



Review

Methamphetamine use: A comprehensive review of molecular, preclinical and clinical findings

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ABSTRACT

Methamphetamine (MA) is a highly addictive psychostimulant drug that principally affects the monoamine neurotransmitter systems of the brain and results in feelings of alertness, increased energy and euphoria. The drug is particularly popular with young adults, due to its wide availability, relatively low cost, and long duration of psychoactive effects. Extended use of MA is associated with many health problems that are not limited to the central nervous system, and contribute to increased morbidity and mortality in drug users. Numerous studies, using complementary techniques, have provided evidence that chronic MA use is associated with substantial neurotoxicity and cognitive impairment. These pathological effects of the drug, combined with the addictive properties of MA, contribute to a spectrum of psychosocial issues that include medical and legal problems, at-risk behaviors and high societal costs, such as public health consequences, loss of family support and housing instability. Treatment options include pharmacological, psychological or combination therapies. The present review summarizes the key findings in the literature spanning from molecular through to clinical effects.

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1. The methamphetamine problem

Methamphetamine (MA) is a psychostimulant drug with significant abuse potential and neurotoxic effects that acts principally to cause the release of central and peripheral monoamines (Gold et al., 2009). The compound was first synthesized from ephedrine in 1893 by the Japanese scientist Nagai Nagayoshi, 6 years after the discovery of amphetamine (see Fig. 1). In 1919, Akira Ogata

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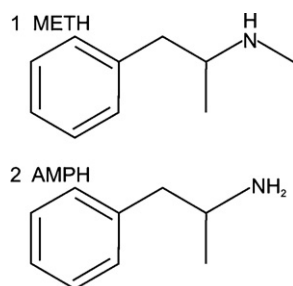


Fig. 1. Chemical structure of methamphetamine (1), as well as the closely related psychostimulant *d*-amphetamine (2).

synthesized crystallized MA by reducing ephedrine using red phosphorous and iodine, providing the basis for production of the drug on a larger scale. MA was not produced in significant quantities for the United States' (US) domestic market until the 1960s, when the first MA "epidemic" appeared on the West Coast (for a comprehensive review, see Anglin et al., 2000). In 1971, MA was restricted by US law, although oral MA (Ovation Pharmaceuticals) continues to be used today in the US as a second-line treatment for a number of medical conditions, including attention deficit hyperactivity disorder (ADHD) and refractory obesity (Kish, 2008).

The primary ingredients used for MA production have, until recently, been widely available in many countries. Synthesis of MA is a straightforward one-step process, involving the reduction of ephedrine or pseudoephedrine; this has led to the expansion of numerous "mom-and-pop" labs. However, much production comes from larger criminal "super labs" in Mexico, supplying Canada and the U.S. (Cunningham et al., 2010; Scott et al., 2007). Methamphetamine is a drug with many "street" names, including ice, meth, crank, jib, speed and crystal, reflecting in part the broad geographical and demographic profile of people who use the drug. The 2008 United Nations Office on Drugs and Crime (UNODC) world drug report estimates that there were approximately 25 million abusers of MA worldwide, exceeding that for cocaine (14 million) and heroin (11 million; UNODC, 2008). The 2011 UNODC report describes the MA problem as a global epidemic, citing an unprecedented rise in use compared to other illicit substances (Misawa et al., 2011).

The recent 2010 National Survey on Drug Use and Health estimated 105,000 new MA users in the United States in 2010, down from almost triple this amount early in the decade. This recent drop is corroborated by the "Monitoring the Future" survey, which monitors adolescent drug use for the National Institutes of Health. These data show that 1.6% of secondary school students used MA in 2010, down from 4.7% in 1999 (Johnston, 2012). A caveat in interpreting these data is the overall long term trend. A similar pattern of waxing and waning use has characterized the MA problem since the 1970s, with use peaking in 1981 (3.7%) followed by a long decline, reaching a nadir in 1992 at 0.4%, and then a steady rise to new highs thereafter (Johnston et al., 2012). Methamphetamine use amongst young individuals is especially common in the western regions of the US and Canada (Gruenewald et al., 2010; Rawson et al., 2002). Use of MA continues to expand eastward, although decreasing availability of pseudoephedrine, a sympathomimetic found in many decongestants, may limit the rate of expansion (DEA, 2010; Maxwell and Rutkowski, 2008).

2. Mechanism of action of amphetamines

Methamphetamine is a potent psychostimulant that acts primarily to cause the release of the monoamines dopamine, serotonin and norepinephrine. Norepinephrine is released most efficiently, followed by dopamine and then serotonin (Rothman et al., 2001).

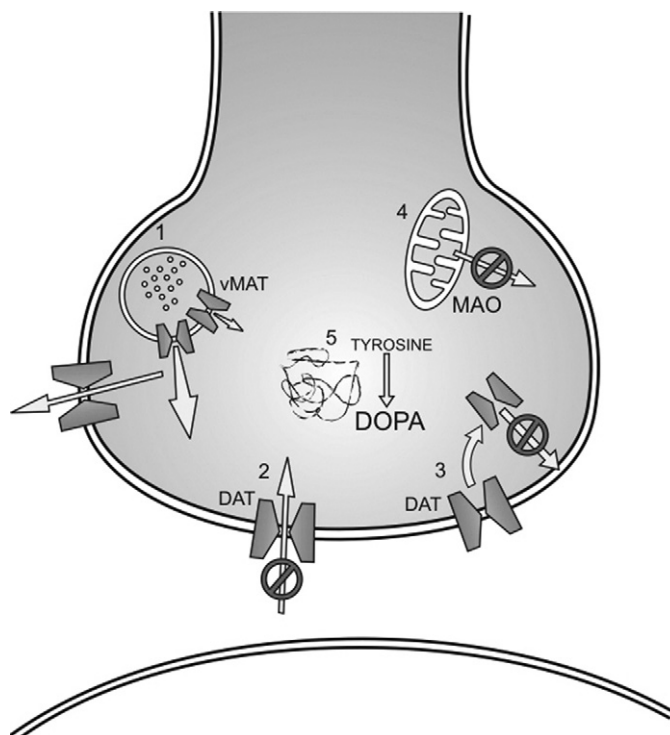


Fig. 2. Physiological mechanisms by which methamphetamine increases synaptic levels of monoamines, principally dopamine. Mechanisms include the redistribution of monoamines from synaptic vesicles to the cytosol (1), and the reverse transport of neurotransmitter through plasma membrane transporters. In addition, amphetamines have been shown to block the activity of dopamine transporters (DATs) (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 tyrosine hydroxylase (5).

