

Developing Treatments for Stimulant Abuse: A Brief Overview

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Abstract

The abuse of stimulants such as cocaine, amphetamine, and methamphetamine is a huge problem in many parts of the world. Abuse of these drugs does not ruin just the user's life, but also adversely affects those around them. Despite many years of research, there are no approved medications for stimulant dependence, and treatment is focused on psychotherapy and abstinence. Over the last 10 to 20 years, there have been some major changes in approach to medication development for stimulant dependence. These include assessing ligands for non-dopaminergic sites, atypical dopamine transporter ligands, blocking long-term potentiation and / or memory reconsolidation, vaccines against the stimulant, and molecular approaches including pharmacogenomics and gene silencing. Also included in this overview are non-drug treatments such as deep brain stimulation and psychosurgery. This overview highlights recent preclinical and clinical studies of treatment development for stimulant dependence.

Key words: Amphetamine; Cocaine; Drug therapy; Methamphetamine; Therapeutics

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Stimulant Misuse Is Widespread and Difficult to Treat

Lots of people take stimulants. In Europe, 5.7 million adults took cocaine and 2.9 million adults took amphetamine in 2015.¹ In 2014 there were 0.9 million cocaine-abusing or cocaine-dependent individuals in the US.² South-East Asia seems to have the biggest problem with amphetamine-type stimulants,³ and Japan has had problems with methamphetamine for over 60 years.⁴ There are currently no approved pharmacotherapies for stimulant abuse. Behavioural therapies work to a certain extent but are limited.⁵ Dropout rates of over 50% are common in cocaine dependence treatment programmes⁶ and it is likely that cocaine withdrawal symptoms greatly contribute to dropout rates.⁷ The need for new treatments for stimulant dependence is thus critical.

Time Course of Stimulant Dependence

Traditionally, pharmacotherapies have aimed to block the reinforcing effects of stimulants (e.g. blocking the dopamine transporter [DAT]) or alleviate the anxiety or depression associated with stimulant withdrawal. Nonetheless, when

the various stages of drug dependence are considered, it becomes clear that there are multiple stages at which therapies can be targeted. In addition, it is likely that different pharmacotherapies will be needed for these different stages. Thus, there are phases of drug-taking that can be targeted (Fig), when stimulant levels and / or extracellular dopamine levels are high. There are also chronic drug withdrawal states where there is dopaminergic hypofunction.⁸ In general, drugs can be targeted at 'abstinence initiation' or 'relapse prevention' and these have been reviewed.⁹ Drug therapies that might be useful in initiating abstinence include modafinil (a mild stimulant currently approved for narcolepsy), propranolol (an anxiolytic), and bupropion (an antidepressant). Relapse prevention pharmacotherapy might include γ -aminobutyric acid (GABA) enhancers such as γ -vinyl GABA, tiagabine, and topiramate to be discussed below.

Nonetheless, if one examines drug dependence more closely we can split the addict's activities or behaviour into numerous subcategories, each of which could be a target for pharmacotherapy. These subcategories include thinking about taking the drug, drug-taking, euphoria / drug-liking, acute drug withdrawal, compulsion to take the drug, relapse, chronic drug withdrawal, withdrawal-associated depression, withdrawal-associated anxiety, and drug-induced cognitive dysfunction.

Treatments for Stimulant Dependence That Have Thus Far Not Worked

Agonist therapies include drugs that act on the same receptor or transporter as the drug of abuse. In the case of cocaine this is the DAT and dopamine D1-5 receptors. Because cocaine's acute action is to increase synaptic dopamine,

