Medication treatment options for amphetamine-type stimulant users
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LeeJenn Health Consultants

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Executive summary

Background

Australia has one of the highest rates of amphetamine-type stimulant (ATS) use in the world. Around 2.5 per cent of people over the age of 14 years have used ATS in the past year, and estimates suggest more than 72 000 may be dependent users.

Amphetamines and their analogues are complex drugs that have multiple mechanisms of action in the brain, including stimulating release of monoamines, blocking re-uptake of adrenergic and dopaminergic neurotransmitters, and inhibiting monoamine oxidase. The effects of these actions manifest differently among people who use ATS during intoxication (e.g. euphoria, increased energy, confidence) and withdrawal (e.g. low mood, agitation, irritability), making the identification of effective pharmaceutical agents a complex endeavour.

Regular long-term use of ATS can result in dependence, especially in those who use by injection or smoking. On cessation, dependent users can experience a range of withdrawal symptoms such as insomnia, irritability, dysphoria, depression and lack of motivation, while strong craving to use is also a common feature.

Neurotoxicity is associated with chronic and long-term exposure to ATS, with imaging studies demonstrating significant dopamine transporter reductions in the brains of methamphetamine users up to one year following abstinence. Serotonin is also thought to be depleted after chronic exposure, particularly in users of 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy. As a consequence, ATS users often experience problems with concentration and memory, impaired decision making, irritability, insomnia, mood swings, loss of interest in pleasurable activities, and lack of motivation.

ATS users are notoriously difficult to attract and retain in treatment, with less than 20 per cent of dependent users entering treatment. Many users attempt to withdraw from ATS without specialist supervision, and the use of other illicit drugs to self-manage the symptoms of withdrawal is common. ATS users tend to seek formal treatment only when the consequences of ATS use are severe and typically when abstinence is the treatment goal. Clinicians and researchers have called for more research into effective pharmacotherapies for this group to broaden treatment options and attract more ATS users into treatment.

In recent years, considerable attention has been focused on developing effective psychosocial interventions for ATS users and psychological interventions are currently the treatment of choice. Yet, despite the effectiveness of psychosocial approaches, treatment attrition and subsequent relapse rates are high, prompting strong interest in pharmacological treatments. Even with considerable research efforts, so far no medications have demonstrated sufficient effectiveness to warrant widespread approval in Australia or internationally for the treatment of ATS dependence or withdrawal, leaving an important gap in evidence-based treatment options for health workers and their clients. There is a broad range of views about the use of pharmacotherapy within the alcohol and other drug treatment sector more generally, and specifically for ATS treatment.
Purpose of this review

This review was designed to examine, in greater detail than previous reviews, whether there are medicines that show promise in forming part of a comprehensive treatment plan, and conversely whether there are medicines that are unsafe to use with people who are dependent on ATS. Both statistical and clinical significance was considered in the review, and an in-depth meta-narrative analysis of identified studies was undertaken.

This review of the evidence for pharmacotherapies for ATS treatment articulates the potential role for medicines in the treatment of ATS dependence and related conditions, including which medicines show potential. The review is also designed to help to guide discussion related to the next steps, including the development and updating of clinical guidelines, and identification of areas for concentration of future research efforts in Australia.

Methods

A systematic review method, coupled with a modified meta-narrative approach to the interpretation of findings, was undertaken. Systematic reviews use a thorough, systematic search method as their primary vehicle and can include any type of study (including qualitative and case studies). They differ from a general review in that the search method and the evaluation of the articles are explicit and replicable. A newer form of review has emerged to help researchers interpret the literature when methods, measures and outcomes vary widely. Rather than presenting and interpreting the evidence as ‘all-or-nothing’ (that is, whether the weight of the evidence is for or against the use of a medicine), meta-narrative review is designed to examine similarities and differences in the data and to look beyond ‘what’ to ‘why’, ‘how’, ‘for whom’ and ‘in what circumstances’.

The databases searched were MEDLINE, PsycINFO, Embase and the Cochrane Database of Systematic Reviews. The search period was January 1997 to January 2013. Hand-searching of specific papers also identified some additional studies.

Included papers were human studies, studies of adult participants, articles published between 1997 and 2013 (last 15 years), manuscripts in English or with available English translation, and at least Level IV methodology (according to the National Health and Medical Research Council levels of evidence). Excluded were animal studies, non-English manuscripts, studies published prior to 1997, qualitative studies, general reviews, studies that included primarily non-dependent participants, studies that included primarily non-treatment participants or contexts (e.g. used healthy volunteers or used dependent volunteers in a laboratory setting), and studies of pharmacotherapy responses to acute toxicity.
Main findings

Withdrawal from amphetamines

Twelve separate studies that reported the effects of medicines on any symptom of ATS withdrawal were reviewed. The evidence was inconclusive but, despite small sample sizes, some positive results were found. Where medicines showed non-significant effects compared to placebo, in general participants in both groups improved.

There was no evidence found for the use of benzodiazepines or other medicines for the management of sleep disturbance or agitation among ATS users in withdrawal, even though these medicines are commonly recommended in clinical guidelines.

Of the four medicines that have been studied for withdrawal from amphetamines, modafinil, mirtazapine and dexamphetamine appear to offer some benefits during ATS withdrawal and may also assist with relapse prevention. The fourth medicine, amineptine, is not available in Australia. Modafinil is thought to act on the dopamine transporter, while mirtazapine is known to enhance noradrenergic and serotonergic transmission. Dexamphetamine and amineptine both work by increasing levels of monoamines at the synaptic cleft.

The evidence from this review, although limited, suggests that modafinil, mirtazapine and dexamphetamine may have a potential role in the range of symptom-management strategies available for methamphetamine withdrawal, and merit further investigation. Future clinical guidelines should detail the circumstances under which these medicines could be used, and for whom, and the medical monitoring strategies that would ensure their safe use.

In summary:

- 60 mg of mirtazapine demonstrated effectiveness in reducing withdrawal symptoms in some participants over a 14-day period; lower doses did not produce convincing effects
- 400 mg of modafinil demonstrated effectiveness, when tolerated by patients, in reducing withdrawal symptoms in some participants over a 7–10 day period; lower doses did not produce convincing effects
- 60–110 mg of dexamphetamine demonstrated effectiveness in reducing withdrawal symptoms in some participants over a 2–8 week period
- although 300 mg of amineptine demonstrated effectiveness in some studies, there is some question about its abuse potential and it is currently unavailable in Australia.

There were no serious adverse events reported in the 12 studies reviewed, but given the small number of studies and the lack of strong evidence either for or against the routine use of these medicines as pharmacotherapy for ATS withdrawal, further research is required to inform the development of clinical guidelines.

Most of the studies reviewed had small sample sizes and the outcomes were variable. In addition, ATS users in treatment drop out at high rates and there is a high relapse rate during and after ATS withdrawal. Further research is warranted to confirm the effectiveness of these medicines.
Treatment for amphetamine dependence

Thirty-nine studies were identified, examining 18 potential pharmacotherapies, though each has been the subject of relatively few studies at the time of writing. Dexamphetamine has been the subject of the greatest number of studies (seven), including four randomised controlled trials (RCTs); followed by modafinil (five) including three RCTs; and bupropion (four), all RCTs. The evidence is sparse for the remainder.

No medicine demonstrated consistent evidence of effectiveness in reducing ATS use or preventing relapse among dependent methamphetamine users. All of the studies conducted to date are smaller-scale feasibility studies. Larger RCTs are required to enable results to be generalised to the broader population of ATS users in Australia and to be interpreted with confidence.

The following medicines were reported to be reasonably well tolerated by research participants and showed some benefit in the studies reviewed:

- Dexamphetamine was found to reduce the severity of ATS dependence and increase treatment retention. The most effective dose was 100 mg per day taken in the morning to limit sleep disturbance.

- Modafinil was found to be superior to placebo in reducing ATS use among those who were medicine-compliant. The most effective dose was 400 mg per day taken in the morning to limit sleep disturbance.

- Bupropion was effective in reducing ATS use by ‘lighter’ ATS users (<18 days use per month) and men. The most effective dose was a starting dose of 150 mg per day increasing to 300 mg per day after three days taken either in the morning or in divided doses (150 mg morning and 150 mg evening).

- Naltrexone may improve retention in treatment and reduce craving. The most effective dose was 50 mg per day (optimal time for daily dosing was unspecified).

- Methylphenidate may improve retention and reduce use. The most effective dose was a starting dose of 18 mg daily increasing to 36 mg daily in the second week, and 54 mg daily from week 3 onwards (optimal time for daily dosing was not specified).

Although these medicines appear to have been beneficial for some participants, they cannot be recommended for routine treatment of methamphetamine dependence due to insufficient evidence. These medicines require further research with large numbers of Australian participants under local conditions of ATS use. Most of the studies reviewed were conducted over 8–12 weeks, so the effectiveness and safety of these medicines for long-term use are unknown.
A number of other medicines showed promise for the treatment of amphetamine dependence but as the number of studies is too small to draw conclusions, additional research is required. Each utilises a different pharmacological approach, including noradrenergic and serotonergic agents, dopamine antagonists and a nicotinic receptor partial agonist. These potential medicines are all used currently for a range of indications, such as depression, psychosis, epilepsy and smoking cessation:

- mirtazapine
- fluoxetine
- topiramate
- risperidone
- varenicline.

Other medicines showed either limited or no benefit, or an unacceptable adverse effect profile. They are not recommended for use or as a high priority for further study:

- baclofen (limited evidence of benefit)
- gabapentin (limited evidence of benefit)
- ondansetron (limited evidence of benefit)
- amlodipine (limited evidence of benefit)
- aripiprazole (unacceptable adverse effect profile)
- vigabatrin (unacceptable adverse effect profile)
- sertraline (unacceptable adverse effect profile)
- Prometa™ protocol of combination flumazenil and gabapentin (unacceptable adverse effect profile).

Overall, many studies were conducted on small numbers of participants and there were high drop-out rates and low medication adherence. Future research that examines ways to retain patients in pharmacotherapy treatment and to improve medication adherence may be useful.

The studies showed variable outcomes and some results were conflicting. Many had small sample sizes while poor participant retention and low adherence to prescribed pharmacotherapy were common barriers to gaining high-quality results. Australians tend to use ATS in patterns that differ from users in other countries (e.g. high rates of injecting) and, as most of the evidence has been gained from international studies, research is needed to examine the effectiveness of medicines that show promise for treating ATS-dependent adults in Australia.
Other considerations in the treatment of amphetamine use

Role of adherence to prescribed medicines

In most of the studies, adherence to taking medicines as prescribed was low. Many studies found a correlation between medication adherence and better outcomes, so careful monitoring of adherence is important for ensuring effectiveness of treatment. In some studies, attrition rates were very high, suggesting that helping clients maintain their motivation for treatment is also necessary for treatment success. Some clinicians argue that providing pharmacotherapies in conjunction with psychosocial therapies will increase the number of ATS users who enter treatment, and the evidence suggests that medicines can increase the length of time they remain in treatment. The use of strategies such as contingency management (that is, a program of planned incentives for treatment goals met) to increase adherence to taking medicines as prescribed may also improve outcomes.

Role of psychosocial interventions

Nearly all of the studies reviewed utilised psychosocial interventions, some quite intensively, in conjunction with pharmacotherapy. Although rates of attendance at counselling sessions varied between studies, psychosocial interventions for both the treatment and placebo groups may have masked the effectiveness of the medicines.

Psychosocial interventions, such as the Matrix Model (Rawson et al., 1995), which is used extensively in the United States of America, and the Baker et al. (Baker et al., 2005) four-session brief cognitive behaviour therapy (CBT) intervention, which is offered widely in Australian treatment settings, have been shown to be effective among methamphetamine users.

Another complicating factor is that many of the studies employed intensive assessment procedures as part of their protocols. There is evidence to suggest that assessment itself is therapeutically beneficial (Kypri, Langley, Saunders & Cashell-Smith, 2007), which may have created a ceiling effect in some studies that is unlikely to be replicated in the clinical setting.

There is some emerging work on ‘third wave’ CBT interventions for ATS users, such as acceptance and commitment therapy (ACT), but these studies remain unpublished in the peer review literature, providing little guidance on whether these interventions are effective with ATS users on their own or in conjunction with medicines. Systematic reviews that have examined ACT have found it to be effective with other disorders, but no more effective than traditional CBT, and have noted that the quality of the research is relatively poor (e.g. Ost, 2008).

Cultural differences

The majority of the studies were undertaken in the United States of America. This is an important consideration for Australia because the nature of methamphetamine use and the treatment systems in each country differ. Among Australians who use drugs by injection, approximately 70 per cent use ATS (Stafford & Burns, 2012) and studies from the United States rarely included injecting methamphetamine users. Care is needed in translating these results for an Australian clinical setting.
Subgroups of amphetamine users
Very little evidence is available about which particular medicines prescribed, under what conditions, might benefit subgroups of amphetamine users.

Elkashef et al. (2008) showed that, for the subgroup of participants who had ‘lighter’ use of methamphetamine at baseline, bupropion treatment increased weekly periods of abstinence (56%) compared to placebo (40%), and less frequent users also showed a greater rate of decrease in urine quantitative methamphetamine than placebo. Shoptaw et al. (2008) also found that less frequent users were nearly three times more likely to have a methamphetamine-free week than heavier users during treatment with bupropion compared with placebo. Although bupropion did not show benefit overall, post-hoc analyses suggest that there may be some benefit for less frequent users (e.g. <18 days of use in the last 30 days).

Shearer et al. (2009) found poorer outcomes for HIV-positive participants taking modafinil and poorer outcomes for methamphetamine-dependent participants with comorbid opioid dependence compared to those with methamphetamine dependence only.

Gender differences in outcomes were rarely reported in the studies reviewed. However, Elkashef et al. (2008) reported that bupropion was associated with reduced methamphetamine use in men but not women.

Treatment of co-occurring mental health problems with amphetamine dependence
The dominance of case studies, coupled with a lack of standard measures, makes it difficult to draw specific conclusions about the effectiveness of these medicines for people with mental health problems who use ATS. A range of medicines, including antipsychotics, dexamphetamine, modafinil and citicoline, were found to be safe in the studies reviewed and may be effective for treatment of co-occurring mental health problems among methamphetamine users if used within existing guidelines for the general population of people with mental health disorders; but, given the lack of specific evidence, additional research is required.

Treatment of other amphetamine-type stimulant dependence
Other than methamphetamine, very few other ATS result in significantly problematic use. Most of the problems associated with MDMA involve acute toxicity and it is rare for MDMA to be associated with chronic heavy use.

Only two studies that examined the role of medicines for treating MDMA dependence were identified for this review and both were single-case designs. Overall, there was little evidence for the effectiveness of pharmacotherapy for MDMA treatment and, with the exceptions of symptomatic relief from withdrawal or co-occurring mental health symptoms, psychosocial intervention remains the treatment of choice for MDMA users.

Only one single-case design was identified that examined the role of medicines for treating ATS dependence other than methamphetamine and MDMA.

Given the very small numbers of dependent users of other ATS, research into pharmacotherapies is likely to be more productive if focused on treating methamphetamine dependence.
Introduction

Amphetamine-type stimulant use in Australia

Amphetamine-type stimulants (ATS) include methamphetamine, MDMA and a range of other synthesised analogues. Australia has one of the highest rates of ATS use in the world. In 2010, 2.5 per cent of people aged 14 years and over (about 400 000) had used methamphetamine in the past year, with 6.8 per cent of 20–29 year olds reporting use in the previous year. In 2010, 3 per cent of 550 000 people aged 14 years and over had used ecstasy (3,4-methylenedioxyamphetamine, MDMA) in the previous year, with the highest use among people aged between 20 and 29 years (10%) (Australian Institute of Health and Welfare, 2011).

A 2011 report showed an increase in methamphetamine use among police detainees, with 21 per cent testing positive, up from 16 per cent in 2010 and 13 per cent in 2009 (Sweeney & Payne, 2012), compared to about 11 per cent of detainees who tested positive for heroin use (Australian Crime Commission, 2012) for which effective pharmacological therapies are widely available.

Primary mechanisms of action of amphetamine-type stimulants

Amphetamines and their analogues are complex drugs that have multiple mechanisms of action in the brain, the effects of which manifest differently during intoxication and withdrawal. The initial effects of ATS are mediated by neurotransmitter systems, primarily through the dopamine system but also through the serotonin and noradrenergic systems. Amphetamines and their structural analogues increase levels of monoamines (dopamine, noradrenaline and serotonin) through a number of mechanisms, including inhibiting re-uptake through various transporter systems, resulting in higher concentrations of monoamines at the synaptic cleft. Stimulant effects are also achieved by increasing release of monoamines, or inhibiting enzymes that break down monoamines (Rose & Grant, 2008).

The dopamine system is involved in movement, attention and memory, and purposeful behaviour. It is the primary pathway for reward, which is thought to influence the development and maintenance of drug dependence and cravings (Volkow, Fowler & Wang, 2002). Serotonin is involved in a variety of important activities including control of mood, appetite, sleeping, thinking, perception, physical movement, temperature and blood pressure regulation, pain control and sexual behaviour. Noradrenaline is primarily involved in the ‘fight or flight’ response: it stimulates the central nervous system to increase heart function and blood circulation, concentration, attention, learning and memory.

Methamphetamine primarily affects the dopamine system, whereas MDMA primarily exerts its action on the serotonergic system (Majumder & White, 2012).

1 Monoamines are a particular class of neurotransmitter that have a single amine group in their molecular structure.
Effects, consequences and harms of amphetamine-type stimulants

The rapid release of neurotransmitters caused by ATS acts to boost energy, promote wakefulness and reduce appetite. Users also report increased self-esteem and sociability, lowering of inhibitions and heightened sexual arousal (Halkitis, Fischgrund & Parsons, 2005), all of which can last for around 8–10 hours due to the long half-life of ATS (Cruickshank & Dyer, 2009).

Short-term physiological consequences can include restlessness and agitation, teeth grinding, elevated blood pressure, rapid heartbeat and palpitations. Acute toxic effects of ATS include chest pain, tremors, dangerously high body temperature, muscle spasm, brain haemorrhage, heart attack and seizures.

Adverse psychological effects, such as anxiety, irritability and insomnia, can also occur, while many long-term users at some time can experience depression, paranoia and psychotic symptoms (McKetin, McLaren, Lubman & Hides, 2006).

Regular long-term use of ATS can result in dependence. Among a sample of regular methamphetamine users in Sydney, McKetin and colleagues found the highest rates of dependence among injectors (62%) and smokers (53%), while 25 per cent of those who usually snorted or ingested methamphetamine were dependent (McKetin, Ross, Kelly & Baker, 2008). On cessation of ATS use, dependent users can experience a range of withdrawal symptoms, such as insomnia, irritability, dysphoria, depression and lack of motivation, while strong cravings to use also commonly feature in ATS withdrawal states (Jenner & Saunders, 2004).

Neurotoxicity is associated with chronic and long-term exposure to ATS, with imaging studies demonstrating significant dopamine transporter reductions in the brains of methamphetamine users up to one year following abstinence (Volkow et al., 2001). Serotonin is thought to be similarly depleted after chronic exposure, particularly in users of MDMA (Barr et al., 2006; Dean, 2004). As a consequence, ATS users often experience problems with concentration and memory, impaired decision making, irritability, insomnia, mood swings, loss of interest in pleasurable activities, and lack of motivation. Newly abstinent methamphetamine users have been found to perform significantly worse on the Stroop Test (a measure of a person’s ability to direct his or her attention) when compared to those who had been abstinent for one year or more, suggesting that attentional focus and executive functioning require many months to recover, during which time impulsive behaviour may be difficult to control (Salo et al., 2009).
Psychosocial treatment for amphetamine-type stimulant users

For more than a decade, clinical researchers have highlighted the reluctance of ATS users to enter treatment (Vincent et al., 1999). In 2005, for example, researchers estimated that among the 100 000 Australians who used methamphetamine regularly, more than 72 000 were likely to be dependent (McKetin, McLaren, Kelly, Hall & Hickman, 2005), yet in the same period there were fewer than 15 000 closed treatment episodes for which amphetamine was the primary drug of concern (Australian Institute of Health and Welfare, 2013).

Many users attempt to withdraw from ATS without specialist supervision, and self-medication (using other illicit drugs) to manage the symptoms of withdrawal is common (Kenny, Harney, Lee & Pennay, 2011). ATS users tend to seek formal treatment only when the consequences of use are severe (Baker, Gowing, Lee & Proudfoot, 2004) and typically when abstinence is the ultimate goal (Kenny et al., 2011).

Considerable attention has been focused on developing effective psychosocial interventions for this group in recent years and structured psychological interventions are currently the treatment of choice. Contingency management, an approach that uses immediate reinforcers such as vouchers to reward drug-free behaviour, and cognitive behaviour therapy (CBT) have both demonstrated effectiveness in assisting ATS users to attain abstinence (Lee & Rawson, 2008). Psychological interventions also have the benefit of addressing co-occurring mental health problems among ATS users. One Australian study, for example, found that four sessions of CBT increased rates of abstinence and also significantly reduced the severity of depression among ATS users (Baker et al., 2005).

Other treatment options available to ATS users include residential rehabilitation, which was found to be associated with short-term reduction in methamphetamine use in about one-third of treatment completers, and detoxification, which was found to have similar outcomes to no treatment at all (McKetin et al., 2012) and should therefore be used only as a first step in a structured treatment program.

Despite the effectiveness of psychosocial approaches, treatment attrition and subsequent relapse rates are high, particularly among people with more severe dependence and longer duration of ATS use (Brecht, Greenwell & Anglin, 2005). Even when psychosocial interventions are tailored specifically for stimulant users, only about 40 per cent complete treatment (Rawson et al., 2004).

