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Pharmacotherapy for amphetamine dependence: A systematic review

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ABSTRACT

Background: Demand for treatment for amphetamine use is increasing internationally. Establishing effective pharmacotherapy provides broader treatment options for people who are dependent on amphetamine and may encourage engagement in evidence-based behavioral treatment. This study aimed to identify medicines that have potential in improving treatment outcomes for people who are dependent on amphetamines.

Methods: Medline, PsycINFO, Embase and the Cochrane Database of Systematic Reviews were searched from 1997 to 2012 and again from 2013 to 2016. Studies on medications for amphetamine/methamphetamine dependence treatment were selected and assessed by two independent researchers. A meta-narrative review approach was used to synthesize results.

Results: A total of 49 studies investigating 20 potential pharmacotherapies were eligible for inclusion. Of these, 35 studies related to 33 level II quality randomized controlled trials (RCTs). Five medications were subject to multiple RCTs. Four of these medicines demonstrated some limited evidence of benefit for reducing amphetamine use: methylphenidate (as reported in three studies), buprenorphine (in three studies), modafinil (two studies), and naltrexone (one study). Four RCTs of dexamphetamine suggest its benefit on secondary outcomes such as treatment retention, but not for reducing amphetamine use. Six other medicines indicate the potential for efficacy, but the number of studies is too small to draw conclusions.

Conclusions: No medicine has as yet demonstrated sufficient, consistent evidence of effectiveness to support its use in routine treatment. High study drop-out and poor medication adherence limits the strength of evidence and raises important clinical questions about how to improve treatment engagement and outcomes.

1. Introduction

Internationally, recent increases in the proportion of people using amphetamines in the community are reported for a number of regions. Though global trends indicate no overall growth (Center for Behavioral Health Statistics and Quality, 2015; United Nations Office on Drugs and Crime, 2016) a rise in use is evident in East and South East Asia (United Nations Office on Drugs and Crime, 2016) and in Europe, where Finland and the Czech Republic showed increased use, although decreased prevalence was reported for Spain and the United Kingdom (European Monitoring Centre for Drugs and Drug Addiction, 2017). A trend is also reported toward riskier methamphetamine use, such as injecting, and the use of the more potent form of crystal methamphetamine (European Monitoring Centre for Drugs and Drug Addiction, 2017).

The amphetamine group of drugs referred to broadly in this review as 'amphetamine', includes amphetamine sulfate and methamphetamine (Cruickshank and Dyer, 2009). They are synthetic central nervous system stimulant drugs with similar profiles of effect and potential for abuse, though methamphetamine is considered a more potent type of amphetamine (Perez-Mana et al., 2013; Darke et al., 2008). Methamphetamine makes up the largest share of the amphetamine-type stimulant (ATS) seizures across the world and dominates the ATS street markets in North America, East and South-East Asia and Oceania, (United Nations Office on Drugs and Crime, 2016). ATS use is related to a range of serious harms, including dependence (Cruickshank and Dyer, 2009; Mcketin et al., 2006a, b). Regular and longer-term use of methamphetamine is particularly associated with extensive physical health consequences (Cruickshank and Dyer, 2009; Darke et al., 2008), elevated risk of psychiatric symptoms including psychosis and depression (Ma et al., 2018; Mcketin et al., 2006b) and increased prevalence of aggressive behaviors (Mcketin et al., 2014; Darke et al., 2008), violent offending (Darke et al., 2010), high-risk sexual activity (Cruickshank and Dyer, 2009) and blood borne viruses (Tavitian-Exley et al., 2015; United Nations Office on Drugs and Crime, 2016).

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The purity of both amphetamine and methamphetamine is reported to have increased in recent years (European Monitoring Centre for Drugs and Drug Addiction, 2017; United Nations Office on Drugs and Crime, 2016) raising further concerns for the potential impact on the prevalence of amphetamine-related harms on public health. Crystal methamphetamine is typically smoked or injected, and compared to the powder or paste forms of methamphetamine, is significantly stronger and associated with a greater likelihood of developing dependence (McKetin et al., 2006a, b). Regions reporting increased use or purity of crystal methamphetamine may be particularly negatively impacted. In Australia, a state showing an overall increase in crystal methamphetamine purity also experienced a drop in purity-adjusted price (United Nations Office on Drugs and Crime, 2016), and found this change was paralleled with substantial methamphetamine-related harms, including a three-fold increase in the number of ambulance attendances specifically related to crystal methamphetamine (Heilbronn et al., 2013; Scott et al., 2015).

