and Washington were found to have toxic levels of precursors and byproducts in their bloodstreams, necessitating treatment or hospitalization.[20] The number of pediatric deaths and ER visits for significant burns suffered in in-home MA labs has increased (Hammond C, personal communication, 15 August 2001), as has the number of pediatric visits for inadvertent MA poisoning.[21] The use of lead acetate as an occasional reagent in MA synthesis has led to an increase in lead poisoning.[22]

Fetal exposure to MA is increasing and has been shown to lead to multiple prenatal complications, such as intraventricular hemorrhage, fetal growth restriction, increased risk of preterm labor, placental abruption, decreased birth weight, cardiac defects, cleft palate, and behavioral effects in neonates.[22–27] Visual recognition memory, which has been correlated with subsequent IQ, is lower in infants with prenatal stimulant exposure.[28] Swedish studies show that prenatal amphetamine exposure is correlated with poor social adjustment and an increased incidence of aggressive behavior in both 4 and 8 year olds,[29–31] with continued behavioral problems at the age of 14 years,[32] with slightly lower IQ,[33] and with delays in mathematical and language skills that impaired school performance and subsequent educational advancement at ages 4, 8, and 14.[29,32,34] Some of these children, however, also had significant prenatal nicotine and alcohol exposure, were raised by mothers who continued to abuse amphetamines, or lived in foster care for significant portions of the study period. A cohort of children aged 6.9 +/− 3.5 years with prenatal MA exposure exhibited deficits in delayed verbal memory and sustained attention that were correlated with reduced volumes in the hippocampus and striatal nuclei.[35]

Needle sharing among MA abusers who use IV administration has resulted in higher rates of hepatitis C and HIV.[36,37] MA abuse has been identified as a contributing factor to the spread of HIV among the population of men who have sex with men. In this same group of men, both MA and amphetamine use have been linked to increased incidence of unprotected sex and other high-risk sexual behaviors.[36,38–41]

EFFECTS OF MA AND MA ABUSE

Pharmacological and Neurobiological Effects

Due to its lipophilic nature, MA has increased central nervous system (CNS) penetration and is more potent than its parent compound amphetamine.[42] It acts similarly to stimulate release of newly synthesized catecholamines in the CNS and, to some extent, blocks presynaptic reuptake of these neurotransmitters. Studies in transgenic knockout mice reveal the target of amphetamines to be the dopamine transporter (DAT), which regulates dopaminergic transmission by facilitating dopamine reuptake.[43–45] Amphetamines block DA reuptake via DAT but primarily reverse the direction of DA transport through the channel, leading to increased DA release.[43]

MA is typically smoked, injected, ingested, snorted, dissolved sublingually, or solubilized and consumed in a beverage such as coffee. Both smoking and injection are reported to result in the immediate sensation of several minutes of intense euphoria. The “high” produced by MA is less immediate, longer lasting, and less intense if the MA is administered via other routes, with slower absorption.[46] Euphoria occurs five minutes after intranasal use and twenty minutes after oral ingestion, but is reported to last 8–12 hours.[22] This long-lasting effect is due, in part, to the 12-hour half-life of MA—in contrast, for example, to the 90-minute half-life of cocaine.[47] The longer half-life of MA, coupled with its inexpensive synthesis, may explain why MA abusers regularly spend roughly 25% as much as cocaine abusers on their drug habits.[48]

MA intoxication initially produces excessive stimulation of the sympathetic nervous system, resulting in marked tachycardia, hypertension, pupillary dilation, diaphoresis, tachypnea, peripheral hyperthermia, and hyperpyrexia. In addition to euphoria, desired effects include a heightened sense of attentiveness, increased energy, heightened curiosity, elevated interest in environmental stimuli, and, initially, hypersexuality and decreased anxiety.[49–51] Repeated MA use results in catecholamine depletion and produces a withdrawal syndrome marked more by psychiatric complaints than by physical manifestations. Labeled “the crash,” stimulant withdrawal characteristically manifests as depression with severe dysphoria,[22,46,50,52,53] irritability and melancholia,[50,52,53] anxiety,[22,46,52] marked fatigue with hypersomnia,[22,50] intense craving for the drug,[22] and even paranoia[22,46] or aggression.[22] Although the severity of the abstinence syndrome appears to be related to the frequency of use, it tends to resolve spontaneously.[53] The intensity of this post-binge dysphoria can, in the short term, lead to lethal suicidal ideation that warrants inpatient psychiatric treatment.