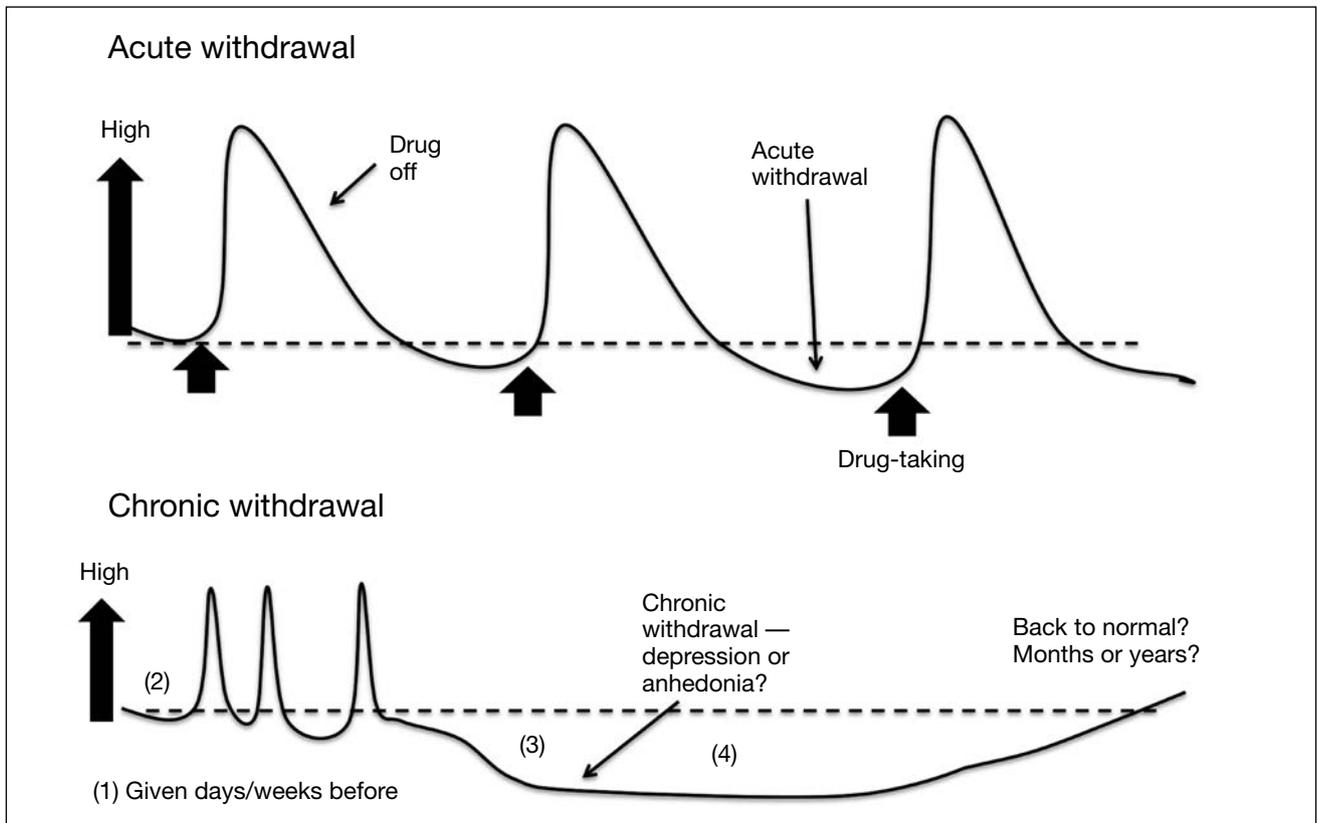


Figure. Treatment opportunities during stimulant treatment and abstinence. (Top) This might represent stimulant bingeing where the stimulant is taken 3 times in quite quick succession. The stimulant has a quick effect and the abuser experiences a high, followed by a slower comedown phase where mood decreases below the norm: an acute withdrawal phase. The abuser may take the stimulant again to overcome the acute withdrawal. (Bottom) After binge drug-taking, the abuser may abstain from drug use for weeks or months and this may lead to a chronic withdrawal phase characterised by anxiety- and depression-like symptoms. It is at this point that many abusers seek medical help. Pharmacotherapy could be targeted at any stage including (1) prophylactic measures such as cocaine vaccine or agonist therapy; (2) dopamine receptor antagonists to reduce the effect of the stimulant; (3) anxiolytic or antidepressants to decrease withdrawal symptoms; and (4) drugs that might block or attenuate 'drug-related memories'.

