

# The need for speed: an update on methamphetamine addiction

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The psychostimulant methamphetamine (MA) is a highly addictive drug that has surged in popularity over the last decade in North America. A burgeoning number of clandestine drug laboratories has led to dramatic increases in MA production, which have resulted in significant public health, legal and environmental problems. Current evidence indicates that exposure to MA is neurotoxic, and neuroimaging studies confirm that long-term use in humans may lead to extensive neural damage. These physiological changes are commonly associated with persistent forms of cognitive impairment, including deficits in attention, memory and executive function. In the present review, we provide a comprehensive description of the factors relating to MA use and the major health-related consequences, with an emphasis on MA-induced psychosis. It is hoped that increased knowledge of MA abuse will provide the basis for future treatment strategies.

La méthamphétamine (MA), un psychostimulant, est une drogue très toxicomanogène dont la popularité a grimpé en flèche au cours de la dernière décennie en Amérique du Nord. Des laboratoires clandestins de plus en plus nombreux ont entraîné des augmentations spectaculaires de la production de MA et, par conséquent, d'importants problèmes pour la santé publique, la loi et l'environnement. Les données actuelles indiquent que l'exposition à la MA est neurotoxique et des études de neuro-imagerie confirment que l'utilisation chronique chez l'être humain peut causer des dommages nerveux étendus. On établit couramment un lien entre ces changements physiologiques et des formes persistantes de déficience cognitive, y compris des déficits de l'attention, de la mémoire et de l'exécution. Nous présentons dans cette analyse critique une description détaillée des facteurs reliés à l'utilisation de la MA et ses principales répercussions sur la santé, en insistant sur la psychose causée par la MA. On espère qu'une meilleure connaissance de l'abus de MA servira de base à de futures stratégies de traitement.

## Introduction

The illicit psychostimulant drugs, which include cocaine and the amphetamines as well as their derivatives, represent a highly addictive class of compounds. In recent years, there has been a dramatic increase in the use of certain drugs of this class. Among these, both methamphetamine (MA) and 3,4-methylenedioxymethamphetamine (MDMA, or "ecstasy") have experienced a surge in popular use. MA (Fig. 1), can be synthesized by a straightforward 1-step process by reduction of ephedrine or pseudoephedrine,<sup>1</sup> ingredients that are widely available in North America in nonprescription al-

lergy medicine and through methods described in detail on the World Wide Web. The relative ease with which the primary ingredients of MA can be acquired and then converted into the final product has led to the widespread existence of numerous "mom-and-pop" laboratories,<sup>2</sup> although larger criminal "super lab" organizations in Mexico, Canada and the United States continue to supply a large proportion of the high-purity drug.

These factors have led to a so-called epidemic of MA addiction in certain regions of the US and Canada. The important long-term health-related consequences of this trend are underscored by evidence of the especially pernicious effects of MA exposure. Numerous preclinical and clinical studies

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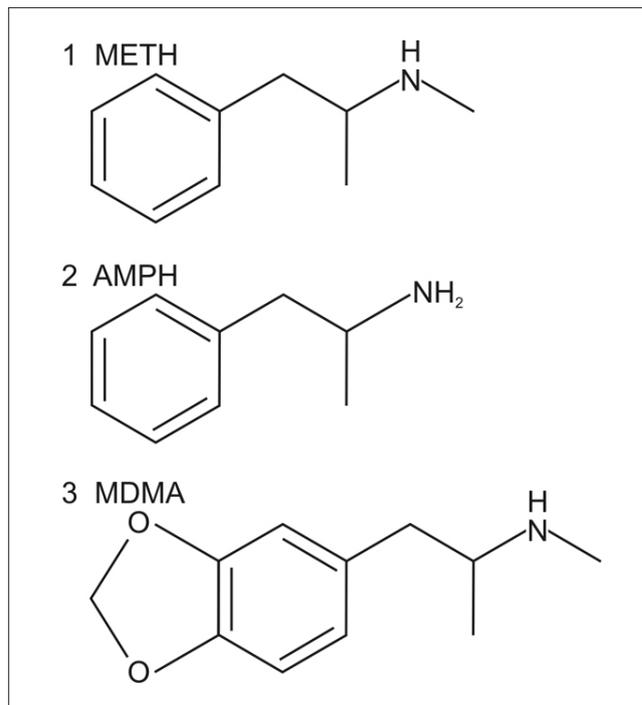
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demonstrate that MA exposure results in extensive neural damage, which is associated with cognitive impairment. At present, the treatment options for MA-induced psychosis and MA addiction are limited, and further clinical trials are required.

In this review, we aim to provide a broad overview of the current state of knowledge regarding MA and the effects of its use, presenting findings from the basic sciences and from clinical fields. We briefly describe the physiological effects of MA and summarize the major findings from the animal literature. Because most of the human studies on the effects of MA abuse have examined changes *in vivo*, we chose to examine the evidence for structural and molecular changes obtained from the neuroimaging techniques, magnetic resonance imaging (MRI) and positron emission tomography (PET). These changes are then compared with reported effects of MA abuse on cognition. After summarizing these data, we describe the social impact of MA abuse and the limited options for treating MA addiction.

## Neurobiology of MA

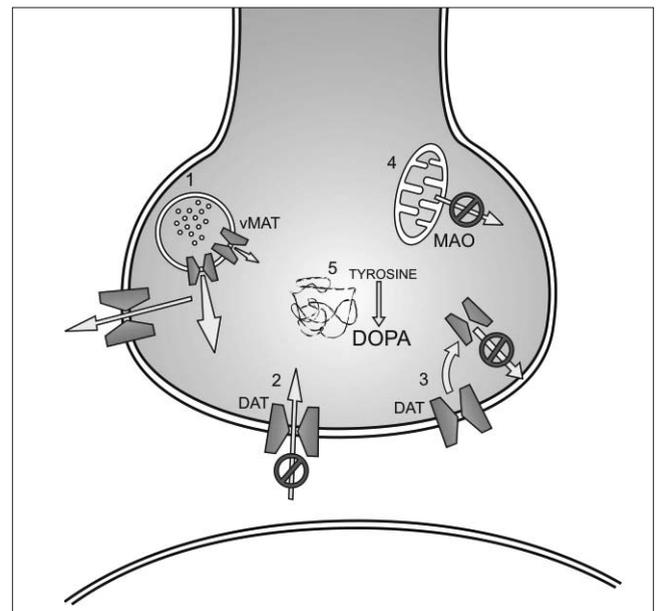
MA is a psychostimulant drug that acts on the central nervous system (CNS) through a non-exocytotic mechanism, causing the release of monoamine neurotransmitters, including dopamine, norepinephrine and serotonin.<sup>13</sup> Unlike cocaine, which works principally by blocking plasma membrane transporters that reuptake monoamines,<sup>4</sup> MA exerts multiple pharmacological effects via different molecular



