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Review

Advances and challenges in pharmacotherapeutics for amphetamine-type stimulants addiction

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ABSTRACT

Addiction to amphetamine-type stimulants (ATS) is a serious worldwide public health problem with major medical, psychiatric and socioeconomic consequences. However, no approved pharmacological therapies are available to treat ATS addiction. Based on the neurobiological mechanisms underlying ATS addiction, the recent research works about pharmacological strategies have been focused on monoamine, glutamate, endogenous opioid peptide and γ-amino butyric acid (GABA) systems. This review summarizes the recent advances in the medications being developed to treat ATS addiction and discusses the remaining challenges. Although no substantial evidence for efficacious medications has emerged, some of these agents, including bupropion, naltrexone and mirtazapine, have demonstrated promise in clinical studies. Moreover, some challenges, such as the development of new preclinical animal models of drug addiction, the design of large-scale clinical trials with strict quality control, and the distinction of patients' genetic polymorphisms, need further attention. Despite the lack of success to date, much effort is being made to develop efficacious medications for treating ATS addiction.

Contents

1. Introduction

Drug addiction is a chronic and relapsing disease characterized by compulsive and uncontrolled drug use that results in serious medical, psychiatric and socioeconomic problems. An estimated

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246 million people used addictive drugs recreationally in 2013. At that time, an estimated 27 million people were problem drug users, suffering from drug use disorders or drug addiction (UNODC, 2015). The abuse of amphetamine-type stimulants (ATS) is increasing worldwide, especially in Southeast and East Asia. The number of people requiring treatment for ATS addiction is also increasing globally; however, no approved pharmacological therapeutic is available to treat addicted individuals. Recent advances in our understanding of the neurobiological mechanisms underlying drug addiction have led to the development of a growing number of pharmacological approaches to treat ATS addiction. Although substantial evidence is not available to support the efficacy of these agents, some agents exhibit great promise. This review focuses on the progress in developing pharmacological approaches to treat ATS addiction and discusses the challenges that may impede the development of these medications in the future.

2. Pharmacology of ATS

ATS are a class of compounds containing a phenyl structure that includes amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA), methcathinone, fenetylline, ephedrine, pseudoephedrine, and methylphenidate (Souza et al., 2012). According to their effects on the central nervous system, ATS can be divided into two groups. One group only acts as psychostimulants, such as amphetamine and methamphetamine. The other group resembles the structure of the hallucinogenic material mescaline, which has a methylenedioxy (–O–CH_2–O–) group attached to positions 3 and 4 of the phenyl structure and thus has both stimulant and hallucinogenic effects, such as MDMA, MDA and MDEA (Kalant, 2001). In this review, we mainly focus on the non-hallucinogenic psychostimulats.

ATS exert their effects by facilitating monoamine neurotransmission. Similar to cocaine, ATS block plasma membrane monoamine transporters, including dopamine transporters (DAT), norepinephrine transporters (NET) and serotonin transporters (SERT), to inhibit the clearance of extracellular monoamines. Unlike cocaine, however, ATS also compete with monoamine neurotransmitters based on their structural similarity, acting as substrates for DAT, NET and SERT and entering the presynaptic neuron. Once inside the neuron, these molecules both inhibit the reuptake of monoamine neurotransmitters through vesicular monoamine transporter 2 (VMAT2) and release the neurotransmitter stores of synaptic vesicles into the cytoplasm by inducing reverse transport of VMAT2, thus elevating cytoplasmic neurotransmitter concentrations. In addition, ATS attenuate monoamine degradation by inhibiting monoamine oxidase, further increasing cytoplasmic monoamine concentrations. Through their actions on the plasma membrane transporters (DAT, NET, and SERT), ATS reduce the uptake of monoamine neurotransmitters to the cytoplasm and facilitate the reverse transport of monoamine neurotransmitters, leading to non-exocytotic monoamine neurotransmitter release into the extracellular space, where they bind to their associated presynaptic autoreceptors and postsynaptic receptors (Courtney and Ray, 2014; Rice and Cragg, 2008; Teixeira-Gomes et al., 2015). Additionally, ATS agonize trace amine-associated receptor 1, which likely contributes to the complex effects of these agents on monoamine activity in the brain (Jing and Li, 2015; Xie and Miller, 2009). Specific ATS also interact with other presynaptic intracellular receptors that promote monoamine neurotransmission (e.g., methamphetamine is an agonist of the σ1 receptor) (Maurice and Su, 2009). Moreover, accumulated ATS and dopamine are oxidized in the cytoplasm, either by monoamine oxidase or by auto-oxidation, to produce neurotoxic reactive species, including superoxide (O_2^-) and peroxynitrite ($ONOO^-$). Mitochondrial disruption also contributes to the production of reactive species by activating NMDA receptors and opening the permeability transition pore (Davidson et al., 2001). Aberrant release of dopamine caused by ATS can increase dopamine D_1 receptor-mediated glutamate release, further increasing oxidative stress by excitatory amino acid toxicity (Mark et al., 2004). Furthermore, our recent research revealed that methamphetamine also directly increases presynaptic glutamate release independent of the dopaminergic system (Zhang et al., 2014). Altogether, these processes lead to the enhancement of monoaminergic and glutamatergic neurotransmissions, ultimately resulting in the pharmacological actions and neurotoxicity of ATS.

Although ATS present similar actions at several transporters, their affinities to different monoamine transporters are distinct, which explains the specificity of their pharmacologic and neurotoxic actions (Steinkellner et al., 2011). Amphetamine and methamphetamine have more potent actions on dopamine release than serotonin release, while MDMA causes a higher release of serotonin than dopamine. Importantly, amphetamine, methamphetamine, and MDMA are more potent norepinephrine releasers than dopamine and serotonin releasers (Rothman and Baumann, 2003).

Acute administration of low to moderate doses of ATS produces euphoria, arousal, and short-term improvement in cognition, while high doses or frequent use also result in psychotic episodes (such as hallucinations and delusions), hypertension, tachycardia and peripheral hyperthermia. Long-term use leads to dependence, cognitive dysfunction, and the irreversible loss of neuronal cell bodies and terminals. Following abrupt cessation after periods of regular use, individuals exhibit psychiatric withdrawal symptoms, including depression, anxiety and drug craving. Even after long-term abstinence, ATS addicts, similar to those addicted to other drugs, will relapse upon re-exposure to drug-related cues and contexts (Ciccarone, 2011).