In this context of shifts in amphetamine use patterns and drug purity, the number of people presenting for treatment for amphetamine-related disorders is seen to be rising internationally. In Europe, the number of first-time treatment entrants for amphetamine use grew by 50% since 2006 (European Monitoring Centre for Drugs and Drug Addiction, 2017) and increased treatment access is reported across Asia and specific regions of North America (United Nations Office on Drugs and Crime, 2016). Such changes in treatment demand suggest a wider trend of increased problem use and health consequences (United Nations Office on Drugs and Crime, 2016).

Current treatment for amphetamine dependence is founded on structured behavioral interventions, with cognitive behavioral therapy (CBT) and contingency management interventions most supported for reducing methamphetamine use (Lee and Rawson, 2008). However, relapse rates are high (Mcketin et al., 2012) and a pharmacotherapy may help attract people who use methamphetamine into treatment (Kenny et al., 2011).

Investigation of medications to treat amphetamine dependence has commonly involved trials of agonist replacement medications, antidepressant and antipsychotic-type medications (Rose and Grant, 2008). The medicines achieve their effects through modulation of key neurotransmitter systems, primarily dopaminergic neurotransmitter systems, but also the serotonergic and GABAergic systems (Rose and Grant, 2008; Panenka et al., 2013). A number of earlier reviews have shown no benefit of pharmacotherapy for amphetamine dependence.

Brensilver et al. (2013) reviewed twenty-one randomized controlled trials (RCTs) of pharmacotherapies for ATS or methamphetamine dependence and concluded that no pharmacotherapy had been found to be broadly effective. Four medications were indicated to have limited evidence but promising results in reducing use and/or increasing abstinence among subgroups of patients: naltrexone among individuals with less severe dependence or with comorbid opioid and amphetamine dependence, mirtazapine among men who have sex with men, methylphenidate with people who use amphetamine by injection and bupropion with lighter amphetamine users (Brensilver et al., 2013).

Reviews by Stoops and Rush (2013, 2014) similarly identify promising directions but no widely effective treatment option. In a review of clinical trials and human laboratory studies of agonist replacement medication options for stimulant dependence (Stoops and Rush, 2013) they included 13 amphetamine treatment studies. Authors highlighted the potential utility of methylphenidate for reducing amphetamine use and the limited but promising evidence for bupropion among lighter amphetamine users.

The review of combination pharmacotherapies for stimulant use disorder (Stoops and Rush, 2014) included four amphetamine specific studies that combined: naltrexone and alprazolam, naltrexone and n-acetylcysteine, and gabapentin with flumazenil. Findings from the limited evidence were mixed, but authors suggest combination pharmacotherapy may be a viable and effective treatment approach for stimulant use disorders, with most promising findings for the use of naltrexone (as a mono- or combination therapy) and GABA agonists in combination with other medications (Stoops and Rush, 2014).

A Cochrane systematic review evaluating the efficacy and safety of psychostimulant medications for amphetamine abuse or dependence (Perez-Mana et al., 2013) reviewed eleven studies involving administration of dexamphetamine, bupropion, methylphenidate, and modafinil. No significant differences were found between these medications and placebo in their effect on reducing amphetamine use or craving, or increasing length of abstinence. The retention in treatment was low, and a similar proportion of adverse events prompting dropout was evident for both psychostimulants and placebo groups.

Since the publication of these reviews, 12 new clinical studies have been published, and this paper provides an update on these previous reviews. We take a broad approach to this update, including both RCT and non-RCT studies to offer a picture of what works and what is promising in pharmacotherapies for dependence on amphetamines.

2. Method

2.1. Review protocol

2.1.1. Approach

A systematic review was undertaken in January 2013 examining pharmacotherapy for amphetamine dependence as part of the Australian Nation Council on Drugs (ANCD) report 'Medication treatment options for amphetamine-type stimulant users' (Lee and Jenner, 2014). An updated search was undertaken for papers published between January 2013 and September 2016.