**Fig. 1:** Chemical structure of methamphetamine (1), as well as the closely related psychostimulants d-amphetamine (2) and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") (3). AMPH = amphetamine; METH = methamphetamine

processes (Fig. 2). The primary mechanisms by which the amphetamine class of drugs increase levels of monoamines (principally, dopamine) include the redistribution of catecholamines from synaptic vesicles to the cytosol<sup>5</sup> and the reverse transport of neurotransmitter through plasma membrane transporters.<sup>6</sup> In addition, amphetamines have been shown to block the activity of monoamine transporters,<sup>7</sup> similar to cocaine, and to decrease the expression of dopamine transporters at the cell surface.<sup>8</sup> There is also evidence that amphetamines can increase cytosolic levels of monoamines by inhibiting the activity of monoamine oxidase (MAO),<sup>9</sup> as well as increase the activity and expression of the dopamine-synthesizing enzyme, tyrosine hydroxylase (TH).<sup>10</sup> As a result of these combined mechanisms, amphetamines act as highly potent releasers of monoamines. Further, MA has a significantly greater elimination half-life than many other psychostimulants, such as cocaine, leading to behavioural and psychological effects that last substantially longer than these other drugs<sup>11</sup> (8–13 h for MA v. 1–3 h for cocaine). MA also has a relatively high lipid solubility, allowing more rapid transfer of the drug across the blood–brain barrier.

The acute effects of MA on neurotransmitter release are feelings of euphoria, well-being and alertness,<sup>12</sup> as well as increased libido and decreased appetite. Immediate somatic side effects of higher doses, which result partly from the



**Fig. 2:** Physiological mechanisms by which methamphetamine increases synaptic levels of monoamines, principally dopamine (DOPA). Mechanisms include the redistribution of catecholamines from synaptic vesicles to the cytosol (1) and the reverse transport of neurotransmitter through plasma membrane transporters. In addition, amphetamines have been shown to block the activity of monoamine transporters (2), similar to cocaine, and decrease expression of dopamine transporters at the cell surface (3). Amphetamines can increase cytosolic levels of monoamines by inhibiting the activity of monoamine oxidase (MAO) (4) and increase activity and expression of the tyrosine hydroxylase (5). DAT = dopamine transporter; vMAT = vesicular monoamine transporter.

effects of MA on epinephrine and norepinephrine release by the adrenal glands,<sup>13</sup> may include increased blood pressure, hyperthermia, stroke, cardiac arrhythmia, stomach cramps and muscle tremor; acute negative psychological side effects include anxiety, insomnia, aggression, paranoia and hallucinations.<sup>2</sup> We recently reviewed the intermediate-term negative effects of withdrawal from sustained higher doses of psychostimulant drugs. Terminating the administration of high doses of these drugs in humans and animals induces physiological and psychological effects that are opposite to the acute effects of the drug (Fig. 3); these include fatigue, anxiety, irritability, depression, inability to concentrate and even suicidality.<sup>15,16</sup>

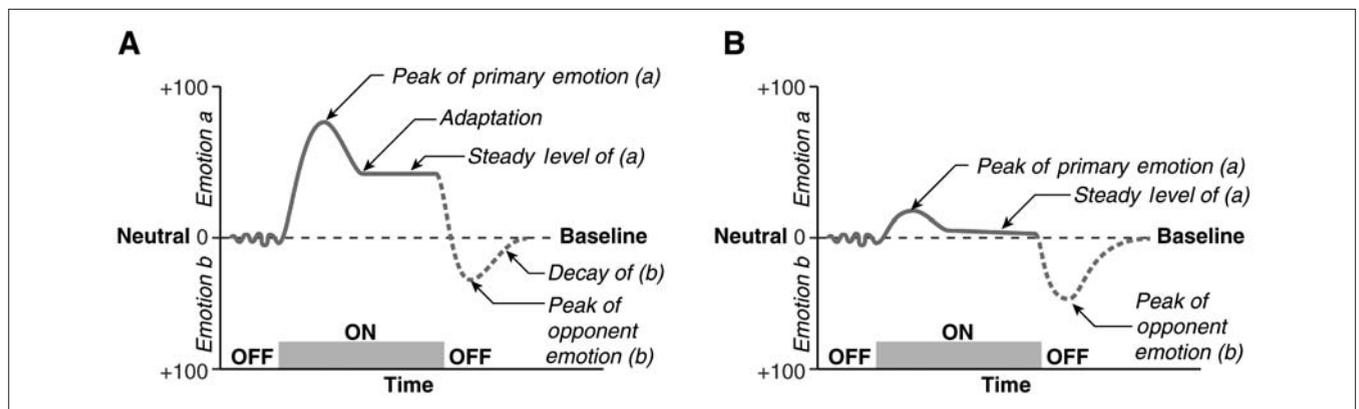
### Animal studies of MA exposure

Numerous preclinical reports used techniques such as in-vivo cerebral microdialysis to measure synaptic levels of neurotransmitters and demonstrated that exposure to amphetamines results in the rapid release of high levels of monoamines in the CNS,<sup>1,3</sup> which are hypothesized to underlie the reinforcing properties of such drugs. Typically, both animals and humans will self-administer amphetamines until the drug supply is curtailed, or the individual will voluntarily cease further drug intake (often due to a lack of additional reinforcing effects of the drug arising from tolerance-related processes). During this early withdrawal period, animal studies have shown that synaptic levels of monoamines are decreased in limbic brain nuclei and that additional administration of non-contingent doses of amphetamines results in reduced levels of neurotransmitter release, compared with drug-naïve animals.<sup>16,17</sup> This period is also associated with the onset of depressive-like symptoms, including anhedonia and decreased motivation.<sup>18–21</sup> These temporary reductions in monoamines normally return to baseline levels over several days, as the psychological symptoms abate.<sup>16</sup> However, the neurotoxic effects of amphetamines, including MA, are measured in terms of months or years rather than days.