it has indirect agonist effects at the dopamine receptors. The theory behind agonist therapy is that by giving the addict a little bit of what he / she wants, they may not take the primary drug of abuse. As we have seen with heroin, however, the addict can become addicted to the agonist therapy (methadone). Typically the agonist (or substitution) therapy is longer-acting (making it less addictive) and with a better safety profile than the drug of abuse. Amphetamine and methylphenidate have both been used in cocaine or methamphetamine abusers, with only modest effects. Similarly bupropion, a relatively weak DAT inhibitor, has had inconsistent effects in cocaine or methamphetamine dependence. Modafinil is a mild stimulant that also enhances glutamate transmission.¹⁰ It has been found to be useful in some small clinical trials, attenuating the euphoric effects of cocaine and reducing cocaine intake.¹¹⁻¹⁵ More recent data have shown that modafinil causes the DAT to prefer its inward (cytosol)-facing state. Thus modafinil appears to

react with the DAT more like a substrate (e.g. dopamine) than an uptake blocker like cocaine, but unlike substrates is not moved intracellularly.¹⁶ Dopamine transporter ligands with this property have been termed 'atypical' DAT inhibitors. More recent long-acting atypical DAT inhibitors include the CTDP series of National Institute on Drug Abuse-sponsored compounds, e.g. CTDP 31345¹⁷ and modafinil analogues.¹⁸ Thus, the quest for a cocaine agonist therapy continues.¹⁹

The opposite treatment of a substitution or maintenance therapy would be an antagonist-based therapy. This type of therapy has worked for opioid abuse, e.g. using the opioid antagonist naltrexone or the partial agonist buprenorphine.²⁰ For cocaine abuse, rather than reducing cocaine intake by providing a low-level dopamine boost, the antagonist therapy blocks dopamine receptors and thus attenuates the rewarding effects of cocaine. Dopamine D3 receptor antagonists have been shown to work in rodent

models of drug abuse²¹ but have not yet been tested in humans. Antagonists at the dopamine D3 receptor may have particular use in the stimulant chronic withdrawal period.^{22,23} Nonetheless, it is always possible that the addict will just increase their dose of stimulant to overcome the antagonist. As a caveat, one should also be wary of dopamine antagonist-induced extrapyramidal side-effects.

Future Treatments

Drugs That Work via Other Membrane Proteins

The main neurotransmitter involved in drug abuse and reward is undoubtedly dopamine. Many other neurotransmitters are also involved either directly, or as modulators of dopamine levels via action on the dopamine terminals or at the cell body region (the ventral tegmental area). In addition, other transmitter systems are involved in drug withdrawal states and their associated craving, depression, and anxiety. Drugs that block corticotrophin-releasing factor (CRF) and / or noradrenaline might decrease the stimulant-induced anxiety that could lead to relapse.

Stimulants not only increase extracellular dopamine levels, but also those of noradrenaline and 5-HT. Potentiation of 5-HT contributes to cocaine reward²⁴ and transgenic mice devoid of the DAT still exhibit cocaine-seeking behaviour, but not when devoid of the DAT and serotonin transporters.²⁵ It is reasonable to assume then that drugs that act on the 5-HT system may be useful in manipulating stimulant dependence. Another advantage of the 5-HT system is that there are 14 known 5-HT receptors (but only 5 for dopamine) allowing quite specific modulation of only part of the 5-HT system to reduce stimulant dependence,²⁶ but hopefully with fewer side-effects. The use of selective serotonin reuptake inhibitors in cocaine dependence has been disappointing.²⁷ Nonetheless, antagonists of the 5-HT₂ and 5-HT₃ receptors have been tested for stimulant dependence^{28,29} with small positive effects, and the role of 5-HT₂ in cocaine use has been recently reviewed.³⁰