3. Pharmacological approaches to treating ATS addiction

The treatment of individuals abusing ATS involves two approaches. The first approach is to treat ATS addiction with the goal of reducing drug use, attenuating craving and preventing relapse. The second approach is to treat ATS-related disorders, such as psychotic episodes and depression. To treat ATS-related disorders, many anti-psychotic and anti-depressive medications and cognitive enhancers could be used. However, at present, no medication is approved for the treatment of ATS addiction. Pharmacological strategies targeting monoamine, glutamate, endogenous opioid peptide and γ-amino butyric acid (GABA) systems have gained attention recently. Numerous classes of medications are currently involved in preclinical and clinical studies, and some candidate pharmaceuticals appear promising in clinical trials.

3.1. Targeting the dopamine system

Brain dopaminergic neurotransmission is thought to mediate reward and positive reinforcement, and ATS can increase extracellular dopamine concentrations. Chronic exposure to ATS also causes long-lasting molecular and cellular adaptations of the dopaminergic system, which may contribute to the addict's continued compulsive and uncontrolled drug use, despite obvious negative consequences. Therefore, targeting the dopamine system is an important strategy for the development of medications to treat ATS addiction. Based on their influence mechanisms on ATS addiction, dopamine-targeted treatments can be classified into two subtypes: substitution therapeutic medications and anti-dopamine system medications.

3.1.1. Substitution therapeutic medications

Of all of the medications that have been evaluated for the treatment of ATS dependence, bupropion has shown the most promising results. As an effective antidepressant, bupropion does not inhibit monoamine oxidase, exerts no effect on serotonin uptake, and minimally inhibits the reuptake of DAT and NET (Bryant et al., 1983). At the preclinical level, bupropion significantly reduces the self-administration of methamphetamine in monkeys at a dose that does not affect operant responding for food (Schindler et al., 2011). In a placebo-controlled human laboratory study, treatment with sustained-release bupropion two times a day significantly reduced methamphetamine-induced subjective effects and cue-induced craving (Newton et al., 2006). Two placebo-controlled double-blind clinical studies have revealed that sustained-release bupropion combined with cognitive behavioral therapy can reduce drug use in light methamphetamine users (less than 18 days of drug use/month) but not in heavy users (Elkashef et al., 2008; Shoptaw et al., 2008). Further analysis revealed that in the bupropion group, 20% of the participants achieved 2 or more weeks end-of-study abstinence, 14% achieved 6 or more weeks end-of-study abstinence, and 6% were abstinent throughout the trial, compared to 7%, 4%, and 1% in the placebo group, respectively (McCann and Li, 2012). Moreover, from a safety perspective, bupropion did not potentiate the cardiovascular effects of intravenous methamphetamine but rather significantly attenuated the ability of methamphetamine to increase heart rate and produced no significant trend in the direction of diminished methamphetamine effects on blood pressure (Newton et al., 2005). These results suggest that bupropion effectively facilitates the achievement of abstinence in light methamphetamine-dependent individuals and is promising for the treatment of ATS addiction.

In addition to bupropion, other medications that enhance dopamine have been evaluated as potential pharmacological interventions for ATS addiction. Methylphenidate, which has a similar mechanism to bupropion, failed to produce beneficial results in placebo-controlled, double-blind clinical trials (Miles et al., 2013). Modafinil is a non-amphetamine-type central stimulant that was first approved to treat narcolepsy and is used as an adjunctive therapy for depression. This medication acts as a weak inhibitor of DAT to elevate extracellular dopamine levels, increase glutamate release, and decrease GABA release (Martinez-Raga et al., 2008; Volkow et al., 2009a). Recently, two double-blind, placebo-controlled clinical trials found no overall therapeutic effect of modafinil on either cocaine or methamphetamine addiction (Anderson et al., 2012; Dackis et al., 2012). However, further analysis of the data revealed that the maximum duration of abstinence was significantly increased in modafinil-compliant methamphetamine-dependent participants compared to the remaining modafinil treatment groups (Anderson et al., 2012), indicating that improving treatment compliance and decreasing the dropout rate should be considered to achieve more definitive conclusions. In addition, several clinical studies have evaluated the effects of dextroamphetamine (D-amphetamine) on ATS addiction. Sustained-released D-amphetamine reduced withdrawal symptoms and craving in methamphetamine-addicted individuals (Galloway et al., 2011; Longo et al., 2010; Shearer et al., 2001), suggesting that treatment with D-amphetamine may be an efficacious substitution therapy. However, in light of the small sample size and high dropout rate of these studies, additional studies are needed to reach definitive conclusions.

Reducing the abuse liability of medications is important for the efficacy of substitution therapies for drug addiction. Lisdexamfetamine, the pro-drug of D-amphetamine, is used to treat attention deficits and hyperactivity disorders and exerts pharmacological actions by hydrolysis to D-amphetamine *in vivo*. After administration of equivalent doses of lisdexamfetamine and D-amphetamine (1.5 mg/kg i.p. of the D-amphetamine base) in rats, the resultant plasma pharmacokinetics profiles were very different. The maximum plasma concentration (C_{max}) observed after lisdexamfetamine administration was 50% lower than that of D-amphetamine, and the time to achieve C_{max} (t_{max}) was doubled. Accordingly, lisdexamfetamine produced a slow and sustained increase in extracellular dopamine levels in the striatum. Compared with D-amphetamine, lisdexamfetamine treatment resulted in reduced hyperactivity in rats (Heal et al., 2013b) and failed to substitute cocaine self-administration (Heal et al., 2013a), suggesting a lower potential for abuse. In addition, repeated administration of lisdexamfetamine for 7 days reduced cocaine self-administration behavior in rhesus monkeys (Banks et al., 2015). One clinical trial (NCT02034201) is underway to examine its efficacy for treating methamphetamine addiction. The results of this clinical study will ascertain the utility of lisdexamfetamine as a treatment for ATS addiction.