Earlier studies identified a selective long-term loss of

dopamine terminal markers in the brains of rodents treated with high doses of MA. These included decreased levels of dopamine, reduced TH activity and altered density of the dopamine transporter (reviewed in Sulzer et al<sup>1</sup>). More recent studies have demonstrated that there is a distinct anatomic degeneration of axon terminals in the rodent striatum following treatment with higher doses of MA.<sup>22</sup> Despite the extensive loss of dopamine terminals, there is minimal evidence for actual loss of dopamine cell bodies, measured in the substantia nigra, pars compacta and ventral tegmental areas.<sup>23</sup> It has been repeatedly observed that the nigrostriatal dopamine pathway is more vulnerable to the neurotoxic effects of MA than are the mesocorticolimbic dopaminergic projections from the ventral tegmental area to forebrain regions, such as the nucleus accumbens.<sup>24</sup> It has been hypothesized that this phenomenon may be due to the greater concentration of dopamine transporters in the terminal regions of the nigrostriatal dopamine pathway (i.e., the striatum).<sup>25</sup> The dopamine transporter plays a major role in MA-induced dopamine release, and genetically engineered mice without the dopamine transporter are significantly less vulnerable to the neurotoxic effects of MA<sup>26</sup>; dopamine uptake blockers, such as bupropion, decrease the magnitude of MA-induced neurotoxicity.<sup>27</sup>

The precise mechanisms by which MA exerts its neurotoxic effects on the dopamine system remain to be fully resolved. Nevertheless, there is strong evidence that endogenous dopamine is an important substrate. The depletion of dopamine from terminal regions by pretreatment with dopamine depleting agents, such as reserpine or  $\alpha$ -methyl p-tyrosine (AMPT), decreases the neurotoxic effects of MA administration in rodents.<sup>28</sup> A proposed mechanism includes the propensity for dopamine, in the presence of high doses of MA, to be rapidly and easily oxidized into reactive oxygen species (ROS), including quinones and semiquinones.<sup>29</sup> Abundant evidence indicates that oxidative stress resulting from free radicals and ROS is necessary for the neurotoxic effects of MA on dopamine terminals, which may be mediated through the production of downstream



**Fig. 3:** (A) The central hypothesis of the opponent-process theory of motivation, as envisioned by Solomon and Corbit (14), is that emotions may be considered as pairs of opposites. Thus, when one emotion or affective state is experienced (Emotion a), an opposing emotion or affective state is triggered after a period of time (Emotion b). (B) With repeated stimulations, the opposing emotion or affective state increases in strength, decreasing the experience of the primary emotion or affective state and producing an enduring aftereffect.

neurotoxic compounds such as peroxynitrite (ONOO<sup>-</sup>). However, Itzhak and Achat-Mendes<sup>30</sup> noted that the neuroprotective effects of dopamine depletion are body core temperature-sensitive; the palliative effects of pretreatment with reserpine and AMPT are mitigated when core temperature is raised.<sup>31</sup> Alternative mechanisms of MA-induced neurotoxicity have been proposed to include activation of apoptotic biochemical cascades involving caspases, proapoptotic *Bcl-2* family genes and the tumour suppressor gene *p53*. In addition, an increasing number of studies indicate the importance of both pro- and anti-inflammatory immune mediators, such as the cytokines, on the neurotoxic effects of MA on dopamine terminals.<sup>30</sup>

More recently, studies have focused on the neurotoxic effects of MA on serotonergic neurons. Similar to its effects on dopamine terminals, the administration of high doses of MA results in significant long-term reductions in markers of serotonergic terminals, which are most commonly measured by changes in the levels of serotonin and in the serotonin transporter.<sup>30,32</sup> However, unlike the relatively discrete effects of MA neurotoxicity on dopamine neurons, which are largely restricted to the striatum, the effects of MA on serotonin neurons are much more diffuse. The list of regions exhibiting MA-induced serotonergic damage includes, but is not limited to, the perirhinal cortex, hippocampus, anterior cingulate cortex, caudate nucleus, nucleus accumbens and septum.<sup>33–35</sup> The mechanism of MA-induced serotonergic toxicity is less well understood than it is for dopamine but is believed to be mediated, in large part, by the production of free radicals.<sup>32</sup> Even less is known about the effects of high doses of MA on the norepinephrine pathways of the CNS, despite the greater capacity of MA to stimulate norepinephrine than either dopamine or serotonin release.<sup>36</sup> Brunswick and colleagues reported decreases in levels of norepinephrine transporter binding sites in specific amygdaloid nuclei and in the dorso-medial hypothalamic nucleus after acute treatment with MA.<sup>33</sup> Because the norepinephrine pathways of the brain play an important role in the regulation of arousal, motivation, attention and executive function,<sup>37,38</sup> further study of this system is warranted.

It has also become clear from the animal literature that the neurotoxic effects of MA are strongly dependent on the type of dosing schedule. Most studies in rodents use acute exposures to multiple high doses of MA over 1 or 2 days (e.g., Itzhak et al,<sup>30</sup> Belcher et al<sup>35</sup>) which typically result in a loss of about 30%–60% of dopamine terminal markers and are often accompanied by cognitive impairment.<sup>35,39</sup> Human patterns of MA use are normally based on years of exposure to the drug.<sup>40–42</sup> Thus, it may be argued that more homologous effects would be produced by exposing animals to longer regimens of MA or by requiring animals to self-administer the drug. These points are theoretically valid, although empirical evidence indicates that the neurotoxic effects of MA are significantly lessened in these latter types of study, perhaps due to the development of drug tolerance.<sup>43,44</sup> A recent study showed that an escalating dose schedule of MA followed by a 1-day binge (0.1–4.0 mg/kg over 14 days plus 4 ∞ 6 mg/kg at 2-h intervals) produced only an 11% decrease in dopamine

levels, whereas the acute 1-day binge alone induced a 37% loss of dopamine<sup>44</sup>; this is closer to results of postmortem human studies, which report decreases of 50%–61%.<sup>45</sup> Because the aim of many preclinical studies is to attain the same post-mortem degree of neurotoxicity in animals as in humans, there is strong rationale to continue using established and reliable regimens of MA administration that induce robust neurotoxic effects, although alternate MA regimens should be evaluated in the future. Further, it is unknown whether neurotoxic effects of MA use in humans result from longer-term exposure to low doses of the drug or from brief exposure to much higher doses.