The α_1 adrenergic antagonist prazosin can reduce cocaine seeking in rats.³¹ The α_{2A} adrenergic agonist guanfacine enhanced inhibitory control and executive function in early abstinent cocaine dependents.³² One might ask how an agonist could reduce noradrenergic function. It is possible that guanfacine preferentially activates the presynaptic α_2 receptors, which are inhibitory autoreceptors,³³ thus the net effect is lower noradrenaline efflux. Propranolol, a beta-blocker with anxiolytic qualities, has also been found to be useful in patients with severe cocaine withdrawal, increasing the number of patients who stayed in treatment^{34,35} or remained abstinent.³⁶ The CRF-1 receptor antagonist CP-154,526 can attenuate cocaine or methamphetamine reinstatement (relapse) in rodents^{37,38} and also reduce cocaine-induced conditioned place preference (cocaine seeking) in rodents.³⁹ Thus far, antagonists at the glutamate N-methyl-D-aspartate (NMDA) receptor, for example, memantine, have been unsuccessful in cocaine dependence.⁴⁰ Nonetheless N-acetylcysteine, which among

other actions stimulates the cysteine-glutamate transporter,⁴¹ normalises glutamate levels in the accumbens after cocaine^{42,43} and may reduce cocaine craving in humans.⁴⁴⁻⁴⁶

Other transmitter systems that might be involved in drug dependence include the orexin, GABAergic and cholinergic systems, as well as pharmacotherapies that act via these systems have been tested. The hypothalamic neuropeptide orexin is released into the accumbens and SB-334867, an orexin-1 receptor antagonist, inhibits relapse in rodents.⁴⁷ Tiagabine, used to treat seizures, increases extracellular GABA levels by blocking GABA reuptake.⁴⁸ It can increase abstinence in cocaine dependence.⁴⁹ Varenicline, a nicotinic acetylcholine receptor partial agonist, decreased cocaine use⁵⁰ but had little effect on cocaine abstinence.⁵¹ Recently, much research has focused on the cannabinoid system and the CB₁ receptor antagonist rimonabant that reversed cocaine sensitisation⁵² and blocked cue-induced reinstatement of cocaine seeking.⁵³ Regrettably clinical use of rimonabant ceased due to potentially serious side-effects. More recent research has focused on the phytocannabinoid cannabidiol, a weak CB_{1/2} receptor antagonist. This drug has shown promise in animal models⁵⁴ and a Canadian trial is currently recruiting for cannabidiol and cocaine dependence (ClinicalTrials.gov identifier: NCT02559167).

Therapeutics That Act via Enzymes

Butyrylcholinesterase is an enzyme that metabolises cocaine. It has been tested in rodents and in people where it may accelerate cocaine metabolism.⁵⁵ Its use in cocaine dependence has been reviewed.⁵⁶ Bacterial cocaine esterases (CocE), which also metabolise cocaine, have been isolated from *Rhodococcus* bacteria that grow in the soil around coca plants. It has had some success in rat models⁵⁷ but is not stable at physiological temperatures. Mutants of CocE have been developed that are stable at physiological temperatures and can reduce cocaine self-administration in rats.⁵⁸ These studies have been reviewed.⁵⁹ The GABAergic drugs have long been known to be useful in anxiety. Benzodiazepines have been tested in stimulant dependence⁶⁰ and has led investigators to test drugs that act via GABAergic enzymes: vigabatrin (γ -vinyl GABA), an antiepileptic and an irreversible inhibitor of GABA transaminase (which breaks down GABA), has been shown to increase abstinence in cocaine dependents.⁶¹⁻⁶³

Therapeutics That Block Long-term Potentiation or Affect Memory Reconsolidation

It has been hypothesised that some of the changes seen with long-term stimulant use are similar to those seen in memory formation, including long-term potentiation.⁶⁴ We can take the memory analogy a step further by considering memory reconsolidation where memories that are reactivated become liable to be modified.^{65,66} It is thought that by disrupting 'drug memory' reconsolidation, when the 'drug memory' is particularly labile, we might be able to attenuate drug dependence and this theory has been tested in rodents. Lee et al⁶⁷⁻⁶⁹ used NMDA receptor antagonists to disrupt

memory reconsolidation for cocaine, and reduced cocaine-seeking and relapse-like behaviour.

