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Review

Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature

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ABSTRACT

Background: Despite initial reports of a decline in use in the early 2000s, methamphetamine remains a significant public health concern with known neurotoxic and neurocognitive effects to the user. The goal of this review is to update the literature on methamphetamine use and addiction since its assent to peak popularity in 1990s.
Methods: We first review recent epidemiological reports with a focus on methamphetamine accessibility, changes in use and disorder prevalence rates over time, and accurate estimates of the associated burden of care to the individual and society. Second, we review methamphetamine pharmacology literature with emphasis on the structural and functional neurotoxic effects associated with repeated use of the drug. Third, we briefly outline the findings on methamphetamine-related neurocognitive deficits as assessed via behavioral and neuroimaging paradigms. Lastly, we review the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial and pharmacological treatments within the context of an addiction biology framework.
Conclusion: Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Contents

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1. Introduction

Methamphetamine use remains a significant public health concern in the United States (U.S.) and worldwide. Research has greatly advanced our knowledge of the epidemiology, consequences, and treatment of methamphetamine use disorders since methamphetamine's peak in popularity in the 1990s. Thus, the goal of this review is to update the literature on methamphetamine use and addiction since its assent to popularity. To do so, we cover recent epidemiological reports, methamphetamine pharmacology, and briefly outline the neurocognitive deficits associated with chronic methamphetamine use. We also discuss the clinical presentation of methamphetamine addiction and the evidence supporting the available psychosocial interventions and pharmacological treatments.

This review is intended to supplement recent, more comprehensive reviews of pharmacologic treatments for methamphetamine addiction (i.e., Brackins et al., 2011; Brensilver et al., 2013; Rose and Grant, 2008) by distinguishing medications that have been tested clinically for reducing methamphetamine use from medications that may be promising based on their anti-craving effects – yet, clinical trials are ultimately needed. A number of other areas of potential interest to the field are also expanded upon, such as the trends in methamphetamine use/abuse rates, associated costs to the individual and society, and recent debates regarding methamphetamine-related neurocognitive impairments. Furthermore, the present review differs from other methamphetamine reviews (e.g., Panenka et al., 2013) by incorporating this wide range of domains of interest and by highlighting the increasingly recognized role for the opioidergic system in the development (i.e., reinforcement), maintenance (i.e., craving), and treatment (i.e., naltrexone) of methamphetamine addiction as an area for greater study in methamphetamine-related research. Taken together, this review provides a broad-based update of the available literature covering methamphetamine research over the past two decades and concludes with recommendations for future research.

Articles for inclusion in this review were identified through an extensive literature search conducted in January 2014 (and repeated in March, April, and July 2014) in PubMed and national survey databases. Search terms included "methamphetamine" (or "amphetamine" where appropriate) and domain specific terms such as "pharmacokinetics," "neurocognition," and "treatment." Efforts were made to include the most recent reports within each section in order to provide an updated summary of the current knowledge of the field.

1.1. Epidemiology of methamphetamine

Methamphetamine remains a widely used illicit drug in the U.S. Estimates from 2012 suggest over 12 million people in the U.S., ages 12 years and older (4.7% of total responders) have used methamphetamine in their lifetimes, 1.2 million people (0.4%) reported using methamphetamine in the past year, and approximately 440,000 (0.2%) of those identified as past month users (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013a). Amphetamine-type simulants (ATS), of which methamphetamine is the most frequently used, are the second most commonly used class of illicit drugs worldwide (United Nations Office on Drugs and Crime (UNODC), 2012); approximately 0.7% of the global population (33.8 million people) aged 15–64 years-old, reported using an ATS in 2010 (UNODC, 2013). Importantly, these estimates appear to be growing, as stated in the 2013 World Drug Report, "The market for ATS appears to be expanding in terms of locations of manufacture and trafficking routes, as well as in terms of demand" (UNODC, 2013).

1.2. History of methamphetamine use in the United States

ATS have a long history of use in the U.S., going as far back as World War II when soldiers used ATS to reduce fatigue and suppress appetite. ATS were widely prescribed in the 1950s and 1960s as a medication for depression and obesity, reaching a peak of 31 million prescriptions in the U.S. in 1967 (Anglin et al., 2000), with a roughly estimated 9.7 million Americans identified as past-year users of amphetamines in 1970 (Rasmussen, 2008). The rates of ATS use declined following the passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970, which reclassified amphetamine to a more restrictive schedule, thereby limiting its accepted medical use (Gonzales et al., 2010). After amphetamine was rescheduled, illicit manufacturers began making methamphetamine using phenyl-2-propanone ("P2P") and methylamine. However, after P2P became a Schedule II controlled substance in 1980, ephedrine and pseudoephedrine became the predominant precursors and large quantities of these chemicals were smuggled from Mexico into the U.S. (Maxwell and Brecht, 2011). The increase in production was followed by a dramatic increase in use, with methamphetamine specifically increasing in popularity during the 1990s and early 2000s (Rawson et al., 2002). For example, estimates from the 2002 U.S. National Survey on Drug Use and Health (NSDUH) suggest that over 210,000 individuals ages 12 and older tried methamphetamine for the first time in 1991, whereas 454,000 individuals did so in 1998 (SAMHSA, 2003). Following the passage of the Combat Methamphetamine Epidemic Act in 2005 which restricted public access to products containing pseudoephedrine, the rates of methamphetamine use finally began to decrease (Gonzales et al., 2010; Maxwell and Brecht, 2011; Maxwell and Rutkowski, 2008), as evinced by a drop to 192,000 of new methamphetamine users in 2005 (SAMHSA, 2006).