The withdrawal syndrome specific to chronic MA abuse can cause much more severe anergia and dysphoria than

seen in cocaine withdrawal and may last up to 12 months.[54] Some authors view the increased severity and duration of these withdrawal symptoms as the clinical manifestations of residual neurotoxicity from chronic MA abuse.[55] Most studies of neurotoxicity, however, have been performed in animal models.

Effects on the Monoamine System

MA use leads to neurotoxicity to both the DA and serotonergic transmitter systems (5HT) across a wide variety of mammalian species. Rodents treated with repeated doses of MA for several weeks show losses of the 5HT transporter (SERT), 5HT depletion, depletion of the major 5HT metabolite 5-hydoxyindole acetic acid, and reductions in tryptophan hydroxylase (TPH).[56,57] Acute and chronic exposure to MA or amphetamines in rodents both lead to striatal DA depletion and physical destruction of striatal DA terminals,[44,58–62] as well as to decreased levels of presynaptic markers of DA function such as tyrosine hydroxylase (TH),[63,64] DAT,[61,62,65] and the vesicular monoamine transporter (VMAT).[66] Nigrostriatal DA cell bodies are preserved in most species, indicating that MA exposure preferentially leads to selective degeneration of striatal DA terminals rather than to cell loss.[67]

MA neurotoxicity in both rodents and higher primates is at least partially reversible when animals are treated with MA in noncontinuous, bingelike administration schedules that more closely approximate a human "meth run."[68] Evoked efflux of striatal 5HT normalizes in rodents six months after MA treatment.[69] MA-related cognitive problems, behavioral disturbances, and decrements in DA functioning normalize with time in both rodents[68,70] and primates,[71,72] although the extent of normalization depends on both the dose and chronicity of MA exposure. MA has been shown to lead to deficits in DA and 5HT function that can persist for up to four years in primates, but these animals show marked recovery between three months and four years after treatment.[73] Data pooled from both rodents and primates is most consistent with a recovery process best explained by a compensatory increase in enzymatic activity in residual DA nerve terminals, DA axonal regeneration, or collateral DA sprouting.[67,71,72]

Human MA abusers report patterns of repeated dosing in the range of 20–40 mg every 2–3 hours,[74] which can result in consumption of 0.3 to 1.0 grams during a 24-hour binge.[75] Primates treated with equivalent dosing regimens develop dose-dependent decreases in striatal DAT density as measured by positron emission tomography (PET) imaging, and have decreased levels of DAT, DA, and the DA metabolite dihydroxyphenylacetic acid (DOPAC) at autopsy.[76] Human studies profiling long-term MA neurotoxicity, however, have been mixed, with conflicting PET and autopsy findings. PET studies reveal that striatal DAT density is markedly reduced in chronic MA abusers after three years of abstinence, suggesting that chronic MA abuse leads to destruction of DA nerve terminals or cell bodies.[77] Yet at postmortem, MA abusers have marked decreases in striatal TH, DAT, and DA, but preservation of the presynaptic DA markers VMAT and DOPA decarboxylase without any signs of pigmented cell loss in the substantia nigra.[78,79] These findings suggest that MA-induced neurotoxicity leads to selective destruction or downregulation of particular DA synthetic and functional proteins rather than to general destruction of DA terminals or cell bodies.[78] This conception complements longitudinal PET data from vervet monkeys showing reductions in TH, DAT, and VMAT that recover with time, and an absence of cell loss in DA-rich areas of the ventral midbrain.[67] Such preserved DA cellular integrity is difficult to explain since both reductions in VMAT density and at least some partial cell loss would be expected to occur consistently in a model of toxicity that leads to extensive terminal degeneration. The absence of these findings and the phenomenon of recovery of DA functional markers may explain why human MA abusers do not have many gross cognitive or behavioral deficits that remain unrecoverable as they progress through treatment.