As pharmacotherapies such as methadone have been shown to increase retention in treatment of people dependent on opioids (Mattick, Breen, Kimber & Davoli, 2009), clinicians and researchers have called for more research into effective pharmacotherapies for ATS users to broaden treatment options and attract and retain more ATS users in treatment (Kenny et al., 2011; Pennay & Lee, 2009).
Medications and their potential uses in amphetamine-type stimulant treatment

The medicines that have been trialled in the reviewed studies target a wide range of underlying mechanisms of ATS dependence, including reward pathways and craving, psychiatric vulnerabilities and common symptoms of withdrawal and dependence. The medicines achieve their effects through modulation of key neurotransmitter systems, primarily dopaminergic neurotransmitter systems, but also the serotonergic and gabaergic systems. For some medicines the exact mechanism of action is still unclear. Medicines known to improve cognition and those that target specific symptoms associated with ATS use, such as depression, have also been investigated. Unlike cocaine, there has been no human trial of a vaccine for amphetamine dependence, though reports from recent animal studies show promise.

Functional agonist pharmacotherapies

Functional agonist pharmacotherapies possess properties similar to the target drug of concern. They work by binding to the same receptors in the central nervous system as the target drug and triggering a similar but moderated or less intense effect. In some cases, functional agonist medicines reduce the effect of the target drug if it is used concurrently, thereby limiting its rewarding effects.

Agonist medicines are currently used to treat opioid dependence (e.g. the opioid agonist methadone and the partial opioid agonist buprenorphine) and tobacco dependence (e.g. nicotine patches). They offer some advantages for dependent users in comparison to illicit drug use by delivering a known and measurable dose, a legal and regular supply, and reduced potential for abuse. Agonist medicines also offer the advantage of being inherently positively reinforcing (that is, activate the reward pathway), which usually improves medication adherence and increases engagement and retention in treatment.

Agonist pharmacotherapies are of particular interest in the treatment of ATS dependence because the most effective pharmacotherapies for opioid and nicotine dependence are agonist therapies. Methadone was introduced into Australia in 1970 in response to concerns about morbidity and mortality, and criminal activity associated with opioid use (McArthur, 1999). Through decades of rigorous investigation, methadone has demonstrated effectiveness in reducing heroin use and retaining people in drug treatment (Mattick et al., 2009), as well as reducing injecting behaviours and risk of mortality (Kimber et al., 2010). Users of ATS and heroin face similar risks and harms, such as needle sharing, exposure to blood-borne viruses, and engagement in criminal activity (McKetin & McLaren, 2005), suggesting agonist therapies are also a viable option as pharmacotherapy for ATS dependence.

The potential roles of agonist medicines in the treatment of ATS dependence include normalising neurochemistry; providing a stable, known and legal dose of a medicine that stimulates the central nervous system in ways that may be acceptable to users but lack the severe adverse effects of illicit ATS; reducing illicit ATS use (quantity and frequency); and minimising physical withdrawal symptoms, including withdrawal-related craving that may trigger relapse (Brensilver, Heinzerling, Swanson & Shoptaw, 2012; Hartz, Frederick-Osborne & Galloway, 2001).
Dopaminergic agents

Due to their primary roles in ATS neurochemistry, the dopamine, serotonin and noradrenaline systems have been the targets for a range of agonist medicine treatment trials for ATS dependence. Dopamine depletion is a hallmark of ATS dependence and withdrawal. Two pharmacotherapies that are functional agonists are dexamphetamine and methylphenidate. They are both structurally similar to methamphetamine and both have similar effects to methamphetamine on these important neurotransmitter systems. Both medicines act primarily on the dopaminergic pathways and on noradrenergic pathways, the latter often to a lesser degree.

Dexamphetamine is the dextrorotatory stereoisomer of the amphetamine molecule and a psychostimulant drug that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. It has been trialled as a replacement pharmacotherapy among dependent ATS users in Australia and elsewhere. Dexamphetamine primarily increases release of monoamines. Dexamphetamine is a functional agonist of methamphetamine, meaning it produces similar pharmacological effects to methamphetamine, but has the advantages of being able to be provided in a known and controlled dosage, similar to opioid–agonists for opioid dependence. Dexamphetamine is structurally similar to endogenous monoamines (noradrenaline, dopamine and serotonin), competing with them for uptake at monoamine transporters, resulting in higher levels of monoamines at the synaptic cleft (Grabowski, Shearer, Merrill & Negus, 2004). Higher doses of dexamphetamine also cause release of noradrenaline and dopamine and, to a much lesser degree, serotonin (Howell & Kimmel, 2008).

Methylphenidate is a dopamine and noradrenaline re-uptake inhibitor approved for treatment of attention deficit hyperactivity disorder; and has also been trialled as a replacement pharmacotherapy among dependent ATS users. Methylphenidate primarily blocks re-uptake of monoamines into the synapse, thereby increasing concentrations of monoamines at the synaptic cleft.

Bupropion is an atypical, non-tricyclic antidepressant and smoking cessation aid thought to act through noradrenaline–dopamine re-uptake inhibition. It also acts as a nicotinic acetylcholine receptor antagonist. It is considered for its role in reducing amphetamine withdrawal symptoms that are associated with dopamine depletion. Bupropion has a mild stimulant effect and antidepressant properties (Brensilver, Heinzerling et al., 2012), probably brought about by restoring depleted levels of dopamine (Rau et al., 2005), and has been approved for the treatment of depression, seasonal affective disorder, and smoking cessation.

Modafinil belongs to a relatively new class of wakefulness-promoting agents known as eugeroics. In Australia it is approved for the treatment of narcolepsy, sleep disorder associated with shift work, and excessive daytime sleepiness associated with obstructive sleep apnoea. The pharmacology of modafinil is complex and the exact mechanism of action is not yet known (Ballon & Feifel, 2006), but recent research has found that modafinil appears

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2 Isomers are molecules that have the same molecular formula as each other but differ in the way the atoms are arranged around the central atom, while dextrorotatory means the molecules rotate the plane of polarised light to the right (such rotation affects the pharmacological activity of molecules).
to act primarily on the dopamine transporter, inhibiting its re-uptake and leading to an increase in extracellular dopamine, though it does have non-dopaminergic mechanisms as well (Zolkowska et al., 2009).

**Amineptine** is an atypical tricyclic antidepressant that selectively inhibits the re-uptake of dopamine, and to a lesser extent noradrenaline, and exerts a short-lived stimulant effect. This medicine is not currently available in Australia.

### Serotonergic agents

Preclinical studies have shown that blocking serotonergic transmission increases amphetamine consumption, which led researchers to investigate if an increase of serotonin at the synaptic cleft would reduce ATS use. In addition, a wide range of methamphetamine withdrawal symptoms appear similar to that of depression, providing a rationale for the use of serotonergic agonists for methamphetamine dependence treatment (Rose & Grant, 2008).

**Fluoxetine** is an antidepressant of the selective serotonin re-uptake inhibitor (SSRI) class. SSRIs work by preventing uptake of serotonin into the neuron, thereby initially increasing serotonin levels at the synaptic cleft, with longer-term effects being attributed to down-regulation of presynaptic autoreceptors. Fluoxetine was found to reduce methamphetamine self-administration in animal studies, sparking interest in its ability to reduce ATS use among humans.

**Sertraline** is an antidepressant of the selective serotonin re-uptake inhibitor class, approved in Australia for the treatment of major depressive disorder, social anxiety disorders and premenstrual dysphoric disorders. Early studies showed that inhibited serotonin signalling caused animals to self-administer more ATS; therefore sertraline, which increases levels of serotonin at the synaptic cleft, was considered a valid target of investigation among human participants.

**Mirtazapine** is a noradrenergic and specific serotonergic antidepressant used primarily in the treatment of major depressive disorders. It is thought to work by enhancing the release of noradrenaline and serotonin (Anttila & Leinonen, 2001). Structurally, mirtazapine can also be classified as a tetracyclic antidepressant. It has been trialled for the treatment of ATS withdrawal symptoms because of the association of amphetamine withdrawal with serotonin depletion.

**Ondansetron** is a serotonin receptor antagonist and modulator of cortico-mesolimbic dopamine function. As many stimulants act through cortico-mesolimbic dopaminergic neurons, it is hypothesised that a 5HT3 receptor antagonist may indirectly reduce cortico-mesolimbic dopamine release (Johnson, 2007). It is approved in Australia for the management of nausea and vomiting associated with radiotherapy being used to treat malignancy. It has been trialled to determine its effectiveness in reducing the subjective rewarding effects of ATS among dependent users and is currently being investigated for the treatment of alcohol use disorders.
**GABAergic agents**

The gamma-aminobutyric acid (GABA) system has been found to play a key role in inhibiting synaptic transmission in the brain (Padgett & Slesinger, 2010). One possible mechanism to reduce the reinforcing effects of ATS and craving is through GABA$_B$ agonists mediating transmission along the mesolimbic dopamine system, which is thought to reduce the rewarding effects of ATS (Cousins, Roberts & de Wit, 2002). Therefore, a number of GABAergic medicines have been investigated for their potential role in treating ATS dependence.

**Baclofen** is a derivative of GABA and an agonist for GABA$_B$ receptors. Baclofen is primarily used to treat involuntary muscle spasm in multiple sclerosis and spinal lesions and is being investigated for the treatment of alcohol use disorders.

**Gabapentin** is a GABA agonist and anticonvulsant that increases GABA concentrations in the central nervous system, possibly via inhibition of GABA-transaminase. Originally developed for the treatment of epilepsy, it can also be used under authority in Australia for the treatment of refractory neuropathic pain not controlled by other drugs. Results from studies showing gabapentin reduced craving for cocaine prompted interest in its role in treating methamphetamine dependence.

**Topiramate** is an anticonvulsant (anti-epilepsy) drug that showed promise in the treatment of alcohol and cocaine use, thus prompting investigations into its usefulness for ATS users. While the proposed mechanism for how topiramate may work for methamphetamine treatment is not clear, topiramate is known to facilitate GABAergic transmission through a non-benzodiazepine site on the GABA$_A$ receptor. Through its action on the GABAergic pathway, it is possible that topiramate may have an effect on the reward system by depressing dopaminergic transmission along the mesolimbic pathway (Elkashef et al., 2012). In Australia, topiramate is indicated only for the treatment of epilepsy in adults and children aged two years and over, and the prevention of migraine headaches in adults.

**Vigabatrin** (Gamma Vinyl GABA or GVG) is an analogue of GABA (but not a receptor agonist) that has been shown to minimise the rapid rise of dopamine, and associated behaviours, following ATS use. The ability of vigabatrin to reduce pharmacological effects of methamphetamine is thought to be how it may reduce methamphetamine use. In preclinical studies, vigabatrin has been shown to block reinstatement of drug-related behaviors, suggesting promise as a relapse prevention medication (DeMarco et al., 2009). It is prescribed in Australia for the treatment of epilepsy that has not been successfully controlled by other medicines.

**Flumazenil** is a GABA antagonist available for injection only and used as an antidote in the treatment of benzodiazepine overdose. It was thought to play a role in restoring balance, impaired through chronic ATS exposure, in the GABA system.
Dopamine antagonists

Medicines that work as antagonists bind to the same receptors as the drug of concern and limit its effects, but unlike agonists, these medicines exert no active effect (Brensilver, Heinzerling et al., 2012). The usefulness of antagonist medicines is thought to be their ability to block the rewarding, and therefore reinforcing, effects of the drug of concern, resulting in the eventual elimination of drug-using behaviours (Herin, Rush & Grabowski, 2010).

Evidence from studies of antagonist pharmacotherapies in the treatment of drug dependencies other than ATS (such as naltrexone for alcohol and opioid dependence) has provided the basis for trialling dopamine antagonist pharmacotherapies, such as the antipsychotics class of medicines, with ATS users. However, the euphoric effects of ATS do not appear to be reduced by the dopamine antagonists risperidone or haloperidol (Rose & Grant, 2008), suggesting that these agents are not useful in the typical ‘antagonist’ approach used with other substances such as opioids. As noted below, dopamine antagonists are commonly used to treat psychosis associated with amphetamine use.

**Haloperidol** is a dopamine antagonist of the typical (first-generation) antipsychotic class. It is a butyrophenone derivative and has pharmacological effects similar to the phenothiazines. Haloperidol is an older antipsychotic used in the treatment of schizophrenia and acute psychotic states and delirium, and was trialled for its effectiveness to treat ATS-induced psychosis.

**Atypical (second-generation) antipsychotics**

Atypical antipsychotics such as aripiprazole, olanzapine, quetiapine and risperidone differ from typical antipsychotics such as haloperidol due to the lesser degree of extrapyramidal (movement) side effects and constipation. The reduced side-effect profile is attributed to a more rapid dissociation from the dopamine receptor than the first-generation antipsychotic medicines, allowing more normal dopamine transmission and less effect of hormones, cognition and extrapyramidal side effects.

**Aripiprazole** is a partial dopamine agonist and atypical antipsychotic with additional antidepressant properties used in the treatment of schizophrenia, bipolar disorder and clinical depression; it has been trialled as a treatment for ATS-induced psychosis.

**Olanzapine** is an atypical antipsychotic. Olanzapine is a serotonin–dopamine antagonist approved in Australia for the treatment of schizophrenia and related psychoses. Olanzapine is structurally similar to clozapine, but is classified as a thienobenzodiazepine and has been trialled for use in ATS-induced psychosis.

**Quetiapine** is an atypical antipsychotic and serotonin and dopamine antagonist, approved in Australia for the treatment of schizophrenia and bipolar 1 disorder. Trialled for its effectiveness in treating mood disorders and ATS dependence.

**Risperidone** is a dopamine antagonist of the atypical antipsychotic class of medicines, approved in Australia as a treatment for schizophrenia and as adjunctive therapy to mood stabilisers for treating acute mania associated with bipolar 1 disorder. Trialled as a treatment for ATS-induced psychosis.
Opioid antagonists

Opioid antagonists block the effect of endogenous (naturally occurring) opioids by binding to opioid receptors in the brain. It is hypothesised that, by blocking endogenous opioids, a change can be effected on the reinforcing properties of methamphetamine.

Naltrexone is an opioid receptor antagonist that exerts effects by blocking the effects of heroin and other opioids. It is authorised for use in Australia in the management of opioid dependence and alcohol dependence. Naltrexone has been shown to reduce cravings for alcohol and limit its rewarding effects when consumed. Opioid receptors are located on dopamine cell bodies, partially modulating dopaminergic effects (Llorens Cortes, Pollard & Schwartz, 1979). Stimulant administration has also been shown to change opioid receptor density in the nucleus accumbens, a brain region known to be associated with reinforcement of drug administration (Azaryan, Coughlin, Buzas, Clock & Cox, 1996). As such, naltrexone has also been examined for its role in tempering the rewarding effects of ATS among dependent users.

Pharmacotherapies to reduce craving

Dopamine pathways in the midbrain are thought to mediate the rewarding effects of methamphetamine and be involved in cravings to use. A number of medicines have been trialled to determine their effectiveness to reduce cravings among ATS users.

Calcium-channel blockers

Amlodipine is a long-acting calcium ion antagonist used as an antihypertensive and in the treatment of angina pectoris. By blocking calcium ion influx selectively on vascular smooth muscle, amlodipine causes vasodilation, reducing vascular tone and blood pressure. Amlodipine is thought to play a role in reducing the rewarding effects of ATS use by blocking central dopamine pathways in the brain. Calcium-channel blockers have been proposed as a treatment for methamphetamine dependence because of their observed ability to reduce subjective effects of methamphetamine, by antagonising the effect of dopamine in central dopaminergic pathways (Johnson et al., 2008).

Nicotinic antagonist

Varenicline is a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, which stimulates nicotine receptors more weakly than nicotine. As a partial agonist, it both reduces cravings for, and decreases the pleasurable effects of, cigarettes and other tobacco products, making it a candidate for trials among ATS users. In Australia, it is prescribed as an anti-smoking aid.
Other medicines

Citicoline is a naturally occurring compound shown to reduce some of the functional impairments associated with acute stroke and is thought to have neuroprotective properties and to increase norepinephrine, dopamine, serotonin and acetylcholine levels in certain brain regions. Used as adjunctive therapy for Parkinson’s disease, it also showed promise in reducing craving for cocaine, and was therefore trialled among dependent ATS users.

N-acetyl cysteine, commonly known as NAC, is the precursor to both the amino acid L-cysteine and glutathione, and is thought to have a role in reversing glutamate dysfunction associated with drug cravings. It is sold over the counter in Australia as a dietary supplement, commonly claiming antioxidant and liver-protecting effects. It is also used as a cough medicine.

Purpose of this review

Despite research efforts so far, no medications have widespread approval in Australia or internationally for the treatment of ATS dependence or withdrawal, leaving an important gap in evidence-based treatment options for clients and the health professionals who work with them. There is a broad range of views about the use of pharmacotherapy within the alcohol and other drug treatment sector generally, and specifically for the treatment of ATS dependence.

In the context of the lack of approval for routine use of medicines with ATS users and the breadth of opinion on the role and function of pharmacotherapy for this group, the purpose of this review of the evidence for pharmacotherapies for ATS treatment was to articulate the potential role for medicines in the treatment of ATS dependence and related conditions, including which medicines show potential, under what circumstances, and with which patients. The review is designed to help to guide the next steps, including the development and updating of clinical guidelines and identification of areas for concentration of future research efforts in Australia.

The reference group that guided the conduct of this review developed a number of research questions:

1. What medication treatment options are currently available, within Australia as well as internationally, for the treatment of dependent ATS users?

2. What are the areas of promising research for the treatment of dependent ATS users and the role Australian research might play?

3. What are the medication treatment options and what is their relationship to other treatment interventions?

4. What are the advantages and disadvantages of each of the medication treatment options?
Methods

This review was undertaken using a systematic review method coupled with a modified meta-narrative approach to the interpretation of findings. Systematic reviews use a thorough systematic search method as the primary vehicle to include all relevant results in a summary of the literature in an effort to answer a specific research question. A systematic review can include any type of study (including qualitative and case studies), and differs from a general review in that the search method and the evaluation of the articles are explicit and replicable. Furthermore, it allows a systematic sorting of the evidence to answer specific questions. A traditional systematic review works best when there are large numbers of studies with similar methodologies and outcome measures.

A newer form of review has emerged to help researchers interpret the literature when methods, measures and outcomes vary widely. A meta-narrative review (Potts, 2012) or realist review (Pawson, Greenhalgh, Harvey & Walshe, 2005) is a pragmatic method of understanding a diverse and disparate literature. Meta-narrative reviews are typically used for distilling complex interventions (that is, areas in which there may be multiple components, multiple target groups or natural variability in the application of the intervention, such as evaluation of psychological treatments or policy interventions). Although the efficacy and effectiveness of medicines are generally considered a ‘simple intervention’ (Wong, Greenhalgh & Pawson, 2009), the complexity of methamphetamine use has resulted in the reporting of widely varied research outcomes.

Rather than presenting and interpreting the evidence as ‘all-or-nothing’ (that is, either the weight of the evidence is for or against the use of a medicine), a realist or meta-narrative review is designed to examine similarities and differences in the data and to look beyond ‘what’ to ‘why’, ‘how’, ‘for whom’ and ‘in what circumstances’ (Wong et al., 2009).

Search strategy

Search terms were developed based on the aims and scope of the review. A combination of MeSH (and other database thesaurus) terms, keyword terms and words in the text and title were used. Groups of key terms were used for searches, then systematically combined for exploring the various sets of clinical questions across all databases. The databases searched were: MEDLINE, PsycINFO, Embase and the Cochrane Database of Systematic Reviews. The search period was January 1997 to January 2013. Hand-searching of specific papers also identified some additional studies.
Inclusion and exclusion criteria

The inclusion criteria were:

• human studies
• adult studies
• articles published between 1997 and 2012 (last 15 years)
• manuscripts in English or with available English translation
• Level IV or above intervention studies (National Health and Medical Research Council levels of evidence).

The exclusion criteria were:

• animal studies
• non-English manuscripts
• studies published prior to 1997
• qualitative studies and general reviews
• studies that included primarily non-dependent participants
• studies that included primarily non-treatment appropriate participants or contexts (e.g. used healthy volunteers or used dependent volunteers in a laboratory setting)
• studies of pharmacotherapy responses to acute toxicity.

Screening and extraction

At the first screen, one reviewer excluded all studies that were not related to ATS. At the second screen, all studies that did not meet inclusion criteria were excluded (e.g. laboratory and animal studies, participants without ATS dependence). Data from each article were extracted by a single reviewer and checked and entered into a summary table by a second reviewer.

Analysis

Qualitative analysis, synthesis and interpretation of the data were undertaken by two reviewers. Elements from the meta-narrative approach were used in the interpretation of the review data. Details of the search, screening and review procedure are shown in Figure 1.
Number of citations retrieved through database searching (including duplicates): 6537

Number of citations identified through other sources: 52

First screen
Number of citations (duplicates & irrelevant records removed): 2179

Second screen
Number of studies excluded at second screen: 2021

Quality check
Number of studies assessed for quality: 158

Final review
Number of studies included in final review: 56

Figure 1: Search, screening and review procedure
Detailed findings

Amphetamine and methamphetamine

Withdrawal from amphetamines

See summary evidence table beginning on page 48 for details of this group of studies.

Overall summary

The results are not conclusive but, despite small sample sizes, some positive results were reported. Where medicines showed non-significant effects compared to placebo, both active treatment and placebo groups improved.

No evidence was found for the use of benzodiazepines or other medicines for the management of sleep disturbance or agitation among ATS users in withdrawal, even though these medicines are commonly recommended in clinical guidelines.

Of the four medicines examined, modafinil, mirtazapine and dexamphetamine appear to have some effect during withdrawal and may also assist with relapse prevention. Although 300 mg of amineptine (the fourth medicine) appears to be effective, there is some question about its abuse potential and it is currently unavailable in Australia.