The phenomenon of psychostimulant-induced “sensitization” refers to the enhanced physiological and behavioural response to a low dose of amphetamines after prior exposure to low, intermittent doses of this drug.<sup>46–48</sup> Although psychostimulant sensitization may induce a range of molecular and behavioural changes, these are generally not considered neurotoxic. However, the findings from drug administration studies in animal paradigms indicate that even low, intermittent doses of MA may be able to induce subtle alterations in brain morphology and motivation, which may be relevant to earlier stages of MA drug abuse in humans. In addition, amphetamines have also been shown to “cross-sensitize” with stress, resulting in greater physiological responses to stress after prior exposure to amphetamines.<sup>48</sup>

## Neurotoxic effects of MA use in humans

Postmortem human data regarding the effects of MA use on monoamine neurotoxicity are surprisingly sparse. Most post-mortem human research has been performed by Kish and colleagues at the Centre for Addiction and Mental Health in Toronto, Ontario. In the first major evaluation of the effects of long-term MA use, Wilson and others noted that the mean striatal (nucleus accumbens, caudate, putamen) dopamine levels were reduced by 50%–61% in the brain of 12 long-term MA users, many of whom had died from drug overdose.<sup>49</sup> In a follow-up study, this research group reported that dopamine levels were as severely depleted in MA users as in people with Parkinson’s disease (PD) in the caudate but not in the putamen subdivision of the striatum.<sup>45</sup> This finding may explain why PD-like symptoms are not more commonly observed in long-term MA users. Further evidence of dysregulation of the dopamine system was obtained in the same postmortem sample set; a 25%–30% decrease in the maximal extent of dopamine-induced stimulation of adenylyl cyclase activity was demonstrated, which was observed in the striatum of the MA users. These data showing reduced levels of dopamine and decreased dopamine receptor function linked to adenylyl cyclase in the striatum suggest that the physiological function of this brain region may be severely impaired in long-term MA users. Future studies, including different postmortem samples, are required to ascertain the effects of long-term MA use in humans on levels of other neurotransmitters and the molecular machinery responsible for neurotransmitter release.<sup>47,50–52</sup>

To date, most research on the neurotoxic effects of MA use

in humans has been performed in vivo with neuroimaging techniques. Recent structural MRI studies in people with MA addiction have reported several morphological changes in the brain. The more prominent of these include a loss of grey matter in the cingulate, limbic and paralimbic cortices of MA abusers, as well as significantly smaller hippocampi and white-matter hypertrophy.<sup>41</sup> Longer-term MA users also displayed an enlarged striatum<sup>42</sup> and subtle alterations in cerebral vasculature.<sup>53</sup> A recent study has identified shape changes of the corpus callosum in abstinent MA users, including increased curvature in the genu and decreased width in posterior midbody and isthmus areas, which connect frontal and parietal cortices.<sup>54</sup>

Several studies have used proton magnetic resonance spectroscopy (MRS) to examine changes in neuronal metabolites in specific brain regions in people with MA addiction (Table 1). This technique allows the measurement of markers of cellular integrity and function, which include N-acetyl aspartate (NAA), high-energy metabolic products (creatine [CR] and phosphocreatine [PCR]), cell membrane synthesis or degradation products (choline [CHO]) and glia markers (myo-inositol [MI] and CHO).<sup>57</sup> Results from this body of research suggest that the effects of MA exposure are region- and metabolite-specific. In the first study of MA users, Ernst and others reported that there was an inverse correlation between levels of NAA in frontal white matter and the logarithm of lifetime MA used.<sup>55</sup> Two more recent studies have noted statistically lower NAA/CR ratios in the anterior cingulate cortex,<sup>2,57</sup> whereas CHO/CR and CHO/NAA ratios were significantly higher in MA abusers. Decreased levels of NAA, or reduced NAA/CR ratios, are associated with neuronal loss and clinical disease (e.g., Ende et al,<sup>59</sup> Ernst et al<sup>60</sup>), whereas the CHO signal is associated with membrane synthesis and turnover,<sup>61</sup> suggesting that increased CHO or CHO

ratios may reflect compensatory responses to MA-induced damage.<sup>57</sup> These combined findings indicate that exposure to MA may result in damage to frontal regions, with resulting adaptive processes.

Data from MRS studies of the basal ganglia reveal a similar pattern of results, with significantly greater CHO/CR ratios in long-term MA users (non-drug using at the time of the study), compared with control subjects. This elevation was significantly correlated with duration of MA abuse and the severity of residual psychiatric symptoms.<sup>40</sup> Levels of NAA and CR, the latter of which is commonly used as a standard reference in MRS studies, were both decreased in the basal ganglia of MA abusers.<sup>55</sup> Similarly, levels of NAA and CR were also decreased in the basal ganglia of people with MA addiction with HIV, compared with non-drug abusing HIV patients.<sup>58</sup> Thus, results from the basal ganglia broadly resemble MRS findings from the frontal brain regions and suggest that drug-induced neuronal damage does occur, with possible compensatory adaptive mechanisms involved in neuronal repair.