Although the molecular mechanism underlying MA-induced neurotoxicity remains unclear, most evidence implicates reactive oxygen species (ROS) and resultant oxidative stress. Pretreatment with inhibitors of DA synthesis protect against MA-induced toxicity to both DA and 5HT systems, while treatment with L-DOPA restores the capability of MA to induce neurotoxicity, indicating that endogenous DA is required for neurotoxicity to occur.[56,80–83] MA treatment leads to a DA-dependent increase in levels of the neurotoxin 6-hydroxydopamine (6-OHDA).[83,84]

Severity of MA-induced neurotoxicity is influenced by the levels of the reducing enzyme superoxide dismutase (SOD),[85–88] the ROS-producing enzyme neuronal nitrous oxide synthase (nNOS),[89,90] and the antioxidants ascorbic acid and glutathione.[91,92] MA appears to redistribute DA from the reducing environment of the synaptic vesicles into the oxidizing environment of the neuron's cytoplasm. The end result is the generation of free radicals and reactive metabolites that likely lead to protein and cell membrane destruction. Consequently, VMAT-2 knockout mice demonstrate increased damage to the DA system when treated with MA, as VMAT-2 maintains sequestration of DA in the reducing environment of the synaptic vesicle.[44]

Pathophysiological Effects

Amphetamine abuse has been documented to produce both significant psychiatric and medical comorbidity—in particular, marked vascular and cardiac toxicity. Chronic MA administration in animals leads to pathological cerebrovascular changes and signs of hemorrhage.[93] Case studies and

a retrospective cohort study have linked death in human MA abusers to an increased frequency of pulmonary edema, cerebral hemorrhage, and congestive heart failure.[94–96] MA intoxication has been implicated in acute aortic dissection and myocardial infarction.[97] The catecholamine excess released by MA can sensitize the abuser's myocardium to ectopic cardiac stimuli, leading to the development of lethal cardiac arrhythmias.

The large catecholamine release induced by MA ingestion also leads to significant hyperpyrexia that can be fatal either directly or via contribution to cerebral hemorrhage, seizures, or rhabdomyolysis.[96,98,99] Direct CNS toxicity in the acute setting can take the form of seizure activity, including status epilepticus.[100,101] Renal failure can result either from infarction secondary to vasospasm or from rhabdomyolysis.[99] While MA use is associated with higher rates of ER utilization, the majority of these visits are for blunt trauma from multivehicular accidents and interpersonal trauma such as gunshot and stab wounds.[99,102]

The discovery that MA leads to DA depletion and striatal neurotoxicity led initially to public health concerns that as MA-abusing populations aged, they would be at increased risk for the development of parkinsonism, but no studies have confirmed this prediction. The explanation may be that the use of MA leads to more DA depletion in the caudate nucleus, which is involved in cognitive function, than in the putamen,[79] which is primarily involved in motor function.[103] In contrast, patients with Parkinson's disease have markedly higher levels of DA loss in the putamen compared to this population,[104] and more loss in the putamen than in the caudate.[105]

A variety of adverse psychiatric effects from MA may result from particular abusers' heightened sensitivity to MA, from repeated administration or an escalation in dose, or from changing the route of administration to injection. This presentation can manifest as euphoric disinihibition, extremely impaired judgment, grandiosity, extreme psychomotor agitation, and even bizarre stereotypies such as the repeated disassembling and reassembling of electrical objects and appliances, and formication (i.e., scratching of imagined insects perceived under skin).[4,22,99,106,107] In fact, marked stimulant intoxication can trigger or resemble manic or hypomanic episodes. Multiple case reports and autopsy case reviews have, over the years, suggested that chronic MA and amphetamine abuse can contribute to increased incidence of violent behavior and violent death, often in the setting of stimulant-induced psychosis (which is the source of the popular antidrug slogan "speed kills").[108–112]