This decline in methamphetamine use was short lived however, as illicit manufacturers of methamphetamine began to use the P2P processes once again (Maxwell and Brecht, 2011). Estimates from the 2012 NSDUH identify over 130,000 individuals as new methamphetamine users in 2012, and the number of past month users in 2012 (440,000 people or 0.2%) remained consistent with reports from the last five years (0.1–0.2%) (SAMHSA, 2013a).

Recent reports of production and supply indicate a probable rise of methamphetamine use in the near future. For example, the number of methamphetamine laboratories reported in the U.S. quadrupled from 2,754 in 2010 to 11,116 in 2011, and the amount of methamphetamine seized by the U.S. government increased from 15 tons in 2010 to 23 tons in 2011 (UNODC, 2013). Furthermore, production methods are refined on an ongoing basis to produce

purer and more potent forms of methamphetamine, and at lower costs. Analysis of data from the System to Retrieve Information on Drug Evidence (STRIDE), which reflects evidence submitted to DEA laboratories for analysis from July 2007 through September 2010, indicates that the price per pure gram of methamphetamine decreased 61%, from $270.10 to $105.49, while the purity increased 114%, from 39% to 83% (Maxwell and Brecht, 2011). Together, the culmination of recent prevalence, production, and supply data forewarn of an impending increase in methamphetamine use in the years to come.

1.3. Current rates of abuse and dependence

Although the prevalence rates of current methamphetamine use have been relatively stable over the past five years, the rates of methamphetamine use disorders in the U.S. are on the rise. In 2012, 535,000 (0.2%) individuals were estimated to meet the Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM-IV; American Psychiatric Association, 1994) criteria of stimulant abuse or dependence, a significant increase from the 329,000 (0.1%) in 2011 (SAMHSA, 2013a). This increase was especially pronounced among individuals aged 18–25 years, with 0.5% meeting criteria in 2012, up from 0.3% in 2011. Over 379,000 of individuals were estimated to meet dependence criteria for methamphetamine in 2012, as compared to 252,000 in 2011 (SAMHSA, 2013a).

Estimates from the Treatment Episode Data Set (TEDS), which provides information on admissions to substance abuse treatment facilities that are licensed or certified by state substance abuse agencies, suggest that treatment admissions for primary methamphetamine increased from 78,248 individuals ages 12 or older (4.4% of admissions) in 2001 to 154,364 individuals (8.1%) in 2005, but then decreased to 102,384 individuals (5.6%) in 2011 (SAMHSA, 2013b). The recently released TEDS data report a slight increase for 2012, with 116,090 individuals (6.6%) being admitted for primary methamphetamine-related problems (SAMHSA, 2014). The rates of methamphetamine dependence appear to be roughly equivalent in men compared to women, with 53% of primary methamphetamine/amphetamine admissions being male. Further, the majority of individuals admitted to treatment were non-Hispanic White (69%), followed by individuals of Mexican origin (12%; SAMHSA, 2014). Thus, methamphetamine dependence is largely a disorder of the White population; however, this may be a byproduct of the regional variability in methamphetamine use, which is currently greatest in the West and parts of the Midwest (NIDA, 2012).

1.4. Burden of care associated with methamphetamine use

In 2009, the RAND Corporation published the first national estimate of the economic burden of methamphetamine use based on information available for 2005 (Nicosia et al., 2009). They estimated the economic burden of methamphetamine use in the U.S. to be approximately $23.4 billion, which includes the costs associated with drug treatment, other health costs, the intangible burden of addiction and premature death, lost productivity, crime and criminal justice costs, child endangerment, and harms resulting from production. These intangible costs of addiction make up a substantial portion of the overall cost, at approximately $12.6 billion; which includes the costs associated with drug treatment at approximately $545 million, primarily delivered in the community-based specialty treatment sector ($491 million; Nicosia et al., 2009). These high costs are consistent with the TEDS data, which indicate that primary methamphetamine/amphetamine admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/residential treatment (16% vs. 7%) (SAMHSA, 2013b).

In summary, methamphetamine use and the associated disorders constitute a significant burden to the individual and to society. Furthermore, the substantial time and resources devoted to the treatment of methamphetamine use disorders in the U.S. underscores the need for more efficacious, cost effective, and easily deliverable treatments.

2. Pharmacology of methamphetamine

2.1. Chemistry of methamphetamine

Methamphetamine, also known as metamfetamine, N-methylamphetamine, methylamphetamine, and desoxyephedrine, is a psychostimulant of the phenethylamine and amphetamine class of psychoactive drugs. Methamphetamine exists in two stereoisomers, the L- and D-forms. D-Methamphetamine, or the dextrorotatory enantiomer, is a more powerful psychostimulant, with 3–5 times the central nervous system (CNS) activity as compared to L-methamphetamine, or the levorotatory enantiomer (Ciccarone, 2011); however, both enantiomers influence dopamine release and can induce stereotypy (i.e., persistent mechanical repetition of speech or movement) and psychosis at high doses (Kuczenski et al., 1995). Illicitly, methamphetamine may be sold as pure D-methamphetamine (dextromethamphetamine) or in a racemic mixture, and presents as powder or crystalline form, the latter commonly referred to as “ice” or “crystal meth” (Cruickshank and Dyer, 2009). Crystalline methamphetamine typically refers to a highly purified form of D-methamphetamine which is intended for smoking, with similar effects to that from an intravenous dose (Cho, 1990). Further, crystalline methamphetamine is associated with an increased incidence of dependence, as compared to the lower purity forms (McKetin et al., 2006).