The evidence from this review, although limited, suggests that modafinil, mirtazapine and dexamphetamine may have a potential role in the range of symptom-management strategies available for methamphetamine withdrawal and merit further investigation. There is some evidence for the use of these medicines, which is more evidence than currently exists to support other commonly recommended pharmacotherapy for ATS withdrawal, such as benzodiazepines, which are used to reduce agitation.

In summary, the research shows that:

• 60 mg of mirtazapine demonstrated effectiveness in reducing withdrawal symptoms in some participants over a 14-day period; lower doses did not produce convincing effects

• 400 mg of modafinil demonstrated effectiveness, when tolerated by patients, in reducing withdrawal symptoms in some participants over a 7–10 day period; lower doses did not produce convincing effects

• 60–110 mg of dexamphetamine demonstrated effectiveness in reducing withdrawal symptoms in some participants over a period of 2–8 weeks.

No serious adverse events were reported in these studies, suggesting that among both moderately and heavily dependent individuals these medicines appear to be safe for use in ATS treatment. However, there were a small number of studies, most with small sample sizes, and a lack of strong evidence either in favour of or against the efficacy of these medicines. Although mirtazapine, modafinil and dexamphetamine show promise, further research is needed to confirm the effectiveness of these medicines for withdrawal. Given ATS treatment has a high drop-out rate and a high relapse rate during withdrawal, this may be a worthy area for future research to assist in retaining users in a supervised withdrawal program.
Future clinical guidelines should detail the circumstances under which these medicines could be used, and for whom, and the medical monitoring strategies that would ensure their safe use.

**Summary of literature reviewed**

Two systematic reviews have been conducted by researchers from the Cochrane Collaboration (Shoptaw, Kao, Heinzerling & Ling, 2009; Srisurapanont, Jarusuraisin & Kittirattanapaiboon, 2001). Both found favourable results overall for two studies involving amineptine; and Shoptaw and colleagues found mixed results for mirtazapine. Since then, another five relevant papers have been published. In total, seven papers from six separate studies of medicines for withdrawal, and two studies of maintenance medicines, which also measured withdrawal symptoms, were included in this review.

Of the nine included studies, two examined mirtazapine (Cruickshank et al., 2008; Kongsakon, Papadopoulos & Saguansiritham, 2005), one studied modafinil (Hester, Lee, Pennay, Nielsen & Ferris, 2010 from the same study; Lee et al., 2013), one trial involved modafinil and mirtazapine (McGregor, Srisurapanont, Mitchell, Wickes & White, 2008), three studied amineptine (Jittiwutikan, Srisurapanont & Jarusuraisin, 1997; Srisurapanont, Jarusuraisin & Jittiwutikan, 1999; Srisurapanont et al., 2001) and two dexamphetamine maintenance trials that reported withdrawal symptom outcomes (Galloway et al., 2011; Longo et al., 2010) were also reviewed.

The results of these studies were mixed, with one modafinil study (Lee et al., 2013) and two mirtazapine studies (Cruickshank et al., 2008; McGregor et al., 2008) finding no differences in withdrawal or other measures compared to placebo, with others finding significant differences in favour of mirtazapine (Kongsakon et al., 2005) and modafinil (McGregor et al., 2008). Both dexamphetamine studies showed a significant reduction in severity of withdrawal symptoms (but not drug use). All of the studies had very small sample sizes.

All four medicines were well tolerated at a wide range of doses given with no serious adverse effects reported and some indication of positive clinical effects from some studies, suggesting that these medicines remain a possibility for assisting with symptom management during withdrawal and merit further investigation.

Modafinil also resulted in neuropsychological improvements and dexamphetamine resulted in reduced craving, both of which could have implications for relapse prevention, although the longer-term benefits of maintenance medication prescribed during withdrawal have not been examined in any studies.
**Meta-narrative analysis**

In each of the reviewed studies, those taking the active medicines improved on measures of withdrawal symptoms and there were no serious adverse effects reported, suggesting that these medicines are generally safe to use during withdrawal under supervised conditions. As with most medicines, there were mild side effects such as nausea and headache in a minority of patients.

All of the studies had relatively small sample sizes: the smallest had 19 participants and the largest had 60 participants. At these sample sizes it would be difficult to detect small differences that may be clinically significant in a withdrawal situation. A meta-analysis may help to clarify whether differences exist but there were only one or two studies of each medicine, and while meta-analysis is possible with small numbers of studies, it is less reliable.

There was no evidence found for the use of benzodiazepines or other medicines for the management of sleep disturbance, agitation or other psychiatric symptoms among ATS users in withdrawal, although benzodiazepines are commonly recommended in clinical guidelines (e.g. Dunlop, Hocking, Lee & Muhleisen, 2004; Dunlop et al., 2008; Kenny et al., 2009; Lintzeris, Dunlop & Thornton, 1996) for use under supervision. Future revisions of these guidelines should carefully consider recommendations for the use of medicines that are based on evidence for other illicit drug withdrawal.

**Modafinil**

Of the three papers that reported withdrawal outcomes after treatment with modafinil, McGregor et al. (2008) reported significant effects on withdrawal symptoms, and Hester et al. (2010) reported significant effects on cognitive functioning, specifically on immediate memory and executive functioning. Lee et al. (2013) found no benefit on withdrawal symptoms or on retention in withdrawal treatment. Of the participants who left withdrawal treatment early, most of those who had been in the placebo group, but not those who had been in the modafinil group, resumed ATS use, suggesting some benefit. However, the sample size for this study was small.

McGorger et al. (2008) found significant differences in withdrawal symptoms using modafinil. This study used higher doses of modafinil (400 mg) than Lee et al. (2013) (200 mg), possibly explaining the differences in response. In addition, the former was an open-label study. Placebo medicines have been shown to positively influence patients' self-reported symptoms (Hróbjartsson & Gøtzsche, 2010) and there may have been a placebo effect in the McGregor study. The larger dose of 400 mg did not produce significant side effects but appeared to result in a better outcome.
Mirtazapine

Two mirtazapine studies showed positive benefits and one did not. Kongsakon et al. (2005) reported significant effects of mirtazapine at 15–30 mg. McGregor et al. (2008) reported large and significant benefits of mirtazapine over treatment as usual (but not modafinil) at 60 mg. Cruickshank et al. (2008) reported small and non-significant effects at 30 mg. Larger doses appeared to produce larger effects with no significant adverse events reported. McGregor et al. (2008) conducted an open-label study and there may have been some placebo effect.

Dexamphetamine

The two studies of dexamphetamine were not originally designed as withdrawal studies but did measure withdrawal symptoms among people who were not abstinent at treatment entry. Galloway et al. (2011) used a dose of 60 mg and found significant effects of dexamphetamine in reducing withdrawal symptoms and craving among mainly moderate methamphetamine smokers (17 days in the previous month), and Longo et al. (2010), using a dose of 20–110 mg, found a non-significant trend (with a small sample size) in reduction of withdrawal symptoms among mainly long-term (11 years) injecting methamphetamine users. Although limited, these results suggest that dexamphetamine is promising for the treatment of ATS withdrawal in moderate users, but further research is required. A meta-analysis may be possible.

Amineptine

Since amineptine is not currently available as a medicine, no further distilling of the results was undertaken.

Research implications

There are numerous guidelines that recommend a range of medicines for the management of withdrawal symptoms in ATS users (e.g. Dunlop et al., 2004; Dunlop et al., 2008; Kenny et al., 2009; Lintzeris et al., 1996). These guidelines are based on recommendations for the management of other drug withdrawal, which reflects the paucity of research into the pharmaceutical management of ATS withdrawal.

Relatively few studies of pharmacotherapy for amphetamine withdrawal were found, highlighting a sizeable research gap. Given the poor treatment completion rates (50%) and high rates of relapse immediately after withdrawal (50%), it appears to be an area that would benefit from more intensive research efforts (Brecht et al., 2005; McKetin et al., 2005).

The variability in results and small sample sizes suggest that the studies suffered from low power, and larger studies are needed to show more conclusive results. Many studies did not report important factors, such as average doses (where a variable dose schedule was used) and outcome means, in enough detail to assist in clinical decision making. This suggests the need for more detailed and standardised approaches to the reporting of pharmacotherapy trials is required. As a start, a meta-analysis pooling the results of multiple studies may assist in clarifying outcomes. This was beyond the scope of the current work.
Treatment for amphetamine dependence

See summary table beginning on page 58 for details of this group of studies.

**Overall summary**

Thirty-nine studies were identified, examining 18 potential pharmacotherapies. None demonstrated consistent evidence of effectiveness in reducing ATS use or preventing relapse among dependent methamphetamine users.

Although there have been many pharmacotherapies examined, each medicine has been the subject of relatively few studies. Dexamphetamine has been the subject of the greatest number (seven, including four RCTs), followed by modafinil (five, including three RCTs) and bupropion (four, all RCTs). The evidence is sparse for the remainder. In addition, the studies conducted to date are all smaller-scale feasibility studies. This is consistent with a treatment area in its relative infancy, but now larger RCTs are required.

The following medicines appear to be well tolerated and showed some significant positive effects in the literature reviewed:

- Dexamphetamine reduced the severity of dependence in some participants and increased treatment retention. The most effective dose reported in the literature appears to be 100 mg per day taken in the morning to limit sleep disturbance.

- Modafinil was found to be superior to placebo in reducing ATS use among those who were medicine-compliant. The most effective dose was 400 mg per day taken in the morning to limit sleep disturbance.

- Bupropion was effective in reducing ATS use by ‘lighter’ ATS users (<18 days use per month). The most effective dose reported was a starting dose of 150 mg per day increasing to 300 mg per day after three days taken either in the morning or in divided doses (150 mg morning and 150 mg evening). Bupropion may be especially useful for men and for those with a lighter pattern of ATS use.

- Naltrexone may improve retention in treatment and reduce craving to use ATS. The most effective dose was 50 mg per day (optimal time for daily dosing was unspecified).

- Methylphenidate may improve retention in treatment and reduce use. The most effective dose seems to be a starting dose of 18 mg increasing to 36 mg in the second week and 54 mg from week 3 (optimal time for daily dosing was unspecified).

Without further research, these medicines cannot yet be considered as routine treatment options for dependent methamphetamine users, but do appear to offer some benefit to some people, and there were few adverse events reported. Most of the studies were conducted over 8–12 weeks, so the effective and safe long-term use of these medicines is unknown. As these medicines showed some benefits, future research efforts could focus on treatment matching and identifying particular subgroups of ATS users that may benefit most from these medicines.
There were a number of other medicines that showed promise and, hence, may also be good candidates for further research:

- mirtazapine
- fluoxetine
- topiramate
- rispiridone
- varenicline.

Other medicines showed either no benefit or an unacceptable adverse effect profile and do not appear to be of value clinically or for future research:

- baclofen (limited evidence of benefit)
- gabapentin (limited evidence of benefit)
- ondansetron (limited evidence of benefit)
- amlodipine (limited evidence of benefit)
- aripiprazole (evidence of adverse effects)
- vigabatrin (evidence of adverse effects)
- sertraline (evidence of adverse effects)
- Prometa™ protocol of combination flumazenil and gabapentin (evidence of adverse effects).

Overall, the studies showed variable outcomes and some results were conflicting, even under robust study conditions. Many had small sample sizes, while poor study retention and failure of many participants to take medicines as prescribed were common barriers to gaining high-quality results. Australians tend to use ATS in patterns that differ from users in other countries (e.g. higher rates of injecting), and as most of the evidence has been gained from international studies, further research is needed to examine the effectiveness of medicines that show promise for treating ATS-dependent adults under local conditions.
Summary of literature reviewed

Thirty-nine studies were identified, examining 18 potential pharmacotherapies. Thirty-five of these studies reported no serious adverse events. All medicines come with some side effects and risks, and on occasion particular individuals may have unusual responses to some medicines, but overall there was no evidence that, at the doses reported, these medicines produced significant adverse effects, even in patients severely dependent on ATS.

None of these medicines showed effects across the main variables of reduced ATS use or abstinence that were strong enough to recommend their routine use, probably due to small sample sizes. But a number did show some promise, which may make their use in particular circumstances with specific patients under well-monitored conditions feasible. Meta-analysis may be useful in further assessing the viability of these medicines. Future clinical guidelines should detail the circumstances under which these medicines could be used, and for whom, and the medical monitoring strategies that would ensure their safe use.

Although a wide variety of medicines have been trialled, most individual medicines have been the subject of only a few studies, with only three medicines having more than three published reports (dexamphetamine (n=7), modafinil (n=5) and bupropion (n=4)), and not all of those studies were RCTs. Thus, although studies have been accruing over a long period of time and with a large number of medicines, the research into pharmacotherapies for amphetamine dependence is in its relative infancy. Many of the studies are typical of early studies of any pharmacotherapy; that is, they are case studies, open-label studies or feasibility RCTs. None has been a study with a very large sample size. For example, the largest sample among the four dexamphetamine randomised controlled trials numbered 60 participants.

Meta-narrative analysis

Medicines showing some benefit in randomised controlled trials

Five medicines (dexamphetamine, methylphenidate, modafinil, bupropion and naltrexone) showed equivocal but promising results, suggesting they may be effective targets for further research. Each of these medicines has been the subject of more than one peer-reviewed report and has shown some benefits over placebo on some variables or within some groups of participants. None reported any serious adverse events.

Dexamphetamine showed benefit over placebo on secondary variables of retention in treatment and attendance at counselling sessions, and may reduce the severity of dependence (Longo et al., 2010; Shearer et al., 2001).

Methylphenidate was superior to placebo in reducing amphetamine use in one study (Tiihonen et al., 2007) but not in a second study (Miles et al., 2013).

Modafinil: Two RCT studies showed that those who were compliant with taking the medicine were significantly more likely to reduce drug use (Anderson et al., 2012; Shearer et al., 2009).
**Bupropion** appears to be associated with reduced methamphetamine use among men but not women (Elkashef et al., 2008), and among those with ‘lighter’ patterns of use (<18 days in a month) (Elkashef et al., 2008; Shoptaw et al., 2008). In a re-analysis of two randomised controlled trials of bupropion, Brensilver, Heinzerling et al. (2012) found that the inability to produce at least three drug-free urine samples in the first week of treatment was associated with a 90 per cent likelihood of treatment failure. They concluded that, in a clinical setting, failure to achieve at least two drug-free urine samples in the first three weekly visits represents a high risk for treatment failure. When abstinence is the goal, urine testing may help to indicate the likelihood of treatment success.

**Naltrexone:** One RCT study (Jayaram-Lindström, Hammarberg, Beck & Franck, 2008) found lower amphetamine use, reduced craving and better retention among the naltrexone group compared to placebo but a second smaller RCT study found no differences.

These findings are consistent with, and were built upon by, a review by Brensilver et al. (Brensilver, Johnson, Grotheer, Heinzerling, Bholat & Shoptaw, 2012), which concluded that bupropion, methylphenidate and naltrexone are among the most promising medicines to date.

**Medicines that may have potential but require further research**

A number of medicines show promise but the number of studies is too small to draw conclusions. Many of them have shown some benefits, but have done so in either a single small n RCT study or one or more non-RCT studies.

**Mirtazapine** has been the subject of only one study, an RCT, which showed significant decreases in methamphetamine use and sexual risk taking (Colfax et al., 2011). Brensilver, Johnson et al. (2012) also highlighted the potential benefits of mirtazapine. But fewer than 50 per cent of participants took the medicine regularly as prescribed, suggesting it may be more useful for those who are highly motivated to reduce their use.

**Fluoxetine:** A single double-blind RCT (Batki et al., 1999) found fluoxetine was not superior to placebo in reducing both self-reported and urinalysis-confirmed methamphetamine use, but craving was lower in the fluoxetine group compared to the placebo group.

**Topiramate:** One large double-blind multi-site RCT (Elkashef et al., 2012) showed topiramate was ineffective among study completers in promoting methamphetamine abstinence but was superior to placebo on reducing use and severity of dependence and increasing general functioning.

**Risperidone:** Two open-label uncontrolled trials by the same research group (Meredith, Jaffe, Yanasak, Cherrier & Saxon, 2007; Meredith et al., 2009) found in favour of oral and injectable risperidone on measures of methamphetamine use, craving, verbal memory and psychiatric symptoms.

**Varenicline:** One recent pilot RCT (Swanson, Shoptaw & Heinzerling, 2011) reported greater retention rates and trends in favour of varenicline over placebo in reducing methamphetamine use and increasing duration of abstinence compared with placebo.
Medicines with limited or no evidence of benefit

**Gabapentin:** One double-blind RCT (Heinzerling et al., 2006) found no effect for gabapentin in reducing methamphetamine use, craving or retention when compared to both baclofen and placebo.

**Baclofen:** One RCT (Heinzerling et al., 2006) found the GABA$_B$ agonist baclofen was not superior to placebo overall on measures of methamphetamine use, craving or treatment retention. However, participants with greater medicine adherence showed a significant reduction in methamphetamine use when compared with placebo, but the short half-life of baclofen compared to the long half-life of ATS may limit its use.

**Ondansetron:** One RCT (Johnson et al., 2008) reported that ondansetron was well tolerated by participants but was not superior to placebo on measures of methamphetamine use, craving or severity of dependence. The treatment groups showed poorer outcomes (non-significant) than the placebo group.

**Amlodipine:** One RCT (Batki et al., 2001) found no effect for amlodipine on any measures. This report was a conference abstract with little detail about the direction of any changes.

Medicines with unacceptable side-effect profiles

The results suggest some medicines should not be used due to unacceptable side effects, including aripiprazole and vigabatrin (both of which appear to have potentially serious adverse effects) and sertraline and the Prometa™ protocol of combination flumazenil and gabapentin (both of which appear to increase amphetamine use).

**Aripiprazole:** The subject of one trial that had to be discontinued because of serious adverse events. Participants in the aripiprazole group produced significantly more positive ATS urine samples and showed a worsening of symptoms.

**Vigabatrin:** A single open-label study of vigabatrin did not show any unusual visual field defects, but given that defects have been reported previously (including permanent vision impairment), and this study was a small open-label trial with few benefits, future research efforts should focus on medicines with greater promise.

**Sertraline:** There were two reports of the outcomes of sertraline (different analyses of the same data set). They showed increases in use during the trial period and one of these analyses also showed poorer retention and more adverse events than placebo (Shoptaw et al., 2006; Zorick, Sugar, Hellemann, Shoptaw & London, 2011).

**Combination flumazenil and gabapentin:** In one study of combination flumazenil and gabapentin, ATS use steadily increased during the trial from day 1 to day 30 in both placebo and treatment groups, although the results show a large decrease in ATS use from 30 days pre-trial to week 1 of the trial (Urschel, Hanselka & Baron, 2011). The initial decrease may have been a response to entering treatment, as the placebo group also showed a similar level of reduction. In addition, the protocol is complex to administer.
Research implications

Numerous studies have been undertaken to identify a pharmacotherapy for methampheta-
mine dependence. All have examined reduction in drug use or abstinence as the treatment
goal across a spectrum of users. Further work should focus on areas of potential benefit
and could include:

- meta-analytic review of modafinil, dexamphetamine and bupropion studies; the data
currently reported in these studies were insufficient for meta-analysis, but access to the
original data sets or further details of these analyses would enable such an analysis

- re-analysis of some of the larger data sets or designing studies that identify subgroups
of ATS users which may show a differential benefit from these medicines as distinct from
the sample as a whole

- studies that examine the relapse–prevention potential of these drugs in abstinent users
(for example, a random discontinuation design in which all patients undergo supervised
withdrawal from ATS and are treated with the target medicine, then one group is with-
drawn from the medicine according to random allocation)

- further trials of methylphenidate, as it showed positive outcomes in one study and rep-
lication is required

- further trials of mirtazapine, baclofen and topiramate, which showed promise but have
been the subject of only one study each.

Many studies had small sample sizes, high drop-out rates and low medication adherence.
Studies that examine ways to retain patients in pharmacotherapy treatment and improve
adherence may be useful. Contingency management shows promise in supporting adherence
to the pharmaceutical protocol. At least one study noted the requirement for daily dosing
may have reduced adherence (Miles et al., 2013), so more flexible dosing regimes could be
considered for future clinical trials.

Other considerations in the treatment of amphetamine dependence

Role of adherence with prescribed medicines

In most of these studies, adherence to taking medicines as prescribed was low. Many stud-
ies found a correlation between adherence and better outcomes, suggesting that if any of
these medicines are used, monitoring of adherence is important for ensuring effectiveness
of treatment. In some studies attrition rates were very high, also suggesting that assistance
with maintaining motivation is an important factor in optimising client outcomes in a
clinical setting.
Role of psychosocial interventions

Nearly all the studies utilised psychosocial interventions, some quite intensively, in conjunction with pharmacotherapy. Although attendance at treatment sessions varied between studies, psychosocial interventions for both the treatment and placebo groups may have masked the apparent effectiveness of the medicines being examined, making it difficult to determine the effect of the medicine itself. Psychosocial interventions, such as the Matrix Model (Rawson et al., 1995) used extensively in the United States and the Australian gold standard four-session brief cognitive behavioural and motivational interviewing (MI) intervention (Baker et al., 2005), have been shown to be effective for methamphetamine users. The Matrix Model is an intensive intervention involving group and individual work designed for dependent users in treatment. Baker and colleagues’ combined MI/CBT intervention has been shown to be effective for a range of users, including those who are dependent.

A further complicating factor is that many of the studies employed intensive assessment procedures as part of the protocol. There is evidence to suggest that assessment itself is therapeutically beneficial (Kypri et al., 2007) and in some studies may have created a ceiling effect in the results that is unlikely to be replicated in the clinical setting.

Cultural issues

The majority of the studies have been undertaken in the United States. This is significant for Australia because the nature of methamphetamine use and the treatment systems are different in the two countries. Among Australians who use drugs by injection, around 70 per cent used ATS (Stafford & Burns, 2012), and studies from the United States rarely included injecting methamphetamine users. Care is needed in translating results from international studies to the Australian clinical setting.