Based on neuroimaging, neuropsychological testing, and psychiatric evaluation, evidence accrued from empirical data implicates heavy use of MA as a contributing agent to a variety of psychiatric pathologies, including psychosis,[107,113–115] mood disturbance,[115–117] anxiety,[114–116] attention-deficit hyperactivity disorder (ADHD),[75,118] motor dysfunction,[119] and cognitive deficits.[75,118–120] Proposed mechanisms for the onset and persistence of psychiatric symptoms, especially psychosis, among MA abusers include: (1) chronicity of MA use, (2) DAT loss in the nucleus accumbens and caudate/putamen, and (3) alterations in cerebral blood flow.[114,121]

Psychotic symptoms—including hypersensitivity to the environment, paranoid ideation, auditory and visual hallucinations, and persecutory delusions—often develop.[98] MA psychosis, which is thought to be due to the excess of synaptic dopamine,[113,122,123] mimics symptoms of schizophrenia.[124] The presence of psychosis and stereotypies is at least partially related to the level of MA metabolites in the blood and urine of acutely psychotic abusers.[107] Risk factors for the development of MA psychosis include younger age at first use, using larger amounts of MA, having more premorbid schizoid or schizotypal characteristics, and having a genetic polymorphism in the gene that encodes the DAT.[125,126] Also, rates of other psychiatric disorders—including major depression, alcohol dependence, and antisocial personality disorder—were higher in individuals with MA psychosis than MA users without psychosis.[125] A deletion in the gene for glutathione S-transferase has been linked to a predisposition toward development of MA psychosis in MA-abusing women,[127] as has a polymorphism in the gene for alpha-synuclein, a structural protein involved in membrane clustering of DAT.[128]

Neurological problems—including traumatic brain injury, birth trauma, learning disabilities, and soft neurological signs—have also been associated with an increased risk of treatment-resistant MA psychosis.[129] Unfortunately, MA psychosis is thought to recur among individuals with a history of MA psychosis—even during times of abstinence that include remission of psychotic symptoms.[130] Although there are no controlled studies available examining the use of antipsychotics in the treatment of MA psychosis, Sato and colleagues[131] have suggested that MA psychosis is mediated by dopamine hypersensitivity and that haloperidol may be prophylactic against paranoid psychosis. There are also published case reports of olanzapine and risperidone effectively treating the psychotic symptoms in outpatients with MA psychosis —both acutely and during early abstinence.[132,133]

While there are no data exploring the association between MA use and bipolar disorder or the likelihood of inducing mania, a number of studies have found depressive symptoms, irritability, and suicidal ideation among MA abusers during active use and also during withdrawal and early abstinence.[53,114–117] In the largest study of psychiatric symptoms among MA users ($n = 1{,}016$), depression was the most common symptom experienced, and 27% of the sample

had attempted suicide at least once in their lifetimes. The severity of depression was highest in females and MA users who injected MA.[115] Beck Depression Inventory scores of MA abusers in early abstinence (4 to 7 days) are positively correlated with the amount of recent MA use and negatively correlated with glucose metabolism in an area of the anterior cingulate involved in mood symptoms.[116] Anxiety and depressive symptoms in MA-dependent inpatients have been shown to improve significantly over an average of three weeks of abstinence[134] but may persist for over a year in some patients.[114] Female MA abusers tend to report more severe symptoms.[115,135]