2.2. Molecular pharmacology of methamphetamine

Methamphetamine is a cationic lipophilic molecule which stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho and Melega, 2002). Due to its structural similarity, methamphetamine substitutes for the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulate postsynaptic monoamine receptors (Cruickshank and Dyer, 2009). Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase (Sulzer et al., 2005), further enabling the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of methamphetamine act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008). The medial basal forebrain, the hippocampus, and the prefrontal cortex (PFC) represent noradrenergic regions of interest, with various functions related to arousal, memory consolidation, and cognitive processing, respectively (Berridge and Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). However, the wide distribution of monoamines throughout the CNS, interactions between

the monoamine pathways, baseline dopamine (and likely other monoamine) functioning, and peripherally mediated effects of methamphetamine add to the complexity of methamphetamine's effect on the monoamine systems (Cruickshank and Dyer, 2009).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid system in the establishment of reinforcement (Boutrel, 2008). Three families of endogenous opioid peptides have been identified (dynorphins, endorphins and enkephalins), each associated with a distinct polypeptide precursor (prodynorphin, proopiomelanocortin, and proenkephalin). These precursors produce a number of active ligands including β-endorphin, met- and leu-enkephalin, dynorphins, and neo-endorphins (Kieffer and Gavériaux-Ruff, 2002). Each ligand expresses a different affinity for each opioid receptor; for example, β-endorphin binds with higher affinity to μ- than δ- or κ-opioid receptors (Mansour et al., 1995b).

Anatomically speaking, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc; Mansour et al., 1995a). Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ- and δ-opioid receptors in the NAcc (Hirose et al., 2005; Murakawa et al., 2004), and by decreasing GABA-inhibition via μ- and κ-opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci and Williams, 1997; Shoji et al., 1999). Many non-opioid drugs of abuse are also known to interact with the endogenous opioid system (for a review see Trigo et al., 2010). For example, preclinical studies in rats have shown that ethanol, cocaine, and D-amphetamine increase extracellular levels of endorphins in the NAcc (Olive et al., 2001), and that ethanol-induced increases in extracellular levels of dopamine in the NAcc are modulated by endogenous opioid system processes (e.g., Acquas et al., 1993; Lee et al., 2005). In humans, the rewarding effects of alcohol have been shown to be mediated by alcohol-induced endogenous opioid release in the NAcc and orbitofrontal cortex (OFC; Mitchell et al., 2012). Further, tobacco use, nicotine dependence severity, and nicotine craving were associated with reduced binding potential of a μ-opioid receptor agonist ([^{11}C]-carfentanil) in a number of mesolimbic regions in an alcohol dependent sample (Weerts et al., 2012). Together, these reports are suggestive of a general mediating role for the endogenous opioid system in the rewarding properties of multiple drugs of abuse.

ATS have also been shown to affect the endogenous opioid system, which may mediate some of the rewarding properties associated with acute ATS use (Boutrel, 2008). For example, acute amphetamine administration has been linked with increased β-endorphin levels in the NAcc (Olive et al., 2001), increased striato-nigral dynorphin-like immunoreactivity (Bustamante et al., 2002; Hanson et al., 1988), and changes in the endogenous opioid mRNA expression in the striatum (Hurd and Herkenham, 1992; Smith and McGinty, 1994; Wang and McGinty, 1995). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of methamphetamine-induced behavioral (locomotor) sensitization (Chiu et al., 2006), analogous to compulsive drug seeking behavior in humans (i.e., drug craving; Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford et al., 2006).

In sum, methamphetamine has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

2.3. Clinical pharmacokinetics of methamphetamine

Methamphetamine is largely metabolized in the liver, resulting in metabolites including amphetamine, 4-hydroxymethamphetamine, norephedrine, hippuric acid, 4-hydroxyamphetamine, and 4-hydroxynorephedrine (Caldwell et al., 1972). It is then excreted by the kidneys, with the majority excreted as unchanged methamphetamine (30–50%), followed by up to 15% as 4-hydroxymethamphetamine, and 10% as amphetamine. Approximately 70% of a single oral dose is excreted in the urine within 24 h (Cook et al., 1993; Kim et al., 2004). With repeated dosing, methamphetamine can accumulate in the urine, with one study showing detection 7 days after a regimen of four daily 10 mg oral doses (Oyler et al., 2002). Based on the pharmacokinetic data reviewed below, the typical assessment of methamphetamine abstinence in clinical studies consists of urinalysis at 3–4 day intervals (i.e., twice weekly).

Methamphetamine is commonly smoked, injected, ingested, snorted, dissolved sublingually, taken rectally, or solubilized and consumed as a liquid. Smoking, the most common route of administration (NIDA, 2012), and intravenous injection result in the near-immediate euphoric sensation which typically lasts for several minutes, as opposed to intranasal and oral injection which take approximately 5 and 20 min to reach peak euphoric state. The "high" through intranasal and oral methods however, is reported to last 8–12 h (Meredith et al., 2005). When smoked, methamphetamine exhibits 90.3% bioavailability, compared to 67.2% for oral ingestion (Caldwell et al., 1972).