The mechanism of action of MA and other amphetamines has been described in extensive detail in several excellent reviews (Weiland-Fiedler et al., 2004; Fleckenstein et al., 2007; Sulzer et al., 2005). However, it is informative to summarize briefly some of the principal mechanisms that are believed to underlie MA's physiological effects (see Fig. 2). Most studies have focused on the capacity of amphetamines to modulate dopamine release, due to this neurotransmitter's crucial role in reward and reinforcement processes. The acute effects of MA modulate dopamine release by acting at two main molecular substrates on dopamine neuronal terminals: the vesicular monoamine transporter-2 (VMAT-2) and the plasmalemmal dopamine transporter (DAT).

One of the key substrates of amphetamines is the plasmalemmal monoamine transporter (Kahlig and Galli, 2003). This has been studied most extensively for the DAT (Schmitt and Reith, 2010). Amphetamines are a substrate of the Na^+/Cl^- -dependent DAT. According to the "exchange-diffusion model" (Fleckenstein et al., 2007), amphetamines compete with synaptic dopamine at the extracellular site on the DAT. Because the DAT can transport dopamine in a bi-directional manner, and concentrations of dopamine are much greater inside the cell, the binding of MA on the extracellular side causes cytosolic dopamine to be reverse transported outside the cell. With higher concentrations of amphetamines, this process of reverse transport may not even require binding to the extracellular site of the DAT, as these lipophilic drugs diffuse directly across the plasmalemmal membrane (Mack and Bonisch, 1979; Sulzer et al., 2005). This mechanism is closely regulated, and the activity of the DAT in the exchange diffusion model is dependent on cell signaling pathways, including calmodulin-dependent protein kinase II (Fog et al.,

2006) and phosphatidylinositol 3-kinase (PI3K; Lute et al., 2008). Data from stably expressed heterologous cell systems indicate that the DAT is also able to cause non-vesicular release of dopamine through a second mechanism. This process involves a conformational change of the DAT into a “channel-like mode” that enables brief bursts of a dopamine efflux at a concentration resembling vesicular exocytotic release (Kahlig et al., 2005). The DAT can also be internalized as part of an endocytotic recycling pathway, thereby removing it from the plasmalemmal membrane and hence negating its capacity to decrease synaptic levels of dopamine. Studies note that amphetamines promote DAT internalization (Li et al., 2010; Saunders et al., 2000). It should be noted, though, that all such studies on DAT internalization have been conducted *in vitro*, and the significance of these findings remains to be determined *in vivo*. The VMAT-2 is an integral membrane protein that transports monoamines from the intracellular cytosol into synaptic vesicles (Brown et al., 2001; Fleckenstein et al., 2009; Weiland-Fiedler et al., 2004). The VMAT-2 transport of molecules is coupled to a vacuolar-type H⁺-pumping ATPase (Schuldiner, 1994); this generates a pH gradient across the vesicle membrane, with a mildly acidic vesicular internal environment of approximately pH 5.5 (Johnson, 1988). According to the “weak base hypothesis” (Fleckenstein et al., 2007), amphetamines cause synaptic vesicles to leak monoamines into the surrounding cytosol by disrupting the proton gradient between the inside and outside of the vesicle. Amphetamines are weak bases, with a pK_a of 9.9 (Sulzer and Rayport, 1990). By entering the vesicle in sufficient concentration, it is posited that the membrane pH gradient is reduced with resultant VMAT-2 compromise and reduced ability to sequester dopamine. However, high concentrations of amphetamines are required to meaningfully disrupt the pH gradient (Floor and Meng, 1996; Schwartz et al., 2006). Only at concentrations above 100 μM is there a strong correlation between gradient disruption and dopamine efflux (Schwartz et al., 2006). With lower concentrations of amphetamines, studies have failed to demonstrate dopamine release (Hondebrink et al., 2009). One possible explanation is that only a small portion of the total dopamine, namely the unbound free dopamine portion, is normally susceptible to proton gradient mediated efflux (Hondebrink et al., 2009). Overall, the free-base theory is therefore a potentially useful construct, although confirmation of its relevance at physiological concentrations of amphetamines and/or dopamine requires further research.

Amphetamines at physiological concentrations also bind the VMAT-2 with micromolar affinity, and competitively inhibit vesicular monoamine uptake. Under physiological concentrations, amphetamines are thought to decrease sequestration of dopamine, and thus lead to increased cytosolic and synaptic monoamine concentrations (Schwartz et al., 2006; Sulzer et al., 1993). An additional role for the VMAT-2 in the activity of amphetamines involves the redistribution of the protein from the synaptic vesicle to an as yet unidentified cellular location (Fleckenstein et al., 2007). Studies of rat striatal preparations have provided converging evidence that multiple, high doses (40 mg/kg) of MA cause decreased vesicular uptake of dopamine. These studies also noted that while levels of the VMAT-2 were decreased in preparations that included only the vesicles, the concentration of VMAT-2 in entire homogenates remained unaltered (Hogan et al., 2000; Riddle et al., 2002), indicating a redistribution of the VMAT-2 to alternate cellular locations, which remain undetermined. However, it should be noted that these represent high doses of the drug, and lower doses (typically in the range of 5–7.5 mg/kg per administration) are used for most studies of MA neurotoxicity (Hanson et al., 2009; Tata et al., 2007).

Some of the interactions between amphetamines and the DAT may be indirect (Schmitt and Reith, 2010). One such example is the trace amine-associated receptor-1 (TAAR1). This G-protein coupled receptor was identified in 2001 as a receptor for trace amines

(Bunzow et al., 2001; Smith et al., 1998) and later shown to mediate MA activity on the DAT (Xie and Miller, 2009). Both *d*-amphetamine and MA are full agonists of the TAAR1 (Reese et al., 2007). Activation of TAAR1 decreases DAT dopamine uptake, enhances dopamine efflux, and leads to DAT internalization; thus, the TAAR1 is being studied as a potential target for therapeutic development (Revel et al., 2012).

Although less of a contemporary research focus, several additional mechanisms have been previously demonstrated to contribute to amphetamines' effects on monoamine release (Fung and Uretsky, 1982; Kuczenski and Segal, 1975). One of note is the inhibition of monoamine oxidases (MAO), the enzymes present on the outer mitochondrial membrane responsible for amine catabolism in presynaptic terminals. Amphetamines are competitive inhibitors of MAO, although MA does not exhibit the greater affinity for MAO-A over MAO-B that other amphetamines do (Robinson, 1985).