The methods and results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses -PRISMA statement (Liberati et al., 2009; Moher et al., 2015). A traditional systematic review works best when there are large numbers of studies with similar methodologies and outcome measures. A more recent review methodology, meta-narrative review (Potts, 2012) is a pragmatic method of understanding a diverse and disparate literature and can help provide better interpretation of the literature when methods, measures, and outcomes between studies vary widely. Although the efficacy and effectiveness of medicines are generally considered a 'simple intervention' (Wong et al., 2009), the complexity of amphetamine use has resulted in the reporting of widely varied research outcomes.

2.1.2. Eligibility criteria

The **inclusion** criteria were:

- Human studies
- Adult studies (participants aged 18 years and over)
- Materials published previous 15 years (1 January 1997–January 2013), an additional search of articles 2013 to September 2016
- Manuscripts in English or with available English translation
- Intervention studies of Level IV study type (case series with either post-test or pre-test/post-test outcomes) or above (National Health and Medical Research Council, 2009)

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 participants or contexts (e.g., used healthy volunteers or used dependent volunteers in a laboratory setting)
- Studies of pharmacotherapy responses to acute toxicity

- Studies specifically targeting other mental health disorder (e.g., attention deficit hyperactivity disorder, depression)

Only published articles and abstracts that met these criteria and contained sufficient comparison information to be extracted were included in the review.

2.1.3. Information sources and search

Four electronic databases were searched: Medline, PsycINFO, Embase and the Cochrane Database of Systematic Reviews. A combination of medical subject headings (MeSH), keywords and title searches were used depending on the database. An example of the specific search strategy, as used for Medline is detailed in Supplement 1. Searching by hand the references within key papers also identified additional studies of relevance.

2.1.4. Data items

An initial screen by 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. Data items extracted during the second stage of screening included: citation details; country research was completed; type of medicine and intervention; setting of study; study objective; number and description of participants (i.e. gender, age, mean days of methamphetamine use in past 30 days, mean years methamphetamine use); intervention and comparison group details where included in study; outcome measures used; response rate; length of follow-up; outcomes, and effect size if reported.

2.2. Risk of bias

Two reviewers undertook the data extraction and quality check. The data extraction sheet was adapted from Torgerson (2003) with each paper also subject to assessment based on a number of criteria that focus on study design elements that research has shown to have a significant effect on the risk of bias in the results reported, including study procedures for randomization, treatment allocation, blinding, outcome measurement and study drop out (Scottish Intercollegiate Guidelines Network (SIGN), 2014). The study type determined the checklist used; copies are available from the Scottish Intercollegiate Guidelines Network (SIGN)[1] website. As recommended by SIGN (Scottish Intercollegiate Guidelines Network (SIGN, 2014) the literature search covered a range of sources and studies, which were appraised by two reviewers. The inclusion of open-label and non-controlled studies in this systematic review aimed to identify important and clinically useful information but is acknowledged as potentially increasing the risk of bias. Findings of high-quality RCTs assessed as low bias risk are more heavily weighted in our synthesis of results.

2.3. Summary measures and synthesis of results

Extracted data were transcribed into a summary table by a single reviewer and checked by a second reviewer consistent with systematic methods of reporting (Higgins and Green, 2008). To synthesize the studies, the meta-narrative review elements of interpretive synthesis and guiding principle of 'pragmatism' (Greenhalgh and Peacock, 2005; Greenhalgh et al., 2009; Potts, 2012) were then applied, aiming to identify what will be most useful to the intended audience. In this context, this pragmatic aim is interpreted as whether medicines show promise in forming part of a comprehensive treatment plan and conversely whether there are medicines identified as unsafe to use with people dependent on ATS. From this process, conclusions could be made and have a chronological order (Kitson et al., 2013).

[1] http://www.sign.ac.uk/methodology/checklists.html

2.4. Study selection

The citations from all database sources and other sources (committee members suggestions) were saved into separate EndNote libraries (Thomson Reuters, 2013). A flow diagram of the search results is provided in Fig. 1.

From the initial search, a total of 6537 citations were returned from database searches, and an additional fifty-two papers were identified through other sources. After removal of duplicates, 2179 articles were assessed for eligibility.

A two-stage screening process was used. During the first screen, one reviewer assessed each article to ensure they met the eligibility requirements. A further n = 2021 articles were removed, leaving n = 158 articles to be further checked for eligibility and quality during the second screen.