2.4. Clinical response and withdrawal of methamphetamine

Methamphetamine is a potent CNS stimulator. As such, the clinical response to methamphetamine administration at low to moderate doses (5–30 mg) includes euphoria, arousal, reduced fatigue, euphoria, positive mood, tachycardia, hypertension, pupil dilation, peripheral hyperthermia, reduced appetite, behavioral disinhibition, short-term improvement in cognitive domains, and anxiety (for a review see Cruickshank and Dyer, 2009). At frequent and high doses, there is also evidence that methamphetamine can induce psychotic episodes (Hermens et al., 2009; Ujike and Sato, 2004).

Frequent use of methamphetamine results in a depletion of presynaptic monoamine stores, down-regulation of receptors, and neurotoxicity (Barr et al., 2006; Meredith et al., 2005), resulting in significant psychiatric withdrawal symptoms following abrupt cessation after periods of regular use. Symptoms of methamphetamine withdrawal include anhedonia, hypersomnia, irritability, anxiety, aggression, and intense cravings for methamphetamine (Cantwell and McBride, 1998; Meredith et al., 2005). Depressive symptomatology has been considered the hallmark of methamphetamine withdrawal, with depressive symptoms lasting beyond two weeks of abstinence (Zorick et al., 2010). The severity of the withdrawal syndrome appears to be related to the frequency of use, yet methamphetamine withdrawal largely resolves spontaneously (Newton et al., 2004), and usually within 14 days of abstinence (Zorick et al., 2010). Protracted withdrawal from methamphetamine may in turn take several weeks to resolve and poses a large obstacle to sustained recovery.

2.5. Neurotoxicity associated with chronic methamphetamine use

Repeated exposure to moderate to high levels of methamphetamine has been related to neurotoxic effects on the

dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies (Cho and Melega, 2002). Although the precise mechanisms remain unclear, the culmination of evidence suggests that the high level of cytoplasmic dopamine released as a result of methamphetamine use leads to the accumulation of reactive oxygen species and severe oxidative stress on the neuron (Berman et al., 2008a). Results of non-human primates given doses of methamphetamine roughly equivalent to a typical human abuse pattern of use (0.5–2 mg/kg given four times at 2-h intervals), indicate that methamphetamine at this (typical) level of use produces long-term reductions in dopaminergic axonal markers in the brain, including decreased striatal DAT density (Villemagne et al., 1998). Human studies using positron emission tomography (PET) and magnetic resonance imaging (MRI) data also provide support for prolonged neurotoxicity following repeated methamphetamine use. Reductions in striatal DAT site density (McCann et al., 1998; Volkow et al., 2001b, 2001d), D2 receptor availability (Volkow et al., 2001a), VMAT-2 density (Johanson et al., 2006), and SERT density (Sekine et al., 2006), have all been reported, with some markers (i.e., DAT density) showing improvement following prolonged (greater than 12 months) abstinence (Volkow et al., 2001b). Neurotoxic effects have been associated with behavioral and cognitive changes, such as memory deficits and impaired psychomotor coordination associated with reduced DAT site density (Volkow et al., 2001d), and increased aggression associated with reduced SERT density (Sekine et al., 2006). Chronic abuse of methamphetamine is also associated with reduced markers of neuronal integrity and increased markers of glial content, possibly indicating the proliferation of glial cells following neural damage (Chang et al., 2007; Ernst et al., 2000).

Structural brain abnormalities among frequent methamphetamine users as compared to healthy controls have also been observed, including, but not limited to, reduced white-matter integrity and/or organization associated with depression severity and positive psychiatric symptoms (Tobias et al., 2010), reduced gray matter in the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004), reduced hippocampal volumes associated with poorer memory performance (Thompson et al., 2004), altered shape of the corpus callosum (Oh et al., 2005), and increased volumes of the putamen and globus pallidus (interpreted as a compensatory effect; Chang et al., 2005). As noted by Berman and colleagues (2008a), lower cortical gray matter density or volume is the most consistently reported structural abnormality in amphetamine users, and studies assessing striatal gray matter report larger volumes in amphetamine abusers when compared to healthy controls, although the latter may reflect a compensatory response to initial neurotoxicity.

A number of functional brain abnormalities have been observed in recently abstinent chronic abusers of methamphetamine. Using glucose metabolism as a marker of functional activity, regions of abnormally high relative activity include the amygdala, ventral striatum, and lateral orbitofrontal cortex (OFC), whereas abnormally low activity was observed in the medial PFC and cingulate cortex (London et al., 2004). Furthermore, glucose metabolism in the anterior and middle cingulate gyrus and the insula was negatively correlated with error rates on an auditory vigilance task in recently abstinent (4–7 days) methamphetamine abusers (London et al., 2005). Relative higher global and parietal cortex glucose metabolism has been noted to accompany continued abstinence (Berman et al., 2008b; Volkow et al., 2001c), along with relatively lower metabolism in striatal and thalamic regions (Volkow et al., 2001c; Wang et al., 2004). Importantly, some degree of recovery has been observed in the neocortical regions (Berman et al., 2008b) and thalamus (Wang et al., 2004) following one and nine months of abstinence, respectively.