An association between MA use and ADHD has recently been identified.[75,136,137] ADHD is a clinical diagnosis characterized by a syndrome of inattention, impulsivity, and hyperactivity that can persist into adulthood.[138–141] Adults meeting DSM-IV criteria for ADHD are characterized primarily by symptoms of inattention; impulsivity and hyperactive symptoms tend to remit after childhood.[141,142] Current understanding of ADHD based on neuroimaging data conceptualizes the disorder as one of relative prefrontal dopamine hypoactivity.[141] Dopamine activity in the frontal lobe is intimately involved in executive function,[143,144] a domain in which both children and adults with ADHD demonstrate clinical impairment.[141,145–147] Since ADHD is associated with a hypo-dopaminergic state, it makes sense that the primary pharmacological treatments for ADHD are methylphenidate and amphetamine.[148–150] While there is a clinical perception of risk in prescribing stimulants, previous data indicate that treating childhood ADHD with a stimulant may reduce the risk of later developing a substance use disorder.[151] The presence of ADHD among MA abusers has been a focus of recent study. Among outpatient adult MA abusers, 33 to 40%[75,136] screen positive for presumptive childhood ADHD based on the Wender Utah Rating Scale (WURS),[152] while a study of MA-dependent inpatients found that 71% of the 51 participants screened positive on the WURS.[137]

Human data overwhelmingly implicate MA abuse in the development of characteristic neurocognitive impairments that are both dose- and duration-dependent in severity. While single doses of amphetamine have been shown to *improve* performance in several domains of neurocognitive functioning in normal humans,[153–155] chronic abusers actively using MA suffer from multiple neurocognitive impairments in dose-dependent fashion. The severity of these deficits depends upon the frequency of MA use[118,156] and the severity of MA dependence.[157]

MA abusers appear to develop different cognitive impairments than do abusers of other stimulants or other classes of illicit drugs. Active abusers of MA and cocaine both have significantly impaired verbal memory, but MA abusers also demonstrate impaired performance on tasks of perceptual speed and information manipulation, and do very poorly on tasks that combine these skills with visuomotor scanning.[158] Compared to cocaine and heroin abusers, abusers of MA or amphetamine also demonstrate deficits on tests of executive function such as the Wisconsin Card Sorting Test (WCST), which suggests frontal dysfunction.[158,159]

Marked impairment in the neurocognitive functioning of MA-dependent patients persists into abstinence, is slow to normalize, and actually worsens initially. MA-dependent patients in early abstinence (5 to 14 days) perform markedly worse than controls on measures of attention and psychomotor speed, and of verbal learning and memory, as well as on fluency-based measures of executive function such as set shifting and inhibition.[120] MA-dependent inpatients show essentially no improvement in visuospatial learning after three weeks of abstinence and remain in the functionally impaired range, while they significantly worsen in verbal learning, throughout this time period.[137] Despite 2 months of abstinence, abusers consistently demonstrate errors in selective attention and priming.[160] After 3 months of abstinence, recovering MA abusers score worse on word recognition and tests of episodic memory than do individuals continuing to use MA, who themselves score worse than MA-naive controls.[161] Decrements in performance on psychomotor and verbal memory tasks do lessen in MA-dependent subjects between 3 and 14 months of abstinence, but this improvement falls short of statistical significance.[162] MA-dependent individuals with an average of 8.0 +/− 2.2 months of abstinence showed little difference in verbal memory compared to controls, but do perform significantly worse on working-memory tasks.[163] Cocaine-dependent samples have been shown to have cognitive deficits, particularly in verbal memory, in early abstinence[164–166] and again 6 months after their last use.[164] Yet cocaine abusers do not differ from normal controls three years after their last use.[167]