At the second screen, all studies (n = 121) that did not meet inclusion criteria were excluded (e.g., laboratory and animal studies, participants without ATS dependence). Thirty-seven studies of medications for ATS dependence were initially included for review.

The updated search conducted in 2016, followed the same procedures and identified an additional twelve papers for inclusion in the review.

Forty-five of these studies reported no serious adverse events. Overall there was no evidence that, at the doses reported, these medicines produced significant adverse effects, even in patients severely dependent on ATS.

3. Results

3.1. Study characteristics

A total of 49 studies were included in the final review, relating to 20 potential amphetamine dependence pharmacotherapies. Table 1 provides a detailed summary of each study.

Overall, thirty-five studies reported on 33 level II quality-controlled trials. The majority of RCTs involved a trial of medication in conjunction with some level of behavioral intervention, and most (n = 28) specified their participant sample included methamphetamine-dependent users.

3.2. Synthesis of results

A synthesis of studies reviewed for the treatment of amphetamine dependence is provided in Table 2.

3.2.1. Dexamphetamine

Dexamphetamine is a functional agonist of methamphetamine, 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 et al., 2004). Dexamphetamine is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy, and at higher doses can cause the release of noradrenaline and dopamine and, to a much lesser degree, serotonin (Howell and Kimmel, 2008). As detailed in Table 1, a total of seven studies investigating the efficacy of dexamphetamine for amphetamine dependence were reviewed, including four randomized trials.

Retrospective studies (levels III and IV) investigated the safety and efficacy of dexamphetamine among specific groups of people who use amphetamine. Studies suggested the medication may provide more overall gains with injectors compared to people who ingest orally (White, 2000); should only be initiated as a last-line treatment for those amphetamine users who are pregnant (White et al., 2006); may achieve comparable outcomes for people who use amphetamine on maintenance doses as for heroin users on methadone (Charnaud and Griffiths, 1998).