3. Neurocognitive functioning associated with chronic methamphetamine use

Chronic methamphetamine use has been associated with discrepancies in numerous cognitive processes dependent upon fronto-striatal and limbic circuits. However, differentiating preexisting deficits from methamphetamine-induced cognitive deficits poses significant challenges (Dean et al., 2013), and concerns regarding the interpretation of these discrepancies and their clinical significance have been raised (Hart et al., 2012). Despite this, the preponderance of evidence from preclinical, cross-sectional human, and brain imaging studies supports the assertion that methamphetamine abuse does indeed cause cognitive decline in at least some individuals (i.e., individuals at the age of early-to-middle adulthood; Dean et al., 2013) and that some cognitive/behavioral changes may be the result of methamphetamine neurotoxicity (Bortolato et al., 2009). Further, individual difference variables such as age, education level, and genotype appear to moderate the relationship between methamphetamine use and cognitive deficits (Dean et al., 2013).

With respect to the specific cognitive domains potentially affected, a meta-analysis of 18 studies found medium effects of methamphetamine use disorders on processes including episodic memory, executive functions (e.g., response inhibition, novel problem solving), complex information processing speed, and psychomotor functions. Small, yet significant, effects were also observed on measures of attention/working memory, language, and visuoconstruction (Scott et al., 2007).

A small number of these cognitive processes have been further examined using functional neuroimaging procedures in chronic methamphetamine users (for a review see Aron and Paulus, 2007). For example, the brain correlates of learning and cognitive control in methamphetamine abusers have been investigated using a color-word Stroop task administered during functional magnetic resonance imaging (fMRI). On this task, methamphetamine abusers display reduced reaction-time (RT) adjustments and reduced PFC activity following conflict (i.e., incongruent) trials (Salo et al., 2013, 2009), and reduced RT, increased error rate, and reduced activation of the right inferior frontal gyrus (IFG), supplementary motor cortex/anterior cingulate gyrus, and the anterior insular cortex during the incongruent condition (Nestor et al., 2011). Using a reversal learning task and PET in a preclinical sample, vervet monkeys given a chronic, escalating-dose regimen of methamphetamine revealed associations between the change in response to positive feedback and individual differences in the change in dopamine D_2-like receptor availability in the striatum, assessed pre- and post-methamphetamine regimen (Groman et al., 2012); thus advancing D_2 specific alterations of the dopaminergic system as a plausible neurobiological pathway subserving some of the disturbances in learning observed with repeated methamphetamine use.

Methamphetamine use disorders are associated with differential brain activity during decision-making, as assessed via fMRI. Methamphetamine abusers displayed reduced activation in the right IFG and the left medial frontal gyrus during a two-choice prediction task (where only 50% of the responses are reinforced with a correct response outcome), and a decrease in dorsolateral PFC (dlPFC) and right OFC activity in the active compared to control conditions, as opposed to the increase of activation in these areas observed in the healthy controls (Paulus et al., 2002). In a follow-up study using the same task, recently abstinent (average 25 days) individuals with methamphetamine dependence displayed reduced activation of the OFC, dlPFC, anterior cingulate cortex (ACC), and parietal cortex irrespective of the outcome, and attenuation of specific "success-related" patterns of brain activation as compared to healthy controls (Paulus et al., 2003). Furthermore, the degree of activation in the right middle frontal gyrus, middle

temporal gyrus, and posterior cingulate during the two-choice prediction task in early remission (3–4 weeks abstinent) was predictive of relapse during a one-year follow-up (Paulus et al., 2005).

Methamphetamine dependence has also been associated with maladaptive reward-related decision-making, as indexed via steeper rates of temporal discounting ("delay discounting") (Hoffman et al., 2006). Contrasting "hard choices", where roughly equivalent preference is obtained for the immediate and delayed reward choices, and "easy choices", in which the choices differ dramatically in value and preference, revealed less activation in the precuneus, right caudate nucleus, ACC, and dlPFC in recently abstinent (2–8 weeks) individuals with methamphetamine dependence (Hoffman et al., 2008), and less activation of the left dlPFC and right intraparietal sulcus in active methamphetamine abusers (Monterosso et al., 2007), as compared to healthy controls. Furthermore, methamphetamine dependent individuals undergoing treatment display disrupted risk-related processing, a component of decision-making, on the Risky Gains Task in both the ACC and insula (Gowin et al., 2013).

In summary, methamphetamine use disorders are associated with specific task-related behavioral and neural processing differences across a number of cognitive domains, which appear to be moderated by individual difference variables. Importantly, evidence is accumulating to suggest some of these differences are associated with altered dopaminergic processing (Groman et al., 2012) and clinically meaningful outcomes (Paulus et al., 2005), suggestive of a functional role for these cognitive differences in the development and perpetuation of methamphetamine addiction.