We have previously tried to disrupt cocaine-evoked pharmacological changes by treating rats with the 5-HT₃ receptor antagonist ondansetron, not before cocaine injection or self-administration, but by giving ondansetron 3.5 hours after cocaine.^{70,71} Ondansetron, given after (but not before) cocaine, was able to reduce cocaine self-administration the following day. Giving cocaine as part of a treatment regimen is probably not a great idea and so we tested a cocaine substitute in a similar regimen. We chose pergolide, a clinically used (Parkinson's disease) dopamine D1/2 receptor agonist as a drug that might evoke a cocaine memory. This pergolide plus ondansetron treatment was able to reverse a previously established cocaine sensitisation⁷² and attenuated methamphetamine reinstatement (relapse) in rats.⁷³ This work has been reviewed⁷⁴ and small clinical trials have been completed to establish safety and efficacy for a methylphenidate plus ondansetron treatment regimen (ClinicalTrials.gov identifiers: NCT01290276, NCT01377662). The disruption of drug memory reconsolidation may yet prove to be a fruitful area in clinical trials.

Vaccines for Stimulants

Vaccines for stimulants have been developed so that antibodies to, for example, cocaine are produced, limiting the amount of cocaine that passes from the bloodstream to the brain, reducing its rewarding effects. In the first trial of a cocaine vaccine in humans the vaccine appeared to reduce the euphoric effects of cocaine and increased cocaine abstinence.⁷⁵ Despite this, results to date have not been as good as hoped due to the relatively long incubation period needed for the required amount of antibodies to be produced. In addition, it is questionable whether enough antibodies could ever be produced to attenuate the effects of the vast amount of cocaine molecules ingested by addicts. A major limitation is that only about 40% of patients treated with the cocaine vaccine actually produced enough antibodies, suggesting that better adjuvants are needed. To this aim, Kosten et al⁷⁶ have tried to improve the immunogenicity by using keyhole limpet haemocyanin as the carrier protein with improved results and a reduction in cocaine-evoked hyperactivity. The same group has also attempted to improve the cocaine hapten, with succinyl butyl norcocaine proving to be the hapten that produced the most cocaine antibodies.⁷⁷ To date, however, clinical trials with cocaine vaccines have been disappointing.⁷⁸ Bacterial proteins have also been tested as both carrier and adjuvant.⁷⁹ Monoclonal antibodies (produced outside the body) are another mechanism to reduce the effects of cocaine. Research in this area would benefit from behavioural pharmacologists and psychiatrists working more closely with immunologists.

Traditional Herbal Medicines

Traditional medicines from South America, Africa, and Asia all have anecdotal evidence suggesting their use in

drug dependence. There are only limited clinical trials but this is certainly an area where more research could be done. In South America, the herbal brew of ayahuasca has been suggested to decrease drug dependence, but research in this area has been hampered by not knowing exactly what is in the brew and concoctions being different in different areas.^{80,81} In addition, there is a religious element to ayahuasca use that might contribute to any therapeutic effects.

Ibogaine, found in the root of the African shrub *Tabernanthe iboga*, may be useful in not only cocaine dependence, but also other drugs of abuse.⁸² Its pharmacology is complicated with affinity at opioid, nicotinic, glutamatergic, and monoamine sites. Levo-tetrahydropalmatine is found in 2 Chinese herbs (*Corydalis* and *Stephania*), has a complex pharmacology and has been shown to be useful in rodent models of drug abuse.²⁷ *Thunbergia laurifolia*, Linn, is a traditional Thai herbal medicine used to treat alcohol and drug addiction and has been tested preclinically and has some mild-stimulant properties that may make it useful as an agonist therapy.⁸³ The use of traditional medicines in the treatment of drug dependence has been reviewed.⁸⁴ This research area would benefit from researchers in the West working more closely with those from the East.

Looking Further Ahead: Cognitive Enhancers, Deep Brain Stimulation, Molecular Biology, and Psychosurgery?