3.1.2. Anti-dopamine system medications

Compared to the agonist approaches described above, antagonist approaches in the dopamine system have been the subject of fewer clinical studies. The dopamine D_3 receptor has been investigated as a potential target for therapeutics to treat ATS addiction, and numerous antagonists and partial agonists have exhibited promise as anti-relapse drugs in preclinical studies. Our group developed the D_3 receptor antagonist YQA_{14}, which reduced the positive reinforcement of methamphetamine and drug- and cue-induced relapse in animal models (Chen et al., 2014). The compound $GSK_{598,809}$, a D_3 receptor antagonist developed by GlaxoSmithKline, reduced early withdrawal symptoms and craving in a smoking cessation study (Mugnaini et al., 2013). Buspirone is a partial agonist of the 5-HT_{1A} receptor that also antagonizes dopamine D_3 and D_4 receptors with high affinity. Buspirone exhibited a similar efficacy to other dopamine D_3 receptor antagonists in animal models of cocaine- and methamphetamine-induced self-administration and relapse. Small-scale clinical trials of buspirone have been performed for cocaine, opioids, cannabinoids and alcohol addiction with mixed results (Elkashef et al., 2008; Johnson, 2004; Newman et al., 2012; Rose et al., 2003). Phase I clinical trials showed that buspirone is safe and well-tolerated in methamphetamine addicts, and further phase IIa trials are needed to assess buspirone as a pharmacotherapy for ATS addiction (Paterson et al., 2014). Clinical investigation of these medications or other novel D_3 receptor ligands will provide a better understanding of the dopamine D_3 receptor as a target for the treatment of ATS addiction.

3.2. Targeting the glutamate system

Changes in glutamate neurotransmission have been implicated in the pathophysiology of drug addiction and appear to be involved in relapse. Moreover, glutamate-induced excitotoxicity contributes to ATS neurotoxicity. In the brain, the basal level of extracellular glutamate is maintained by a glutamate-cysteine exchanger that mediates the exchange of extracellular cysteine for intracellular glutamate. Chronic administration of addictive drugs down-regulates cysteine-glutamate exchange, leading to reduced extracellular glutamate and lowered mGluR2/3 stimulation, which in turn relieves inhibition of the synaptic release of glutamate (Kalivas, 2009; McClure et al., 2014). Therefore, N-acetylcysteine (NAC), a pro-drug of cysteine, has been examined for its therapeutic potential in treating drug addiction. Although preclinical and clinical studies have demonstrated some benefit of NAC in cocaine, heroin and cannabinoid addiction (Asevedo et al., 2014; Kalivas, 2009; Zhou and Kalivas, 2008), two small clinical trials in methamphetamine addicts yielded contradictory results (Grant et al., 2010; Mousavi et al., 2015), perhaps due to their small sample sizes or high dropout rates. In addition to NAC, many agents targeting the glutamate system (i.e., mGluR2/3, mGlu5 and NMDA receptors) have produced positive results in animal models of ATS addiction

(Forray and Sofuoglu, 2014), and more clinical studies are required.

3.3. Targeting the endogenous opioid peptide system

In addition to the dopamine and glutamate systems, endogenous opioid peptides and their receptors also play important roles in ATS addiction, mainly through influencing the function of the mesolimbic dopamine system. Naltrexone is a non-selective opioid receptors antagonist, with a higher affinity for μ-opioid receptors than for δ-and κ-opioid receptors. Naltrexone is approved to treat opioid addiction and alcoholism (Krupitsky et al., 2012; Ray et al., 2010), and a large number of preclinical and clinical reports describe its therapeutic effect on ATS addiction. Naltrexone reduces ATS-induced behavioral sensitization and relapse in rats, and also attenuates ATS-induced self-administration and relapse in rhesus monkeys (Anggadiredja et al., 2004b; Chiu et al., 2005; Haggkvist et al., 2009; Jimenez-Gomez et al., 2011). Recent clinical trials studying the effect of naltrexone treatment on ATS addiction have generated encouraging results. In an open-label clinical trial with 20 amphetamine-dependent patients receiving 12 weeks of naltrexone (50 mg) along with cognitive behavior therapy, naltrexone significantly reduced the frequency and amount of amphetamine consumption and was well tolerated with moderate rates of compliance (Jayaram-Lindstrom et al., 2005). Furthermore, a larger randomized double-blind placebo-controlled trial was performed in which naltrexone was well tolerated. Naltrexone outperformed the placebo in the mean number of negative urine samples and continuous abstinence rates in methamphetamine addicts, except for retention (Jayaram-Lindstrom et al., 2008a). Moreover, in another randomized double-blind placebo-controlled trial with 20 amphetamine-dependent patients, naltrexone significantly attenuated subjective responses to methamphetamine and cue-induced craving (Jayaram-Lindstrom et al., 2008b). Recently, in another double-blind, randomized, placebo-controlled human laboratory study, naltrexone significantly blunted cue-induced craving for methamphetamine and attenuated several of the hedonic subjective effects of methamphetamine (Ray et al., 2015). Because adherence to oral naltrexone tends to be suboptimal in this population, a naltrexone implant has also been developed. In a 10-week trial of individuals with comorbid opioid and amphetamine dependence, the naltrexone implant outperformed the placebo implant in terms of retention and the proportion of drug-free urine samples (Tiihonen et al., 2012). Thus, naltrexone appears to be a highly promising medication for treating ATS addiction.

3.4. Targeting the GABA system

GABA is an inhibitory neurotransmitter in the mammalian central nervous system that plays a vital role in drug addiction. Activation of the GABA system reduces mesolimbic dopaminergic neurotransmission. Thus, agonists of the GABA system may be effective for the treatment of ATS addiction. However, GABA agonists, such as gabapentin, baclofen, vigabatrin and tiagabine, have yet to reduce of methamphetamine use in human studies (Karila et al., 2010). These studies were limited by small sample size and a high dropout rate.