4. Clinical presentation of methamphetamine use disorders

A methamphetamine use disorder represents a complex psychiatric condition characterized by a set of maladaptive behaviors which result in clinically significant functional impairment (American Psychiatric Association, 1994, 2013). A diagnosis made using the DSM-IV criteria necessitates the experience of at least 1 symptom of abuse or 3 symptoms of dependence occurring within a 12-month period (American Psychiatric Association, 1994), whereas the fifth edition of the DSM (DSM-5) combines these criterion (with a few notable changes) to form a single "methamphetamine use disorder" with an added severity specification (American Psychiatric Association, 2013). The DSM-specified criteria include maladaptive behaviors such as "continued use despite persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of methamphetamine", the development of "tolerance" and "withdrawal," and "persistent desire or unsuccessful efforts to stop or cut down or control methamphetamine use."

The two most notable changes to the DSM-5 criteria include the removal of "legal problems" and the addition of "drug craving" to the symptom list. The addition of "craving" as a possible symptom represents an effort to increase consistency between DSM-5 and the International Classification of Diseases (ICD-10; World Health Organization, 2010), as well as acknowledgment of a vast amount of scientific research highlighting the importance of craving for understanding the pathogenesis and maintenance of addiction (e.g., Robinson and Berridge, 1993, 2001). Specific to methamphetamine addiction, research suggests individuals with this disorder exhibit cognitive performance deficits that are more pronounced during exposure to methamphetamine-related cues (Tolliver et al., 2012), and that level of craving for methamphetamine is associated with neural and behavioral measures of self-control (Tabibnia et al., 2011), together suggestive of a strong neural relationship between craving and clinically relevant behavioral markers of addiction. Furthermore, methamphetamine craving has been observed to be present for at least 5 weeks into abstinence, rendering the user particularly vulnerable to relapse during 7–14 days of abstinence (Zorick et al., 2010), and is a significant predictor of subsequent use during outpatient treatment (Galloway and Singleton, 2009; Hartz et al., 2001). Craving beliefs, or interpretations and decisions about cravings, have also been shown to predict relapse in a sample of regular methamphetamine users (Lee et al., 2010). On this basis, methamphetamine craving has been advanced as a surrogate marker of methamphetamine dependence (Galloway and Singleton, 2009). As with other substance use disorders, methamphetamine addiction is considered a chronic and relapsing disorder characterized by neurobiological changes that subserve the observed functional impairment in the individual (Koob et al., 2004).

5. Treatment of methamphetamine use disorders

At present, few effective options exist for individuals seeking treatment for methamphetamine use disorder, and to date these options have been limited to psychosocial interventions. Twelve-Step programs, such as Narcotics Anonymous, remain a common intervention pursued by many individuals with methamphetamine use concerns (Galanter et al., 2013) despite a lack of evidence supporting the efficacy of these programs as a stand-alone treatment (Donovan and Wells, 2007; Shearer, 2007). There is some, albeit modest, evidence to suggest that other psychological interventions are effective for stimulant users (Knapp et al., 2007; Shearer, 2007; Vocci and Montoya, 2009). However, the majority of the treatment efficacy research has been done with cocaine abusing populations, and given the known differences between individuals seeking treatment for methamphetamine versus cocaine (i.e., age of first use, route of administration, frequency of use, demographics, and prior exposure to treatment; Huber et al., 1997), it remains unclear whether the efficacy of these interventions is generalizable to individuals with a methamphetamine use disorder.

5.1. Psychosocial treatments

A systematic review of cognitive and behavioral treatments as applied specifically to methamphetamine use disorders concluded that good clinical outcomes are achieved with Cognitive-Behavioral Treatment (CBT; with and without Motivational Interviewing [MI]) and Contingency Management (CM) therapies involving the systematic use of reinforcement (Lee and Rawson, 2008). A number of caveats must be considered when interpreting these conclusions however, such as the durability of treatment effects (especially with respect to CM programs). Furthermore, the effectiveness of psychosocial interventions is compromised by poor rates of treatment induction and retention (Shearer, 2007), and methamphetamine-related cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments ineffective (Baicy and London, 2007).

5.2. Pharmacologic treatments

Given these important caveats of psychosocial interventions, and the heavy focus on the neurobiology of methamphetamine dependence, attention has shifted to the development of efficacious pharmacotherapies for methamphetamine addiction (NIDA, 2005). At present, no medication is approved by the U.S. Food and Drug Administration (FDA) for use in methamphetamine dependence. Numerous classes of medication are currently under study, primarily in small clinical trials (for a recent focused review see Brensilver et al., 2013). Medications presumed to have potential for the treatment of methamphetamine addiction frequently

target dopaminergic, serotonergic, GABAergic, and/or glutamatergic brain pathways (for a review see Vocci and Appel, 2007), as well as opioidergic pathways (e.g., Brensilver et al., 2013). Additionally, cognitive enhancing medications such as modafinil (an analeptic drug with known cognitive-enhancing properties) have garnered attention given the known cognitive deficits associated with chronic methamphetamine use (e.g., Ghahremani et al., 2011).

5.2.1. Medications associated with reduced methamphetamine use. A focused review on pharmacological treatments for methamphetamine/amphetamine dependence identified only three double-blind placebo-controlled trials that have shown positive results for reducing use of the substance (Karila et al., 2010). The first two trials found treatment effects within a specific subpopulation of users; namely buproprion was associated with a reduction of methamphetamine use among baseline light, but not heavy, methamphetamine users (identified in a posthoc analysis; Shoptaw et al., 2008), and modafinil combined with CBT was associated with reduced methamphetamine use within a small sample of HIV+ gay men dependent on methamphetamine (McElhiney et al., 2009), although recent trials have not found strong support for a direct effect of modafinil on abstinence outcomes (e.g., Anderson et al., 2012; Heinzerling et al., 2010). The third trial found support for reduced amphetamine use and greater abstinence rates with naltrexone treatment (50 mg) in a sample of amphetamine-dependent individuals (Jayaram-Lindstrom et al., 2008).