Subgroups of amphetamine users

Very little evidence is available concerning which medicines prescribed under what conditions might benefit particular subgroups of ATS users. Clinical experience suggests that people who use lower quantities of ATS at initial presentation may do better in treatment than those who are heavy users. This view was supported by results from two separate studies. Elkashef et al. (2008) showed that, for the subgroup of participants who had lighter use of methamphetamine at baseline, bupropion treatment increased weekly periods of abstinence (56%) compared to placebo (40%), and lighter users also showed a greater rate of decrease in urine quantitative methamphetamine than placebo. Shoptaw et al. (2008) also found that lighter users were nearly three times more likely to have a methamphetamine-free week than heavier users during treatment with bupropion compared with placebo. Although bupropion did not show benefit overall, post-hoc analyses suggest that there may be some benefit for lighter users (e.g. <18 days of use in the last 30 days).
Gender differences in outcomes were rarely reported in the studies reviewed. However, Elkashef et al. (2008) showed that bupropion was associated with reduced methamphetamine use in males but not in females.

Comorbid disorders may also complicate clinical responses to medicines. Shearer et al. (2009) found poorer outcomes for HIV-positive participants taking modafinil and poorer outcomes for methamphetamine-dependent participants with comorbid opioid dependence compared to those dependent solely on methamphetamine.

Vaccines for amphetamine dependence

There were no Phase II or III studies of vaccines identified, but they have been mooted for ATS users after successful trials with cocaine users.

Effective vaccines for many common illnesses, such as measles and polio, have been available for many years. Vaccines are designed to boost the body’s immune response against the target pathogen. Vaccines can be both active and passive in nature. Active vaccines introduce molecules that trigger the immune system to develop its own antibodies, while passive vaccines introduce pre-generated antibodies.

Promising results from trials of vaccines for cocaine dependence (e.g. Martell et al., 2009) prompted a search for a vaccine for methamphetamine dependence. Methamphetamine vaccines are designed to sequester the methamphetamine molecules in the bloodstream and allow natural clearance to occur (Gentry, Ruedi-Bettschen & Owens, 2009). Without antibodies crossing the blood brain barrier, the highly rewarding central nervous system effects of methamphetamine would also be blocked.

To date, all trials of methamphetamine vaccines have been conducted in animal models. Early trials of active methamphetamine vaccines in rats found that while anti-methamphetamine antibody titres increased, behavioural effects of methamphetamine (e.g. locomotor activity) did not reduce (Gentry et al., 2009), indicating that methamphetamine was still active in the central nervous system, which is undesirable following vaccination. In later trials, six methamphetamine immunoconjugates were tested in mice with some found to result in high methamphetamine-antibody titres and high affinity (binding of molecules in the bloodstream) (Moreno, Mayorov & Janda, 2011). One of these promising immunoconjugates, MH6, was recently re-tested and found to again produce high methamphetamine-antibody titres and methamphetamine blood concentrations, and lower brain methamphetamine concentrations in rats (Miller et al., 2012), which adds to the promising pool of results in these pre-clinical trials of methamphetamine vaccines.

Researchers suggest that a successful vaccine could be a highly effective adjunct to preventing relapse to methamphetamine use if used in combination with supportive psychosocial therapy in long-term users, and as a treatment for methamphetamine overdose in acute medical settings (Gentry et al., 2009).
## Table 1. Overview of studies reviewed for the treatment of amphetamine-type stimulant dependence

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Fluoxetine and gabapentin combination</th>
<th>Anticonvulsants</th>
<th>Antipsychotics</th>
<th>Medication adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmopressine</td>
<td>Modafinil</td>
<td>Bupropion</td>
<td>Naltrexone</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Number of studies</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Number of RCTs</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>AFS use reduced?</td>
<td>Yes, but not more than placebo</td>
<td>Yes, but evidence equivocal</td>
<td>Yes, if compliant with medicine</td>
<td>Yes, but no more than placebo; but reductions among lighter users</td>
</tr>
<tr>
<td>Other effects</td>
<td>Appears to reduce severity of dependence</td>
<td>May improve retention slightly</td>
<td>No effect on craving or treatment retention</td>
<td>Is probably more effective with light users, also reduces tobacco smoking</td>
</tr>
<tr>
<td>Safety</td>
<td>Safe and well tolerated</td>
<td>Safe and well tolerated</td>
<td>Safe and well tolerated</td>
<td>Safe and well tolerated</td>
</tr>
<tr>
<td>Comments</td>
<td>Studies had a high drop-out rate</td>
<td>Studies had a high drop-out rate</td>
<td>Studies had low medication adherence</td>
<td>Studies had high drop-out rate</td>
</tr>
<tr>
<td>Evidence of benefit rating</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Key points</td>
<td>Shows some benefits in reducing severity of dependence, but not use</td>
<td>Shows some benefits in reducing use and potential in increasing retention</td>
<td>Shows some benefits in reducing use if medication-compliant</td>
<td>Shows some benefits in reducing use, especially for lighter users (&lt; 18 days in last 30 days)</td>
</tr>
</tbody>
</table>

### Evidence of benefit rating legend:
- *** Shows some benefit
- ** Shows potential benefit but current evidence is limited
- * Shows little or no evidence of benefit
- X Shows evidence of harm

### Detailed findings
Treatment for co-occurring mental health problems among amphetamine-type stimulant users

See summary table beginning on page 102 for details of this group of studies.

**Overall summary**

It is difficult to draw any firm conclusions about the prescription of medicines for mental health disorders co-occurring with amphetamine use because of the nature of the studies.

A range of medicines, including antipsychotics, dexamphetamine, modafinil and citicoline, are probably safe and may be effective for methamphetamine users if used within existing guidelines for general population prescribing under close supervision.

Dexamphetamine and modafinil did not appear to exacerbate psychotic symptoms in the participants taking part in these studies, although Shearer et al. (2009) advise caution when using modafinil in those with pre-existing psychotic conditions. Dexamphetamine, risperidone and a combination of modafinil, quetiapine and divalproex appeared to have some positive effects on both psychotic symptoms and amphetamine use.

Although there was a paucity of well-controlled studies, those available suggest that medicines for mental health disorders in the general population are also suitable for amphetamine users with these disorders, under close supervision. Medicines to treat mental health disorders in the general population are probably useful and safe for people using amphetamines but, given the lack of specific evidence, additional monitoring may be required.

The dominance of case studies with the lack of standard measures makes it difficult to draw specific conclusions about the effectiveness of these medicines for people who use amphetamines and further research is needed.

**Summary of literature reviewed**

A total of eight studies, two controlled trials (Brown & Gabrielson, 2012; Nejtek et al., 2008) and six case studies or open-label trials (Camacho, Ng & Frye, 2010; Camacho & Stein, 2002; Carnwath, Garvey & Holland, 2002; Misra & Kofoed, 1997; Misra, Kofoed, Oesterheld & Richards, 2000; Sulaiman et al., 2012) were reviewed.

There were very few studies that examined medication for co-occurring mental health problems among dependent amphetamine users, making it difficult to draw conclusions for clinical practice.

One study (Brown & Gabrielson, 2012) was a randomised trial that found improvement in depressive symptoms, but no change in drug use using citicoline, a naturally occurring compound thought to have neuroprotective properties, which is available as an over-the-counter supplement in the United States but not in Australia.
A second randomised trial (Nejtek et al., 2008) compared risperidone and quetiapine, two antipsychotic medicines, for amphetamine use and bipolar disorder and showed that both medicines improved manic and depressive symptoms and reduced cravings among this group. As no placebo control was employed, the most that can be said is that risperidone and quetiapine are equally effective, but it is unclear whether they are better than no treatment or other treatments. A number of other antipsychotic preparations have been examined for amphetamine users experiencing psychotic symptoms, including risperidone (Misra & Kofoed, 1997), olanzapine (Misra et al., 2000) and aripiprazole (Sulaiman et al., 2012), all of which were effective in reducing acute and residual psychotic symptoms in amphetamine users.

In a report of a single case, Camacho et al. (2010) concluded that a combination of modafinil, quetiapine and divalproex for methamphetamine users with bipolar affective disorder improved depressive symptoms and reduced craving for methamphetamine with no exacerbation of manic symptoms. The same group (Camacho & Stein, 2002) found that modafinil was also useful in treating a single case of social phobia and amphetamine dependence. It is important to note, however, that Shearer et al. (2009) suggest caution when prescribing modafinil for people with pre-existing anxiety or psychotic disorders, as the few reports of thought disorder or anxiety symptoms found in that study were unique to the modafinil group.

One case study (Carnwath et al., 2002) found that dexamphetamine, prescribed as replacement therapy for amphetamine dependence, did not exacerbate psychotic symptoms among a group of eight dependent amphetamine users with schizophrenia. Six of the eight patients showed ‘good’ or ‘some’ improvement in both drug use and mental health symptoms.

Overall, these studies do not offer sufficient evidence on which to base recommendations for the treatment of amphetamine use and co-occurring mental health problems. However, similar to general studies of co-occurring drug use and mental health disorders, they appear relatively safe for use with this group and may be helpful in treating symptoms of mental health problems among the cohort of amphetamine users of interest to this review.

Research implications

There were few studies examining medicines for amphetamine use and co-occurring mental health disorders, and only two of the studies reviewed were controlled trials. All others were either open-label trials with no control group and small sample sizes, or single-case designs. Additional high-level studies of the efficacy and effectiveness of prescribed medicines for co-occurring mental health and ATS dependence are required.
MDMA

Overall summary
There were only two studies of treatment for MDMA, both single case studies of little value to clinical settings.

There is little evidence for the effectiveness of pharmacotherapy for MDMA and, with the exceptions of symptomatic relief from co-occurring mental health symptoms, psychosocial intervention remains the treatment of choice for this group.

Research efforts are better directed towards treatment of methamphetamine dependence because, although there have been reports of MDMA dependence and long-term problems, these are unusual and rarely in isolation from polydrug dependence. MDMA use is generally considered to be self-limiting over time. Most issues with MDMA are acute and more amenable to harm reduction strategies.

Summary of literature reviewed
Only two studies that examined the role of medicines for treating 3,4-methylenedioxymethylamphetamine (MDMA) use problems were identified and both were single-case designs. The first described the case of a 28-year-old man using MDMA two to four times per week for four years, who reported a dramatic reduction in MDMA use during three months of treatment with topiramate and a reduction in subjective effects of MDMA when it was taken (Akhondzadeh & Hampa, 2005). The second study reported the case of 28-year-old woman who reported depression and anxiety, which she linked to a period of one year when she used MDMA weekly; she had been abstinent for six years at the time of the study (Fetter, 2005). The patient self-reported decreased panic attacks and improved functioning use following three months treatment with mirtazapine.

Research implications
Most of the problems associated with MDMA involve acute toxicity and it is rare for MDMA to be associated with chronic heavy use. There are a few reports of MDMA dependence in clinical settings and there is some evidence that a dependence syndrome potentially exists (Degenhardt & Hall, 2010), but presentation for treatment is relatively rare as a primary drug of concern. In 2011–12, for example, there were 720 closed treatment episodes across Australia for ecstasy as a main drug of concern, compared to 12 528 for amphetamines (Australian Institute of Health and Welfare, 2012). Given the small numbers of dependent users, research into pharmacotherapies is likely to offer more productive public health benefits if focused on treating amphetamine dependence.
Other amphetamine-type stimulants

Only one study that examined the role of medicines for treating stimulants other than methamphetamine and MDMA was identified in this review and it was a single-case design. The study described the case of a 37-year-old woman with a history of major depression, eating disorder and compulsive behaviour who had used ephedrine for 20 years for weight management. She was treated successfully with fluoxetine plus aripiprazole for eight weeks and was ephedrine-abstinent after four months.

Very few ATS other than amphetamines become problematic among users. Given the small numbers of users, research efforts are likely to be better focused on treating methamphetamine dependence.
Conclusions

Amphetamine-type stimulants have been available on the illicit drug market in Australia for decades and, like many drugs of abuse, their popularity has waxed and waned over the years in accordance with availability, cost and cultural trends among people who use drugs. ATS include amphetamines (amphetamine and methamphetamine), as well as MDMA and a handful of other analogues not commonly seen among clients in treatment settings. Methamphetamine has dominated the market since a significant spike in reported use in 1998 (Australian Institute of Health and Welfare, 2011), and recent data from the Drug Use Monitoring in Australia project (Sweeney & Payne, 2012) suggest that ATS use is once again on the increase since downturns were first reported in 2004.

The acute effects of ATS in general, and methamphetamine in particular, are highly rewarding for most people and users report feeling intense pleasure that is unrivalled by endogenous processes. Conversely, adverse effects can also be severe and include a range of significant physical and psychological health problems, including neurotoxicity. Despite this, people who use ATS tend not to present for treatment until their problems are extreme (Baker et al., 2004).

Research suggests that services generally have difficulty attracting ATS users into treatment and retaining them until treatment goals are met (Vincent et al., 1999). This could be due in part to the traditional focus of the alcohol and other drugs treatment sector on treating opiate and alcohol-use disorders, coupled with a previous paucity of evidence-based interventions to offer people who use ATS.

There is now a significant body of evidence for the effectiveness of psychological therapies for problematic ATS use which can be used to guide clinical responses in all alcohol and drug treatment services (Lee & Rawson, 2008). Despite this, substantially fewer ATS users present for treatment than estimates suggest would benefit from it, and drop-out among people who do begin psychological therapy is high.

Practitioners have identified the lack of a pharmacotherapy for ATS as a barrier to treatment (Kenny et al., 2011), but to date the role that pharmacotherapy might play in better supporting people who are dependent on ATS is still unclear.

It is possible that offering dependent ATS users access to effective medicines may have several benefits. Firstly, it may serve to attract more people into treatment, and attract them earlier when evidence suggests they will benefit most. Secondly, offering pharmacotherapy in concert with psychosocial interventions may help to retain people in care until such time as treatment gains are made. This is particularly important for those people who have had multiple attempts at quitting or reducing ATS use on their own or under supervision, or for those who have been unsuccessful in maintaining engagement with psychosocial treatment services and have dropped out of treatment multiple times.

To date, there are insufficient data to demonstrate a universal benefit for any one particular medicine in the treatment of ATS use disorders over another, thus no medicines are authorised in Australia for this purpose and none can be recommended as a first-line treatment option.
Findings from some of the 56 studies examined for this review suggest that some medicines (dexamphetamine, bupropion, modafinil, methylphenidate and naltrexone) may be effective and suitable for some people in some circumstances, particularly when pharmacotherapy forms part of a comprehensive and individualised treatment plan, and are prescribed within a quality use of medicines framework. Each of these medicines showed a good safety profile with amphetamine users in the trials reviewed.

Given the likely widespread off-label prescribing of medicines for people dependent on methamphetamine (e.g. Dunlop et al., 2008), this discussion paper has also identified a number of medicines that should be avoided because they have been shown to be harmful to use with methamphetamine users.

Additional research, particularly among Australian ATS users, is still required to understand the role of pharmacotherapy among people who are ATS-dependent, and to further identify how best the medicines that show promise can be appropriately prescribed.
References


**Studies included in the systematic review**


### Appendix: Summary tables

#### Amphetamine withdrawal

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medicine</th>
<th>Number and description of participants</th>
<th>Intervention and comparison if relevant</th>
<th>Primary outcomes including measures used</th>
<th>Level of evidence</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, N. et al. (2013). A pilot randomised controlled trial of modafinil during acute methamphetamine withdrawal: feasibility, tolerability and clinical outcomes. Drug and Alcohol Review, 32(1): 88–95. Australia</td>
<td>Modafinil</td>
<td>19 dependent methamphetamine users (inpatients) who had used methamphetamine in the 48 hours prior to recruitment and not dependent on substances other than methamphetamine, cannabis and nicotine. Males n=13 (68%). Mean age: 34.3 years. Mean years of methamphetamine use: approx. 6.5 years. Mean use in last month: approx. 18 days. % injectors: not reported. Randomised to modafinil (n=9) or placebo (n=10).</td>
<td>Modafinil or placebo crushed in capsules for seven days (200 mg of modafinil or matching placebo for days 1-5, and 100 mg for days 6 &amp; 7, to titrate the dose before discharge)</td>
<td>Measures</td>
<td>Level II – double-blind placebo-controlled RCT (pilot)</td>
<td>Well-conducted pilot study, but small sample size. Cohort were not daily users but had been using for more than six years on average and were all injectors. This is similar to, but slightly less severe than, a large cohort of methamphetamine users in treatment reported by McKetin et al. (2012). Same dataset as Hester et al. (2010).</td>
</tr>
<tr>
<td>Hester, R. et al. (2010). The effects of modafinil treatment on neuropsychological and attentional bias performance during 7-day inpatient withdrawal from methamphetamine dependence. Experimental and Clinical Psychopharmacology, 18(6): 489–497. Australia</td>
<td>Modafinil</td>
<td>19 dependent methamphetamine users (inpatients) who had used methamphetamine in the 48 hours prior to recruitment and not dependent on substances other than methamphetamine, cannabis and nicotine. 13 of the 19 eligible patients underwent neuropsychological assessment at both baseline and follow-up. Males n=13 (68%). Mean age: 34.3 years. Mean years of methamphetamine use: approx. 6.5 years. Mean use in last month: approx. 18 days. % injectors: not reported. Randomised to modafinil (n=9) or placebo (n=10).</td>
<td>Modafinil or placebo crushed in capsules for seven days (200 mg of modafinil or matching placebo for days 1-5, and 100 mg for days 6 &amp; 7, to titrate the dose before discharge)</td>
<td>Measures</td>
<td>Level II – double-blind placebo-controlled RCT (pilot)</td>
<td>Well-conducted pilot study, but small sample size and low follow-up for neuropsychological testing. Inpatient study.</td>
</tr>
</tbody>
</table>

#### Measures

- **Neuropsychological test battery including:** literacy (National Adult Reading Test); verbal and visual memory (Rey Auditory Verbal Learning test (RAVLT) and Rey Complex Figure test (RCFT)); working memory (Digit Span test, Psychomotor speed – Digit–Symbol Substitution test); executive function (Controlled Oral Word Association test (COWAT), Trail Making test, Stroop test, methamphetamine word emotional Stroop task). **Summary**

  - Treatment was associated with a significant improvement in immediate verbal memory recall and a non-significant trend toward improvement on executive function and delayed memory tasks. No benefit was seen for measures of verbal learning, visual memory, processing speed, or verbal fluency. All participants showed a significant attentional bias for methamphetamine-related stimuli on the emotional Stroop task. The magnitude of bias predicted both retention in treatment and relapse potential at follow-up but was not significantly alleviated by modafinil treatment. While non-significant, the effect sizes of modafinil-related improvements in executive function and memory were consistent with those found in more robustly powered studies of cognitive benefits in attention-deficit hyperactivity disorder and schizophrenia.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Medicine</th>
<th>Number and description of participants</th>
<th>Intervention and comparison if relevant</th>
<th>Primary outcomes including measures used</th>
<th>Level of evidence</th>
<th>Quality assessment</th>
</tr>
</thead>
</table>
Males n=27 (55%)  
Mean age: 31.3 years  
Mean years of methamphetamine use: 10 years  
Mean use in last month: 23.6 days  
% injectors: not reported  
Randomised to mirtazapine (n=13) or modafinil (n=14). A historical comparison group who had received treatment as usual (TAU) (n=22) | Modafinil (400 mg/day) and mirtazapine (60 mg/day for up to 10 days) were compared to a historical comparison group receiving pericyazine as per necessary (PRN) which was treatment as usual (TAU) (2.5–10 mg/day)  
Symptomatic medications were available PRN for all groups (diazepam (5–10 mg) for anxiety, either nitrazepam (5–10 mg) or temazepam (10–20 mg) for insomnia, and non-opioid analgesia was administered for pain) | Measures  
Severity of Dependence Scale; Amphetamine Cessation Symptoms Assessment (ACSA); Clinical Global Impression Scale; Beck Depression Inventory II; St Mary’s Hospital Sleep Questionnaire.  
Summary  
Modafinil and mirtazapine were well tolerated, producing minimal positive subjective effects and no discontinuation effects in this open-label study. Side effects were mild and transient. Both modafinil- and mirtazapine-treated participants showed milder withdrawal symptoms compared to TAU-treated participants; modafinil-treated participants had a milder withdrawal syndrome and less sleep disturbance in comparison to mirtazapine. | Level II — double-blind randomised trial (pilot) | Pilot open-label study, small sample size. No placebo control.  
Cohort were near daily users and had been using for 10 years on average. This is similar to a large cohort of methamphetamine users in treatment reported by McKetin et al. (2012). |
Two studies of amineptine and two of mirtazapine compared to placebo | Summary  
Two studies found that amineptine significantly reduced discontinuation rates and improved overall clinical presentation, but did not reduce withdrawal symptoms or craving compared to placebo. The benefits of mirtazapine over placebo for reducing amphetamine withdrawal symptoms were not as clear. One study suggested that mirtazapine may reduce hyperarousal and anxiety symptoms associated with amphetamine withdrawal. A more recent study failed to find any benefit of mirtazapine over placebo on retention or on amphetamine withdrawal symptoms. | Level I — systematic review | High-quality Cochrane review. |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Medicine</th>
<th>Number and description of participants</th>
<th>Intervention and comparison if relevant</th>
<th>Primary outcomes including measures used</th>
<th>Level of evidence</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cruickshank, C.C. et al. (2008).</td>
<td>Mirtazapine</td>
<td>31 dependent methamphetamine users (outpatients) who had used methamphetamine in the 72 hours prior to recruitment and not at significant risk of withdrawal from other drugs</td>
<td>Mirtazapine 15 mg or placebo on the first two nights and 30 mg mirtazapine nocte for a further 12 nights. Medications were self-administered unsupervised, + five sessions of 45 mins narrative therapy both groups</td>
<td>Measures: A range of clinical measures including: Treatment retention; Amphetamine Cessation Symptoms Assessment (ACSA); Athens Insomnia Scale (AIS–5); Brief Symptom Inventory (BSI) subscale BSI–GSI; Depression–Anxiety–Stress Scale (DASS); Severity of Dependence Scale; Opiate Treatment Index (OTI) Drug Use subscale.</td>
<td>Level II – double-blind RCT (pilot)</td>
<td>Well-conducted pilot study, but small sample size and high drop-out (52% completed the two-week medication phase and 32% completed the five-week study). Difficult to assess any ceiling effects of added psychotherapy.</td>
</tr>
<tr>
<td>Kongsakon, R. et al. (2005). Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. International Clinical Psychopharmacology, 20(5): 253–256.</td>
<td>Mirtazapine</td>
<td>20 dependent methamphetamine users in a probation centre (inpatients)</td>
<td>Mirtazapine 15–60 mg per day or placebo with an initial dose of 15 mg and titrated according to the participants’ clinical response over 14 days. Participants were followed up on days 3 &amp; 14 after initiation of treatment.</td>
<td>Measures: Depression was measured using the Montgomery–Asberg Depression rating scale (MADRS) and ATS withdrawal symptoms measured by the Amphetamine Withdrawal Questionnaire (AWQ).</td>
<td>Level II – placebo-controlled trial (pilot)</td>
<td>Small sample size, unclear whether study was double blinded.</td>
</tr>
<tr>
<td>Reference</td>
<td>Medicine</td>
<td>Number and description of participants</td>
<td>Intervention and comparison if relevant</td>
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<tr>
<td>Srisurapanont, M. et al. (1999). Amphetamine withdrawal: II. A placebo-controlled, randomised, double-blind study of amineptine treatment. <em>Australian and New Zealand Journal of Psychiatry</em>, 33(1): 94–98. Thailand</td>
<td>Aminetpine</td>
<td>44 methamphetamine-dependent inpatients</td>
<td>Aminetpine 300 mg daily for 14 days (plus lorazepam 0.5–1.5 mg/day for 5–14 days as per necessary for anxiety)</td>
<td>Measures</td>
<td>Level II – double-blind placebo-controlled trial (pilot)</td>
<td>Well-conducted pilot RCT with small sample size. Cohort was young; nearly all men with less than two years of ATS use, so results may not be generalisable to older users with longer histories of ATS use.</td>
</tr>
<tr>
<td>Jittiwutikan, J. et al. (1997). Aminetpine in the treatment of amphetamine withdrawal: a placebo-controlled, randomised, double-blind study. <em>Journal of the Medical Association of Thailand</em>, 80(9): 587–592. Thailand</td>
<td>Aminetpine</td>
<td>30 dependent oral amphetamine-using inpatients, with DSM–IV amphetamine withdrawal</td>
<td>Aminetpine 300 mg/day titrated over the first five days and matching placebo for 14 days</td>
<td>Summary</td>
<td>Level II – double-blind placebo-controlled randomised trial</td>
<td>Well-conducted but small RCT. All participants used oral amphetamine, were young, nearly all men and had been using for less than two years which limits generalising findings to long-term, heavier users of amphetamine.</td>
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**Reference Medicine**