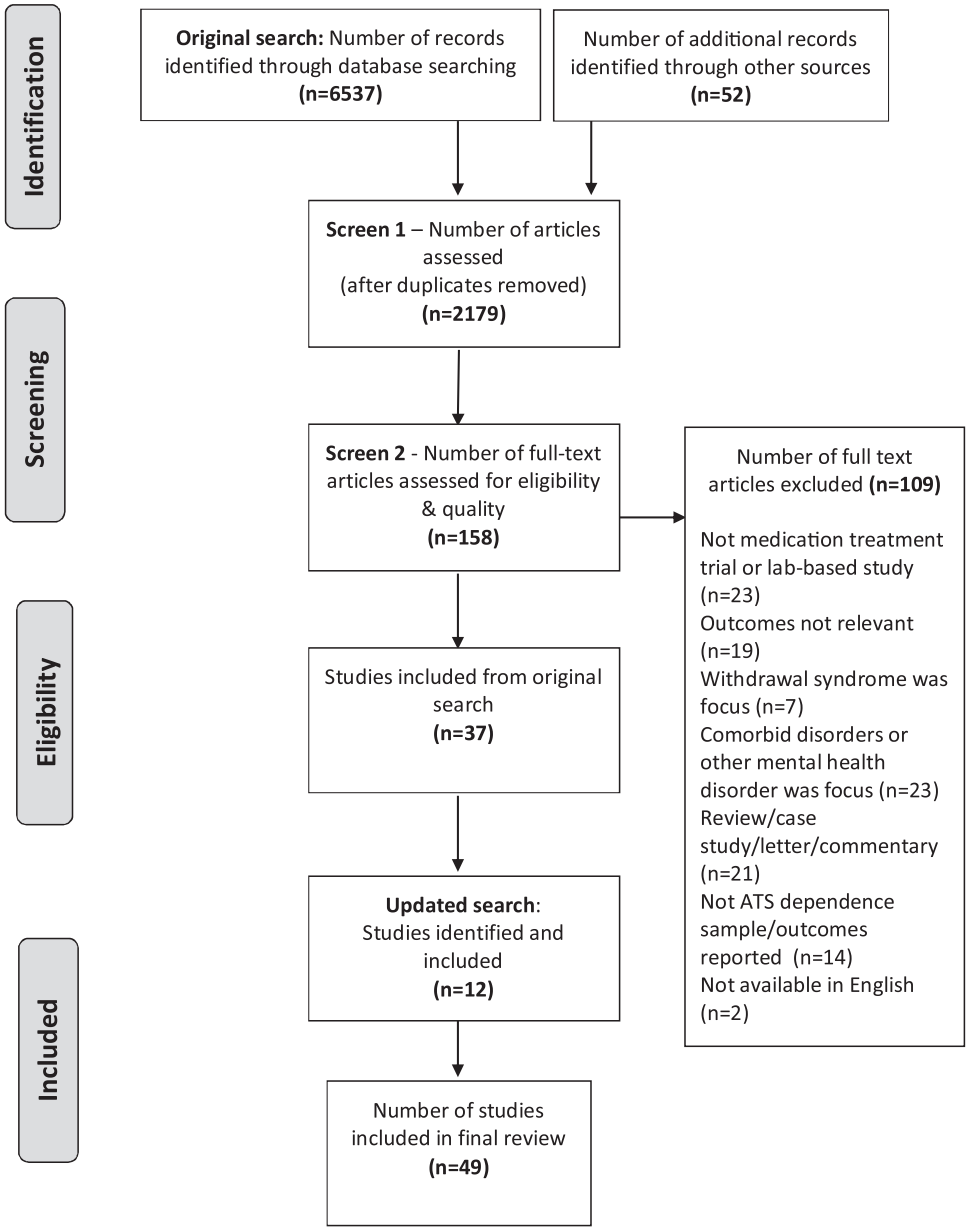

Fig. 1. Flow diagram of systematic review.

In a randomized controlled trial of dexamphetamine for methamphetamine dependence, administered at average daily doses of 80 mg (Longo et al., 2010) dexamphetamine showed benefit over placebo on secondary variables of retention in treatment and reduced severity of dependence. In RCTs administering lower doses (21–60 mg daily), dexamphetamine showed benefit on attendance at counselling sessions (Shearer et al., 2001) and craving symptoms (Galloway et al., 2011), however, no trials reported evidence of greater reductions in amphetamine use compared with placebo (Longo et al., 2010; Galloway et al., 2011; Shearer et al., 2001). An open-label RCT with no placebo control (Merrill et al., 2005) administered up to 100 mg dexamphetamine daily and also found no benefit of the medication in reducing amphetamine use compared with treatment as usual.

3.2.2. *Methylphenidate*

Methylphenidate is a dopamine agonist approved for the treatment of attention deficit hyperactivity disorder. Methylphenidate is a dopamine and noradrenaline reuptake inhibitor and primarily blocks reuptake of monoamines into the synapse, thereby increasing concentrations of monoamines at the synaptic cleft (Karila et al., 2010). Six studies of methylphenidate treatment of amphetamine dependence were identified.

In four RCTs, sustained release methylphenidate was compared to placebo using daily dosing regimen of 18 mg at week 1, 36 mg week 2 and 54 mg for remainder of trials (7–17 weeks) (Ling et al., 2014; Miles et al., 2013; Rezaei et al., 2015; Tiihonen et al., 2007). Methylphenidate was superior to placebo in reducing the number of amphetamine-positive urine samples in two of these studies (Rezaei et al., 2015; Tiihonen et al., 2007), and the self-reported days of methamphetamine use in a third trial (Ling et al., 2014), but not in a fourth study (Miles et al., 2013).

Benefits were demonstrated on secondary outcomes of reducing craving symptoms (Ling et al., 2014; Rezaei et al., 2015) though methylphenidate at 10 mg daily was found to be less effective when compared to risperidone (Solhi et al., 2014).

One RCT found reductions in amphetamine use were most notable among dependent users with baseline moderate- to severe-level use (Ling et al., 2014); one retrospective case series study (level IV)

Table 1
Summary table of studies.