Biological markers of impaired brain function that are specific to MA abuse also persist into abstinence. Chronic abusers with an average of 5.9 +/− 9.0 months of abstinence still have significantly reduced striatal DAT density—which is correlated with both their years of MA use and the severity of their impairments in verbal memory and psychomotor function.[119] With additional abstinence, DAT density fully recovers, but baseline neurocognitive function lags behind[162]—a result that complements PET studies in primates and that suggests the possible involvement of other transmitter systems.[67] Increased levels of MA use leads to increased reductions of DAT density in the striatum and nucleus accumbens, which results in a higher likelihood and higher severity of residual psychotic symptoms as measured by the Brief Psychiatric Rating Scale.[114] In contrast to MA, chronic cocaine use is associated with increases in DAT density, which return toward normal with abstinence. These increases in DAT density are correlated with the depressive

symptoms seen in stimulant withdrawal, but have not been implicated in cognitive deficits.[168–171]

Based on human neuroimaging and animal data, it is unclear whether changes in DAT density represent terminal degeneration or compensatory downregulation of the transporter protein in response to a MA-induced hyperdopaminergic state. Human and primate histological studies are suggestive of preserved DA terminal integrity,[67,78,172] but given the short life span of the DAT protein, the 17 months needed for full DAT recovery is not consistent with MA-induced changes being solely due to protein downregulation.[162] Additionally, the persistence of DAT losses after three years of abstinence in some populations is certainly suggestive of permanent terminal or transporter loss.[77] Volkow[162] has proposed that DAT recovery via either increased arborization or transporter protein upregulation on surviving DA terminals could lead to normalized ligand binding in imaging studies, but that it may not be sufficient to fully restore the dopaminergic neurotransmission that subjects need in order to resume baseline neuropsychological functioning.

This question of what causative mechanism actually reduces DAT density in response to chronic MA use is further complicated by a lack of knowledge concerning DAT levels prior to MA abuse. It is possible that MA abusers may have an intrinsically low level of DAT to begin with, which could predispose them to abuse stimulants in an effort to compensate for an intrinsically hypoactive dopaminergic system. PET studies have shown low right-sided putamen DAT levels to be correlated with schizoidal traits such as amotivation, asociality, and poor drive.[173] Data from craving studies also suggest that levels of DA-system activity may significantly differ between individuals, since high D2 levels in stimulant-naive subjects predict reinforcing effects of methylphenidate administration.[174]

Finally, metabolic irregularities are common in MA abusers and have been linked to the behavioral manifestations of MA-induced psychiatric impairment. Measures of cellular energy regulation are decreased in the basal ganglia of chronic MA abusers in dose-dependent fashion, suggesting impairments in energy production at the cellular level.[175,176] In view of the similar findings for the anterior cingulum, it has been proposed that such a decrease contributes to the development of attention deficits and alterations in the reward system in MA abusers.[177] These deficits have been linked to hypoactivity in orbitofrontal and dorsolateral prefrontal cortex within this population.[178] Dysregulation of glucose metabolism in limbic and cingulate cortex, as well as significant structural loss of limbic, paralimbic, and cingulate gray matter, has been strongly correlated to the elevated depressive and anxiety symptoms in active chronic MA abusers.[116,179] Verbal memory impairments in this same subject group were correlated with severity of hippocampal shrinkage, which averaged 8% in the MA group.[179]

TREATMENTS FOR MA ABUSE AND DEPENDENCE

The primary modality of treatment for MA dependence is behavioral. In a nonrandomized, uncontrolled, retrospective analysis of cocaine and MA abusers in inpatient treatment, chemical and electrical aversion therapies resulted in a self-reported abstinence rate of 53% for 12 months.[180] The most adequately tested treatment approach, however, is the Matrix Model, a 4-month, manualized, intensive outpatient therapy that, in order to maintain abstinence, combines cognitive-behavioral therapy, family education, 12-step program participation, and behavioral approaches such as positive reinforcers.[181,182] MA abusers remained active in treatment for an average of 17 weeks and submitted an average of eight random urine toxicology screens (just under 20% of which were positive for MA).[183]

Two to five years after completion of treatment in the Matrix Model, subjects reported markedly less MA use and higher occupational and psychiatric functioning, and only 6.5% of urine analyses at follow-up were positive for MA.[46] Subjects were sampled nonrandomly, however, since this follow-up analysis was limited to the first 25% of the original 500 Matrix subjects to be located. While it is apparent that a significant number of prior MA abusers are able to obtain long-term benefits from the Matrix approach, it is difficult to draw detailed conclusions about the efficacy of this model.