Number and description of participants

Intervention and comparison if relevant

Primary outcomes including measures used

Level of evidence

Quality assessment
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</thead>
<tbody>
<tr>
<td>Galloway, G.P. et al. (2011). A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. <em>Clinical Pharmacology &amp; Therapeutics</em>, 89(2): 276–282. United States of America</td>
<td>Dexamphetamine (d-AMP)</td>
<td>60 dependent methamphetamine users (outpatients) Males n=34 (57%) Mean age: 37 years Mean years of use: 2 years Mean use in last month: approx. 16 days % injectors: not reported (80% active group and 67% placebo group smoked MA primarily) Randomised to either placebo (n=30) or d-AMP (n=30)</td>
<td>Participants received either 60 mg d-AMP sustained-release (SR) or placebo daily for eight weeks. This was given as a single dose on the first day and as two equally divided doses on subsequent days. All received 50-min. manual-based individual motivational enhancement therapy sessions once a week for nine weeks.</td>
<td>Measures Number of methamphetamine-negative urine drug screens (collected twice weekly); self-reported methamphetamine use (Time Line Follow Back — TLFB); Amphetamine Withdrawal Questionnaire (AWQ); The Desire for Speed Questionnaire (visual analogue craving scale); medication adherence self-report. Summary The dexamphetamine group reported significantly less craving and fewer withdrawal symptoms. No serious adverse events occurred during the trial, but n=30 reported mild adverse events.</td>
<td>Level II — double-blind multi-site placebo-controlled RCT</td>
<td>Well-conducted double-blind RCT, originally designed to examine treatment for dependence but measures withdrawal in dependent methamphetamine users. Cohort were not daily users and had been using for an average of two years.</td>
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<tr>
<td>Longo, M. et al. (2010). Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. <em>Addiction</em>, 105(1): 146–154. Australia</td>
<td>Dexamphetamine</td>
<td>49 dependent methamphetamine-using outpatients who had used methamphetamine on three or more days per week over the previous 12 months. 86% were IV users. Males n=24 (61%) Mean age: 31.9 years Mean years of methamphetamine use: not reported Mean use in last month: not reported Mean age first use: approx. 20 years Median use in past 3 months: 69 days % injectors: 86% Randomised to receive either dexamphetamine (n=23) or placebo (n=26)</td>
<td>The study period comprised an initial stabilisation period of up to 14 days, with an initial dose of 20 mg/day of a SR formulation of dexamphetamine increased by 10 mg daily as required until stabilised or in receipt of a maximum of 110 mg/day for 90 days. All participants underwent stabilisation (withdrawal assessed by AWQ), with the placebo group receiving increasing numbers of placebo capsules. Plus all participants received four sessions of cognitive behaviour therapy (CBT) for amphetamine users.</td>
<td>Measures Self-reported methamphetamine use and hair analysis at three time-points (baseline, the end of maintenance, and follow-up); degree of dependence over time (Leeds Dependence Questionnaire — LDQ); treatment retention. Summary Dexamphetamine was well tolerated and safe under pharmacist-supervised, daily dosing conditions. There was a trend toward greater reduction of reduced withdrawal symptom severity during stabilisation in the dexamphetamine group.</td>
<td>Level II — double-blind, placebo-controlled RCT</td>
<td>Well-conducted, Australian double-blind RCT, originally designed to examine dexamphetamine for methamphetamine dependence but also measured withdrawal symptoms. Small sample size and high rate of attrition from the trial among the placebo group. Unclear how long or how much methamphetamine the participants had been using at the beginning of the trial.</td>
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## Treatment for amphetamine dependence

### Dexamphetamine and other psychostimulants

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Males n=15 (50%)  
Mean age: 37 years  
Mean 18.9 days of methamphetamine use in last 30 days  
Randomised to dextroamphetamine (n=30) or placebo (n=30) | Participants received either 60 mg d-AMP SR or placebo daily for eight weeks. This was given as a single dose on the first day and as two equally divided doses on subsequent days.  
All received 50-min., manual-based, individual motivational enhancement therapy sessions once a week for nine weeks. | Measures  
Primary measure: Number of methamphetamine-negative urine drug screens (collected twice weekly).  
Secondary measures: self-reported methamphetamine use (TLFB); Amphetamine Withdrawal Questionnaire (AWQ); The Desire for Speed Questionnaire (visual analogue craving scale); and medication adherence self-report. | Level II — double-blind multi-site placebo-controlled RCT | Well-conducted RCT with a sufficient sample size, reasonable medication adherence and low loss to follow-up rate. |
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<tr>
<td>Longo, M. et al. (2010). Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. <em>Addiction</em>, 105(1): 146–154. Australia</td>
<td>Dexamphetamine</td>
<td>40 dependent methamphetamine users who had used methamphetamine on three or more days per week over the previous 12 months. 86% were IV users Males n=24 (61%) Mean age: 31.9 years Mean years of methamphetamine use: not reported Mean use in last month: not reported Mean age first use: approx. 20 years Median use in past 3 months: 69 days Randomised to receive either dexamphetamine (n=23) or placebo (n=26)</td>
<td>The study period comprised an initial stabilisation period of up to 14 days, with an initial dose of 20 mg/day of a SR formulation of dexamphetamine increased by 10 mg daily as required until stabilised or until the participant was in receipt of a maximum of 110 mg/day for 90 days. All participants underwent stabilisation (withdrawal assessed by AWQ), with the placebo group receiving increasing numbers of placebo capsules. At the end of the maintenance period, participants were tapered off the medication over one month in order to minimise any withdrawal symptoms experienced. Participants were followed up two months after completing treatment. Plus all participants received four sessions of CBT for amphetamine users.</td>
<td>Measures Self-reported methamphetamine use and hair analysis at three time-points (baseline, the end of maintenance, and follow-up); degree of dependence over time (Leeds Dependence Questionnaire); treatment retention. Summary Dexamphetamine was well tolerated and safe under pharmacist-supervised, daily dosing conditions. Intention to treat (ITT) analysis showed that participants taking dexamphetamine stayed in treatment significantly longer (86.3 days) compared to placebo (48.6 days).</td>
<td>Level II – double-blind, placebo-controlled RCT</td>
<td>A well-conducted, Australian double-blind RCT. Small sample size and high rate of attrition from the trial among the placebo group. Originally designed to examine dexamphetamine for methamphetamine dependence but also measured withdrawal symptoms.</td>
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<tr>
<td>White, R. et al. (2006). Dexamphetamine substitute prescribing in pregnancy: a 10-year retrospective audit. <em>Journal of Substance Use</em>, 11(3): 205–216. United Kingdom</td>
<td>Dexamphetamine</td>
<td>47 amphetamine-using women who were prescribed dexamphetamine. 41 women who were not amphetamine-using, and two equivalent groups of heroin users and members of the general population Females only Mean age: 26.7 years Injecting use: 56.8% Mean years of methamphetamine use: not reported Mean use in last 30 days: not reported</td>
<td>Dexamphetamine substitution, with typical doses of an orally administered elixir being between 30 mg and 60 mg, is offered to pregnant amphetamine users. There was an emphasis on reducing the dose of dexamphetamine through the pregnancy and an expectation that this can usually be done at a faster rate than for a woman on methadone. Thus, ideally, patients are detoxified before the third trimester. Pregnant heroin users are offered methadone as the treatment of choice, but dihydrocodeine is also used on an occasional basis.</td>
<td>Measures Cigarette and alcohol use, outcome by prescription regime and drug use. Summary There was a high rate of low birth-weight babies in both groups, which was not considered to be substantially related to prescribed dexamphetamine, as birth weights were very similar in those not prescribed dexamphetamine. There was no association demonstrated with duration of receipt of a maximum of 110 mg/day for 90 days. All participants underwent stabilisation (withdrawal assessed by AWQ), with the placebo group receiving increasing numbers of placebo capsules. At the end of the maintenance period, participants were tapered off the medication over one month in order to minimise any withdrawal symptoms experienced. Participants were followed up two months after completing treatment. Plus all participants received four sessions of CBT for amphetamine users.</td>
<td>Level IV – secondary data analysis using retrospective cohort with historical controls</td>
<td>Well-analysed retrospective cohort study but relied on record keeping of clinical records and some data were missing, although other data were considered reliable. The control or comparison group was opportunistic and not randomised.</td>
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<td>Merrill, J. et al. (2005). Dexamphetamine substitution as a treatment of amphetamine dependence: a two-centre randomised controlled trial. Drugs: Education, Prevention and Policy, 12(Suppl. 1): 94–97.</td>
<td>Dexamphetamine</td>
<td>59 dependent amphetamine users, 56% injectors; Males n=42 (71%); Mean age: not reported; Mean years of methamphetamine use: not reported; Mean use in last 7 days: 19.3 g; Randomised to dexamphetamine n=32 or best available treatment alone (BATA) n=27</td>
<td>Random assignment to dexamphetamine tablets up to 100 mg per day dispensed daily by a pharmacist (maintenance for four months, then taper for three months) plus best available treatment (BATA), or BATA alone. BATA consisted of providing literature on amphetamines; motivational interviewing (MI); drug use diary; discussion of cues, coping and lapse management; advice on healthy lifestyles; harm minimisation advice; referral for other supports; symptomatic prescribing for depression, anxiety and insomnia; and the possibility for inpatient detoxification if clinically indicated. After randomisation, participants received weekly clinical appointments for four weeks, then fortnightly until seven months (end of dex. prescribing period).</td>
<td>Measures: Standard questionnaires on drug use, physical and psychological health, social functioning and quality of life, offending behaviour, and satisfaction with treatment (no measure specified). Summary: There was no significant difference between groups on use measures with both groups reporting reductions and no difference in injecting behaviour between the groups. A trend toward the reduction of polydrug use and improvements in psychological health and significant improvement in the dexamphetamine group on physical health indicators.</td>
<td>Level II RCT. Blinding not reported</td>
<td>A well-designed trial but reporting was brief and lacked detail. Small sample size and no placebo control.</td>
</tr>
<tr>
<td>Shearer, J. et al. (2001). Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. Addiction, 96(9): 1289–1296.</td>
<td>Dexamphetamine</td>
<td>41 dependent amphetamine users; 32% homosexual or bisexual men; 95% injecting drug users; Males n=24 (83%); Mean age: 29 years; Mean years of methamphetamine use: 10 years; 31% shared injecting equipment in month prior to intake; Randomised to dex. plus counselling n=21 or counselling only n=20</td>
<td>All participants received psychological counselling. In addition, the treatment group were prescribed dexamphetamine to a maximum daily supervised oral dose of 60 mg. Induction began at 20 mg, increasing by 5 mg daily until a maximum dose was achieved. The dose was reduced in the final two weeks to a maximum dose of 40 mg at week 12.</td>
<td>Measures: Urine screens at baseline, 6 weeks and 12 weeks; self-reported amphetamine use (Opiate Treatment Index — OTI); Severity of Dependence Scale (SDS). Summary: Non-significant reductions in street amphetamine use and amphetamine dependence were observed in both groups. Treatment participants were significantly more likely to attend counselling. There was no significant difference between groups in amphetamine use. The severity of dependence reduced significantly more among the active treatment group compared with controls at post-treatment but not follow-up. There were no reports of adverse events.</td>
<td>Level II — double-blind RCT (pilot)</td>
<td>Well-conducted study with a small sample size and high drop-out and low medication adherence. A relatively large proportion of gay or bisexual men were included.</td>
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<td>White, R. (2000). Dexamphetamine substitution in the treatment of amphetamine abuse: an initial investigation. <em>Addiction</em>, 95(2): 229–238. United Kingdom</td>
<td>Dexamphetamine</td>
<td>The standardised records of 220 users receiving dexamphetamine prescriptions were examined retrospectively and cross-sectional socio-demographic data and longitudinal outcome data were obtained for 148 users.</td>
<td>Dexamphetamine was prescribed exclusively in elixir form. Initial dosing was based on self-reports of levels of use up to a maximum of 90 mg. The prescription was continued until street-use ceased. Injection sites were routinely counted.</td>
<td>Measures Ceasing illicit use; treatment retention. Summary Oral and injecting users had similar outcomes, with injecting users making more overall gains in treatment. Over half the injectors stopped injecting, more than one-third within two months of coming into treatment. Failure to stop injecting was related to shorter time in treatment. Variables predicting a good outcome differed between oral and intravenous users, although for both groups being female was associated with a slower change in drug-use behaviours, but a longer period in treatment. 13.6% (n=13) of injectors and 9.4% (n=5) of oral users relapsed into street-use after successfully stopping. Relapse occurred later with a median of 16.0 months for injecting users.</td>
<td>Level IV — secondary data analysis using retrospective cohort</td>
<td>Well-analysed, low-level retrospective cohort study.</td>
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<tr>
<td>Charnaud, B. &amp; Griffiths, V. (1998). Levels of intravenous drug misuse among clients prescribed oral dexamphetamine or oral methadone: a comparison. <em>Drug and Alcohol Dependence</em>, 52(1): 79–84. United Kingdom</td>
<td>Dexamphetamine</td>
<td>180 clients of a community drug treatment service in the UK who were injecting heroin or amphetamine on a daily basis for at least six months prior to receiving replacement pharmacotherapy Males n=52 (87%) (dexamphetamine), n=98 (82%) (methadone) Mean age: 28 years dexamphetamine (32 years methadone group) Median years of injecting methamphetamine: 7 years (9 years injecting heroin for methadone group) Mean use in last 30 days: not reported Either on methadone (n=120) or dexamphetamine elixir (n=60)</td>
<td>Dose usually calculated as 1 g street amphetamine to 20 ml dexamphetamine elixir – mean dose of dexamphetamine for the amphetamine sample was 43 ml (range 15–75 ml) vs mean dose of methadone of 44 ml (11–80 ml), at 1 mg per ml elixir (dex. dose negotiated with clients)</td>
<td>Measures Demographic characteristics, age of first drug use, duration of use, duration of treatment, psychotic episodes, and level of injecting at discharge (assessed by visual observation of injection sites). Summary There were no differences between groups at the beginning of treatment. There were no differences in outcomes between the groups, including injecting rates, median time in treatment, suggesting that amphetamine users on dexamphetamine maintenance did just as well as heroin users on methadone.</td>
<td>Level IV – retrospective chart review over two years (1995–96)</td>
<td>A well-conducted but low-level retrospective chart review using clinical, not standardised, outcome measures, but with real world application.</td>
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<td>Miles, S.W. et al. (2013).</td>
<td>Methylphenidate</td>
<td>79 dependent amphetamine/methamphetamine users n=41 from New Zealand (mainly smokers of methamphetamine) and n=38 from Finland (mainly injectors of amphetamine)</td>
<td>Methylphenidate (or a placebo equivalent) 18 mg daily for the first week, 36 mg daily for the second week, and 54 mg daily for 20 weeks until the end of the 22-week trial. Participants attended the clinics daily for dosing.</td>
<td>Measures&lt;br&gt;Urine drug screens for methamphetamine; previous and current substance use (Pompidou questionnaire); Severity of Dependence Scale (SDS); methamphetamine craving (visual analogue scale); alcohol use (Alcohol Use Disorders Identification Test – AUDIT); and adverse medication effects.</td>
<td>High-quality, well-designed and conducted trial. Findings limited by high attrition rate.</td>
<td>Double-blind placebo-controlled RCT</td>
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<tr>
<td>Tiihonen, J. et al. (2007).</td>
<td>Aripiprazole, methylphenidate</td>
<td>53 dependent amphetamine users</td>
<td>Aripiprazole 15 mg/day&lt;br&gt;Methylphenidate 18 mg/day for the first week, 36 mg/day for the second week, and 54 mg/day thereafter&lt;br&gt; Equivalent gel capsule placebo</td>
<td>Measures&lt;br&gt;The primary outcome measure was the proportion of amphetamine-positive urine samples during pharmacological treatment.</td>
<td>Level II – double-blind placebo-controlled randomised trial</td>
<td>A well-conducted study with ITT analysis but small sample size and high proportion of missing data for analysis.</td>
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### Modafinil