3. Physiological and psychological effects of methamphetamine

Methamphetamine is a potent psychomotor stimulant drug with strong physiological effects on peripheral and central systems, resulting in both physical and psychological alterations. The drug can be consumed in multiple different ways and the physiological effects of MA occur rapidly and last for hours (see Table 1 for pharmacokinetics of MA). Through its action on epinephrine and norepinephrine release by the medulla of the adrenal glands, MA simulates the activation of the sympathetic division of the central nervous system (Schneider, 1972). Thus, MA acutely causes an acceleration of heart and lung action through vasoconstriction and bronchodilation (Kiyatkin et al., 2007), while muscle activity is primed via transient hyperglycemia and dilation of blood vessels in skeletal muscle. Non-essential physiological activity, such as stomach and intestinal function, is inhibited. Levels of stress hormones, including cortisol and adrenocorticotrophic hormone, are increased by over 200% in humans following administration of MA (Harris et al., 2003b) and remain elevated for hours after the final exposure. Evidence in rodents indicates that stress hormone responses may be cross-sensitized after amphetamine exposure (Barr et al., 2002a; King et al., 2010b), whereby previous exposure to amphetamines can enhance the release of stress hormones upon subsequent presentation of a stressful stimulus. In theory, this could increase both the intensity and duration of physiological activation of the HPA-axis in response to daily stressors by MA users. MA also alters the function of the murine immune system, with a direct suppression in response to acute exposure to MA of dendritic cells and macrophages, and T-cell antigen presentation (Tallosy et al., 2008). This is thought to occur by collapsing the pH gradient of acidic organelles, which include lysosomes and associated autophagic organelles. Similar effects in humans could render the user more prone to develop viral, as well as bacterial infections, and likely contribute to the rapid progression of human immunodeficiency syndrome (HIV) in MA users (Tallosy et al., 2008). Use of MA increases a multitude of cytokines, chemokines, and cellular adhesion molecules, and these inflammatory molecules likely serve to prolong and exacerbate the acute and chronic neuropsychiatric symptoms associated with its use (Loftis et al., 2010).

While the body is designed to respond acutely in an adaptive manner to activation of these sympathetic pathways, sustained overstimulation of the stress response, caused by chronic MA use, may exceed the capacity of the organism to maintain normal health, i.e., lead to an “allostatic” load (McEwen and Gianaros, 2010). Long term use of MA by humans can result in a host of medical problems. These include severe cardiovascular complications related to chronic hypertension and cardiovascular disease, such as angina,

Table 1
Pharmacokinetic parameters of methamphetamine (MA).

Route	Study comparing smoked vs. IV ($n = 6$) ^c		Study comparing low and high oral doses ($n = 6$) ^d		Study comparing intranasal vs. smoked ($n = 8$) ^e	
	Data reported as mean \pm SE		Data reported as mean \pm SD		Data reported as mean \pm SD	
	Smoked	IV	Oral	Oral	Intranasal	Smoked
Dose (mg)	21.8 \pm 0.3	15.5 \pm 0.1	0.125 mg/Kg	0.25 mg/Kg	50	40
Half-life (h)	11.8 \pm 1.4	13.1 \pm 1.5	8.5 \pm 0.7	11.5 \pm 1.6	10.7 \pm 2.4	10.7 \pm 2.1
Bioavailability (%)	90.3 \pm 10.4 ^a	100	67.2 \pm 3.1	79.4 \pm 13.1	67.6 \pm 1.5 ^a	
V_d (l/kg)	3.2 \pm 0.4	3.7 \pm 0.6	nd	nd	nd	nd
Cl_T (l/h)	nd	15.9 \pm 0.7	26.8 ^b	22.9 ^b	nd	nd
Cl_R (l/h)	6.7 \pm 0.8	7.0 \pm 1.3	12.7 ^b	8.3 ^b	nd	nd
C_{max} (ng/ml)	nd	nd	19.8 \pm 2.7	37.2 \pm 1.3	113 \pm 23.1	50.9 \pm 24.7
T_{max} (h)	nd	nd	3.6 \pm 0.6	3.2 \pm 0.4	2.7 \pm 1.2	2.5 \pm 3.9
% dose in urine	36.8 \pm 4.3	45.0 \pm 9.5	54.1 \pm 5.8	34.6 \pm 4.3	39.3 \pm 24.5	36.0 \pm 17.7
Amphetamine						
C_{max} (ng/ml)	4.2 \pm 0.6	4.0 \pm 0.6	1.6 \pm 0.2	4.0 \pm 0.5	9.1 \pm 2.4	3.7 \pm 2.9
T_{max} (h)	12 \pm 2.3	17 \pm 3.3		11.7 \pm 0.8	17.3 \pm 6.0	15.3 \pm 5.1

IV: intravenous; SE: standard error; SD: standard deviation; V_d : volume of distribution; Cl_T : total clearance; Cl_R : renal clearance; C_{max} : maximum plasma concentration; T_{max} : time of maximum concentration; nd: not determined.

• Bioavailability of smoked MA may be affected by pipe temperature and smoking technique.

• There may be two absorption phases associated with smoking MA.

◦ Quick absorption from inhaled vapor

◦ Slower absorption from trapped or absorbed MA on mucosa, swallowed MA, or slowly released MA from lungs.

• Plasma concentration of MA remains elevated long after the subjective effects suggestive of acute tolerance.

• Large amounts of MA are excreted in the urine.

• Much smaller amounts of the major urinary metabolites (4-hydroxymethamphetamine and amphetamine) are found in the urine.

• Renal clearance of MA

◦ Increases with renal flow and urine acidification.

◦ Decreases with dose suggesting that renal excretion is a saturable.

^a Bioavailability based on delivered dose.

^b No SD as we converted units from ml/min to l/h from aggregate data.

^c Cook et al. (1993).

^d Cook et al. (1992).

^e Harris et al. (2003a).

arrhythmias, valvular disease, hemorrhagic/ischemic strokes, and a high incidence of myocardial infarction (Darke et al., 2008). If MA is smoked, the user may experience respiratory symptoms, which include bronchitis and pulmonary hypertension. Rates of infectious disease, including HIV and hepatitis C, are increased by intravenous MA use due to a greater frequency of risky sexual behavior, needle-sharing, and immune system dysregulation (Cheng et al., 2010). Chronic MA use is associated with malnourishment (Werb et al., 2010), while administration of the drug orally can result in “meth mouth” (Rhodus and Little, 2008), which is a dental condition associated with severe decay and loss of teeth. This latter syndrome results from physiological properties of the drug, such as its acidic residue properties, combined with poor oral hygiene. Xerostomia (dry mouth) also contributes to the dental sequelae resulting from MA use (Hamamoto and Rhodus, 2009), and is caused by vasoconstriction of the salivary glands, decreasing salivary flow. Skin lesions are commonly observed in MA users, as a result of the compulsive scratching that accompanies drug use. The lesions frequently become infected, resulting in bacterial cellulitis (Kerr et al., 2005), extending to bacteremia and sepsis in some cases.

The effects of MA in the central nervous system are mediated mainly by its effects on stimulation of the monoaminergic dopamine, norepinephrine, and serotonin systems. Levels of specific monoamines increase in a regionally dependent manner, based partly on the local density of monoamine terminals. Estimation of extracellular brain levels of monoamine release by amphetamines in humans is challenging, and typically inferred using techniques that assess reductions in binding potential of exogenous radioligands, using positron emission tomography (PET; Barr et al., 2006; Lee et al., 2009). Preclinical studies in non-human primates permit use of invasive procedures, such as cerebral microdialysis, which enable direct measurement of synaptic levels of monoamines. These studies have consistently noted that monoamine levels are increased dramatically after acute MA administration; for example,

a dose of 1 mg/kg of MA in adult male rhesus monkeys elevated dopamine levels in the striatum by 1350% compared to baseline within 30 min, and levels remained close to 500% above baseline two and a half hours later (Tsukada et al., 1999).