Positron emission tomography (PET) with radiolabelled ligands has been used to measure the levels of dopamine-relevant proteins in the brains of MA users in vivo. These studies have found consistent decreases in levels of the dopamine transporter in brain regions, including the orbitofrontal cortex, dorsolateral prefrontal cortex, striatum, nucleus accumbens and amygdala,<sup>62-65</sup> which have been associated with cognitive impairment and severity of psychiatric symptoms. MA use for longer than 1 year was also associated with significantly lower levels of the dopamine D<sub>2</sub> receptor in the striatum<sup>66</sup> (however, see Iyo et al<sup>67</sup>). A recent study reported that the density of the serotonin transporter was significantly lower in global brain regions in longer-term MA abusers than in control subjects and that levels of the transporter were inversely related to duration of MA use. Further, people who abused MA were more aggressive, which was related to levels of the serotonin transporter in orbitofrontal, temporal and anterior cingulate areas.<sup>68</sup> Measurement of glucose metabolism in MA users by PET has observed increased global metabolism but showed lower relative levels of striatal and thalamic metabolism.<sup>69,70</sup> A global pattern of metabolic activity similar to that observed in major depressive disorder was also noted in MA users during early abstinence, which corresponds to the period of withdrawal that is associated with depressive-like features, such as dysphoria and anhedonia.<sup>15,71</sup> It would be interesting to measure alternate PET indices of long-term MA use and withdrawal that are related to mood and cognitive dysregulation, such as serotonin synthesis,<sup>72</sup> in this clinical population.

Although structural MRI and MRS have provided invaluable in-vivo information about the morphological and metabolite alterations in people who abuse MA, the results of the above studies are limited in their interpretation by several potential confounds. Perhaps the most important of these is lack of knowledge about the premorbid condition of MA abusers before the onset of addiction. Knowledge of brain morphology and/or metabolites before drug use, as well as functional indicators of these parameters, such as

**Table 1: Significant alterations reported in neuronal metabolites or metabolite ratios in methamphetamine users, measured by magnetic resonance spectroscopy**

Study	Brain region	Metabolite	Direction of change
Ernst et al <sup>55</sup>	Basal ganglia	NAA, CR	↓
	Frontal white matter	NAA	↓
	Frontal gray matter	CHO, MI	↑
Nordahl et al <sup>56</sup>	Anterior cingulate	NAA/CR	↓
		CHO/CR	↑
Sekine et al <sup>40</sup>	Basal ganglia	CHO/CR + PCR	↑
Nordahl et al <sup>57</sup>	Anterior cingulate	NAA/CR	↓
		CHO/NAA	↑
Chang et al <sup>58</sup>	Basal ganglia	NAA, CR	↓
		NAA	↓
	Frontal gray matter	CHO	↑
		MI	↑

CHO = choline-containing compounds; CR = creatine; NAA = N-acetyl aspartate; MI = myo-inositol; PCR = phosphocreatine.

premorbid cognition, is sparse. Thus, it remains unknown whether the differences observed with MRI and MRS and functional deficits, such as cognitive impairment, between MA users and control subjects reflect a deleterious effect of drug exposure or a natural (but abnormal) condition of the brain that predisposes to addiction.<sup>40</sup> Longitudinal studies that aim to observe changes at different times after admission to determine whether structural or metabolite alterations will reverse over time in the absence of the MA are complicated by extremely high rates of recidivism in people with addiction and uncertainty over self-reports of abstinence, drug dose or usage pattern.<sup>73,74</sup> In addition, most MA addicts are poly-drug abusers, leaving open the question of whether observed changes are due to a specific drug or to its interaction with additional drugs.<sup>41</sup> Many MA abusers with psychosis are treated with antipsychotic drugs, which have well-established effects on brain morphology. Members of our research group recently reported that schizophrenia patients treated with typical antipsychotic drugs exhibited increased basal ganglia volumes (measured by structural MRI) that are reversible following replacement with olanzapine (an atypical antipsychotic).<sup>75</sup> More recently, we reported that typical antipsychotic drugs increase the volume of the thalamus.<sup>76</sup> Thus, the use of animal paradigms will be invaluable in elucidating the influence of these potential confounds: cognition, brain structure and metabolites can be measured before specific treatment with MA and at predetermined times afterward, in the absence of further illicit or therapeutic drugs.

### Cognitive effects of MA use

Numerous studies have confirmed that MA abuse is associated with cognitive impairment. Unlike the acute effects of a single low dose of MA, which can improve cognitive processing speed, attention, concentration and psychomotor performance,<sup>77,78</sup> long-term exposure to MA may result in profound neuropsychological deficits (see Nordahl et al<sup>2</sup>). A recent study indicated that MA use was associated with a 40% prevalence of global neuropsychological impairment.<sup>79</sup> Nevertheless, despite the broad nature of such deficits, some of the most consistent and severe changes include specific impairments in working memory, attention and executive function.<sup>80–86</sup> It has been hypothesized that this specificity is due to the denser dopaminergic innervation of neural circuits that subservise these cognitive processes, including dopamine-rich fronto striatal thalamo cortical pathways,<sup>83</sup> which are the primary substrate of neurotoxic doses of MA. People with a history of MA use displayed working memory deficits in such tasks as the immediate recall component of the auditory verbal learning test<sup>63</sup> and took 18%–30% longer to complete the working memory components of the California computerized assessment package.<sup>87</sup> Consistent with the greater distractibility of MA users, as widely observed in the clinic,<sup>82</sup> attentional deficits have been noted in the Stroop Colour Word and Trail Making tests.<sup>88,89</sup> Alternate procedures have demonstrated that the primary explicit attentional deficits in MA users may be related to reduced

cognitive inhibition<sup>82</sup> and an inability to suppress irrelevant task information.<sup>2</sup> Impairments in executive function, which include the cognitive domains of abstract reasoning, planning and behavioural flexibility, are evident in MA users in the Stroop Interference Task.<sup>89</sup> Episodic memory tasks typically have both a strategic-frontal component and an associative-hippocampal component; Woods and colleagues recently demonstrated that, although there is an episodic deficit in MA users in the Hopkins Verbal Learning Test, it is of a strategic (i.e., executive, planning and organizational) nature and is not purely mnemonic.<sup>83</sup> Interestingly, the above deficits parallel, to some degree, the nature of cognitive impairment observed in attention-deficit hyperactivity disorder (ADHD) — a disorder that is frequently treated with amphetamines, including MA.<sup>90</sup> Whether such similarity reflects an increased sensitivity to amphetamines in people with ADHD<sup>84</sup> or a consequence of high doses of MA remains an ongoing matter for study.<sup>91</sup>