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Males n=124 (59%)  
Mean age: 39 years  
>18 days of methamphetamine use in past 30 n=125 (59.8%)  
Mean years of methamphetamine use: not reported  
Randomised to modafinil 200 mg daily (n=72), modafinil 400 mg daily (n=70), or placebo (n=68) | 12 weeks of medication: modafinil 200 mg/day, modafinil 400 mg/day, or placebo  
All participants received standardised 90-minutes of CBT group counselling three times per week for 12 weeks.  
All participants received one session of motivational enhancement at week 3. | Measures  
Methamphetamine non-use weeks assessed by urine samples for methamphetamine metabolites; abstinence at termination of treatment; Addiction Severity Index (ASI); Hamilton Depression Rating Scale (HAM–D); adverse events; Brief Substance Craving Scale; Clinical Global Impression Scale (CGI); HIV Risk-Taking Behaviour Scale.  
Summary  
Participants in all three groups had an increase in methamphetamine-free weeks over the duration of the study, with no differences between groups on methamphetamine non-use weeks overall or on maximum number of methamphetamine non-use days or on ‘terminal abstinence’ at the completion of the study as assessed by urine screens.  
Participants who were compliant with modafinil dosing had a longer duration of consecutive non-using days than less compliant participants and showed better study retention.  
No differences between groups for ASI, CGI, craving, or HIV risk-taking behaviours.  
Of the four serious adverse events that occurred during the study period, none was related to modafinil. | Level II — multi-site double-blind placebo-controlled randomised trial | High-quality study that was well conducted across eight sites and well reported. |
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<tr>
<td>Heinzerling, K.G. et al. (2010). Randomized, double-blind, placebo-controlled trial of modafinil for the treatment of methamphetamine dependence. Drug and Alcohol Dependence, 109(1–3): 20–29. United States of America</td>
<td>Modafinil</td>
<td>71 dependent methamphetamine users Males n=50 (70%) Mean age: 39.1 years Mean years of methamphetamine use: 15.6 years Mean use in last month: 9.4 days Randomised to modafinil n=34 or placebo n=37</td>
<td>Twelve weeks of medication: modafinil 200 mg per day (two 100 mg tablets per day taken in the morning) for the first three days of the study followed by an increase to 400 mg per day (four 100 mg tablets per day taken at one time in the morning) until the last three days of the trial, when the dose was titrated down to 200 mg per day for the final three days. Weekly individual CBT sessions during the medication phase of the study plus contingency management (vouchers for goods and services for methamphetamine-free urines ... the maximum that could be earned for providing methamphetamine- and metabolite-free urine samples at all visits throughout the entire study was $537 in vouchers).</td>
<td>Measures Urine samples collected three times a week; ASI-Lite to measure the severity of addiction-related problems in seven areas of functioning: medical; employment; drug use; alcohol use; legal; family/social; and psychiatric; Beck Depression Inventory (BDI); methamphetamine craving measured weekly using a visual analogue scale; pill count for medication adherence. Summary There were no differences between the groups on drug use, retention, depression or craving. There were no medication-related adverse events. Depressive symptoms decreased during the medication treatment period, but there were no significant differences between groups. Methamphetamine cravings decreased but there were no significant differences between groups. Participants in the modafinil group received on average $113 of the $537 possible from the contingency management intervention reinforcing methamphetamine-free urine drug screens, while participants in the placebo group received $139 (t=–0.70, d.f.=69, p=0.49). Participants with baseline high-frequency of methamphetamine use were more likely to have low CBT attendance in comparison with those with low-baseline methamphetamine use (x²=3.8, d.f.=69, p=0.05).</td>
<td>Level II — double-blind, placebo-controlled RCT</td>
<td>A well-conducted RCT with reasonable sample size, but low treatment completion (41% modafinil and 35% placebo). All groups participated in intensive behavioural interventions.</td>
</tr>
<tr>
<td>McElhiney, M.C. et al. (2009). Provigil (modafinil) plus cognitive behavioral therapy for methamphetamine use in HIV+ gay men: a pilot study. American Journal of Drug and Alcohol Abuse, 35(1): 34–37. United States of America</td>
<td>Modafinil</td>
<td>13 gay men n=11 (85%) HIV+ and n=7 with DSM–IV stimulant abuse (54%) and n=6 DSM–IV stimulant dependence (46%) Males n=13 (100%) Mean age: 38 (SD 6) years Mean years of methamphetamine use: not reported Mean estimated duration of abuse or dependence: 43 months Mean use in last 30 days: 12 days</td>
<td>Twelve weeks of modafinil followed by four weeks of placebo. Starting modafinil dose was 50 mg/day for those taking HIV antiretroviral medications and 100 mg/day for others. The dose was increased to 200 mg/day in the absence of clinical response and significant side effects. The 16-week therapy component started with two weeks of twice-weekly sessions with a motivational enhancement emphasis followed by weekly CBT sessions for the remaining 14 weeks.</td>
<td>Measures Urine drug screen; methamphetamine use self-report; Hamilton Rating Scale for Depression (HAM–D); University of Minnesota Cocaine Craving Scale; Obsessive Compulsive Drinking Scale adapted for methamphetamine. Summary Results are provided for completers only. Six of the 10 completers showed a greater than 50% reduction in methamphetamine days per week. The authors concluded that modafinil appeared to be more useful to patients with a diagnosis of abuse rather than dependence and may be most effective as a short-term abstinence-induction agent, which can then be discontinued. The addition of CBT to address sexual issues appears to promote treatment retention. Ten participants (77%) completed the 16-week trial.</td>
<td>Level III–3 — single blind within subjects pilot</td>
<td>Well conducted, a Level III pilot with small sample. Analysis of completers only. Small number of ATS-dependent participants. Low dose of modafinil compared to other studies.</td>
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<td>McGaugh, J. et al. (2009). Open-label pilot study of modafinil for methamphetamine dependence. <em>Journal of Clinical Psychopharmacology</em>, 29(5): 488–491. United States of America</td>
<td>Modafinil</td>
<td>Seven dependent methamphetamine users</td>
<td>Participants were started on modafinil 200 mg daily for the first three days, then increased to 400 mg daily. They were maintained on modafinil for five weeks and then observed for five days during week 6 after modafinil was discontinued. Weekly manual-driven, individualised CBT for relapse prevention plus contingency management with monetary rewards in exchange for returning medication blister packs, submitting urine samples thrice weekly for analysis, and attending cognitive behaviour therapy sessions.</td>
<td>Measures: Urine screen and vital sign measure three times a week; self-reported amphetamine use weekly using analogue scales; weekly Hamilton depression and anxiety scales (HAM–D/HAM–A), modafinil side effects checklist.</td>
<td>Level IV — open-label clinical trial without a control group</td>
<td>Well-conducted but small open-label study.</td>
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<tr>
<td>Shearer, J. et al. (2009). A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. <em>Addiction</em>, 104(2): 224–233. Australia</td>
<td>Modafinil</td>
<td>80 dependent methamphetamine users</td>
<td>Modafinil 200 mg/day dispensed weekly for 10 weeks using medication event monitoring system (MEMS) cap bottles to record unsupervised regimen adherence. All participants were offered a brief four-session cognitive behavioural intervention developed specifically for methamphetamine users.</td>
<td>Measures: Self-reported ATS use: The Opiate Treatment Index (OTI) and 28-day drug use diaries; Brief Symptom Inventory (BSI); Severity of Dependence Scale (SDS); methamphetamine craving in the past week on a 100-mm visual analogue scale (VAS); weekly urine specimens during treatment; adverse events.</td>
<td>Level II — double-blind placebo-controlled RCT (pilot)</td>
<td>Well-conducted study with a very high drop-out rate and low medication adherence. ITT analysis was used.</td>
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### Bupropion

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<td>Das, M. et al. (2010). Feasibility and acceptability of a phase II randomized pharmacologic intervention for methamphetamine dependence in high-risk men who have sex with men. AIDS, 24(7): 991–1000. United States of America</td>
<td>Bupropion</td>
<td>30 men dependent methamphetamine users who had anal sex with men in the past three months while using methamphetamine (43% HIV+)</td>
<td>Bupropion 150 mg and matching placebo taken daily for one week, increased to 300 mg from week 2 to week 12, plus weekly 30-min. CBT/MI counselling sessions for methamphetamine use, plus medication adherence counselling by the study clinician (frequency not reported, but possibly one-off)</td>
<td>Medication adherence – MEMS caps, self-reported adherence using the 4-day Structured Self-Report; medication safety – weekly self-report, symptom-driven physical exams and safety laboratory monitoring were done at weeks 4, 8, and 12 and classified according to Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences for HIV Prevention Trials Network. Drug use, risks, depression using audio computer-assisted self-interview (ACASI) – frequency and route of administration of methamphetamine and other drug use; AOD treatment; Severity of Dependence Scale (SDS); Center for Epidemiologic Studies Depression Rating Scale (CES–D); sexual risk behaviour; reasons for non-adherence; attitudes about trial participation.</td>
<td>Level II – double-blind placebo-controlled RCT (feasibility pilot)</td>
<td>A well-conducted pilot study. Small sample size. Good study completion rates, but low to moderate medication adherence. Low phone pre-screen to randomisation rate (9%), but 56% for those assessed in person.</td>
</tr>
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</table>

**Measures**

- Medication adherence – MEMS caps, self-reported adherence using the 4-day Structured Self-Report; medication safety – weekly self-report, symptom-driven physical exams and safety laboratory monitoring were done at weeks 4, 8, and 12 and classified according to Division of AIDS (DAIDS) Table for Grading Severity of Adult Adverse Experiences for HIV Prevention Trials Network. Drug use, risks, depression using audio computer-assisted self-interview (ACASI) – frequency and route of administration of methamphetamine and other drug use; AOD treatment; Severity of Dependence Scale (SDS); Center for Epidemiologic Studies Depression Rating Scale (CES–D); sexual risk behaviour; reasons for non-adherence; attitudes about trial participation.

**Summary**

- Both groups showed improvements on all measures. There was no significant difference between the two groups in treatment completion, self-reported medication adherence (both groups over-estimated their medication adherence on self-report), reduction in methamphetamine-metabolite positive urine drug screens, sexual risk-taking behaviours, or depression. There were no serious adverse events from the medications. Ninety-six per cent of participants were highly satisfied or satisfied with study participation. Authors conclude that the study demonstrates the feasibility of enrolling and retaining a typically hard-to-engage group of methamphetamine users into treatment.

- Ninety per cent completed the trial: 89% of monthly ACASIs were completed; 81% of study visits were attended; and 81% of urine samples were collected. Adherence by MEMS cap was 60% and by self-report was 81% and did not differ significantly by treatment assignment.

- The median number of positive urine samples was 5.5 out of a possible 11 (50%). Participants in both arms reported similar non-significant decline in the median number of sex partners.

- No serious adverse events occurred and there were no significant differences in adverse events by treatment assignment.
### Medication Treatment Options for Amphetamine-Type Stimulant Users

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medicine</th>
<th>Number and Description of Participants</th>
<th>Intervention and Comparison if Relevant</th>
<th>Primary Outcomes including Measures Used</th>
<th>Level of Evidence</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elkashef, A.M. et al. (2008) Bupropion for the treatment of methamphetamine dependence. <em>Neuropsychopharmacology</em>, 33(5): 1162–1170. United States of America</td>
<td>Bupropion</td>
<td>151 dependent methamphetamine users: Males n=101 (67%); Mean age: 36 years; Mean years of use: 10.19 years; Mean use in last month: ≤18 days n=71 (47%); and &gt;18 days n=80 (53%); Randomised to bupropion n=79 or placebo n=72</td>
<td>Film-coated sustained-release bupropion 150 mg or matched placebo once daily for three days, then 300 mg daily (one tablet twice a day) for 11 weeks, then dose was reduced to 150 mg daily on the last three days of the 12-week treatment period</td>
<td>Measures: Percentage of abstinence was measured by urine drug screens three times a week for methamphetamine; Brief Substance Craving Scale (BSCS); Hamilton Depression Scale (HAM–D); Timeline follow-back; Addiction Severity Index (ASI–Lite); adherence was assessed by weekly tablet count. <strong>Summary:</strong> There was no significant difference between groups on probability of a non-use week, but subgroup analysis showed that bupropion had a significant effect, compared to placebo, among male patients who had a lower level of methamphetamine use at baseline. The authors concluded that bupropion, in combination with behavioural group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence in male patients.</td>
<td>Level II – double-blind placebo-controlled RCT</td>
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<tr>
<td>McCann, D.J. &amp; Li, S-H. (2012). A novel, nonbinary evaluation of success and failure reveals bupropion efficacy versus methamphetamine dependence: reanalysis of a multisite trial. <em>CNS Neuroscience and Therapeutics</em>, 18(5): 414–418. (Also see Elkashef et al. 2008 above for original data analysis.) United States of America</td>
<td>Bupropion</td>
<td>151 dependent methamphetamine users: Males n=101 (67%); Mean age: 36 years; Mean years of methamphetamine use: 10.42 years; Mean use in last 30 days: 17 days; Randomised to bupropion (n=79) or placebo (n=72)</td>
<td>Sustained-release bupropion 150 mg and matched placebo. Participants received doses of bupropion 150 mg SR or placebo, once daily for three days, then increased to 300 mg daily (one tablet twice a day) for about 11 weeks of treatment, until the final dose taper. The dose was reduced to 150 mg daily on the last three days of the 12-week treatment period. Adherence was assessed by weekly tablet count.</td>
<td>Measures: Primary outcome assessment was urine drug screens three times per week; Brief Substance Craving Scale (BSCS); Hamilton Depression Scale (HAM–D); self-report of methamphetamine use (TLFB); Addiction Severity Index (ASI–Lite). <strong>Summary:</strong> This study re-analysed data from Elkashef et al. 2008. The original study failed to demonstrate an effect for bupropion, but found some subgroups benefited from bupropion. The current paper used a different method of analysis to demonstrate a positive effect of bupropion based on FDA evaluations of medicine to treat alcohol and tobacco dependence. Throughout the course of the study, the success rate in the bupropion group seemed to increase in a biphasic fashion, with a plateau at 11% (9/79) from study weeks 4–6, which then increased steadily to 20% (16/79). In the placebo group, only 7% (5/72) were able to achieve two or more weeks of EDOSA. Of the 16 treatment participants who did attain two or more weeks of methamphetamine abstinence during the trial (range 2–12 weeks during the trial, the only factor that was significantly associated with a ‘successful outcome’ with bupropion treatment was the self-reported level of methamphetamine use during the 30 days immediately before screening; the proportion of ‘treatment successes’ reporting 18 days or less of baseline methamphetamine use (69%) was significantly greater than the proportion of treatment failures reporting this level of baseline use (40%; P=0.04).</td>
<td>Level II – double-blind, placebo-controlled RCT</td>
<td>Complex reanalysis of a well-conducted, double-blind RCT (Elkashef et al. 2008). Criteria for success have limited clinical application.</td>
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<tr>
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<tr>
<td>Shoptaw, S. et al. (2008). Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. <em>Drug and Alcohol Dependence</em>, 96(3): 222–232. United States of America</td>
<td>Bupropion</td>
<td>73 dependent methamphetamine users recruited from three sites, predominantly smokers of methamphetamine (64%) Males n=22 (61%) Mean age: 34.6 years Mean years of methamphetamine use: 9.6 years Mean use in last 30 days: 15.6 days Randomised to bupropion (n=36) or placebo (n=37)</td>
<td>Slow-release bupropion 150 mg (or placebo) per day for days 1–3 of the first week followed by an increase to 300 mg per day (one 150 mg capsule taken twice daily) until week 12 when the dose was decreased to 150 mg of bupropion SR for the last three days Weekly individual CBT sessions for 12 weeks Non-cash vouchers for methamphetamine-free urine screens (max. value $537)</td>
<td>Measures Methamphetamine use as assessed via urine drug screens; treatment retention; depressive symptoms (Beck Depression Inventory — BDI); methamphetamine cravings (visual analogue scale); and adverse events. Summary There were no significant effects for bupropion relative to placebo on methamphetamine use verified by urine drug screens, for reducing the severity of depressive symptoms or methamphetamine cravings, or on study retention. In a post hoc analysis, there was a statistically significant effect of bupropion treatment on methamphetamine use and completion rates among participants with lighter (0–2 methamphetamine-positive urines), but not heavier (3–6 methamphetamine-positive urines) use at baseline. Bupropion treatment was also associated with significantly reduced cigarette smoking, by almost five cigarettes per day. No significant differences in depression scores, which decreased among both groups. No significant differences in methamphetamine craving, which decreased among both groups. No differences in the number of counselling sessions attended (5/12 for bupropion, 4/12 for placebo). No treatment-related serious adverse effects.</td>
<td>Level II — double-blind placebo-controlled RCT</td>
<td>High-quality well-conducted trial, but low completion rates (around 35%).</td>
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### Naltrexone

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<th>Quality assessment</th>
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<tbody>
<tr>
<td>Grant, J.E. et al. (2010). A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. European Neuropsychopharmacology, 20(11): 823–828. United States of America</td>
<td>N-acetyl cysteine (NAC) plus naltrexone</td>
<td>31 dependent methamphetamine users Males n=22 (71%) Mean age: 36.6 years Mean age first used methamphetamine: 24.2 years Mean years of methamphetamine use: not reported Mean days used methamphetamine in past two weeks: 7.18 days Randomised to NAC + naltrexone (n=14) or NAC + placebo (n=17)</td>
<td>600 mg/day NAC plus 50 mg/day naltrexone for two weeks, then 1200 mg/day NAC plus 100 mg/day naltrexone for two weeks, and 1800 mg/day NAC plus 150 mg/day naltrexone for two weeks, and to 2400 mg/day NAC plus 200 mg/day naltrexone for the final two weeks</td>
<td>Measures Penn Craving Scale; frequency of methamphetamine use; urine drug screen; Clinical Global Impression (Severity) scale (CGI); Hamilton Rating Scale for Depression (HAM–D); Hamilton Rating Scale for Anxiety (HAM–A); Sheehan Disability Scale (SDS); the Quality of Life Inventory (QoL).</td>
<td>Level II – double-blind, placebo-controlled RCT (pilot)</td>
<td>A well-conducted pilot study. Small sample size and high drop-out.</td>
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</tbody>
</table>

| Jayaram-Lindström, N., Wennberg, P., Beck, O. & Franck, J. (2005). An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. Nordic Journal of Psychiatry, 59(3): 167–171. Sweden | Naltrexone | 20 dependent methamphetamine users who had used amphetamine at least 12 days in the last 12 weeks Males n=13 (65%) Mean age: not reported Mean years of methamphetamine use: not reported Mean use in last month: not reported | 50 mg naltrexone daily, dispensed weekly for 12 weeks, plus 30 mins weekly of manual-driven individualised CBT for relapse prevention | Measures Self-reported amphetamine use (TLFB); Craving Visual Analog Scale (VAS); weekly urine screen for illicit drugs and naltrexone; tolerability of naltrexone — adverse events (AE) blood samples weeks 4, 8 & 12; adherence — self-report; pill counts; urine screen for naltrexone metabolites; number of treatment days attended. | Level IV – open-label clinical trial without control group (feasibility) | Well-conducted feasibility trial, but small sample size and high drop-out. |

| Jayaram-Lindström, N. et al. (2008) Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. American Journal of Psychiatry, 165(11): 442–448. Sweden | Naltrexone | 80 dependent amphetamine users Males n=63 (79%) Mean age: 39.4 years Mean years of methamphetamine use: 10.19 years Mean use in last month: not reported Mean days of amphetamine use in last 12 weeks: 45.4 days Randomised to naltrexone n=40, placebo n=40 | 50 mg naltrexone daily for 12 weeks and matching placebo, plus 60 mins of individual manualised CBT-based relapse prevention weekly | Measures Urine drug screens; Addiction Severity Index (ASI); self-reported amphetamine use (TLFB); Craving Visual Analog Scale (VAS); and medication adverse events. | Level II – double-blind, placebo-controlled RCT | Well-conducted study with good sample size but moderately high drop-out. |
### Antipsychotics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medicine</th>
<th>Number and description of participants</th>
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<th>Primary outcomes including measures used</th>
<th>Level of evidence</th>
<th>Quality assessment</th>
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</thead>
<tbody>
<tr>
<td>Coffin, P.O. et al. (2013). Aripiprazole for the treatment of methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. <em>Addiction</em>, 108(4): 751–761. United States of America</td>
<td>Aripiprazole</td>
<td>90 dependent methamphetamine users Males n=79 (87.8%) Mean age: 38.7 years Frequency of methamphetamine in past 4 weeks: daily n=19 (21%); 3–6 days week n=43 (47.8%); 2 days or less n=28 (31.1%) Mean years of methamphetamine use: not reported</td>
<td>Participants started on 1 mg nightly (one dose before sleeping) with dose escalation over four days to 4 mg nightly (or highest tolerated dose). Participants attended weekly visits with a study psychiatrist and remained on risperidone for four weeks. The dose of risperidone was decreased if intolerable side effects occurred.</td>
<td>Measures Urine drug screens for methamphetamine; medication adherence (self-report and medication event monitoring system); sexual risk-taking behaviour; methamphetamine craving; Severity of Dependence Scale (SDS). Summary Both groups reduced methamphetamine use, sexual risk taking, craving and severity of dependence. Aripiprazole was not superior to placebo in reducing methamphetamine use or any of the other measures. Aripiprazole participants reported more akathisia, fatigue and drowsiness than placebo. Adherence by MEMS and self-report was low at 42% and 74% respectively, but not significantly different; 78% of weekly substance use counselling sessions (839 out of 1080) were completed (aripiprazole 76% (408 sessions), placebo 80% (431 sessions); p=0.11).</td>
<td>Level II – double-blind placebo-controlled randomised trial</td>
<td>Well-conducted and -reported double-blind RCT with good retention but fairly low medication adherence.</td>
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<tr>
<td>Meredith, C. et al. (2007). An open-label pilot study of risperidone in the treatment of methamphetamine dependence. <em>Journal of Psychoactive Drugs</em>, 39(2): 167–172. United States of America</td>
<td>Risperidone</td>
<td>11 dependent methamphetamine users Males n=10 (90.9%) Mean age: 42 years Mean years of methamphetamine use: 8.5 (6.3) years Mean use in last 30 days: 9.9 (7.6) days</td>
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<td>Measures Clinical charts, which included demographics, medical and substance abuse history, and medications; weekly measures of vital signs monitored urine drug screen, self-reports of substance use, reports of adverse events and concomitant medication use; Brief Symptom Inventory (BSI), a neuropsychological testing battery that assessed a range of functions including speed of information processing learning and memory, executive functioning and abstraction, language and verbal fluency, and psychomotor function. Summary Risperidone was well tolerated and treatment completers showed significant reduction in days of methamphetamine use. It is possible that treatment effects may have occurred due to the increased access and support as a result of participation in the study itself rather than the risperidone. This makes it difficult to draw clear conclusions about the efficacy of risperidone in this population. Participants continued with psychological therapy during the study. Participants completing the study had a final mean daily risperidone dose of 3.6 mg (SD=0.52).</td>
<td>Level IV – open-label clinical trial without a control group</td>
<td>A well-conducted low-level study. Limitations of this study include a small sample size, lack of control group and short-term follow-up timeframe.</td>
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<tr>
<td>Meredith, C.W. et al. (2009).</td>
<td>Risperidone</td>
<td>34 dependent methamphetamine</td>
<td>Participants entered a seven-day open-</td>
<td>Measures</td>
<td>Level IV — open-label clinical trial without a control group</td>
<td>A well-conducted but low-level study. There were difficulties with retention and though numbers were higher at the commencement, the final N is small.</td>
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<td>users entered the study, 22 received</td>
<td>label run-in with oral risperidone</td>
<td>At screening, all participants received a complete medical history, physical examination and routine laboratory tests, and serum prolactin levels. In addition: Structured Clinical Interview; 60-day timeline follow-back interview to quantify self-reported methamphetamine and other substance use over the prior 60 days; a neurocognitive test battery; Addiction Severity Index (ASI); Brief Symptom Inventory (BSI); Barnes Akathisia Scale; Simpson–Angus Scale; and the Abnormal Involuntary Movement Scale were administered to assess movement disorders.</td>
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<td>injectable risperidone</td>
<td>Those who tolerated oral risperidone</td>
<td>Summary</td>
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<td>Males n=19 (86.4%)</td>
<td>(n=22) were started on</td>
<td>No serious adverse events occurred. Methamphetamine used was significantly reduced among those who received injections. Improvements were seen in verbal memory and psychiatric symptoms.</td>
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<td>Mean age: 38 years</td>
<td>long-acting injectable</td>
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<td>Mean years of methamphetamine</td>
<td>risperidone 25 mg intramuscular</td>
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<td></td>
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<td>use: 12.2 years</td>
<td>medication with subsequent injections</td>
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<td>Mean use in last 30 days: 17.1 days</td>
<td>every two weeks to a total of</td>
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<td>four injections.</td>
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<td>Participants remained on</td>
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<td>oral risperidone during the first three weeks after initial injection.</td>
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<td>Participants were offered eight weekly individual sessions of relapse prevention counselling.</td>
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<tr>
<td>Tiihonen, J. et al. (2007).</td>
<td>Aripiprazole, methylphenidate</td>
<td>53 dependent amphetamine users</td>
<td>Aripiprazole 15 mg/day</td>
<td>Measures</td>
<td>Level II — double-blind placebo-controlled randomised trial</td>
<td>A well-conducted study with ITT analysis but small sample size and high proportion of missing data for analysis.</td>
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<td></td>
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<td>Males n=36 (68%)</td>
<td>Methylphenidate 18 mg/</td>
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<td>Mean age: 32.2 years</td>
<td>day for the first week,</td>
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<td>Mean years of methamphetamine</td>
<td>36 mg/day for the second week,</td>
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<td>use: approx. 14 years</td>
<td>and 54 mg/day thereafter</td>
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<td>Randomised to aripiprazole (n=19),</td>
<td>Equivalent gel capsule placebo</td>
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<td></td>
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<td>methylphenidate (n=17) or placebo</td>
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<td>(n=17)</td>
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### Anticonvulsants