Because both GABAergic and glutamatergic neurons are important modulators of the brain reward system, medications that affect both GABAergic and glutamatergic neurotransmission may be more effective than those that activate the GABA system alone to reduce ATS addiction. Topiramate, an anticonvulsant, has attracted attention in recent years. This compound blocks voltage-gated sodium channels and ionotropic glutamate receptors (i.e., AMPA receptors and kainate receptors), enhances GABA neurotransmission by acting on the non-benzodiazepine site of the $GABA_A$ receptor, and inhibits carbonic anhydrase activity. One double-blind, placebo-controlled pilot trial showed that topiramate indeed decreased relapse in cocaine abusers (Kampman et al., 2004). Another multi-site placebo-controlled clinical study of methamphetamine addicts demonstrated that topiramate reduced drug use; however, no abstinence-promoting effect was observed (Elkashef et al., 2012). Further analysis of the data revealed that a small subgroup of patients exhibited consistent reductions in methamphetamine use or achieved abstinence criteria (Ma et al., 2013), suggesting different responses to topiramate treatment among the patients. Taken together, these data support the notion that targeting both the glutamate and GABA systems may be an effective approach for the treatment of ATS addiction.

3.5. Targeting the serotonin system

ATS use not only increases extracellular dopamine levels but also elevates serotonin; thus, the serotonin system is another important area for study. Mirtazapine is a pharmacologically distinct antidepressant with sedative and anxiolytic properties that enhances both noradrenergic and serotonergic activity. Mirtazapine acts differently on the serotonergic system than the selective serotonin reuptake inhibitors. With negligible affinity for reuptake proteins, the drug instead enhances transmission of $5\text{-}HT_{1A}$ receptors and blocks $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors (Anttila and Leinonen, 2001). One open-label study reported that mirtazapine reduced symptoms of methamphetamine withdrawal over 10 days of abstinence (McGregor et al., 2008). In a randomized, double-blind, placebo-controlled study conducted in homosexual men, mirtazapine reduced methamphetamine use in patients receiving counseling (Colfax et al., 2011). Moreover, a meta-analysis concluded that mirtazapine has promise as a pharmacotherapy for methamphetamine addiction (Rose and Grant, 2008). Risperidone, an atypical anti-psychotic medication used to treat schizophrenia, blocks the $5\text{-}HT_{2A}$ and dopamine D2 receptors. Clinical trials demonstrated that risperidone not only relieved the psychotic symptoms of ATS addicts but also reduced the frequency of drug use and craving compared to baseline (Meredith et al., 2007; Nejtek et al., 2008). However, further clinical studies are needed because neither of these studies included a placebo-controlled group. Paliperidone, the active metabolite of risperidone, has similar pharmacological characteristics to risperidone. Our group found that paliperidone, similar to risperidone, relieved methamphetamine-induced psychotic disorders, including positive and negative syndromes. Moreover, in a 12-week, double-blind, placebo-controlled clinical trial studying the effect of paliperidone on relapse, we found that paliperidone not only reduced craving but also increased abstinence, as measured by urine negativity and weeks of continuous non-use. Because psychotic symptoms are one of the main clinical manifestations seen in ATS addicts, targeting the serotonin system may prove to be an effective pharmacological approach to prevent relapse.

Other studies targeting the acetylcholine and endocannabinoid systems are underway but are mainly in the preclinical stage (Anggadiredja et al., 2004a; De La Garza et al., 2008a, 2008b; Landa et al., 2006).

4. Challenges to the development of medications for treating ATS addiction

Although many medications have been evaluated for their potential to treat ATS addiction, we still lack substantial evidence to confirm their efficacy. Despite the large number of agents that reduce ATS rewards and positive reinforcement and that inhibit drug- or cue-induced drug-seeking behavior in preclinical animal models, few agents have proven effective in clinical studies. To improve the pace of medication development for ATS addiction

treatment, several challenges should be considered in further investigations.

First, the gap between human addictive behaviors and experimental animal models limits the prediction of clinical outcomes from preclinical studies. The development of drug addiction is a continuous progression from recreational and regular drug use to compulsive use, accompanied by a behavioral transition from the initially goal-directed behavior with an action-outcome association to the habitual behavior with a stimulus-response association (Vanderschuren et al., 2005). This behavioral transformation coincides with a functional transition of the dopamine system from the ventral striatum to the dorsal striatum (Everitt and Robbins, 2013; Lesscher and Vanderschuren, 2012). Compulsive and uncontrolled drug use is generally recognized as a hallmark of addiction. More recently, several studies have revealed that the mechanism underlying compulsive drug use may be different from that underlying regular drug use and that dopamine, serotonin and glutamate functions are involved (Ben-Shahar et al., 2012; Caine et al., 2007; Lobo and Nestler, 2011; Muller and Homberg, 2015; Pelloux et al., 2012; Ramoa et al., 2014; Volkow et al., 2009b; Wilson et al., 1996). Although a range of animal models are used to explore the neurobiological mechanisms and emergent treatments for drug addiction, including intravenous self-administration 10–14 daily 3-h sessions of training under a low-rate, fixed-ratio reinforcement schedule), conditioned place preference and behavioral sensitization models, these models often do not reflect key characteristics of compulsive and uncontrolled drug seeking and taking. This factor may be the main reason why many agents exhibiting efficacy in preclinical models of ATS addiction fail in clinical studies. Establishing preclinical models that mimic human addictive behaviors remains a challenge. Recently, a series of new models in rats, including long-term self-administration (training for at least two months), escalation of self-administration, and punishment- or conflict-based models of relapse, have been developed that better represent characteristics of drug addiction and resemble clinical diagnostic criteria (Ahmed and Koob, 1998; Cooper et al., 2007; Deroche-Gamonet et al., 2004; Economidou et al., 2009). In particular, the long-term self-administration model in rats resembles some of the human diagnostic criteria for drug addiction described in the DSM-IV and more recently the DSM-5. In this model, animal addiction-like behaviors include 1) increased motivation to take the drug, as measured in a challenging progressive ratio; 2) an inability to refrain from drug seeking, as measured during periods when the drug is signaled as unavailable; and 3) maintained drug use despite aversive consequences, as measured by maintained drug self-administration despite punishment. Addiction-like behaviors are not present after a short period of self-administration but develop, as do addictions in humans, only after prolonged exposure to the drug. Furthermore, as do human addicts, rats showing addiction-like behaviors have a high propensity to relapse, even after a long period of withdrawal. Finally, the percentage of rats (17%) that show a high score for all three addiction-like criteria is similar to the percentage (15%) of human cocaine users diagnosed as addicts (Belin-Rauscent et al., 2016; Deroche-Gamonet et al., 2004). We believe that the use of these new preclinical models in future studies will yield valuable information about the mechanisms underlying ATS addiction and will also reveal the most suitable strategies for therapeutic intervention.