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
Galloway et al. (2011). A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. *Clinical Pharmacology & Therapeutics*, 89(2): 276–282. United States of America	Dexamphetamine	60 dependent methamphetamine users Males n = 15 (50%) Mean age: 37 years Mean 18.9 days of methamphetamine use in last 30 days Randomized 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 Desires for Speed Questionnaire (visual analogue craving scale); and medication adherence capsule count and self-report. **Summary** There were no significant differences between groups on methamphetamine use measures (self-reported methamphetamine using days, number of methamphetamine-free urine samples), but the dextroamphetamine group reported significantly less craving and fewer withdrawal symptoms. No serious adverse events occurred during the trial. There was no significant difference between groups on medication adherence or attendance at psychosocial treatment sessions. Around 75% of both groups reportedly took the dispensed medication.	Level II — double-blind multi-site placebo-controlled RCT
Longo et al. (2010). Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. *Addiction*, 105(1): 146–154. Australia	Dexamphetamine	49 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 Randomized to receive either dexamphetamine (n = 23) or placebo (n = 26)	The study period comprised an initial stabilization 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 stabilized or until the participant was in receipt of a maximum of 110 mg/day for 90 days. Daily supervised dosing. All participants underwent stabilization (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 minimize any withdrawal symptoms experienced. Participants were followed up two months after completing treatment. Plus all participants received four sessions of CBT for amphetamine users.	**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). Both groups showed significant reductions in methamphetamine use over time ($P < 0.0001$), with no difference between groups. Dexamphetamine increased treatment retention, reduced degree of dependence and withdrawal symptom severity during stabilization. Those on dexamphetamine were significantly less likely to drop out of the study (n = 8/23) than those in the placebo group (n = 18/26) ($P = 0.040$); 61% in the dexamphetamine group and 54% in the placebo group attended at least one CBT session (NS).	Level II — double-blind, placebo-controlled RCT
White et al. (2006). Dexamphetamine substitute prescribing in pregnancy: a 10-year retrospective audit. *Journal of Substance Use*, 11(3): 205–216. United Kingdom	Dexamphetamine	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	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.	**Measures** Cigarette and alcohol use, outcome by prescription regime and ATS or heroin use. **Summary** Well-analyzed 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 randomized. 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 prescribing or maximum dose. 'On-top' use was the best predictor of adverse birth outcomes. The authors concluded that dexamphetamine substitution should be initiated with caution and used as a last-line treatment. Clients should be informed of possible risks, including those relating to continued use of street-drugs.	Level IV — secondary data analysis using retrospective cohort with historical controls

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
Merrill et al. (2005). Dexamphetamine substitution as a treatment of amphetamine dependence: a two-center randomized controlled trial. *Drugs: Education, Prevention and Policy*, 12(Suppl. 1): 94–97. United Kingdom	Dexamphetamine	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 Randomized to dexamphetamine n = 32 or best available treatment alone (BATA) n = 27	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 minimization advice; referral for other supports; symptomatic prescribing for depression, anxiety and insomnia; and the possibility for inpatient detoxification if clinically indicated. After randomization, participants received weekly clinical appointments for four weeks, then fortnightly until seven months (end of dex. prescribing period).	**Measures** Standard questionnaires on drug use, physical and psychological health, social functioning and quality of life, offending behavior, 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 behavior 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.	Level II RCT. Blinding not reported, no placebo control.
Shearer et al. (2001). Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. *Addiction*, 96(9): 1289–1296. Australia	Dexamphetamine	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 Randomized to dex. plus counselling n = 21 or counselling only n = 20	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.	**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. Rate of compliance to daily treatment attendance of 74%, and 57% of active treatment group completed treatment, there were no reports of adverse events.	Level II — open RCT (pilot)
White (2000). Dexamphetamine substitution in the treatment of amphetamine abuse: an initial investigation. *Addiction*, 95(2): 229–238. United Kingdom	Dexamphetamine	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.	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.	**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 behaviors, 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.	Level IV — secondary data analysis using retrospective cohort
Charnaud and Griffiths (1998). Levels of intravenous drug misuse among clients prescribed oral dexamphetamine or oral methadone: a comparison. *Drug and*	Dexamphetamine	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	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)	**Measures** Demographic characteristics, age of first drug use, duration of use, duration of treatment, psychotic episodes, level of injecting at discharge (assessed by visual observation of injection sites), and random urine tests assessed medication compliance. **Summary** There were no differences between groups at the beginning of treatment. There were no differences in outcomes between the	Level IV — retrospective chart review over two years (1995–96)