Extensive use of MA has also been repeatedly associated with deficits in episodic memory. These are most evident as impairment in word recall tasks, which measure recall at specific times after stimulus presentation.<sup>41,63,88</sup> Unlike the cognitive domains of attention and executive function, which depend on the functional integrity of fronto-striatal circuits that are densely innervated by dopamine terminals, episodic memory relies predominantly on the hippocampus and related structures,<sup>92</sup> where dopaminergic innervation is more sparse. However, animal studies indicate that MA is also neurotoxic to norepinephrine and serotonin terminals in the hippocampus, which play a critical role in regulating cognitive processing.<sup>93</sup>

One of the most prominent effects of MA abuse on cognitive function pertains to the development of drug-related psychosis. Aside from the sudden psychosis-inducing effects of high doses of MA, prior exposure to MA, following metabolism and excretion of the drug, can also lead to an enduring form of psychosis. Studies conducted in Japan, where high levels of MA use have been prevalent for decades, report that between 36% and 64% of MA users who have experienced psychotic symptoms continue to present with these symptoms for more than 10 days after the cessation of MA use, even though the MA is eliminated from the blood stream in less than 5 days.<sup>53</sup> Another study investigating female inmates in Japan observed that 21% of those having experienced MA psychosis remained in a psychotic state for more than 6 months, whereas 49% returned to their premorbid state but experienced “flashbacks” (i.e., spontaneous recurrence of psychotic symptoms that would fit criteria for a paranoid-schizophrenia psychotic relapse) during their 15–20 months of incarceration.<sup>53</sup> Studies in Japan show that MA users with MA psychosis are much more likely to experience psychotic symptoms again if they use MA and are also more likely to have a psychotic relapse when confronted with stressful situations, even years after cessation of MA use.<sup>53</sup> MA users with persistent or recurrent psychotic symptoms become vulnerable to environmental stress and may benefit from antipsychotic medication in a manner similar to individuals with schizophrenia.<sup>53</sup>

## Genetics and MA abuse

Evidence from twin studies reveals that most forms of substance abuse exhibit a strong degree of heritability, with liabilities of up to 71% for certain classes of drugs.<sup>94</sup> This finding strongly suggests that there are inherited functional variants of genes that predispose individuals to acquiring and maintaining drug use. Regarding MA specifically, several studies have reported significant associations between different genes and MA use or the development of MA-induced psychosis. To our knowledge, all significant associations have been obtained in Chinese and Japanese cohorts (Table 2), although other reports have been measured in samples with Czechoslovakians (Table 3). The list of genes related to MA use and drug-induced psychosis includes a number pertinent to the dopaminergic system, which represents an important substrate for both the reinforcing properties of MA and, presumably, most forms of psychosis. The Val158Met polymorphism of catechol-O-methyltransferase (COMT), which represents a high-activity allele, occurred with significantly greater frequency in MA users than in control subjects. In the same group of Han Chinese from Taiwan, a haplotype of the 120-bp variable number tandem repeat (VNTR) polymorphism and the exon 3 VNTR in the dopamine D<sub>4</sub> receptor was significantly associated with MA use.<sup>96</sup> Moreover, there were significant interactions between the COMT and D<sub>4</sub> receptor polymorphisms and MA use. The dopamine transporter has been investigated in several studies as a genetic locus with a possible link to MA use. In 2 studies, there was no association between the DAT 3'-VNTR and MA use or psychosis in Han Chinese,<sup>106,107</sup> although a study in a Japanese sample noted that fewer repeat alleles of this 40-bp region were significantly linked to increased likelihood of long-term psychosis following drug termination.<sup>99</sup> In another study of a Japanese cohort, the A1 allele of the *TaqI* A polymorphism of the dopamine D<sub>2</sub> receptor was significantly associated with both the symptoms and progression of MA psychosis or abuse (see Harano et al<sup>102</sup>). In apparent contrast, there was no significant association between this polymorphism and MA

use in a Chinese male cohort, although this group was selected to exclude subjects with psychosis.<sup>108</sup> The *TaqI* A polymorphism of the dopamine receptor D<sub>2</sub> was also not associated with MA dependence in a Czechoslovakian sample, although data about psychosis in this group were not provided.<sup>109</sup>

Additional genes associated with MA use include the gamma aminobutyric acid (GABA)<sub>A</sub> receptor gamma 2 subunit. A Japanese cohort of MA users, most of whom exhibited drug-induced psychosis, showed a significant association with a haplotype of the 2 single nucleotide polymorphisms (SNP), 315C > T and 1128 + 99C > A for the GABA<sub>A</sub> receptor gamma 2 subunit.<sup>100</sup> In a study of Han Chinese, multiple haplotypes, all of which contained rs4480617, a novel SNP located at nucleotide-69 in the 5'-UTR of the (A) receptor

**Table 3: Studies with no association between genes and methamphetamine (MA) use or MA psychosis**

Gene	Variant	Ethnic group	Reference
Dopamine transporter	SNP	Han Chinese	106
Serotonin transporter	SNP	Han Chinese	106
Dopamine transporter	SNP	Han Chinese	107
Dopamine D <sub>2</sub> receptor	SNP	Han Chinese*	108
Dopamine D <sub>4</sub> receptor	SNP	Han Chinese*	108
Dopamine D <sub>2</sub> receptor	SNP	Czechoslovakian	109
Angiotensin-converting enzyme	SNP	Czechoslovakian	109
Angiotensinogen	SNP	Czechoslovakian	109
Brain-derived neurotrophic factor	SNP	Japanese	110
Type-1 Sigma receptor	SNP	Japanese	111
Tissue-plasminogen activator	SNP	Japanese	112
Fatty acid amide hydrolase	SNP	Japanese	113
X-box binding protein 1	SNP	Japanese	114

SNP = single nucleotide polymorphism.  
\*men only

**Table 2: Studies with significant association between genes and methamphetamine (MA) use or MA psychosis**

Gene	Variant	Ethnic group	Reference
AKT1	SNP and haplotype	Japanese	95
COMT	SNP	Han Chinese	96
DD4R	Haplotype	Han Chinese	96
COMT/DD4R	Haplotype	Han Chinese	96
Glutathione S-transferase P1	SNP	Japanese	97
Glutathione S-transferase M1	Allele deletion	Japanese*	98
Dopamine transporter	SNP	Japanese	99
GABA <sub>A</sub> receptor gamma 2 subunit	Haplotype	Japanese	100
GABA <sub>A</sub> receptor $\alpha$ 1/ gamma 2 subunits	SNP and haplotype	Han Chinese*	101
Dopamine D <sub>2</sub> receptor	SNP	Japanese	102
Mu-opioid receptor	SNP	Japanese	103
Brain derived neurotrophic factor	SNP	Han Chinese†	104
Alpha-synuclein	SNP	Japanese*	105

COMT = catechol-O-methyltransferase; DD4R = dopamine D<sub>4</sub> receptor; SNP = single nucleotide polymorphism.