Since the review (Karila et al., 2010), a few medications have received support for reducing methamphetamine use, namely mirtazapine, topiramate, and naltrexone. Specifically, 12-weeks of mirtazapine treatment combined with CBT/MI counseling was associated with significant reductions in methamphetamine use (percent positive urines at the week 12 visit) in a sample of methamphetamine-dependent men who have sex with men (MSM) (Colfax et al., 2011). Topiramate was associated with more patients achieving a 50% or 25% reduction in baseline level of methamphetamine use in large multi-site clinical trial; however, no effects on total abstinence (negative urines during 6–12 week follow-up) were observed (Elkashef et al., 2012). Further analysis of this data identified a small subgroup of patients who exhibited consistent reductions or achieved abstinence during follow-up, which were associated with topiramate treatment. This subgroup consisted of individuals who were more likely to have discontinued methamphetamine use (i.e., have a negative last urine) during the week prior to randomization (Ma et al., 2013), suggesting that topiramate may function best for relapse prevention. An additional study has found support for of the use of implant naltrexone for the treatment of problematic amphetamine use, noting patients with high levels of naltrexone ($\geq$2 ng/ml) in their blood were 2.27 times more likely to be abstinent than patients with low naltrexone blood levels (<2 ng/ml; Grant et al., 2010). Clinical and preclinical laboratory models have also found support for reduced ATS use with naltrexone treatment. Specifically, clinical laboratory studies of naltrexone found reductions of both heroin and amphetamine use in a sample of individuals dependent on both substances (Tiihonen et al., 2012), and decreases in quality/liking ratings of administered amphetamine in a sample comprised of predominant cocaine users (Comer et al., 2013). Preclinical studies have observed naltrexone-related decreases in d-amphetamine and alcohol self-administration in adult rhesus monkeys (Jimenez-Gomez et al., 2011), and attenuated amphetamine-induced reinstatement with no effect on food taking behavior in the rat (Haggkvist et al., 2009).

The potential efficacy of naltrexone, an opioid antagonist with greatest affinity for the μ-opioid receptor and to a lesser but meaningful extent κ- and δ-opioid receptors (Ashenhurst et al., 2012), may lie in its ability to block drug-induced β-endorphin, and subsequent dopamine, release in the NAcc and through the blockade of drug-induced β-endorphin inhibition of GABAergic inhibitory interneurons in the VTA, as in the case of alcohol (Johnson, 2008; Zalewska-Kaszubska et al., 2006). The decrease in amphetamine-induced dopamine levels in the NAcc following blockade of the μ-opioid receptor by naltrindole (a selective δ-opioid receptor antagonist) and β-funaltrexamine (an irreversible μ-opioid receptor antagonist) provides support for this hypothesis (Schad et al., 1996). However, the efficacy of naltrexone treatment for methamphetamine dependent individuals remains unclear.

5.2.2. Medications associated with reduced methamphetamine craving. Given the putative role of craving in the maintenance of addiction, numerous medications have also been tested for their ability to alleviate methamphetamine craving. These medications include ondansetron (Johnson et al., 2008), methylphenidate (Miles et al., 2013), a combination of flumazenil, gabapentin and hydroxyzine (Ling et al., 2012), modafinil (Shearer et al., 2009), topiramate (Johnson et al., 2007), aripiprazole (Newton et al., 2008), sertraline (Zorick et al., 2011), and isradipine (Johnson et al., 2005). Unfortunately, none of these medications have shown associated reductions in subjective methamphetamine craving, and two of these medications, namely aripiprazole and sertraline, have even been associated with increased (Newton et al., 2008) or sustained (Zorick et al., 2011) craving following treatment, respectively.

Nevertheless, a few medications have shown potential to reduce methamphetamine craving. Treatment with dextroamphetamine, as a potential substitution therapy, has been shown to reduce craving, but not methamphetamine use, in treatment seeking individuals with methamphetamine dependence (Galloway et al., 2011). Rivastigmine, a cholinesterase inhibitor, was observed to reduce participant's endorsement of "Likely to Use Meth" when exposed to acute methamphetamine via intravenous infusion in a sample of non-treatment seeking methamphetamine dependent individuals (De La Garza et al., 2012). Buproprion, an antidepressant which inhibits the reuptake of dopamine and norepinepherine, has also been associated with reduced methamphetamine craving in response to video cues in a laboratory model of non-treatment seeking individuals with a methamphetamine use disorder (Newton et al., 2006). Nicotine has shown promise in rodent models of craving. Specifically, methamphetamine-seeking behavior was found to be attenuated by repeated nicotine administration during methamphetamine withdrawal. Further, this attenuating effect was antagonized by the nicotinic antagonist mecamylamine (Hiranita et al., 2004).