Studies in rodents have used both acute and chronic drug-exposure paradigms to measure the effects of MA treatment on monoamine release in the brain, as well as metabolic mapping with the 2-[¹⁴C] deoxyglucose method to measure regional brain activity (Pontieri et al., 1990). Acute exposure to MA at doses designed to simulate human pharmacokinetic values has typically resulted in large increases in dopamine levels in the dorsal striatum (1300% of baseline values; Segal and Kuczenski, 2006). However, drug tolerance may occur after extended MA exposure during the same drug session, resulting in attenuated dopamine release (O’Neil et al., 2006). This should not be confused with MA-induced sensitization, by which prior exposure to lower, intermittent doses of the drug can result in a long lasting enhanced dopamine release with a subsequent MA challenge (Narita et al., 2004).

It should be noted that many of the earlier rodent studies on the central effects of MA were based on acute studies in which the drug was administered non-contingently to the subject. However, more recently there has been an increased use of rodent “self-administration” paradigms in which the animal can administer the drug itself, typically intravenously, and often over an extended period (Kobeissy et al., 2012; Lominac et al., 2012). Due to the numerous and diverse studies that use self-administration procedures, a full discussion of the results of these studies is beyond the current scope, but such paradigms are clearly more homologous to the clinical literature (McFadden et al., 2012a) and represent optimal protocols for in vivo studies, particularly when modeling “dependence.”

Given the ubiquitous functions and distribution of monoamines in the brain, it is not surprising that many other neurotransmitters and neuropeptides are altered following treatment with MA

and elevation of monoamines in the CNS. One example in rats is an increase in levels of glutamate in the frontal cortex and striatum in response to MA (Qi et al., 2009; Shoblock et al., 2003). Glutamate release may be mediated through a cascade involving both the dopaminergic and GABAergic systems (Mark et al., 2004) or alternatively through α -7 nicotinic receptors via a MA-induced increase in acetylcholine (Northrop et al., 2011). Numerous studies have demonstrated a potent effect of MA on neurotensin levels in the rodent brain. This neuropeptide is synthesized in dorsal striatal cell bodies and interacts with dopamine neurons to antagonize dopamine-mediated signaling through dopamine D1 and D2 receptors (Chartoff et al., 2004). Non-contingent administration of MA resulted in increased tissue levels of neurotensin in the dorsal striatum (Castel et al., 1994), while a series of MA self-administration studies by the same research group demonstrated specific regional changes in neurotensin levels (Frankel et al., 2011, 2008), which were greater in the nucleus accumbens shell and dorsal striatum after 15 days of treatment with MA (Hanson et al., 2012). Interest remains in this neuropeptide as a potential target for development in treating MA addiction. Acute treatment with MA increased preprodynorphin mRNA levels throughout the striatum, although this was anatomically restricted to the patch-matrix division of the striatum (Adams et al., 2000, 2003). The effects of MA on brain levels of met-enkephalin were shown to be dose-dependent, with a lower dose of the drug causing transient decreases in limbic structures, while a higher dose increased levels of met-enkephalin in the frontal cortex and anterior striatum 12 h after drug administration (Albargues et al., 2001). Both doses of drug decreased levels of met-enkephalin 24 h after treatment. In contrast, using the same doses of MA, the high dose (10 mg/kg) had no immediate effect on levels of Substance P in either the substantia nigra, globus pallidus or striatum, whereas the low dose (0.5 mg/kg) caused a rapid increase in Substance P in the substantia nigra (Hanson et al., 2002). Interestingly, when levels of neuropeptides were examined in post-mortem brain tissue from human chronic MA users, it was noted that levels were either normal or decreased in most regions (Frankel et al., 2007), in contrast to short-term animal studies where levels typically increase. The authors posited that this difference may be due to long-term adaptive processes in the human subjects.

The psychological effects of MA resemble those of other amphetamines, and vary depending on both the method of administration, as well as the amount of drug used. The fastest onset of effects occurs after either smoking or injecting MA, whereupon near-instantaneous drug-induced psychological effects are experienced. Oral ingestion produces a delayed onset of psychological effects and reduces bioavailability of MA (see Table 1; Cook et al., 1993, 1990, 1992). Single, low-to-moderate doses of MA, as used in many research studies, cause cognitive changes including increased arousal and alertness, with improved attention and concentration particularly evident in subjects who are sleep-deprived. Affective changes include decreased appetite and increased libido, increased confidence and elevated mood (De La Garza et al., 2009; Hart et al., 2001). Higher doses of MA may cause dysphoria due to excessive stimulation; symptoms are evident as restlessness and anxiety, and are associated with tremors and dyskinesia. In the case of “binge” drug use, which lasts over a period of days, the euphoric effects of the drug diminish over time while dysphoria and compulsive behavior increases, the latter known as “tweaking.” Binge users may exhibit highly focused and repetitive behaviors, known as “punding” (Fasano et al., 2008), such as the stereotyped handling and sorting of objects. Particular attention has been paid to the capacity of high and sustained doses of MA to cause psychological changes that resemble the symptoms of psychosis (Barr et al., 2006), although it is important to note that relatively few studies have observed this effect in people using only MA, and with no prior history of mental illness (Iwanami et al., 1994; Iyo et al., 1997,

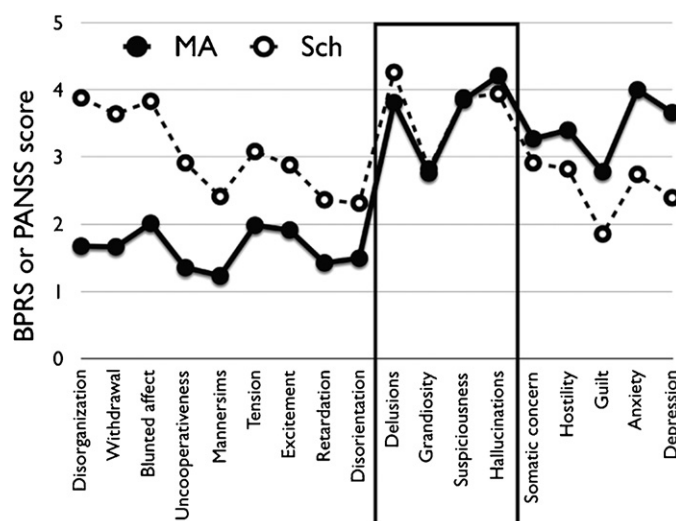


Fig. 3. Psychiatric symptom severity scores in research participants using methamphetamine (MA; $n=235$) and with a history of associated psychosis (Lecomte et al., 2010), compared with patients with treatment refractory schizophrenia (Sch, $n=234$) at admission to a tertiary care hospital (Smith et al., manuscript in revision). Scores were most similar for the positive symptoms of psychosis: delusions, grandiosity, suspiciousness, and hallucinations. BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale.