Second, good study design and strict controls are important for clinical studies. Many current findings have been obtained in small sample clinical trials (i.e., less than 20 cases), and small sample sizes limit our interpretation of the findings due to their low statistical power and poor generalizability. For example, small-size clinical trials of modafinil combined with behavioral therapy generated positive outcomes in the treatment of ATS addiction (McElhiney et al., 2009), whereas a subsequent large-scale trial failed to demonstrate efficacy (Anderson et al., 2012). Thus, large-scale clinical investigations are needed in the future to reach definitive conclusions. In addition, the lack of a placebo-controlled group complicates the interpretation of a number of current studies. Even if statistical differences are found compared with baseline data, natural recovery cannot be eliminated in these cases. Another problem is that high dropout rates and low compliance with therapy often occur in clinical trials of drug addiction, which complicates the results. To obtain definitive conclusions, therefore, large-scale clinical investigations will need to be conducted with strict quality control and a deep analysis of the data.

Third, the effects of patient genetic polymorphism on treatment outcomes should be considered. Treatment responses can be influenced by polymorphisms in drug metabolic enzymes (e.g., CYP2A6 and CYP2B6) that affect drug metabolism. Additionally, variants in medication target genes may also contribute to the diversity of treatment responses. The A118G SNP of the μ-opioid receptor is associated with the treatment response to naltrexone in alcoholism, and patients with the G/G or A/G genotype achieved better efficacy compared to those with the A/A genotype (Crist and Berrettini, 2014). Thus, dividing the subjects into subgroups with different genotypes prior to data analysis may be helpful for reaching clear conclusions.

5. Conclusions

ATS addiction is a serious and growing problem worldwide, and the need for effective treatments is urgent. The development of pharmacotherapies to treat ATS addiction is at an early stage, and no substantial evidence for efficacious treatment programs has emerged. However, the dopamine and norepinephrine reuptake inhibitor bupropion, the opioid receptors antagonist naltrexone, and the serotonin neurotransmission enhancer mirtazapine appear to be highly promising. An improved understanding of the neurobiological mechanisms underlying ATS addiction may pave the road for novel pharmacotherapeutic strategies. Despite the lack of success to date, constant effort is being made to develop efficacious medications to treat ATS addiction.

Conflicts of interest

The authors report no conflict of interest.

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References

Ahmed, S.H., Koob, G.F., 1998. Transition from moderate to excessive drug intake: change in hedonic set point. Science 282, 298–300.

Anderson, A.L., Li, S.H., Biswas, K., McSherry, F., Holmes, T., Iturriaga, E., Kahn, R., Chiang, N., Beresford, T., Campbell, J., Haning, W., Mawhinney, J., McCann, M., Rawson, R., Stock, C., Weis, D., Yu, E., Elkashef, A.M., 2012. Modafinil for the treatment of methamphetamine dependence. Drug. Alcohol Depend. 120, 135–141.

Anggadiredja, K., Nakamichi, M., Hiranita, T., Tanaka, H., Shoyama, Y., Watanabe, S., Yamamoto, T., 2004a. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. Neuropsychopharmacology 29, 1470–1478.

Anggadiredja, K., Sakimura, K., Hiranita, T., Yamamoto, T., 2004b. Naltrexone attenuates cue- but not drug-induced methamphetamine seeking: a possible