Naltrexone (12.5 and 50 mg) was associated with a decrease in cocaine craving, but not positive subjective effects, during acute cocaine and D-amphetamine (versus placebo) administration in a sample comprised of predominant cocaine users (Comer et al., 2013). With respect to methamphetamine craving specifically, preclinical work suggests naltrexone inhibits reinstatement of drug-seeking behavior, a plausible marker of drug craving in the animal, induced by methamphetamine-associated cues in mice following 12 days of methamphetamine self-administration and extinction (Anggadiredja et al., 2004). These results were related to the changes in dopamine and dopamine metabolite levels (Lan et al., 2008), as well as to the binding of a D1 agonist and D2 antagonist (SKF38393 and sulpiride, respectively) to dopamine receptors in the striatum (Tien et al., 2007). Naltrexone was found to have no effect on methamphetamine-priming-induced reinstatement, possibly indicating a separate pathway for drug priming effects (Anggadiredja et al., 2004). Further, μ-opioid receptor knockout mice are unaffected by methamphetamine-induced behavioral sensitization (Shen et al., 2010), suggestive of naltrexone's mechanism of action in craving instatement. The blockage

of methamphetamine-induced dopamine release in the mesolimbic dopamine system has been proposed as the neural mechanism underlying naltrexone's effect on cue-induced craving (Ashenhurst et al., 2012; Jayaram-Lindstrom et al., 2004); however, no study to date has been conducted in humans to test this hypothesis.

In summary, a number of pharmacotherapies are currently under study for the treatment of methamphetamine use disorders, many with promising preliminary results. Treatment development for methamphetamine use disorders, both behavioral and pharmacological, has been a challenging enterprise, yet consistent with the addiction field broadly (Litten et al., 2012) efforts to refocus the field toward medications with novel therapeutic targets hold considerable promise for this complex disorder.

6. Conclusions and future directions

Methamphetamine, a potent central nervous system stimulant, continues to pose a significant public health problem in the U.S. and worldwide. At present, the burden of care associated with methamphetamine use far exceeds what would be expected given the prevalence estimates, underscoring the pervasive impairments associated with methamphetamine use and addiction. Importantly, the culmination of recent prevalence, production, and supply reports warn of the potential for a "second wave" of increased methamphetamine use and associated problems, thus indicating the immediate need for advancements in basic and clinical methamphetamine research.

Through its actions on the brain's major dopaminergic, noradrenergic, serotonergic, and opioidergic pathways, repeated use of methamphetamine is associated with significant neurotoxic effects and neurocognitive deficits, with only a few of such effects known to remediate following sustained abstinence. Thus, early identification of problematic methamphetamine use and effective treatment implementation is critical to successful outcomes. Unfortunately, the available treatments for methamphetamine dependence are at best only modestly effective. There is modest evidence for the efficacy of psychosocial interventions, cognitive behavioral therapy (CBT) in particular; however, these treatments are time-intensive, expensive, and the outcomes are relatively poor at longer follow-up periods. Furthermore, there are no medications currently approved by the FDA to treat methamphetamine use disorders.

Following what appears to be a sequence of failures in medication development for methamphetamine dependence, the field has engendered renewed interest in the development of medications with novel molecular targets (e.g., endocanabinoid and opioidergic systems, neuroinflammation; Brensilver et al., 2013; Snider et al., 2013; Vocci and Appel, 2007). Increasing evidence for the opioidergic system's role in the development (i.e., via reinforcement mechanisms) and maintenance (i.e., craving) of stimulant addiction has advanced pharmacologic agents targeting this pathway as plausible treatments for methamphetamine use disorders. Further, the few medications that have shown some promise for the treatment of methamphetamine use disorders, namely buproprion, modafinil, and naltrexone (as identified by this review), may exhibit greatest effectiveness through novel mechanisms such as enhancing the effectiveness of existent psychosocial interventions (e.g., via decreasing cognitive impairment) and by targeting intermediate phenotypes of addiction (e.g., relapse prevention/craving) (NIDA, 2005). Much more targeted, well-controlled research is indicated to fully understand the mechanisms and potential efficacy of these agents in the treatment of methamphetamine use disorders specifically, particularly given that these medications were commonly studied in small trials, distinct subpopulations, and/or predominately amphetamine using samples.

A number of gaps remain in the treatment literature for methamphetamine addiction. As described above, research is critically needed in pharmacologic treatment development (NIDA, 2005), particularly with novel targets and potentially novel delivery systems (e.g., vaccines; Kosten et al., 2014). By integrating basic neuroscience into treatment development research, one may elucidate how these novel interventions function to reduce methamphetamine use. This would allow in turn for the evaluation of neurotoxic and neurocognitive effects of prolonged methamphetamine use in the context of treatment outcomes and enable the identification of biomarkers with predictive validity. Further, given the poor retention rates, difficulties with treatment adherence, and overall poor outcomes associated with the interventions currently available, it is possible that the outpatient model employed for the treatment of many drugs of abuse is not suitable for methamphetamine addiction. If so, robust treatments studied within controlled inpatient/partial inpatient programs may prove more fruitful. As highlighted by this review and consistent with some conclusions reached by NIDA's Methamphetamine Addiction Treatment Think Tank (NIDA, 2005), research endeavors on the identification of biomarkers (to predict treatment response), relapse prevention (i.e., managing craving and stress), and remediation of associated cognitive impairment are advanced as crucial gaps in the knowledge base. Future research that can systematically address these gaps are thought to provide a roadmap for effective treatment development for methamphetamine addiction.

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Conflict of interest

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