\*women only

†men only

gamma 2 subunit gene, were significantly associated with MA use but not MA-induced psychosis.<sup>101</sup> Interestingly, significant genetic links in this study were only evident for female MA users. Other examples of significant sex-dependent, genetic associations with MA use include the genes glutathione S-transferase M1<sup>98</sup> and  $\alpha$ -synuclein,<sup>105</sup> both of which are present only in women. The reasons for these sex-dependent effects are unknown but they indicate that the nature of genetic factors on MA use and psychosis is likely to be more complicated than initially thought.

## The MA problem

According to the World Health Organization, at least 35 million people regularly used MA worldwide in 1996, making it the second most commonly used illicit drug after cannabis.<sup>115</sup> More recent surveys indicate that MA is the fastest-growing illicit drug in North America.<sup>116</sup> MA abuse among youth is especially common, leading some to describe the MA problem as an "epidemic," particularly in the Western regions of the US and Canada.<sup>117–119</sup> The MA phenomenon started on the West Coast<sup>118,120,121</sup> and has spread to other Canadian cities.<sup>119,122</sup> In Vancouver, BC, 57% of "street kids" (adolescents under 19 years of age who are living on the street or who are involved with street life to a significant extent<sup>123</sup>) reported having used MA more than 10 times in their lifetime.<sup>124</sup> Similar statistics have been reported in Victoria, BC, with 47% of street kids and 10% of all high school students surveyed reported having used the drug. Particular ethnographic groups may be at increased risk for the effects of MA. For instance, Aboriginal groups represent approximately 27% of transient population of Vancouver's Downtown Eastside,<sup>125</sup> an area with among the highest rates of polysubstance abuse in North America. This contrasts with a demographic population frequency of 2% for Aboriginals in Vancouver as a whole.<sup>126</sup> MA abuse within the male homosexual and bisexual community has become a major concern, particularly because of the increased rate of high-risk sexual behaviours associated with MA abuse<sup>127,128</sup>; furthermore, long-term MA use can exacerbate the cognitive impairments associated with HIV.<sup>79</sup> Increasing evidence indicates that prenatal exposure to MA results in severe morphological changes in the brain, with associated cognitive deficits.<sup>129</sup> Recreational users (i.e., "ravers") often take MA either voluntarily or inadvertently in combination with other drugs (i.e., MDMA).<sup>130</sup>

Forty-five percent of youth in Vancouver mentioned being able to obtain MA in less than 24 hours,<sup>131</sup> and the drug can be absorbed in multiple ways: smoked (vaporized), snorted, intravenously injected or swallowed. Typically, users can maintain their dependence for less than Can \$5 a day and experience intoxication effects for 6–16 hours.<sup>131</sup> A recent qualitative survey conducted among street youth in Vancouver described how people intoxicated with MA believe the drug "makes them feel normal" and helps them cope with traumatic experiences and depression, but it also makes them feel more reactive and threatened by authority

figures. Most of them perceived an important deterioration in their quality of life due to MA abuse.<sup>132</sup> Other studies support an increase in violence that is linked to MA abuse.<sup>133</sup> The survey reported that more than 80% of the street youth who regularly abused MA also suffered from MA psychosis and that psychotic symptoms increased with duration of MA use. Of great concern is the finding that repeated psychotic episodes may lead to increased treatment resistance, with symptoms becoming less responsive to medication following successive relapses and, in some cases, residual symptoms appearing that were not present before relapse.<sup>134</sup>

The recent rise in popularity of MA use is also reflected in US government crime statistics. The Drug Enforcement Agency reports that authorities seized 1370 kg of MA along the Mexico–US border in 2001, compared with only 6.5 kg in 1992.<sup>135</sup> In addition, the number of treatment admissions to publicly funded treatment facilities for MA has increased from approximately 20 000 in 1993 to over 110 000 in 2003.<sup>136</sup> It was recently estimated that 600 000 people in the US use the drug on a weekly basis.<sup>137</sup> Within Canada, the number of MA laboratories dismantled by Canadian law enforcement has increased, with 24 laboratories seized in 2000 and 39 in 2003. In 2000, the first "super laboratory" was uncovered in Vancouver, BC.<sup>138</sup> In addition to the mental health problems involved with the longer-term consumption of MA, use of the drug is associated with numerous additional physical problems, including dental caries, infection, heart failure and malnutrition.<sup>139</sup> A recent survey by the US National Association of Counties reported that "methamphetamine was responsible for more emergency department visits than any other drug and that the need for treatment programmes is growing dramatically."<sup>140</sup> Even the manufacture of the drug itself has dire consequences. In the US, the Hazardous Substances Emergency Events Surveillance (HSEES) system, which monitors data about the public health consequences (e.g., morbidity, mortality and evacuations) of acute hazardous substances in 16 American states, reported that 1791 of the 40 349 events reported to the HSEES system during January 2000 to June 2004 were associated with illicit MA production.<sup>116</sup> This proportion was considerably higher in certain Western states, such as Washington and Oregon (399 and 246 events, respectively; figures were unavailable for California). These numbers are clinically significant; for example, a review of patients admitted to a burns unit in rural Iowa revealed that a substantial proportion were related to MA use or production, with a mean treatment cost of US\$77 580 per patient.<sup>141</sup>