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<tr>
<td>Elkashef, A. et al. (2012). Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. <em>Addiction</em>, 107(7): 1297–1306. United States of America</td>
<td>Topiramate</td>
<td>140 dependent methamphetamine users Males n=89 (64%). Mean age: 38 years Mean years of use: not reported Mean use in last month: 21.3 days Randomised to topiramate (n=69) or placebo (n=71)</td>
<td>Oral topiramate or placebo was initiated at 25 mg/day and escalated over the first 35 days of the study up to 200 mg/day or the maximum tolerable dose was achieved. Over weeks 6–12, this dose was maintained. Daily dose could be reduced once during maintenance, to the highest previously tolerated dose. Only those tolerating &gt;50 mg/day were included. Over the last week of treatment (week 13), the dose was tapered to 100 mg/day for three days, 50 mg/day for two days and then 25 mg/day for two days. Medication adherence was measured by pill count. All participants received weekly brief behavioural compliance enhancement treatment (BBCET), a manualised, low-intensity supportive program to promote medication adherence and retention.</td>
<td>Measures Primary outcome assessment: urine drug screens three times a week for % of abstinence. Secondary assessments: Clinical Global Impression Scale – Observer (CGI–O) and Self (CGI–S); Brief Substance Craving Scale (BSCS); Addiction Severity Index (ASI–Lite); Montgomery–Asberg Depression Rating Scale; drug use self-report; medication adherence by pill count.</td>
<td>Level II – double-blind multi-site placebo-controlled RCT</td>
<td>A well-conducted multi-site RCT. Low completion rate (55%), and ITT analysis conducted but conclusions based on completers.</td>
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### Medication treatment options for amphetamine-type stimulant users

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<tr>
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<th>Quality assessment</th>
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<tr>
<td>Heinzerling, K.G. et al. (2006). Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. <em>Drug and Alcohol Dependence, 85</em>(3): 177–184. United States of America</td>
<td>Baclofen and gabapentin</td>
<td>88 dependent methamphetamine users Males n=61 (69%) Mean age: 32 years Mean years of methamphetamine use: 9.5 years Mean use in last month: approx. 15 days Randomised to baclofen (n=25), gabapentin (n=26) and placebo (n=37)</td>
<td>Baclofen 10 mg three times per day (tid) for days 1–3 of the first week followed by 20 mg tid until week 16 when the dose was decreased to 10 mg tid for the last three days Or gabapentin 400 mg tid for days 1–3 of the first week followed by 800 mg tid until week 16 when the dose was decreased to 400 mg tid for the last three days Medication was dispensed in blister packages. First dose was taken under supervision of the study physician and then were dispensed a one-week supply of medication in blister packages. All participants received a standard manual-driven psychosocial counselling program, consisting of thrice-weekly, 90-min. relapse prevention group sessions.</td>
<td>Measures Urine samples collected three times a week; ASI–Lite to measure the severity of addiction-related problems in seven areas of functioning; medical, employment, drug use, alcohol use, legal, family/social, and psychiatric; Beck Depression Inventory (BDI); methamphetamine craving measured weekly using a visual analogue scale; pill count for medication adherence. Summary There were no significant main effects for baclofen or gabapentin in reducing methamphetamine use, craving or retention. For baclofen, but not gabapentin, participants who reported taking a higher percentage of study medication showed significant reductions in use compared to placebo. No differences in medication taken or psychosocial sessions attended. Attendance at counselling sessions, lower depression symptoms and less severe baseline methamphetamine use were significantly associated with a higher probability of providing a methamphetamine-free urine sample during the treatment period, but no difference between groups. The authors concluded that gabapentin does not appear to be effective in treating methamphetamine dependence but baclofen may have a small treatment effect relative to placebo, but the short half-life of baclofen may limit its use as an anti-craving agent for methamphetamine-dependent individuals.</td>
<td>Level II – double-blind, placebo-controlled RCT</td>
<td>A well-conducted study, but drop-out high and variable (Baclofen 60% completion, gabapentin 35% completion, and placebo 40% completion).</td>
</tr>
<tr>
<td>Brodie, J.D. et al. (2005). Safety and efficacy of gamma vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. <em>Synapse, 55</em>(2): 122–125. United States of America</td>
<td>Vigabatrin (Gamma Vinyl GABA (GVG))</td>
<td>30 participants: n=27 methamphetamine-dependent entered and 18 completed the study; 17 participants were also cocaine-dependent Males n=29 (96%) Mean age: not reported Mean years of methamphetamine use: 12.8 years Mean daily reported use of nearly 1 g of methamphetamine for 12 years</td>
<td>Vigabatrin was initiated at 500 mg twice daily for three days, then 1.5 g/day for the next four days and 2 g/day for the next week. On day 15, participants were placed on 3 g/day, maintained at that dose for the next 28 days, and then tapered to zero over the next three weeks. Completers received a cumulative dose of 137 g. All participants were encouraged to participate in weekly group therapy (no indication of how many did participate).</td>
<td>Measures Urine samples twice a week; daily vital signs. Summary At this dose GVG did not produce any visual field defects or alterations in visual acuity or changes in vital signs even with continued use of methamphetamine and cocaine. The authors concluded that vigabatrin is safe to use with methamphetamine and cocaine users. Completers reported increased appetite and showed a significant weight gain over non-completers. Based on urine samples taken under supervision, completers were methamphetamine- and cocaine-free for four consecutive weeks (no slips) while two were never drug-free although use was markedly reduced by self-report. The mean drug-free interval was 40.1 +/- 2.4 consecutive days with an average use of 0.03 +/- 0.02 g/day over the last three weeks of the study. The median onset time to the first day drug-free was 10 days.</td>
<td>Level IV – open-label safety trial</td>
<td>Well-conducted, briefly reported open-label study, but with high drop-out and no control group. Outcome data were not reported separately for amphetamine users.</td>
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### Appendix: Summary tables

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<tr>
<th>Outcome data</th>
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<tr>
<td>No significant main effects for baclofen or gabapentin in reducing methamphetamine use, craving or retention. For baclofen, but not gabapentin, participants who reported taking a higher percentage of study medication showed significant reductions in use compared to placebo. No differences in medication taken or psychosocial sessions attended. Attendance at counselling sessions, lower depression symptoms and less severe baseline methamphetamine use were significantly associated with a higher probability of providing a methamphetamine-free urine sample during the treatment period, but no difference between groups. The authors concluded that gabapentin does not appear to be effective in treating methamphetamine dependence but baclofen may have a small treatment effect relative to placebo, but the short half-life of baclofen may limit its use as an anti-craving agent for methamphetamine-dependent individuals.</td>
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<td>Measures Urine samples collected three times a week; ASI–Lite to measure the severity of addiction-related problems in seven areas of functioning; medical, employment, drug use, alcohol use, legal, family/social, and psychiatric; Beck Depression Inventory (BDI); methamphetamine craving measured weekly using a visual analogue scale; pill count for medication adherence. Summary There were no significant main effects for baclofen or gabapentin in reducing methamphetamine use, craving or retention. For baclofen, but not gabapentin, participants who reported taking a higher percentage of study medication showed significant reductions in use compared to placebo. No differences in medication taken or psychosocial sessions attended. Attendance at counselling sessions, lower depression symptoms and less severe baseline methamphetamine use were significantly associated with a higher probability of providing a methamphetamine-free urine sample during the treatment period, but no difference between groups. The authors concluded that gabapentin does not appear to be effective in treating methamphetamine dependence but baclofen may have a small treatment effect relative to placebo, but the short half-life of baclofen may limit its use as an anti-craving agent for methamphetamine-dependent individuals.</td>
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<tr>
<td>Level II – double-blind, placebo-controlled RCT</td>
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<td>A well-conducted study, but drop-out high and variable (Baclofen 60% completion, gabapentin 35% completion, and placebo 40% completion).</td>
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## Antidepressants

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<th>Reference</th>
<th>Medicine</th>
<th>Number and description of participants</th>
<th>Intervention and comparison if relevant</th>
<th>Primary outcomes including measures used</th>
<th>Level of evidence</th>
<th>Quality assessment</th>
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<tbody>
<tr>
<td>Batki, S.L. et al. (1999).</td>
<td>Fluoxetine</td>
<td>60 dependent methamphetamine users Gay bisexual n=21 (50%), HIV+ n=9 (15%) Males n=42 (70%) Mean age: 35 years Mean years of methamphetamine use: 7.4 years Mean days per week methamphetamine use: 2.6 days Mean amount methamphetamine used per week: 2.4 g Randomised to fluoxetine (n=30) daily or placebo (n=30)</td>
<td>One week single-blind placebo lead-in followed by seven weeks of double-blind fluoxetine 40 mg daily or placebo</td>
<td>Measures Methamphetamine craving; self-reported methamphetamine use; urine screens for methamphetamine. Summary Methamphetamine use declined in both groups. Craving was lower in active treatment group but no other significant differences between the groups on self-reported methamphetamine use or in methamphetamine urine screens for the 30 participants for whom data were available at the time of reporting. No adverse events data reported.</td>
<td>Level II – double-blind placebo-controlled pilot RCT</td>
<td>Preliminary data only reported in the conference proceedings. No detailed report of the data was published subsequently.</td>
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<td>Colfax, G.N. et al. (2011).</td>
<td>Mirtazapine</td>
<td>60 dependent methamphetamine users who were sexually active MSM Those with major depression or antidepressant use in last four weeks, and HIV-positive men with a CD4 cell count below 200/μL, were excluded. Males n=60 (100%) Mean age: 40.5 years Mean years of use: not reported Mean use in last month: 60% used more than 3 times a week, n=10 used (17% daily) Randomised to mirtazapine (n=30) or placebo (n=30)</td>
<td>Gel capsules containing either mirtazapine or placebo were administered: 1 capsule (15 mg) nightly for one week, and then 2 capsules (30 mg) nightly for 11 weeks. All participants were offered weekly 30-minute substance use CBT and MI-based counselling.</td>
<td>Measures Primary outcome was reduction in methamphetamine metabolite-positive urine test results. Secondary outcomes were study medication adherence and sexual risk behaviour. Summary Mirtazapine group significantly decreased methamphetamine use and sexual risk-taking behaviours. Participants assigned to the mirtazapine group had significantly fewer methamphetamine-positive urine test results compared to the placebo group. The number needed to achieve a negative weekly urine test result was 3.1. Adherence was 48.5% by medication event monitoring systems and 74.7% by self-report; adherence was not significantly different between arms. Sexual risk behaviours decreased significantly more among the mirtazapine group (number of male partners with whom methamphetamine was used, number of male partners, episodes of anal sex with serodiscordant partners, episodes of unprotected anal sex with serodiscordant partners, episodes of insertive anal sex with serodiscordant partners). There were no serious adverse events related to study drug or significant differences in adverse events by arm.</td>
<td>Level II – double-blind placebo-controlled RCT</td>
<td>Well-conducted and reported study with good retention rates, but moderate to low medication adherence. ++</td>
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<td>Shoptaw, S. et al. (2006). Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence, Drug and Alcohol Dependence, 85(1): 12–18. United States of America</td>
<td>Sertraline</td>
<td>229 participants with a diagnosis of methamphetamine abuse or dependence (n=227 dependent) Males n= (60%) Mean age: 33 years Mean years of methamphetamine use: 9.3 years Mean use in last 30 days: approx. 13 days Randomised to sertraline plus CM (n=61), sertraline-only (n=59), placebo plus CM (n=54), or placebo-only (n=55)</td>
<td>Sertraline or placebo at 50 mg/day at randomisation. On the eighth day following randomisation, dose was increased to 50 mg twice daily maintained for the 12-week duration of the trial. Contingency management participants observed urine samples on Mondays, Wednesdays and Fridays. Samples free of methamphetamine metabolites qualified for a voucher (from US$2.50), which became increasingly valuable (by US$1.25) with US$10 bonus voucher each third metabolite-free urine sample. Plus all participants received 90-min. Matrix Model relapse prevention groups three times per week.</td>
<td>Measures Methamphetamine use (urine screen); retention in treatment; craving for methamphetamine (visual analogue scale); depression (BDI); and adherence to study medication (pill count, adverse events). Summary No statistically significant main or interaction effects for sertraline or CM in reducing methamphetamine use were observed using a generalised estimating equation (GEE), although post hoc analyses showed the sertraline-only condition had significantly poorer retention than other conditions ($\chi^2(3) = 8.40, p &lt;0.05$). Sertraline conditions produced significantly more adverse events than placebo conditions. A significantly higher proportion of participants in CM conditions achieved three consecutive weeks of methamphetamine abstinence than those in non-CM conditions. More participants in the sertraline condition increased methamphetamine use during treatment (n=13) than in the placebo condition. Drop-outs: sertraline plus CM (30/61), sertraline-only (15/59), placebo plus CM (24/54), or placebo-only (22/55). Drop-outs NS between groups, however sertraline-only participants were retained in treatment for significantly less time than participants in all other treatment conditions ($\chi^2(3) = 8.40, p &lt;0.05$).</td>
<td>Level II – double-blind placebo-controlled RCT</td>
<td>High-quality well-conducted trial, but low completion rates (around 50%).</td>
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<tr>
<td>Zorick, T. et al. (2011). Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine, Drug and Alcohol Dependence, 113(2–3): 500–503. United States of America</td>
<td>Sertraline</td>
<td>229 participants with a diagnosis of methamphetamine abuse or dependence (n=227 dependent) Males n= (60%) Mean age: 33 years Mean years of methamphetamine use: 9.3 years Mean use in last 30 days: approx. 13 days Randomised to sertraline plus CM (n=61), sertraline-only (n=59), placebo plus CM (n=54), or placebo-only (n=55)</td>
<td>Sertraline or placebo at 50 mg/day at randomisation. On the eighth day following randomisation, dose was increased to 50 mg bid maintained for the 12-week duration of the trial. Participants receiving contingency management observed urine samples on Mondays, Wednesdays and Fridays. Samples that did not contain metabolites of methamphetamine qualified participants for a voucher (from US$2.50) which became increasingly valuable (by US$1.25) with US$10 bonus voucher each 3rd metabolite-free urine sample. Plus all participants received 90-min. Matrix Model relapse prevention groups three times per week.</td>
<td>Measures Increase in methamphetamine use &gt;15% during the last month of treatment in the trial, participant-level factors associated with this increase. Summary More participants in the sertraline condition increased methamphetamine use during treatment (n=13) than in the placebo condition (n=5; p=0.03). The study looked at multiple factors from both pre-treatment and in-treatment data that were associated with increased methamphetamine use during treatment. Elevated in-treatment craving for methamphetamine specifically characterised participants in the sertraline group who increased their methamphetamine use.</td>
<td>Level II – double-blind placebo-controlled RCT</td>
<td>Re-analysis of Shoptaw (2006). High-quality well-conducted trial, but low completion rates (around 50%).</td>
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### Flumazenil and Gabapentin Combination

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<th>Quality assessment</th>
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<tr>
<td>Ling, W. et al. (2012). Double-blind placebo-controlled evaluation of the PROMETA™ protocol for methamphetamine dependence. <em>Addiction</em>, 107(2): 361–369. United States of America</td>
<td>Prometa™ protocol (flumazenil and gabapentin)</td>
<td>120 dependent methamphetamine users Males n=89 (80%) Mean age: 38.5 years Mean use in past 30 days: approx. 17.5 days Mean years of methamphetamine use: approx. 10 years Randomised to flumazenil/gabapentin/hydroxyzine (n=60) or placebo (with hydroxyzine) (n=60)</td>
<td>Flumazenil 2 mg infusion on days 1, 2, 3, 22 and 23 (or matched saline infusion). On day 1, participants began gabapentin or placebo, increasing by one capsule (300 mg) per day to reach the maximum dose of 1200 mg on study day 4. Down-titration began on study day 38 with the final gabapentin or placebo dose on day 40. As hydroxyzine is not considered the key element of the Prometa protocol, all participants received active hydroxyzine in order to reduce the anxiety that might be experienced during the medical procedures, and to assist with sleep. Participants in both active treatment and placebo groups were administered a 50 mg dose of oral hydroxyzine, with 50 mg take-home hydroxyzine to day 10 prior to each infusion on days 1, 2, 3, 22 and 23. All participants received weekly individual CBT-based relapse prevention sessions (up to n=14).</td>
<td>Measures&lt;br&gt;Percentage of urine samples testing negative for methamphetamine during the trial (collected at every clinic visit); self-reported drug use; Brief Symptom Craving Scale (BSCS); retention measured by the number of days between the first infusion and the last clinic visit. Summary&lt;br&gt;No effect of the protocol over placebo on measures of methamphetamine use, craving or retention in treatment. All participants improved over the trial. There was a three- to four-fold reduction in the number of days of self-reported methamphetamine use in the past 30 days from baseline. No significant difference between the groups in CBT session attendance: the experimental group attended a mean of 2.95 sessions; and the placebo group attended a mean of 2.86 sessions. The investigators concluded that, in comparison to positive outcomes from another recent trial of the protocol, their null findings may have been influenced by a strong placebo effect due to considerable publicity about the protocol.</td>
<td>Level II — double-blind, placebo-controlled RCT</td>
<td>A high-quality, well-designed and conducted double-blind RCT. Adequate sample but high drop-out rate, especially in the treatment group, and large numbers adverse events.</td>
</tr>
<tr>
<td>Urschel, H.C. et al. (2007). Open-label study of a proprietary treatment program targeting type A γ-aminobutyric acid receptor dysregulation in methamphetamine dependence. <em>Mayo Clinic Proceedings</em>, 82(10): 1170–1178. United States of America</td>
<td>Flumazenil and gabapentin</td>
<td>50 dependent methamphetamine users and had used methamphetamine within seven days prior to screening Males n=26 (52%) Mean age: 35.2 ± 7.3 years Mean years of methamphetamine use: not reported Mean use in past 90 days: 71.4 ± 19.4 days</td>
<td>Medication therapy for four weeks: Flumazenil infusion on days 1, 2, 3, 22 and 23 50 mg oral hydroxyzine prior to infusions Gabapentin up to 1500 mg daily + 11 weekly individual support sessions</td>
<td>Measures&lt;br&gt;Methamphetamine craving (visual analogue scale); urine drug screens; self-reported methamphetamine use (TLFB); adherence to treatment (number infusions, pill count). Summary&lt;br&gt;Significant reduction in methamphetamine cravings (including thoughts, intensity and frequency), self-reported methamphetamine use from 70% of 90 days to 42% of 84 days and self-reported use was correlated with urine screen results. 90% completed infusions and oral medications. There were no serious adverse effects.</td>
<td>Level IV – open-label trial</td>
<td>Well-conducted open-label study as pilot for Urschel et al., 2011.</td>
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| Urschel, H.C. et al. (2011)   | Flumazenil and gabapentin            | 135 dependent methamphetamine users who had used methamphetamine within previous three days  
Males n=67 (49%)  
Mean age: not reported  
Mean years of methamphetamine use: not reported  
Age started drugs: approx. 21 years  
Mean use in last 30 days: not reported  
Self-reported frequency 30 days before: 89% treatment; 88% placebo | Active treatment group received flumazenil, 2 mg administered intravenously on days 1, 2, 3, 21 & 22, oral gabapentin up to 1200 mg/day and hydroxyzine 50 mg for pre-infusion and PRN for sleep (n=68). Placebo control group received inactive formulations of the medications (n=67). All participants received Matrix Model psychosocial intervention and nutritional support. To encourage adherence to protocol, participants received incentives if they completed their appointed visits +1 day (US$50 voucher for food or gasoline). | Measures  
Methamphetamine craving (six visual analogue scales and four categorical scales); self-report methamphetamine use (TLFB); urine drug screens as indices of methamphetamine use and correlates of self-report; adverse events.  
Summary  
Results showed an effect for a combination of flumazenil and gabapentin in reducing craving in methamphetamine-dependent participants, with the greatest effect demonstrated at day 6 of a 30-day trial. Self-reported methamphetamine use was significantly reduced in the treatment group but this was not supported by urine methamphetamine screening in an ITT analysis. Although frequency of use was significantly lower in the treatment group than the placebo group at each time point, the frequency of use increased in both groups throughout the trial. Seventy-four per cent of the treatment group and 79% of the placebo group experienced adverse event, most (97%) of which were mild. Close to half in the treatment group (compared to 21% in the placebo group) had injection site reactions. Authors suggest that these medications may offer an option for clinicians seeking to reduce patient craving and increase engagement in psychosocial treatment. | Level II — double-blind, placebo-controlled RCT | Well-conducted and designed RCT with sizeable sample but drop-out rate not reported. |
### Medicines not otherwise specified