2004). Binge-like use of MA has been reported to induce sleeplessness, hallucinations and paranoia (Leamon et al., 2010), which may be associated with irritability and unprovoked aggression (Payer et al., 2011). Preclinical studies have reported “psychosis”-like phenomena in rats following treatment with higher doses of MA. These include sensorimotor gating deficits (Hadamitzky et al., 2011), agitation and abnormal locomotor activity (Segal and Kuczenski, 1999).

We have recently characterized drug use and associated mental illness in a predominantly MA-using population in the urban setting of Vancouver, British Columbia, Canada (Lecomte et al., 2010). Of 295 subjects using MA, 70% of the participants interviewed reported a prior diagnosis of mental illness (20% schizophrenia-spectrum disorder, 17% depression, 14% bipolar disorder). However, it remains an ongoing effort to determine whether recent psychiatric symptoms contributed to or resulted from concurrent recent MA use. Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis II disorders were common among MA users, and antisocial personality disorder was diagnosed in 68% of our sample. Interestingly, 30% had been diagnosed with ADHD as children. These high rates of comorbid disorders highlight the complexities in ascribing specific observations in MA users as an exclusive consequence of drug use: many MA users are polysubstance users with additional confounding psychiatric issues. However, despite these issues, important observations can be made with this population. For example, consistent with other reports (McKetin et al., 2010), psychotic symptoms were common among participants in our study. When we compared the profile of their psychosis against that of a group of inpatients with refractory schizophrenia at a tertiary care hospital, some important differences were evident (see Fig. 3). Both the MA users and the schizophrenia patients showed similar levels of psychosis for “positive” symptoms, which included delusions, grandiosity, suspiciousness and hallucinations. By contrast, the MA users had lower scores than the schizophrenia patients on the “negative” symptoms, which included variables such as blunted affect, disorganization and social withdrawal. Methamphetamine users had higher scores than the schizophrenia patients on affective symptoms, such as hostility, anxiety and depression. These observations indicate that MA-induced psychosis shares both similarities

and differences with schizophrenia, which may have important implications with regards to diagnosis and treatment.

If amphetamines are administered in sufficient quantities, and/or over sufficient time, the user may experience “withdrawal” symptoms (Glasner-Edwards et al., 2009; Zorick et al., 2010), which can be modeled in rodents using techniques that have been well validated for other indices of affective modulation (Barr et al., 2000; Bruijnzeel et al., 2010). We have reviewed in detail the negative effects of withdrawal from sustained, higher doses of psychostimulants (Barr and Markou, 2005; Barr et al., 2002b). Termination of high doses of these drugs in humans and animals induces psychological effects opposite to the acute effects of the drug (Koob and Volkow, 2010). Thus, the positive effects of energy, confidence and elevated mood are replaced by fatigue, anxiety, depression, inability to concentrate and even suicidality. These effects decrease linearly over time, and largely return to baseline within seven to 10 days of drug termination. In animals, this has been demonstrated as anhedonia and decreased motivation (Barr and Phillips, 1999; Barr et al., 2002c), loss of sexual interest (Barr et al., 1999), and greater sensitivity to “frustration” in negative contrast paradigms (Barr and Phillips, 2002), as well as greater anxiety and increased immobility in the forced swim test (Jang et al., 2012). Unlike other classes of drugs of abuse, such as alcohol and opiates, there are relatively few physical symptoms associated with MA withdrawal, with the exception of somnolence (Mahoney et al., 2012).

Long term use of MA frequently has severe psychosocial consequences (Gonzales et al., 2009). Similar to other forms of addiction, MA use impairs executive function and results in poor coping skills, including disorganized lifestyle and interpersonal difficulties. These effects may be particularly evident in MA users, as chronic MA use causes greater irritability, aggression and impulsivity than many other classes of illicit drugs. These factors impact strongly on social activities such as employment and housing, as well as social support. For example, in our recent study of MA users, 28% were homeless and another 48% lived in sheltered or transitional housing (Lecomte et al., 2010).

4. Neurotoxicity of methamphetamine

In the animal literature, numerous studies have documented dopamine neuron terminal damage or loss after MA exposure (Krasnova and Cadet, 2009; Ricaurte et al., 1984), while a significantly smaller proportion of studies have reported actual cell loss via apoptosis in the striatum (Commings and Seiden, 1986; Tulloch et al., 2011). The relationship between these two different types of neurotoxicity remains unclear, particularly as the phenotype of apoptotic cells require further study. As of yet, cell loss has not been conclusively demonstrated in humans. However, based on a limited number of retrospective studies, MA users may be at possible increased risk of movement disorders (Callaghan et al., 2010, 2012; Rusyniak, 2011) and chronic neuropsychiatric symptoms can persist despite long periods of abstinence. A wide range of clinical evidence, largely derived from structural and functional imaging studies (discussed below), provides evidence for perturbation in signaling mechanisms and cytoarchitectural changes in the human central nervous system after extended MA use.

Although there have been numerous deaths associated with MA overdose, there is a relative paucity of human post-mortem data regarding the effects of MA use on neurotoxicity. The first well-characterized evaluation of the effects of chronic MA use examined dopamine levels in striatal sub-regions, including the nucleus accumbens, caudate and putamen (Wilson et al., 1996). Levels of dopamine and the DAT were measured in twelve chronic MA users, many of whom had died from drug overdose and therefore were likely using high amounts of the drug. MA users exhibited

a mean 50–61% reduction in dopamine levels throughout the striatum (Wilson et al., 1996). In concert, there was reduction in levels of the DAT by at least a third in all striatal regions. For comparison, dopamine levels were depleted in the caudate, but not putamen, of MA users as severely as in a group of Parkinson's Disease patients (Moszczynska et al., 2004). Despite these abnormalities, there were normal levels of the VMAT, which is considered to be a surrogate marker of dopaminergic neuronal integrity. As such, despite the marked changes in neurotransmitter concentrations, no neuronal death was inferred. More recently the assumption that VMAT-2 levels accurately reflect viable neuronal numbers has, however, been questioned (Boileau et al., 2008). Additional studies of dopamine dysregulation in the same post-mortem series noted that there was a 25–30% decrease in the maximal extent of dopamine-induced stimulation of adenylyl cyclase activity in the striatum (Tong et al., 2003). Combined, these data suggest that dopamine signaling in the striatum of heavy MA users may be impaired both presynaptically, by reduced amounts of dopamine available for neurotransmission, as well as postsynaptically, by impaired second-messenger signaling mediated through adenylyl cyclase. These impairments may be important in mediating the dysphoric effects of the drug (low dopamine), and the tolerance that occurs after repeated dosing (Tong et al., 2003). However, it is important to consider potential confounds in this case-series, such as the acute pharmacological effects of MA versus effects of chronic exposure. In addition, many MA users are polysubstance users and may have had pre-existing brain abnormalities.