mechanism for the dissociation of primary and secondary reward. Brain Res. 1021, 272–276.
Anttila, S.A., Leinonen, E.V., 2001. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug. Rev. 7, 249–264.
Asevedo, E., Mendes, A.C., Berk, M., Brietzke, E., 2014. Systematic review of N-acetylcysteine in the treatment of addictions. Rev. Bras. Psiquiatr. 36, 168–175.
Banks, M.L., Hutsell, B.A., Blough, B.E., Poklis, J.L., Negus, S.S., 2015. Preclinical assessment of lisdexamfetamine as an agonist medication candidate for cocaine addiction: effects in rhesus monkeys trained to discriminate cocaine or to self-administer cocaine in a cocaine versus food choice procedure. Int. J. Neuropsychopharmacol., 18.
Belin-Rauscent, A., Fouyssac, M., Bonci, A., Belin, D., 2016. How preclinical models evolved to resemble the diagnostic criteria of drug addiction. Biol. Psychiatry 79, 39–46.
Ben-Shahar, O.M., Szumlinski, K.K., Lominac, K.D., Cohen, A., Gordon, E., Ploense, K. L., DeMartini, J., Bernstein, N., Rudy, N.M., Nabhan, A.N., Sacramento, A., Pagano, K., Carosso, G.A., Woodward, N., 2012. Extended access to cocaine self-administration results in reduced glutamate function within the medial prefrontal cortex. Addict. Biol. 17, 746–757.
Bryant, S.G., Guernsey, B.G., Ingrim, N.B., 1983. Review of bupropion. Clin. Pharm. 2, 525–537.
Caine, S.B., Thomsen, M., Gabriel, K.I., Berkowitz, J.S., Gold, L.H., Koob, G.F., Tonegawa, S., Zhang, J., Xu, M., 2007. Lack of self-administration of cocaine in dopamine D1 receptor knock-out mice. J. Neurosci. 27, 13140–13150.
Chen, Y., Song, R., Yang, R.F., Wu, N., Li, J., 2014. A novel dopamine D3 receptor antagonist YQA14 inhibits methamphetamine self-administration and relapse to drug-seeking behaviour in rats. Eur. J. Pharmacol. 743, 126–132.
Chiu, C.T., Ma, T., Ho, I.K., 2005. Attenuation of methamphetamine-induced behavioral sensitization in mice by systemic administration of naltrexone. Brain Res. Bull. 67, 100–109.
Ciccarone, D., 2011. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. Prim. Care. 38, 41–58, v–vi.
Colfax, G.N., Santos, G.M., Das, M., Santos, D.M., Matheson, T., Gasper, J., Shoptaw, S., Vittinghoff, E., 2011. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. Arch. Gen. Psychiatry 68, 1168–1175.
Cooper, A., Barnea-Ygael, N., Levy, D., Shaham, Y., Zangen, A., 2007. A conflict rat model of cue-induced relapse to cocaine seeking. Psychopharmacol. (Berl.) 194, 117–125.
Courtney, K.E., Ray, L.A., 2014. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug. Alcohol Depend. 143, 11–21.
Crist, R.C., Berrettini, W.H., 2014. Pharmacogenetics of OPRM1. Pharm. Biochem Behav. 123, 25–33.
Dackis, C.A., Kampman, K.M., Lynch, K.G., Plebani, J.G., Pettinati, H.M., Sparkman, T., O'Brien, C.P., 2012. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. J. Subst. Abus. Treat. 43, 303–312.
Davidson, C., Gow, A.J., Lee, T.H., Ellinwood, E.H., 2001. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res. Brain Res. Rev. 36, 1–22.
De La Garza, R., Shoptaw, S., Newton, T.F., 2008a. Evaluation of the cardiovascular and subjective effects of rivastigmine in combination with methamphetamine in methamphetamine-dependent human volunteers. Int. J. Neuropsychopharmacol. 11, 729–741.
De La Garza 2nd, R., Mahoney 3rd, J.J., Culbertson, C., Shoptaw, S., Newton, T.F., 2008b. The acetylcholinesterase inhibitor rivastigmine does not alter total choices for methamphetamine, but may reduce positive subjective effects, in a laboratory model of intravenous self-administration in human volunteers. Pharm. Biochem. Behav. 89, 200–208.
Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science 305, 1014–1017.
Economidou, D., Pelloux, Y., Robbins, T.W., Dalley, J.W., Everitt, B.J., 2009. High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. Biol. Psychiatry 65, 851–856.
Elkashef, A., Kahn, R., Yu, E., Iturriaga, E., Li, S.H., Anderson, A., Chiang, N., Ait-Daoud, N., Weiss, D., McSherry, F., Serpi, T., Rawson, R., Hrymoc, M., Weis, D., McCann, M., Pham, T., Stock, C., Dickinson, R., Campbell, J., Gorodetzky, C., Haning, W., Carlton, B., Mawhinney, J., Li, M.D., Johnson, B.A., 2012. Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. Addiction 107, 1297–1306.
Elkashef, A.M., Rawson, R.A., Anderson, A.L., Li, S.H., Holmes, T., Smith, E.V., Chiang, N., Kahn, R., Vocci, F., Ling, W., Pearce, V.J., McCann, M., Campbell, J., Gorodetzky, C., Haning, W., Carlton, B., Mawhinney, J., Weis, D., 2008. Bupropion for the treatment of methamphetamine dependence. Neuropsychopharmacology 33, 1162–1170.
Everitt, B.J., Robbins, T.W., 2013. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci. Biobehav Rev. 37, 1946–1954.
Forray, A., Sofuoglu, M., 2014. Future pharmacological treatments for substance use disorders. Br. J. Clin. Pharmacol. 77, 382–400.
Galloway, G.P., Buscemi, R., Coyle, J.R., Flower, K., Siegrist, J.D., Fiske, L.A., Baggott, M. J., Li, L., Polcin, D., Chen, C.Y., Mendelson, J., 2011. A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. Clin. Pharm. Ther. 89, 276–282.
Grant, J.E., Odlaug, B.L., Kim, S.W., 2010. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. Eur. Neuropsychopharmacol. 20, 823–828.
Haggkvist, J., Lindholm, S., Franck, J., 2009. The opioid receptor antagonist naltrexone attenuates reinstatement of amphetamine drug-seeking in the rat. Behav. Brain Res. 197, 219–224.