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<tr>
<td>Swanson, A. et al. (2011). Varenicline for the treatment of methamphetamine dependence: a pilot study. Paper presented at the 73rd Annual Scientific Meeting of the College on Problems of Drug Dependence, Hollywood, Florida, United States of America</td>
<td>Varenicline</td>
<td>20 dependent methamphetamine users</td>
<td>Varenicline 1 mg twice daily or placebo for eight weeks Weekly individual counselling using cognitive behaviour therapy</td>
<td>Measures&lt;br&gt;Urine screens for methamphetamine metabolites; adverse events of medication.&lt;br&gt;Summary&lt;br&gt;The varenicline group had higher rates of retention as measured by days retained in the trial (p=0.009; 21 vs 43 days) and study completion (10% vs 60%) with trends toward more mean days of abstinence (1.7 vs 12 days) and greater mean proportion of methamphetamine-negative urine drug screens (9.6% vs 31%). There were no significant differences between treatment groups with respect to changes in depression, craving, or in reported adverse events. No statistically significant main effect for varenicline in reducing methamphetamine use was observed. A main effect of smoking status was found in GEE indicating that smokers provided fewer methamphetamine-negative urine drug screens.</td>
<td>Level II – double-blind placebo-controlled trial (pilot)</td>
<td>Briefly reported (conference abstract). Note: A larger scale RCT is currently being conducted by this research group.</td>
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<tr>
<td>Johnson, B.A. et al. (2008). A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. International Journal of Neuropsychopharmacology, 11(1): 1–14, United States of America</td>
<td>Ondansetron</td>
<td>150 dependent methamphetamine users&lt;br&gt;Males n=96 (64%)&lt;br&gt;Mean age: 36 years&lt;br&gt;Mean years of methamphetamine use: 18.4 years&lt;br&gt;Mean use in last month: 11.7 days Randomised to ondansetron 0.25 mg (n=37), 1 mg (n=29), or 4 mg (n=38) orally twice daily and matched placebo (n=46)</td>
<td>Participants were given ondansetron 0.25 mg, 1 mg, or 4 mg orally twice daily (bid) or matched placebo (n=46). All participants: CBT-based relapse prevention 90-min. group sessions, three times per week from weeks 1–8</td>
<td>Measures&lt;br&gt;Weekly proportion of methamphetamine-free urine samples; urine methamphetamine level; Substance Use Report (SUR); success vs failure at achieving at least three consecutive weeks of abstinence; ASI–Lite; Hamilton Depression Rating Scale (HAM–D); Brief Substance Craving Scale (BSCS); Clinical Global Impression – observer (CGI–O) and self (CGI–S); Methamphetamine Withdrawal Questionnaire (MAWQ) created for the study; study retention.</td>
<td>Level II – double-blind, placebo-controlled RCT</td>
<td>High-quality and well-conducted RCT. Adequate sample size but low retention rates.</td>
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<td>Reference</td>
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<td>Heinzerling, K.G. et al. (2006). Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. Drug and Alcohol Dependence, 85(3): 177–184. United States of America</td>
<td>Baclofen and gabapentin</td>
<td>88 dependent methamphetamine users</td>
<td>Baclofen 10 mg three times per day (tid) for days 1–3 of the first week followed by 20 mg tid until week 16 when the dose was decreased to 10 mg tid for the last three days. Or gabapentin 400 mg tid for days 1–3 of the first week followed by 800 mg tid until week 16 when the dose was decreased to 400 mg tid for the last three days.</td>
<td>Measures&lt;br&gt;Urine samples collected three times a week; ASI–Lite to measure the severity of addiction-related problems in seven areas of functioning; medical, employment, drug use, alcohol use, legal, family/social, and psychiatric; Beck Depression Inventory (BDI); methamphetamine craving measured weekly using a visual analogue scale; pill count for medication adherence. Summary&lt;br&gt;There were no significant main effects for baclofen or gabapentin in reducing methamphetamine use, craving or retention. For baclofen, but not gabapentin, participants who reported taking a higher percentage of study medication showed significant reductions in use compared to placebo. No differences in medication taken or psychosocial sessions attended. Attendance at counselling sessions, lower depression symptoms and less severe baseline methamphetamine use were significantly associated with a higher probability of providing a methamphetamine-free urine sample during the treatment period, but no difference between groups. The authors concluded that gabapentin does not appear to be effective in treating methamphetamine dependence while baclofen may have a small treatment effect relative to placebo, but the short half-life of baclofen may limit its use as an anti-craving agent for methamphetamine-dependent individuals.</td>
<td>Level II — double-blind, placebo-controlled RCT&lt;br&gt;A well-conducted study, but dropout high and variable (baclofen 60% completion, gabapentin 35% completion, and placebo 40% completion).</td>
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<tr>
<td>Batki, S.L. et al. (2001). Amlodipine treatment of methamphetamine dependence, a controlled outpatient trial: preliminary analysis. Paper presented at the Annual Meeting of the College on Problems of Drug Dependence, Scottsdale, Arizona. United States of America</td>
<td>Amlodipine</td>
<td>77 dependent methamphetamine users</td>
<td>Parallel outpatient groups were given amlodipine 5 mg, or amlodipine 10 mg per day, or placebo</td>
<td>Measures&lt;br&gt;Depression (BDI); retention; methamphetamine use in grams; craving. Summary&lt;br&gt;No difference in retention, methamphetamine use (amount, dollar value), craving, quality of high, or general functioning. The authors concluded that amlodipine treatment may be ineffective in the outpatient treatment of methamphetamine dependence.</td>
<td>Level II — randomised double-blind placebo-controlled trial&lt;br&gt;Briefly reported (conference abstract).</td>
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### Comorbidity

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<th>Reference</th>
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<th>Level of evidence</th>
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<tr>
<td>Brown, E.S. &amp; Gabrielson, B. (2012). A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. <em>Journal of Affective Disorders</em>, 143(1–3): 257–260. United States of America</td>
<td>Citicoline</td>
<td>60 amphetamine-dependent outpatients aged 18–70 years, diagnosed with bipolar I, II or NOS, currently depressed or with major depression; methamphetamine use in last four weeks. 48 participants included in ITT analysis (12 dropped out after initial assignment) Citicoline group (n=28) mean age: 41.6 years; 15 female, 13 male Control 20 participants mean age: 34 years; 7 female, 13 male</td>
<td>Citicoline 500 mg/day increasing to 1000 mg/day in week 2, 1500 mg/day at week 4, and 2000 mg/day at week 6, compared with placebo of identical appearance for 12 weeks</td>
<td>Measures: Mood (Inventory of Depressive Symptomatology: Clinician Version — IDS–C); cognition (Hopkins Auditory Verbal Learning Test (HVLT)); and drug use assessed by urine drug screens. Summary: Citicoline was associated with an improvement in depressive symptoms, and longer study survival than placebo. No differences in cognitive outcomes or drug use were found.</td>
<td>Level II — double-blind placebo-controlled RCT</td>
<td>Well-designed and conducted study with reasonable sample size and drop-out within acceptable limits. ++</td>
</tr>
<tr>
<td>Carnwath, T. et al. (2002). The prescription of dexamphetamine to patients with schizophrenia and amphetamine dependence. <em>Journal of Psychopharmacology</em>, 16(4): 373–377. United Kingdom</td>
<td>Dexamphetamine</td>
<td>Eight men aged 23–46 years with schizophrenia and amphetamine use</td>
<td>Dexamphetamine daily – dose calculated by matching the estimated dose of street amphetamine used, assuming the usual local level of 5% purity, usually started at approximately one-half this dose, and adjusted upwards only if considered clinically appropriate. Starting doses in the range of 20 mg/day – 80 mg/day</td>
<td>Measures: Urine drug screens; regular visual observation of injecting sites; unspecified psychiatric assessments were undertaken at least monthly. Summary: Dexamphetamine did not exacerbate psychosis among this group. Four patients had good outcomes for both mental health and amphetamine use (three patients abstinent and one significantly reduced use), two patients had some improvement in both symptoms and use, and two patients showed no improvement on either domain.</td>
<td>Level IV – case study of eight patients</td>
<td>Low-level study with small sample size and variable application of treatment. High risk of bias. –</td>
</tr>
<tr>
<td>Camacho, A. et al. (2010). Modafinil for bipolar depression with comorbid methamphetamine abuse. <em>American Journal on Addictions</em>, 19(2): 190–191. United States of America</td>
<td>Modafinil, quetiapine, divalproex</td>
<td>38-year-old female with bipolar mixed type and methamphetamine use. Patient self-reported depression, poor family functioning, craving for methamphetamine</td>
<td>Modafinil 200 mg/day with a further increase up to 600 mg/day over a three-month period, stabilised on modafinil 600 mg/day, quetiapine 800 mg at night, and divalproex 1000 mg/day</td>
<td>Measures: No formal measures were used. Descriptive clinical opinion only. Summary: Patient reported a reduction in fatigue and depressive symptoms without subsequent induction of manic symptoms. Her family support improved. She was able to live again with her mother and help with chores around the house. She described a decrease in her cravings for methamphetamine and achieved six months of abstinence.</td>
<td>Level IV – case study of one patient</td>
<td>Low-level study with single case. High risk of bias. –</td>
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<td>Misra, L. &amp; Kofoed, L. (1997). Risperidone treatment of methamphetamine psychosis. <em>American Journal of Psychiatry</em>, 154(8): 1170. United States of America</td>
<td>Risperidone</td>
<td>A 45-year-old Caucasian man who had become dependent on methamphetamine 12 years earlier and had increased his use during the past 5 years. There had been no psychiatric symptoms until four months before admission, when he reported the onset of hallucinations.</td>
<td>Risperidone 1 mg twice per day</td>
<td>Measures No formal measures were used. Descriptive clinical opinion only. Summary Within three days the patient noted reduced hallucinations, delusions and paranoia. After one week mood, affect, organisation of thought, delusional beliefs, memory, attention, insight and judgment improved. After the dose was increased to 1.5 mg twice daily the auditory hallucinations and delusions ceased. Two weeks into treatment he stopped taking risperidone, and his auditory hallucinations recurred. He also resumed smoking and craved methamphetamine. Upon resumption of risperidone treatment one week later, his hallucinations and craving for methamphetamine promptly ceased. Insomnia, impulsivity, and anhedonia also improved.</td>
<td>Level IV — case study of one patient</td>
<td>Low-level study with single case. High risk of bias.</td>
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<td>Sulaiman, A.H. et al. (2012). An open-label study of aripiprazole for methamphetamine induced psychosis. <em>Bulletin of Clinical Psychopharmacology</em>, 22(2): 121–129. Malaysia</td>
<td>Aripiprazole</td>
<td>49 dependent methamphetamine users with psychosis, 62% smoking Males n=46 (93.9%) Mean age: 34.2 years Mean years of methamphetamine use: 5.6 years Mean amount spent on methamphetamine use in last 30 days: Ringgit Malaysia 1,386.1 (approximately 40% of mean income)</td>
<td>Eligible patients were treated with an initial dose of 5–10 mg aripiprazole followed by flexible doses (5–15 mg/day) from day 2 to day 14.</td>
<td>Measures MINI; Amphetamine Withdrawal Questionnaire (AWQ); Brief Substance Craving Scale (BSCS); Positive and Negative Symptoms Scale (PANSS); Abnormal Involuntary Movements Scale (AIMS); Barnes Akathisia Scale (BARS); Simpson Angus Scale (SAS); Clinical Global Impression Scale (CGI–S); Hospital Anxiety Depressions Scale (HADS). Summary Out of 49 patients enrolled, 41 (83.7%) completed the study. There was a significant decline in the mean PANSS-total and CGI–S scores over the course of the study. The mean reduction was 27.6±21.4 point from baseline on day 14 for total PANSS score and 2.0±1.2 point for CGI–S. Aripiprazole was generally well tolerated during the study. Adverse events were reported in 10 (20.4%) patients. No statistically significant changes were noted with respect to movement-related adverse events.</td>
<td>Level IV – open-label clinical trial without a control group</td>
<td>Well-conducted open-label study with no control group; of very short duration with only 14-day follow-up but high retention rates.</td>
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<td>Reference</td>
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<td>Intervention and comparison if relevant</td>
<td>Primary outcomes including measures used</td>
<td>Level of evidence</td>
<td>Quality assessment</td>
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<td>Nejtek, V.A. et al. (2008). Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. <em>Journal of Clinical Psychiatry</em>, 69(8): 1257–1266. United States of America</td>
<td>Risperidone and quetiapine</td>
<td>80 dependent cocaine or methamphetamine users with diagnosis of bipolar disorder with current manic, hypomanic or mixed symptoms Males n=44 (47%) Mean age: 35.7 years Randomised to risperidone (n=46) or quetiapine (n=48)</td>
<td>Participants attended for weekly visits for 20 weeks. Study medications were randomly assigned to two groups under blinded conditions. Weekly dosing of quetiapine was 50 mg/day for the first week, 100 mg/day for the second week, and up to 600 mg/day by 12 weeks Weekly dosing for risperidone was 0.5 mg/day for the first week, 1 mg/day for the second week, and up to 6 mg/day by week 12.</td>
<td>Measures YMRS – 11 items; IDS–C-30 – 30-item depression scale; SCQ-10 – measures mood and drug craving; PRD–III – somatic complaints. Higher scores on the YMRS, IDS–C-30, SCQ-10 and PRD–III indicate greater severity of mood, cravings and somatic complaints. Summary Of 124 consenting outpatients and 94 participants in the intention to treat sample that received one week of study medication, an evaluable sample of 80 patients who attended baseline and at least one follow-up study visit was available. The mean ± SD exit dose for quetiapine was 303.6 ± 151.9 mg/day and 3.1 ± 1.2 mg/day for risperidone. Both quetiapine (n=42) and risperidone (n=38) significantly improved manic and depressive symptoms and reduced drug cravings (p &lt;.0005) compared to baseline. Decreased drug cravings were related to less frequent drug use (p=.03). The two medications did not significantly differ in their effects on mood symptoms, drug craving or drug use.</td>
<td>Level II – double-blind randomised trial</td>
<td>Good-quality study with high drop-out rate and two group RCT with no placebo control.</td>
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<td>Camacho, A. &amp; Stein, M.B. (2002). Modafinil for social phobia and amphetamine dependence. <em>American Journal of Psychiatry</em>, 159(11): 1947–1948. United States of America</td>
<td>Modafinil</td>
<td>45-year-old Caucasian woman, dependent on amphetamine since age 28 years</td>
<td>200 mg modafinil twice daily. 40 mg/day fluoxetine</td>
<td>Measures Self-reported amphetamine craving, depression and anxiety symptoms. Summary Self-reported decrease in craving for amphetamine, improvement in depression and anxiety. Reported she no longer spent a lot of time looking for street amphetamine so was able to obtain employment, and she reported not experiencing the same ‘high’ with modafinil that she experienced with amphetamine.</td>
<td>Level IV – case study of one patient</td>
<td>Brief letter to the editor about the clinical application of modafinil.</td>
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<td>Shoptaw, S. et al. (2009). Treatment for amphetamine psychosis. <em>Cochrane Database of Systematic Reviews</em>, 2009(1): CD003026. United States of America</td>
<td>Olanzapine and haloperidol</td>
<td>A review of one randomised controlled trial involving 58 participants (Leelahanaj et al. (2005) below)</td>
<td>One study of olanzapine compared to haloperidol</td>
<td>Summary Results from a single study showed that both the atypical antipsychotic olanzapine and the older, typical antipsychotic haloperidol administered at therapeutic doses were effective in treating amphetamine-induced psychosis. Participants taking olanzapine had significantly fewer extrapyramidal side-effect symptoms than participants taking haloperidol.</td>
<td>Level I – systematic review</td>
<td>High-quality Cochrane review.</td>
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<td>Leelahanaj, T. et al. (2005). A 4-week, double-blind comparison of olanzapine with haloperidol in the treatment of amphetamine psychosis. <em>Journal of the Medical Association of Thailand</em>, 88(3): 43–52. Thailand</td>
<td>Olanzapine and haloperidol</td>
<td>58 participants with DSM-IV amphetamine psychosis. All were smokers of amphetamine with a baseline score on the Brief Psychiatric Rating Scale (BPRS) of 36 or higher. Men n=54 (93%) Mean age: 22.7 years Mean years of amphetamine use: 4.5 years Exclusion criteria included diagnosis of schizophrenia or other psychotic disorder, diagnosis of substance abuse or dependence in past month. Randomised to olanzapine (n=29) or haloperidol (n=29)</td>
<td>All participants treated as outpatients and started with 5–10 mg/day of the study drug. After each seven-day period, the study drug could be adjusted in 5 mg increments or decrements within the allowed dose range of 5–20 mg/day during the four-week double-blind period. Limited use of benzodiazepine for severe agitation or violent behaviour was permitted. Trihexyphenidyl up to 4 mg/day for &lt;2 days to treat extrapyramidal side effects was permitted.</td>
<td>Measures Brief Psychiatric Rating Scale (BPRS); Clinical Global Impression Scale (CGI); adverse events; medication safety profile (SAS &amp; BAS). Summary Both medications were effective in treating symptoms of psychosis, with at least 40% improvement in the first week. One-third of the haloperidol patients discontinued treatment due to extrapyramidal side effects compared to none of the olanzapine patients. But olanzapine patients experienced more weight gain than haloperidol patients. More olanzapine patients completed the study than did haloperidol patients. The olanzapine group (n=27, 93%) were significantly more likely to have completed treatment than the haloperidol group (n=19, 65.5%, x²=6.73, df=1, p=0.01)).</td>
<td>Level II — double-blind randomised trial</td>
<td>Well-conducted, high-quality study. No placebo control.</td>
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<tr>
<td>Misra, I. et al. (2000). Olanzapine treatment of methamphetamine psychosis. <em>Journal of Clinical Psychopharmacology</em>, 20(3): 393–394. United States of America</td>
<td>Olanzapine</td>
<td>Male aged 50 years with history of alcohol, cannabis and cocaine dependency. Developed persistent paranoid-hallucinatory state after one year of methamphetamine use. Patient was given an outpatient trial of olanzapine (5 mg/day), later increased (to 5 mg twice daily)</td>
<td>Measures No formal measures were used. Descriptive clinical opinion only. Summary The authors report that olanzapine on two separate occasions effectively treated both acute and residual psychotic states of a methamphetamine-dependent patient. Within two weeks, his acute psychotic symptoms were reduced, but he admitted to missing several olanzapine doses and to occasionally using methamphetamine. An increased olanzapine dose and abstinence from methamphetamine subsequently eliminated his psychotic symptoms. The authors suggest that atypical antipsychotics can be effective in the treatment of acute and residual methamphetamine-induced psychosis.</td>
<td>Level IV — case study of one patient</td>
<td>Low-level single case report with few systematic measures.</td>
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## MDMA

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<th>Level of evidence</th>
<th>Quality assessment</th>
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<tr>
<td>Akhondzadeh, S. &amp; Hampa, A.D. (2005). Topiramate prevents ecstasy consumption: a case report. Fundamentals of Clinical Pharmacology, 19(5): 601–602. Iran</td>
<td>Topiramate</td>
<td>28-year-old male patient used MDMA 2–4 times per week for 4 years; multiple drug dependence (opiates and alcohol) and long history of use. No other details provided.</td>
<td>50 mg of topiramate on the first day, which was titrated up to 200 mg/day during the second week. He was on this dose for three months.</td>
<td>Measures</td>
<td>Self-report MDMA consumption. No formal measures were used. Summary</td>
<td>Level IV – single case study</td>
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<tr>
<td>Fetter, J.C. (2005). Mirtazapine for MDMA-induced depression. American Journal on Addictions, 14(3): 300–301. United States of America</td>
<td>Mirtazapine</td>
<td>28-year-old female used MDMA weekly for one year. Abstinent for six years, with depression and anxiety, which the patient said was linked to the start of MDMA use.</td>
<td>Mirtazapine 30 mg nightly; hydroxyzine 25 mg as needed for panic attacks</td>
<td>Measures</td>
<td>Self-reported symptoms of depression, anxiety and sleep. Summary</td>
<td>Level IV – single case study</td>
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## Other amphetamine-type stimulants

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<tr>
<td>Arnold, K.K. &amp; Yager, J. (2007). A case of unexpected and selective remission of a 20-year history of ephedrine dependence following treatment with low-dose aripiprazole. [Case Reports Letter]. Journal of Clinical Psychiatry, 68(10): 1620–1621. United States of America</td>
<td>Fluoxetine plus aripiprazole</td>
<td>37-year-old female, using ephedrine for 20 years to maintain weight, history of major depression, eating disorder, compulsive shopping, illegal activity (forgery)</td>
<td>80 mg/day fluoxetine and 2.5 mg/day aripiprazole</td>
<td>Summary</td>
<td>Patient tapered herself off ephedrine over a period of eight weeks. Remained ephedrine-free for the following four months. The case reports on a patient who was using 1.5 mg ephedrine daily, which is a very small dose (e.g. the recommended dose of pseudoephedrine daily for cold and flu is 120 mg, equivalent to about 48 mg of ephedrine (see jap.physiology.org/content/81/6/2611.full)), so these results are unlikely to have clinical application for dependence.</td>
<td>Level IV – single case study</td>
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