In addition to alterations in dopaminergic signaling pathways, MA exposure has also been associated with neurotoxic effects on the central serotonergic systems. An increasing number of studies have examined the neurotoxic effects of MA on serotonergic neurons in the brain. In parallel with its effects on dopamine terminals, exposure to high doses of MA causes significant long-term reductions in markers of serotonergic terminals (although see Krasnova et al., 2010); these are most commonly measured by changes in levels of serotonin and the serotonin transporter (Kaushal et al., 2012). However, dissimilar from dopamine, in which neurotoxic effects are anatomically limited to relatively few regions, primarily the striatum, treatment with MA causes neurotoxic effects that are much more diffuse. Numerous regions display MA-induced serotonergic damage, including the perirhinal cortex, hippocampus, anterior cingulate cortex, caudate nucleus, nucleus accumbens, amygdala and septum (Armstrong and Noguchi, 2004; Belcher et al., 2005; Gross et al., 2011; Reichel et al., 2012). It is worth noting, though, that serotonergic neurotoxicity in the hippocampus was not evident when MA was self-administered by rats, in contrast to most studies which have used high-dose non-contingent drug administration (McFadden et al., 2012b). At present, mechanisms underlying MA-induced serotonergic toxicity are less well understood than for dopamine, but are believed to be mediated in large part by production of free radicals (Hanson et al., 2004) as well as hyperthermia (Farfel and Seiden, 1995).

Methamphetamine use in humans leads to a plethora of structural and metabolic CNS changes. Multiple imaging techniques have been used to address this issue. Magnetic resonance imaging (MRI) has been used to measure structural changes in the brain. While results are not always consistent, reflecting the heterogeneity of clinical populations, evidence for morphological alterations include a loss of gray-matter in the frontal cortices of MA users (Berman et al., 2008; Daumann et al., 2011), in addition to reduced hippocampal volume and white-matter hypertrophy in chronic-use subjects consuming an average of 3 g/week for 10 years (Thompson et al., 2004). Subjects using MA more than four times a week for over 2 years exhibited larger striatal volumes (Chang et al., 2005a). White matter abnormalities in abstinent MA users include structural changes of the corpus callosum, such as increased

curvature in the genu and decreased width in posterior mid-body and isthmus areas, which connect frontal and parietal cortices (Oh et al., 2005). The integrity of frontal white matter has been assessed using diffusion tensor imaging. Prior MA use was associated with reduced white matter integrity in the bilateral frontal region at the plane of the anterior commissure–posterior commissure, as well as right frontal white matter (Alicata et al., 2009; Chung et al., 2007; Tobias et al., 2010) and corpus callosum (Kim et al., 2009). Methamphetamine use has also been associated with changes in cerebral vasculature (Iyo et al., 1997).

By using magnetic resonance spectroscopy (MRS) it is possible to infer CNS integrity by evaluating changes in neuronal metabolites in specific brain regions. Measured metabolites include the neuronal marker N-acetyl aspartate (NAA), cell membrane synthesis or degradation products (choline [CHO]), high-energy metabolic products (creatine [CR] and phosphocreatine [PCR]) and glial markers (myo-inositol [MI] and CHO) (Nordahl et al., 2005). Similar to findings from MRI, there has been substantial variability when examining the effects of MA use. The first MRS study noted an inverse correlation between levels of NAA in frontal white matter and the logarithm of lifetime MA used (Ernst et al., 2000). More recent studies reported lower NAA/CR ratios in the anterior cingulate cortex (Nordahl et al., 2003, 2005; Salo et al., 2007), while CHO/CR and CHO/NAA ratios were significantly higher. As lower levels of NAA and NAA/CR ratios are related to neuronal loss (Ende et al., 1997; Ernst et al., 1997), the findings indicate that MA use may be associated with a loss of neuronal integrity in frontal regions, although a study of chronic MA users with an average 12 years of MA who were in longer-term abstinence (average 4 years) showed recovery of NAA/CR ratios in the cingulate cortex (Salo et al., 2011). The CHO signal is related to membrane synthesis and turnover (Tedeschi et al., 1996); therefore, increased CHO/CR ratios may reflect adaptive and compensatory responses to MA-induced damage (Nordahl et al., 2005). Similar patterns of change in the striatum have been noted in MRS studies of the effects of MA use. Both NAA and CR were decreased in the basal ganglia of subjects using MA at least 5 times a week for 1 year (Ernst et al., 2000), while levels of NAA and CR were decreased in the basal ganglia of HIV-positive MA users compared to HIV-positive non-MA using subjects (Chang et al., 2005b). Abstinence MA users exhibited greater CHO/CR ratios, which correlated with duration of MA use and the severity of residual psychiatric symptoms (Sekine et al., 2002). It is important to remember, though, that the use of nuclear magnetic resonance techniques, which include MRI and MRS, has limitations (Di Costanzo et al., 2007), and the relationship between in vivo changes and the molecular basis of these observations remains an area of ongoing study.

The neurotoxic effects of MA on monoamine pathways in the brain have been determined using positron emission tomography (PET) with radiolabelled ligands. One consistent finding in the neuroimaging of MA use has been a decrease in the concentration of the DAT in multiple brain regions during MA abstinence. Studies have observed lower levels of the DAT in brain regions that include the dorsolateral prefrontal cortex, orbitofrontal cortex, amygdala, striatum and nucleus accumbens (McCann et al., 2008, 1998; Sekine et al., 2001; Volkow et al., 2001a,c), and these decreases have been associated with MA-related behavioral symptoms. More recently, it was shown that MA-dependent subjects had lower dopamine D2/D3 receptor availability in the striatum, which was linked to impulsivity (Lee et al., 2009). Regarding the SERT, levels were lower throughout the brain in subjects with a chronic history of MA compared to controls, and reduced levels of the SERT were inversely related to lifetime drug use. The density of SERTs in orbitofrontal, temporal, and anterior cingulate areas (Sekine et al., 2006) was directly related to the level of aggression in MA users. Interestingly, a PET study determined that levels of the vesicular transporter

VMAT-2 were greater in the striatum of recently abstinent MA users than controls (Boileau et al., 2008), an unexpected consequence of ingestion of potentially neurotoxic amounts of MA. This finding is in contrast to decreased levels of the VMAT-2 in the striatum of MA users who had been drug-free for at least 3 months (Johanson et al., 2006). The reason for the discrepancy between the two studies is uncertain, but may be related to duration of abstinence. Other PET studies have focused on differential patterns of brain activity, measured by glucose metabolism, in MA users. The studies noted increased global metabolism in MA abstinence, although metabolism was decreased specifically in the striatum and thalamus (Volkow et al., 2001b; Wang et al., 2004). During early abstinence from MA, which represents the period of drug withdrawal associated with depressed mood and dysphoria (Barr and Markou, 2005; London et al., 2004), a global pattern of metabolic activity comparable to that observed in major depressive disorder was observed. As a caveat to the findings described above in imaging studies, the majority of observations do not present a unique profile, and similar findings have been observed with other drugs of abuse, or even psychiatric disorders, particularly with regards to the findings from functional studies. There may also be considerable differences between studies based on the duration since last exposure to MA.