Due to the significant cognitive impairments that typically develop in the setting of chronic MA abuse, patients entering treatment can have extreme difficulty participating in psychologically based treatments such as the Matrix Model and could benefit greatly from effective pharmacological therapies for MA dependence. Data on pharmacological treatments for MA abuse are sparse, however, and there are currently no medications that are FDA approved for treatment of MA dependence.[184] Although imipramine dosed at 150 mg/day has been shown to keep both MA and cocaine abusers in treatment longer than controls dosed with 10 mg/day, it led to no measurable reduction in MA use or craving.[185,186] The addition of desipramine to the standardized Matrix treatment program led to no significant differences compared to a Matrix treatment plus placebo group or to Matrix treatment alone.[187] Fluoxetine decreases MA self-administration in animal studies, and an unpublished double-blind, placebo-controlled study in MA-dependent adults demonstrated decreased subjective cravings for MA in the treatment group.[184] Fluoxetine did not, however, decrease either subjective reports of MA use or positive urine toxicology screens.[188]

While the calcium channel blocker amlodipine has shown no benefit for treatment of MA dependence in a small unpublished trial,[184] isradipine may have future promise as an anti-reward or anti-craving medication for MA

dependence. In MA-naive volunteers, isradipine reduces some of the positive subjective effects of MA administration and subsequent craving for MA. Since isradipine has not been studied in MA-dependent patients, however, it needs to be further evaluated to determine its potential utility.[189] The anticonvulsant vigabatrin has been shown to reduce cocaine use and craving in human studies, but due to a high incidence of visual-field problems in earlier studies and in clinical use in other countries, it is not yet available in the United States.[190] Although it has not yet been tested in controlled trials, vigabatrin failed to produce any visual-field defects in a recent nine-week, open-label, pilot study primarily in MA abusers, and subjects appeared to have lower drug use than otherwise expected.[191] In animal studies, olanzapine, risperidone, and clozapine decreased the ability of subjects to discriminate dextroamphetamine from placebo, suggesting that atypical antipsychotics may be effective in attenuating the positive subjective effects of MA and subsequent craving for the drug.[192–194] Risperidone has recently been shown to limit the ability of humans to correctly identify dextroamphetamine after administration[195] and also to limit the subjective "high" from experimentally administered cocaine.[196] A recent, four-week, open-label pilot study of risperidone in 11 MA-dependent subjects entering treatment resulted in a single MA-positive specimen out of 36 weekly urine samples collected throughout the study.[197] Given the ability of atypical antipsychotics to improve cognitive function in schizophrenia, it is likely that future studies will investigate whether they can also improve the cognitive deficits that arise with chronic MA abuse.[198,199]

FUTURE DIRECTIONS

The MA epidemic continues to spread, with MA use increasing particularly among younger cohorts. Chronic MA abuse in our society has contributed to overwhelming public health concerns and has been demonstrably linked to physiological, neurocognitive, and psychiatric comorbidity. Of particular concern, chronic MA abusers develop characteristic neurocognitive impairments that affect information processing, verbal memory, and other domains of cognition. These impairments make it quite challenging to retain these individuals in CBT and case management–based psychosocial treatments. Nevertheless, these modalities are both the best studied and the most effective treatment strategies developed to date for MA abusers attempting to enter recovery. The development of pharmacological treatments that could decrease MA craving, decrease MA use, improve cognitive function, and increase treatment retention in early abstinence would greatly improve our ability to treat MA dependence. Possible candidates for future research in this area include the atypical antipsychotics, the calcium channel blocker isradipine, and the anticonvulsant vigabatrin.

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