## Treatment of MA-related disorders

The earliest trials of addiction to amphetamines focused on agonist-like replacement pharmacotherapies, similar to the opiate–methadone model. Dextroamphetamine has been the drug of choice in these studies, and although the literature is comprised mainly of uncontrolled, retrospective studies, there have been mixed results (summarized in Grabowski et al<sup>142</sup>), with one indication that dextroamphetamine substitution produced

beneficial effects in a subgroup of patients.<sup>143</sup> The only randomized controlled trial of dextroamphetamine substitution, which used 60 mg daily over 12 weeks in 41 participants, demonstrated a trend toward efficacy that did not reach significance.<sup>142,144</sup> Over the past decade, several trials have hoped to capitalize on the successes in treating cocaine addiction by replicating these studies and substituting MA dependence. To this end, compounds including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressant drugs, MAO inhibitors, the GABAergic drugs gabapentin and baclofen, and the anti-nauseant drug ondansetron have been studied with inconclusive or negative results.<sup>145</sup>

The efficacy of the second-generation atypical antipsychotics have been described only anecdotally to date; however, a National Institute on Drug Abuse (NIDA)-sponsored phase 1 study is currently underway with aripiprazole,<sup>146</sup> and risperidone and quetiapine are being tested in a phase IV head-to-head trial for comorbid MA use in schizophrenia.<sup>147</sup> As mentioned above, MA causes a general loss of dopaminergic terminals and transmission in the CNS. Thus agents that increase dopamine levels may be effective in treating MA addiction. By this reasoning, the antidepressant selegiline, an MAO-B inhibitor that increases dopaminergic neurotransmission, has progressed to a Phase II, controlled, double-blind, NIDA-sponsored study.<sup>148</sup> Similarly, a recent laboratory-controlled study of bupropion (a dopamine reuptake inhibitor) noted significantly reduced acute MA-induced subjective effects of doses up to 30 mg i.v. and decreased cue-induced craving in a small sample of MA abusers. However, as the authors of this study observed, the impact of these findings with respect to future outpatient trials may be limited by the relatively low dose of MA used and the capacity for higher doses of MA to overcome the modest effects found in this trial.<sup>149</sup>

Lobeline, a tobacco plant derivative that inhibits uptake of dopamine into synaptic vesicles, is currently entering Phase I clinical trials.<sup>148</sup> A safety and efficacy trial involving 30 subjects was recently completed with vigabatrin, an antiepileptic drug. This drug is an irreversible inhibitor of GABA-transaminase and has shown preliminary effectiveness in cocaine dependence. Of the 18 patients who completed the study, 16 tested negative for MA for the duration of the 6-week trial.<sup>150</sup> Additional compounds soon to enter or be involved in Phase I trials include the acetylcholinesterase inhibitor rivastigmine, the antiepileptic topiramate, the wake promoting GABA/glutamatergic agent modafinil and the experimental dopamine uptake inhibitor GBR 12909.<sup>148</sup> Several compounds are in later stages of preclinical development, representing diverse approaches to treating MA abuse. Among the more promising of these platforms is immunopharmacotherapy, which is based on the generation or administration of antibodies that are capable of binding to MA before it can reach the brain.<sup>151,152</sup>

Finally, the effectiveness of psychotherapy and behavioural treatments has reliably demonstrated a clinical benefit with minimal potential for side effects. Much attention has recently been devoted to creating a standardized protocol.

The "Matrix" model, a manualized 16-week intensive multi-component cognitive-behavioural/addictions model recently underwent a multisite trial involving 978 patients. Matrix participants initially showed significantly better attendance and longer periods of drug abstinence; however, at follow up, these differences became nonsignificant.<sup>153</sup> Further research is underway to determine which of the many facets of this psychosocial intervention program were most effective.

Regarding treatment for MA-induced psychosis, there is a paucity of data and, currently, no controlled trials for the treatment of post-drug psychosis. The standard of care parallels the management of acute psychosis from other etiologies, such as schizophrenia. By extension, the current trend is for initial treatment with antipsychotics, with a bias toward the atypical antipsychotics as first-line treatment in Canada. Evidence for atypical antipsychotic use is limited to isolated case reports, suggesting some measure of efficacy.<sup>154,155</sup> The length of appropriate pharmacological intervention is largely unstudied, and no consistent guidelines exist in the literature. A small case series indicated that antipsychotic treatment beyond the acute psychotic episode may protect against future psychotic episodes, even at very low doses.<sup>156</sup> These data, however, remain to be replicated.

Current research indicates that people presenting with co-occurring disorders, such as MA-induced psychosis, warrant specific treatments that deal with both the psychosis and the addiction issue.<sup>157,158</sup> Indeed, a comprehensive review of treatment programs for people with drug abuse and mental health problems revealed that the best outcomes stem from programs that are considered evidence-based and that integrate mental health and substance abuse treatment.<sup>157,159</sup> Most MA treatments investigated so far have used only an "addiction" treatment model for stimulant dependence and have excluded people with comorbid mental health problems, such as persistent or recurrent psychotic symptoms.<sup>160-162</sup> Further research is required to develop a more thorough understanding of the profiles of people who suffer from persistent or recurrent MA psychosis, in order to address their specific needs.

## Conclusion

MA is a highly addictive psychostimulant drug, whose abuse has reached epidemic proportions in many parts of the US and Canada. Current patterns of use include higher rates of MA abuse in Western regions of North America, although availability and use of the drug appears to be spreading eastward. Longer-term use of MA can result in substantial cognitive deficits, especially to memory, attention and executive function, possibly from neurotoxicity. Studies of the neurochemistry and structural morphology of the brain in MA users reveal numerous alterations, some of which show a direct relation to functional changes in behaviour and cognition. At present, the best understood factors influencing MA use are environmental, although various candidate genes may predispose to MA addiction and drug-induced psychosis. Priorities for further research include better knowledge of the progressive neurobiological effects

of MA use, as well as treatment and health care strategies for MA users.

We aimed to study MA psychosis from a clinical, biomedical and health services perspective. Specifically, we evaluated the treatment needs of people with MA psychosis in terms of addiction and clinical and psychosocial issues, as well as neurocognitive deficits, and to document their service use and pathways to care. Such a descriptive and exploratory study will enable us to gather the information that will undoubtedly lead to the development and validation of effective treatments for this population.

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