We might use a personalised medicine approach where we take into account the drug misuser's gender, age, and so on. We could also target the misuser's cognitive dysfunction or psychiatric co-morbidity that may contribute to drug misuse and has been reviewed.⁸⁵ For example, many drugs of abuse can lead to cognitive deficits including response inhibition and memory and attention problems. By treating drug abusers with cognitive enhancers they may be able to better use coping strategies. Galantamine, an acetylcholinesterase inhibitor cognitive enhancer, can reduce cocaine use.⁸⁶ With the incredible research effort now focused on dementia treatments, it is likely that there will be many new cognitive enhancers becoming available soon, some of which may be useful in stimulant dependence. Similarly, if we could successfully treat the abuser's co-morbid disorder, we may be able to reduce their drug dependence.⁸⁷

Deep brain stimulation (DBS) of, for example, basal ganglia circuits, may prove useful in drug dependence. Drug dependence is defined by a compulsion to take the drug and so can be viewed in a similar way to other compulsive disorders such as obsessive-compulsive disorder. Obsessive-compulsive disorder has been treated with DBS and has been reviewed by Pepper et al⁸⁸ and van Westen et al⁸⁹ who state that DBS appears to counteract striatal dysfunction through an increase in striatal dopamine and through improvement of reward processing. This sounds very promising for the use of DBS in drug dependence, another condition underpinned by striatal dysfunction.

Genome-wide association studies have identified numerous genes that contribute to drug abuse including *CHRNA3-5* for nicotine dependence and *ADH1B* and *ADH1C* genes for alcohol dependence. The *DRD2* gene is the dopamine D2 receptor gene and may be involved in numerous central nervous system disorders, including cocaine dependence.⁹⁰ Other polymorphisms associated with stimulant addiction include *DAT*⁹¹⁻⁹³ and dopamine receptors,^{92,94} dopamine beta-hydroxylase,^{95,96} and brain-derived neurotrophic factor.⁹⁷ Most recently it has been suggested that numerous genes are involved in drug dependence. Many of these genes were not expected to be involved but have been found to contribute greatly to dependence, for example, genes associated with cell adhesion molecules.⁹⁸ These studies throw up numerous new targets for developing new treatments for stimulant dependence. Knowing which faulty proteins are involved in drug misuse is the first step in a gene therapy, epigenetic therapy or gene silencing for addictions.⁹⁹ Finally, from a molecular viewpoint, optogenetics would also be a way to inhibit or activate dysfunctional brain pathways in psychiatric disorders¹⁰⁰ including addictions.¹⁰¹⁻¹⁰³ Nonetheless, due to ethical reasons, its use in humans would appear unlikely in the near future.

Finally, it is likely that neurosurgery for addiction will be tested to a greater degree in the future. Ablation of the nucleus accumbens core or shell has been examined in rats with respect to heroin self-administration^{104,105} with the core being shown to be important in heroin-seeking behaviour. Studies in human heroin abusers have had some positive outcomes^{106,107} but issues have been raised¹⁰⁸ including appropriate personality follow-up tests and the possibility of improved DBS treatment being more ethical. Given that the psychostimulants act predominantly via DATs in the accumbens, while μ -opioid receptors are more widely distributed within the brain, one wonders if this surgery might work best in stimulant abusers. Recently, a book has been written on the use of neurosurgery in psychiatric disorders including a chapter on addiction.¹⁰⁹ Brain lesions can also happen through strokes and damage to the insula decreases nicotine addiction in humans.¹¹⁰ Lesions of the insula also decrease amphetamine seeking in rats.¹¹¹ Thus, the insula might be another target, in addition to the accumbens, for DBS or psychosurgery in stimulant addiction.

Concluding Remarks

Some of the pharmacotherapies tested in stimulant dependence as well as some more novel therapies have been highlighted. Some therapies, for example, bupropion, tested for cocaine dependence but with little effect, may nevertheless be useful for methamphetamine dependence.¹¹² We should be aware that a therapeutic drug that fails for one stimulant or drug of abuse may be useful for another, or may be useful in a subpopulation as with a stratified medicine approach. We should also be aware of advances in other areas of the biomedical sciences that might open

up new windows of opportunity for drug abuse treatments. Vaccines for cocaine dependence or the use of DBS to attenuate compulsive behaviours are good examples. Advances in molecular biology might lead to gene therapies and optogenetic therapies. Finally, one should always remember that these therapies can or should be used with psychological treatments. It is likely that a combination of drug therapy and psychotherapy will provide the greatest impact.

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