The molecular mechanisms that underlie MA-induced neurotoxicity are extensive, including excitotoxicity, blood-brain barrier breakdown, microglial activation, oxidative stress, apoptotic pathways and DNA damage (Cadet and Krasnova, 2009). Preclinical studies have also indicated an important role for hyperthermia as a causative agent in MA-induced neurotoxicity (Krasnova and Cadet, 2009; Riddle et al., 2006), particularly with higher doses of the drug. Increased glutamate levels resulting from MA exposure may contribute to neurotoxicity as well, based on studies which have prevented MA-induced neurotoxicity by using glutamate receptor antagonists (Riddle et al., 2006).

5. Neurocognitive effects of methamphetamine

Cognitive deficits have been widely described in “chronic” MA users. Chronicity is variably defined in the literature, with a meta-analysis indicating that 10 years of MA use is the approximate average for subjects enrolled in the various studies of MA use and cognitive sequelae (Scott et al., 2007). Chronic exposure to MA can result in severe neuropsychological deficits (summarized in Nordahl et al., 2003; Scott et al., 2007). Cognitive impairment is a serious concern for MA users, as it has been estimated that approximately 40% of MA users exhibit global neuropsychological impairment (Rippeth et al., 2004). Important insight into the cognitive sequelae of MA use has been provided by studies that have evaluated separate and discrete cognitive domains. It is increasingly clear that chronic MA use does not affect all aspects of cognition equally. This may be due to the differential distribution of monoamines in the brain, which serve as the substrate for neurotoxicity. However, it should be noted that it is difficult to be certain of what proportion of all cognitive impairment may be ascribed specifically to the neurotoxic effects of MA on the brain. Methamphetamine may have physiological effects on the brain below the threshold of “toxicity,” and drug use can be associated with other lifestyle habits and medical comorbidities that contribute to worsened cognition (Lecomte et al., 2010).

When multiple cognitive domains have been measured concurrently, the most consistent and severe changes include impairments in memory, attention and executive function (Cherner et al., 2010; Gonzalez et al., 2004; Iudicello et al., 2010; Mehrjerdi et al., 2012; Woods et al., 2005). For example, chronic MA users

exhibit working memory deficits in tasks such as the immediate recall component of the auditory verbal learning test (Volkow et al., 2001c) and the Tic-Tac-Toe working-memory test (van der Plas et al., 2009), while also taking up to 30% longer to complete the working memory components of the California computerized assessment package (Chang et al., 2002). Cognitive assessment procedures that assess the integrity of attentional processes, such as “vigilance,” have noted clear impairments in tasks including the Trail-Making test and the Stroop color word task (Kalechstein et al., 2003; King et al., 2010a; Salo et al., 2009). The results of these and other studies indicate that the primary explicit deficits in attentional processing by MA users are related to an inability to suppress irrelevant task information (Nordahl et al., 2003) and reduced cognitive inhibition (Salo et al., 2002). Executive function represents the cognitive domains of planning and abstract reasoning, reflected in behavioral flexibility and adaptability. Numerous studies have provided evidence for impaired executive function in chronic MA users, using tasks such as the Stroop interference task (Kalechstein et al., 2003) and Wisconsin Card Sorting test (Chung et al., 2007). Non-working memory tasks, such as episodic memory, may consist of both a strategic-frontal component and an associative-hippocampal component. Methamphetamine users exhibited significant deficits in the Hopkins verbal learning test, results that were consistent with an episodic deficit that was of a strategic, rather than purely mnemonic nature (Woods et al., 2005). Other studies noted substantial deficits in episodic memory that were more clearly mnemonic. Episodic memory relies predominantly on the hippocampus and related neuronal structures, which are densely innervated with serotonin and norepinephrine monoamine terminals, 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 deficits in MA users have been commonly demonstrated as impairment in word recall tasks, which measure recall at specific time points after stimulus presentation (Simon et al., 2000; Thompson et al., 2004; Volkow et al., 2001c). While most studies evaluate cognitive performance in previous MA users who have been abstinent for weeks or longer, the duration of abstinence is important to consider for each individual study. Acute exposure to MA can increase cognitive performance in prior MA users (Mahoney et al., 2011). The long-term cognitive impairment associated with MA use can improve over time (Iudicello et al., 2010), and so the time since previous MA use should always be considered when evaluating cognitive deficits.

6. Treatment of methamphetamine-related disorders

Different pharmacological approaches have been tried in the treatment of MA addiction. The most common classes of drugs include antidepressants, antipsychotics and substitution/replacement therapies (Rose and Grant, 2008). Indirect evidence supports a rationale for the use of antidepressants – particularly those with a serotonergic mechanism of action, based on efficacy in preclinical models, clinical efficacy in treating compulsive behavior, and potential for ameliorating the affective symptoms of stimulant withdrawal (Barr and Markou, 2005). However, most studies with antidepressants have not found clinically meaningful benefits of these drugs on a range of MA abuse-related measures, including drug craving, affective dysregulation and drug abstinence. These antidepressants include the selective serotonin reuptake inhibitors paroxetine, fluoxetine and sertraline as well as the tricyclic antidepressant drug imipramine (Rose and Grant, 2008). One possible exception to this frustrating therapeutic landscape is the recent demonstration that mirtazapine, a selective serotonin and noradrenergic receptor antagonist, appears to reduce

MA use and risky sexual behavior. In a double-blind, randomized, controlled trial involving 60 men-who-have-sex-with-men subjects, mirtazapine reduced urine-positive drug screens from 73% to 44% with a concomitant decrease in high risk sexual activity (Colfax et al., 2011). The number-needed-to-treat to achieve one negative weekly urine test was 3.1. Larger trials are urgently needed, but based on this work and mirtazapine's excellent safety profile, initial evidence suggests that this drug may have potential as a therapeutic intervention for MA dependence, especially when faced with a comorbid mood disorder. Mirtazapine has inverse agonist activity at constitutively active 5-HT_{2C} receptors. It is this latter mechanism that may mediate the attenuation of drug seeking effect. Recently Graves and Napier demonstrated that selective inverse agonists at 5-HT_{2C} attenuate MA seeking behavior in rats, whereas full receptor antagonists do not (Graves and Napier, 2011, 2012). Promising results were also initially observed on MA craving with the antidepressant drug bupropion (Newton et al., 2006), which inhibits dopamine and norepinephrine reuptake and serves as a functional agonist. More recent studies, with larger numbers of subjects, failed to support the earlier beneficial effects of bupropion on MA use (Shoptaw et al., 2008), although the antidepressant may be effective selectively in male subjects with low-to-moderate MA dependence (Elkashef et al., 2008).