Heal, D.J., Buckley, N.W., Gosden, J., Slater, N., France, C.P., Hackett, D., 2013a. A preclinical evaluation of the discriminative and reinforcing properties of lisdexamfetamine in comparison to d-amfetamine, methylphenidate and modafinil. Neuropharmacology 73, 348–358.
Heal, D.J., Smith, S.L., Gosden, J., Nutt, D.J., 2013b. Amphetamine, past and present–a pharmacological and clinical perspective. J. Psychopharmacol. 27, 479–496.
Jayaram-Lindstrom, N., Wennberg, P., Beck, O., Franck, J., 2005. An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. Nord J. Psychiatry 59, 167–171.
Jayaram-Lindstrom, N., Hammarberg, A., Beck, O., Franck, J., 2008a. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. Am. J. Psychiatry 165, 1442–1448.
Jayaram-Lindstrom, N., Konstenius, M., Eksborg, S., Beck, O., Hammarberg, A., Franck, J., 2008b. Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. Neuropsychopharmacology 33, 1856–1863.
Jimenez-Gomez, C., Winger, G., Dean, R.L., Deaver, D.R., Woods, J.H., 2011. Naltrexone decreases d-amphetamine and ethanol self-administration in rhesus monkeys. Behav. Pharmacol. 22, 87–90.
Jing, L., Li, J.X., 2015. Trace amine-associated receptor 1: A promising target for the treatment of psychostimulant addiction. Eur. J. Pharmacol. 761, 345–352.
Johnson, B.A., 2004. Role of the serotonergic system in the neurobiology of alcoholism: implications for treatment. CNS Drugs 18, 1105–1118.
Kalant, H., 2001. The pharmacology and toxicology of ecstasy (MDMA) and related drugs. CMAJ 165, 917–928.
Kalivas, P.W., 2009. The glutamate homeostasis hypothesis of addiction. Nat. Rev. Neurosci. 10, 561–572.
Kampman, K.M., Pettinati, H., Lynch, K.G., Dackis, C., Sparkman, T., Weigley, C., O'Brien, C.P., 2004. A pilot trial of topiramate for the treatment of cocaine dependence. Drug. Alcohol Depend. 75, 233–240.
Karila, L., Weinstein, A., Aubin, H.J., Benyamina, A., Reynaud, M., Batki, S.L., 2010. Pharmacological approaches to methamphetamine dependence: a focused review. Br. J. Clin. Pharmacol. 69, 578–592.
Krupitsky, E., Zvartau, E., Blokhina, E., Verbitskaya, E., Wahlgren, V., Tsoy-Podosenin, M., Bushara, N., Burakov, A., Masalov, D., Romanova, T., Tyurina, A., Palatkin, V., Slavina, T., Pecoraro, A., Woody, G.E., 2012. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Arch. Gen. Psychiatry 69, 973–981.
Landa, L., Sulcova, A., Slais, K., 2006. Involvement of cannabinoid CB1 and CB2 receptor activity in the development of behavioural sensitization to methamphetamine effects in mice. Neuro Endocrinol. Lett. 27, 63–69.
Lesscher, H.M., Vanderschuren, L.J., 2012. Compulsive drug use and its neural substrates. Rev. Neurosci. 23, 731–745.
Lobo, M.K., Nestler, E.J., 2011. The striatal balancing act in drug addiction: distinct roles of direct and indirect pathway medium spiny neurons. Front Neuroanat. 5, 41.
Longo, M., Wickes, W., Smout, M., Harrison, S., Cahill, S., White, J.M., 2010. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. Addiction 105, 146–154.
Ma, J.Z., Johnson, B.A., Yu, E., Weiss, D., McSherry, F., Saadvandi, J., Iturriaga, E., Ait-Daoud, N., Rawson, R.A., Hrymoc, M., Campbell, J., Gorodetzky, C., Haning, W., Carlton, B., Mawhinney, J., Weis, D., McCann, M., Pham, T., Stock, C., Dickinson, R., Elkashef, A., Li, M.D., 2013. Fine-grain analysis of the treatment effect of topiramate on methamphetamine addiction with latent variable analysis. Drug. Alcohol Depend. 130, 45–51.
Mark, K.A., Soghomonian, J.J., Yamamoto, B.K., 2004. High-dose methamphetamine acutely activates the striatonigral pathway to increase striatal glutamate and mediate long-term dopamine toxicity. J. Neurosci. 24, 11449–11456.
Martinez-Raga, J., Knecht, C., Cepeda, S., 2008. Modafinil: a useful medication for cocaine addiction? Review of the evidence from neuropharmacological, experimental and clinical studies. Curr. Drug. Abus. Rev. 1, 213–221.
Maurice, T., Su, T.P., 2009. The pharmacology of sigma-1 receptors. Pharm. Ther. 124, 195–206.
McCann, D.J., Li, S.H., 2012. A novel, nonbinary evaluation of success and failure reveals bupropion efficacy versus methamphetamine dependence: reanalysis of a multisite trial. CNS Neurosci. Ther. 18, 414–418.
McClure, E.A., Gipson, C.D., Malcolm, R.J., Kalivas, P.W., Gray, K.M., 2014. Potential role of N-acetylcysteine in the management of substance use disorders. CNS Drugs 28, 95–106.
McElhiney, M.C., Rabkin, J.G., Rabkin, R., Nunes, E.V., 2009. Provigil (modafinil) plus cognitive behavioral therapy for methamphetamine use in HIV+ gay men: a pilot study. Am. J. Drug. Alcohol Abus. 35, 34–37.
McGregor, C., Srisurapanont, M., Mitchell, A., Wickes, W., White, J.M., 2008. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. J. Subst. Abus. Treat. 35, 334–342.
Meredith, C.W., Jaffe, C., Yanasak, E., Cherrier, M., Saxon, A.J., 2007. An open-label pilot study of risperidone in the treatment of methamphetamine dependence. J. Psychoact. Drugs 39, 167–172.
Miles, S.W., Sheridan, J., Russell, B., Kydd, R., Wheeler, A., Walters, C., Gamble, G., Hardley, P., Jensen, M., Kuoppasalmi, K., Tuomola, P., Fohr, J., Kuikanmaki, O., Vorma, H., Salokangas, R., Mikkonen, A., Kallio, M., Kauhanen, J., Kiviniemi, V., Tiihonen, J., 2013. Extended-release methylphenidate for treatment of

amphetamine/methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. Addiction 108, 1279–1286.
Mousavi, S.G., Sharbafchi, M.R., Salehi, M., Peykanpour, M., Karimian Sichani, N., Maracy, M., 2015. The efficacy of N-acetylcysteine in the treatment of methamphetamine dependence: a double-blind controlled, crossover study. Arch. Iran. Med. 18, 28–33.
Mugnaini, M., Iavarone, L., Cavallini, P., Griffante, C., Oliosi, B., Savoia, C., Beaver, J., Rabiner, E.A., Micheli, F., Heidbreder, C., Andorn, A., Merlo Pich, E., Bani, M., 2013. Occupancy of brain dopamine D3 receptors and drug craving: a translational approach. Neuropsychopharmacology 38, 302–312.
Muller, C.P., Homberg, J.R., 2015. The role of serotonin in drug use and addiction. Behav. Brain Res. 277, 146–192.
Nejtek, V.A., Avila, M., Chen, L.A., Zielinski, T., Djokovic, M., Podawiltz, A., Kaiser, K., Bae, S., Rush, A.J., 2008. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. J. Clin. Psychiatry 69, 1257–1266.
Newman, A.H., Blaylock, B.L., Nader, M.A., Bergman, J., Sibley, D.R., Skolnick, P., 2012. Medication discovery for addiction: translating the dopamine D3 receptor hypothesis. Biochem Pharmacol. 84, 882–890.
Newton, T.F., Roache, J.D., De La Garza 2nd, R., Fong, T., Wallace, C.L., Li, S.H., Elkashef, A., Chiang, N., Kahn, R., 2005. Safety of intravenous methamphetamine administration during treatment with bupropion. Psychopharmacol. (Berl.) 182, 426–435.
Newton, T.F., Roache, J.D., De La Garza 2nd, R., Fong, T., Wallace, C.L., Li, S.H., Elkashef, A., Chiang, N., Kahn, R., 2006. Bupropion reduces methamphetamine-induced subjective effects and cue-induced craving. Neuropsychopharmacology 31, 1537–1544.
Paterson, N.E., Vocci, F., Sevak, R.J., Wagreich, E., London, E.D., 2014. Dopamine D3 receptors as a therapeutic target for methamphetamine dependence. Am. J. Drug. Alcohol Abus. 40, 1–9.
Pelloux, Y., Dilleen, R., Economidou, D., Theobald, D., Everitt, B.J., 2012. Reduced forebrain serotonin transmission is causally involved in the development of compulsive cocaine seeking in rats. Neuropsychopharmacology 37, 2505–2514.
Ramoa, C.P., Doyle, S.E., Lycas, M.D., Chernau, A.K., Lynch, W.J., 2014. Diminished role of dopamine D1-receptor signaling with the development of an addicted phenotype in rats. Biol. Psychiatry 76, 8–14.
Ray, L.A., Chin, P.F., Miotto, K., 2010. Naltrexone for the treatment of alcoholism: clinical findings, mechanisms of action, and pharmacogenetics. CNS Neurol. Disord. Drug. Targets 9, 13–22.
Ray, L.A., Bujarski, S., Courtney, K.E., Moallem, N.R., Lunny, K., Roche, D., Leventhal, A.M., Shoptaw, S., Heinzerling, K., London, E.D., Miotto, K., 2015. The effects of naltrexone on subjective response to methamphetamine in a clinical sample: a double-blind, placebo-controlled laboratory study. Neuropsychopharmacology 40, 2347–2356.
Rice, M.E., Cragg, S.J., 2008. Dopamine spillover after quantal release: rethinking dopamine transmission in the nigrostriatal pathway. Brain Res. Rev. 58, 303–313.
Rose, J.S., Branchey, M., Wallach, L., Buydens-Branchey, L., 2003. Effects of buspirone in withdrawal from opiates. Am. J. Addict. 12, 253–259.
Rose, M.E., Grant, J.E., 2008. Pharmacotherapy for methamphetamine dependence: a review of the pathophysiology of methamphetamine addiction and the theoretical basis and efficacy of pharmacotherapeutic interventions. Ann. Clin. Psychiatry 20, 145–155.
Rothman, R.B., Baumann, M.H., 2003. Monoamine transporters and psychostimulant drugs. Eur. J. Pharmacol. 479, 23–40.
Schindler, C.W., Gilman, J.P., Panlilio, L.V., McCann, D.J., Goldberg, S.R., 2011. Comparison of the effects of methamphetamine, bupropion, and methylphenidate on the self-administration of methamphetamine by rhesus monkeys. Exp. Clin. Psychopharmacol. 19, 1–10.
Shearer, J., Wodak, A., Mattick, R.P., Van Beek, I., Lewis, J., Hall, W., Dolan, K., 2001. Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. Addiction 96, 1289–1296.
Shoptaw, S., Heinzerling, K.G., Rotheram-Fuller, E., Steward, T., Wang, J., Swanson, A. N., De La Garza, R., Newton, T., Ling, W., 2008. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. Drug. Alcohol Depend. 96, 222–232.
Souza, D.Z., Boehl, P.O., Comiran, E., Prusch, D.S., Zancanaro, I., Fuentefria, A.M., Pechansky, F., Duarte, P.C., De Boni, R.B., Froehlich, P.E., Limberger, R.P., 2012. Which amphetamine-type stimulants can be detected by oral fluid immunoassays? Ther. Drug. Monit. 34, 98–109.
Steinkellner, T., Freissmuth, M., Sitte, H.H., Montgomery, T., 2011. The ugly side of amphetamines: short- and long-term toxicity of 3,4-methylenedioxymethamphetamine (MDMA,'Ecstasy'), methamphetamine and d-amphetamine. Biol. Chem. 392, 103–115.
Teixeira-Gomes, A., Costa, V.M., Feio-Azevedo, R., Bastos Mde, L., Carvalho, F., Capela, J.P., 2015. The neurotoxicity of amphetamines during the adolescent period. Int. J. Dev. Neurosci. 41, 44–62.
Tiihonen, J., Krupitsky, E., Verbitskaya, E., Blokhina, E., Mamontova, O., Fohr, J., Tuomola, P., Kuoppasalmi, K., Kiviniemi, V., Zwartau, E., 2012. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. Am. J. Psychiatry 169, 531–536.
UNODC (United Nations Office on Drugs and Crime), 2015. World Drug Report 2015. United Nations publication, Sales No. E.15.XI.6.
Vanderschuren, L.J., Di Ciano, P., Everitt, B.J., 2005. Involvement of the dorsal striatum in cue-controlled cocaine seeking. J. Neurosci. 25, 8665–8670.
Volkow, N.D., Fowler, J.S., Logan, J., Alexoff, D., Zhu, W., Telang, F., Wang, G.J., Jayne, M., Hooker, J.M., Wong, C., Hubbard, B., Carter, P., Warner, D., King, P., Shea, C., Xu, Y., Muench, L., Apelskog-Torres, K., 2009a. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301, 1148–1154.
Volkow, N.D., Fowler, J.S., Wang, G.J., Baler, R., Telang, F., 2009b. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56 (Suppl 1), 3–8.
Wilson, J.M., Kalasinsky, K.S., Levey, A.I., Bergeron, C., Reiber, G., Anthony, R.M., Schmunk, G.A., Shannak, K., Haycock, J.W., Kish, S.J., 1996. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat. Med. 2, 699–703.
Xie, Z., Miller, G.M., 2009. A receptor mechanism for methamphetamine action in dopamine transporter regulation in brain. J. Pharm. Exp. Ther. 330, 316–325.
Zhang, S., Jin, Y., Liu, X., Yang, L., Ge, Z., Wang, H., Li, J., Zheng, J., 2014. Methamphetamine modulates glutamatergic synaptic transmission in rat primary cultured hippocampal neurons. Brain Res. 1582, 1–11.
Zhou, W., Kalivas, P.W., 2008. N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. Biol. Psychiatry 63, 338–340.