The critical role of dopamine neurotransmission in the psychostimulant and addictive properties of MA and other amphetamines has driven research of the efficacy of dopamine D₂ receptor antagonists (i.e., antipsychotics) as potential treatments for stimulant abuse. Despite well-characterized possible motoric and cardiometabolic side-effects of these drugs (Boyda et al., 2010; Leung et al., 2012; Procyshyn et al., 2010, 2007), antipsychotics represent the first line pharmacotherapy for patients presenting with MA-induced psychosis. The high-potency dopamine D₂ receptor antagonists haloperidol and risperidone failed to reduce the stimulant-like effects of a single 20 mg/kg dose of MA in a laboratory study in humans (Wachtel et al., 2002). However, a recent study of the atypical antipsychotic drugs risperidone and quetiapine in subjects with co-occurring bipolar disorder and stimulant dependence noted that both drugs equally decreased craving for MA (Nejtek et al., 2008), although the interpretation of the results of this study are complicated by the lack of a placebo control group. Preliminary evidence with low doses of the antipsychotic aripiprazole suggested that the drug could reduce the subjective effects of *d*-amphetamine (Lile et al., 2005; Stoops et al., 2006), but a more recent, double-blind study found no effect of aripiprazole of multiple measures of MA dependence, and some subjective effects of MA were actually increased by aripiprazole (Newton et al., 2008), similar to effects reported for the anticonvulsant drug topiramate (Johnson et al., 2007). In a related manner, aripiprazole was found to *increase* intravenous amphetamine use in drug-dependent subjects compared to placebo (Tiihonen et al., 2007). To our knowledge, there has never been a controlled clinical trial of antipsychotic drugs specifically for the treatment of MA-induced psychosis, despite case study reports of antipsychotic drugs efficacy for this indication (Misra and Kofoed, 1997; Misra et al., 2000).

Substitution therapies for MA dependence have provided mixed results. The rationale for these trials is based in part on the success of replacement therapies for other classes of drugs of abuse, such as nicotine and the opiate-methadone model. Dextroamphetamine has been used in several studies. In the first randomized controlled trial of dextroamphetamine substitution treatment for amphetamine dependence, subjects received up to 60 mg immediate-release dextroamphetamine or vehicle for 12 weeks; counseling was available to both groups. Overall, both treatment groups improved, with a non-significantly greater effect observed in the dextroamphetamine group (Shearer et al., 2001).

A second, double blind placebo-controlled trial using up to 110 mg a day observed that dextroamphetamine increased the duration that subjects stayed in treatment for MA dependence, and subjects exhibited a strong trend to decrease MA use (Longo et al., 2010). The most recent randomized placebo-controlled trial involving 60 patients taking 60 mg of dextroamphetamine, however, showed no reduction in the number of MA-positive urine samples over an 8-week period (Galloway et al., 2011). Overall, the practice of prescribing amphetamines is most likely beneficial in reducing withdrawal symptoms and aiding in treatment engagement, with more equivocal effects on promoting abstinence.

The prescription stimulant methylphenidate also exhibits potential for the treatment of MA addiction. Case studies of amphetamine dependence in subjects without psychiatric comorbidity reported that methylphenidate provided long-term help for MA use (Laqueille et al., 2005), while methylphenidate also decreased intravenous amphetamine use, assessed by number of positive urine screens, compared to placebo and aripiprazole (Tiihonen et al., 2007). The mild stimulant modafinil had no effect on MA use, depressive symptoms, or MA cravings in a recent double blind study (Heinzerling et al., 2010).

A number of additional drugs, from diverse pharmacological classes, have been tested as pharmacotherapies for stimulant addiction. In 2005, an open-label safety and efficacy trial involving 28 subjects was completed with the anti-epileptic drug vigabatrin (Brodie et al., 2005). This drug is an irreversible inhibitor of GABA-transaminase, and has shown preliminary effectiveness in cocaine dependence. Of the 18 patients that completed the study, 16 tested negative for MA in the last 6 weeks of this 9 week trial. The GABA agonist baclofen was also shown to decrease MA use (Heinzerling et al., 2006), compared to vehicle and gabapentin-treated subjects, although this effect was only significant in the high protocol adherence subjects. A recent multi-dose study reported that the 5-HT₃ receptor antagonist ondansetron was not effective on any of multiple measures of MA dependence (Johnson et al., 2008). Additional compounds are also in later stages of preclinical development, including entirely novel classes of pharmacotherapies. For example, one of the more promising platforms is immunopharmacotherapy, which acts by generation or administration of antibodies that are bind MA directly in the bloodstream before it can enter the brain (Meijler et al., 2004).

As an adjunct to pharmacotherapy, psychotherapy and behavioral treatments represent a treatment strategy with reliable clinical benefits and minimal risk of physiological side effects (Lee and Rawson, 2008). Emphasis has been placed on creating a standardized protocol; for example, the “Matrix” model is a 16-week intensive multi-component, cognitive-behavioral/addictions paradigm. In a multi-site trial involving 978 patients, Matrix subjects initially demonstrated significantly better attendance and longer periods of drug abstinence. By follow up, however, group differences were no longer significant (Rawson et al., 2004). Additional research is underway to determine which of the many facets of this psycho-social intervention program were most effective. Combined treatment programs are increasingly being recommended for MA abuse and related issues, such as risky sexual behaviors, and integrated therapy for MA abuse and comorbid mental health problems likely represents a major focus of future treatment strategies (Halkitis, 2009).

7. Conclusion

Methamphetamine is a highly addictive psychostimulant drug that acts on the central nervous system through multiple physiological pathways to cause the release of central and peripheral monoamine neurotransmitters. Recreational use of MA remains

high in many parts of the United States and Canada and is increasing in other parts of the world. The highly addictive properties of this drug result in widespread psychosocial issues that include medical and legal problems, at-risk behaviors, and substantial societal costs. The chronic use of MA may result in cognitive deficits, especially to the cognitive domains of memory, attention and executive function, likely resulting in part from the direct neurotoxic effects of the drug. Imaging studies of the neurochemistry and structural morphology of the brain in MA users reveal numerous alterations, some of which show a direct relationship to functional changes in behavior and cognition. A number of medications have been tried to treat dependence, with mirtazapine and amphetamine substitution displaying some efficacy. We find a logical approach to treatment is to carefully examine comorbidities; if there is evidence of a mood component then mirtazapine may represent a reasonable choice, while if an attention-deficit picture predominates, stimulant substitution may be a better first choice. In addition, psychotherapy should be instituted if available. 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.

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Conflict of interest

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