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
Alcohol Dependence, 52(1): 79–84. United Kingdom		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)		groups, including injecting rates, median time in treatment, suggesting that amphetamine users on dexamphetamine maintenance did just as well as heroin users on methadone.	
Minarik et al. (2016). Methylphenidate substitution for methamphetamine addiction and implications for future randomized clinical trials: A unique case series. *Journal of Substance Use* Volume: 21 Issue: 4 Pages: 435-438 Czech Republic	Methylphenidate	24 methamphetamine dependent and active intravenous users, seeking outpatient treatment at a single facility between 2007 and 2013. Males n = 7 (29%) Mean age 30.4 years (females); 34.2 (males) Years of methamphetamine use: 5 or more years Use in last month: daily users n = 17, binge users (average twice week) n = 7	Short acting, individually dosed Methylphenidate (MPH) and psychotherapy. MPH dosing commenced at 10 mg twice daily for each patient, and was titrated individually; mean daily dose was 37.6 mg (SD 20.38). Interventions were not standardized or controlled but generally included: psychiatric pharmacotherapy for co-occurring disorders, individual psychotherapy and social counselling, initially weekly visits reduced to less < 1 month once stabilized.	**Measures** Toxicology and clinical evaluations to monitor methamphetamine abstinence; treatment retention; self-reported adverse effects; clinical team observations of health and quality of life. **Summary** At end of observation period: mean duration of treatment was 8 months (< 1–31 months); 10 cases (42%) achieved full abstinence; 7 cases (29%) had dropped out; 3 cases still in treatment and 4 cases had changed treatment type or setting. MPH was well tolerated, and stabilization and improvement in health and quality of life was observed for patients receiving 1 month or more of treatment. A greater proportion of regular, lower dose users were abstinent (n = 9) compared to high-dose binge users (n = 1). Authors reported MHP replacement with psychotherapy achieved favorable outcomes and low dropout rate with regular, low dose intravenous methamphetamine users, but that an alternative pharmacotherapy may be required to keep episodic high-dose users in treatment.	Level— IV Retrospective case series
Rezaei et al. (2015). Sustained-release methylphenidate in methamphetamine dependence treatment: a double-blind and placebo-controlled trial. *Daru Journal of Pharmaceutical Sciences*, 23(1):2. Iran	Methylphenidate	56 dependent methamphetamine users, mainly smokers (80%, n = 45) Males n = 41 (73%) Mean age: approx. 35 years Mean age: 36 years Mean years of methamphetamine use: approx. 13 years Mean use in last month: 10 days Randomized to sustained-released methylphenidate or placebo	Sustained-released methylphenidate 18 mg/day during week 1, 36 mg/day during week 2 followed by 54 mg/day for 8 weeks, with a matched 10-week placebo group. Outpatient setting with medication given daily under staff supervision.	**Measure** Methamphetamine craving was assessed by a visual analogue craving scale (ranges from 0 to 100). Severity of addiction was assessed by Addiction Severity Index (ASI). Weekly urine sampling screening test for methamphetamine. Depressive symptoms measured using the Beck Depression Inventory II (BDI-II). **Summary** Overall 39% of sample dropped out before week 6 of treatment. Intention to treat analysis showed that compared to the placebo group, significantly fewer participants in the methylphenidate group tested positive for methamphetamines use at week 10 (approx. 18% vs 32%, P = 0.03), and the treatment group showed significantly less craving scores. The active treatment group also showed greater reductions in depressive symptoms.	Level II — double-blind, placebo-controlled RCT
Ling et al. (2014). Sustained-release methylphenidate in a randomized trial of treatment of methamphetamine use disorder. *Addiction*, 109(9):1489-500. United States of America	Methylphenidate	110 dependent methamphetamine users Males n = 90 (81.8%) Mean age: *MPH group* 38.7 years, *placebo* 39.5 years. Mean years of methamphetamine use: *MPH group* 10.8 years (sd = 7.8), *placebo* 11.9 years (sd = 9.9) Mean use in last 30 days: *MPH group* 13.1 days (sd = 9.7), *placebo* 11.4 days (9.8) Randomly assigned to MPH (n = 55) and placebo (n = 55).	A placebo group matched to active treatment group involving sustained-release methylphenidate 18 mg daily for one week, 36 mg for week 2 and 54 mg for weeks 3–10, followed by a 4-week period of single blind placebo. All participants received weekly group CBT and twice-weekly clinic visits with assessments, urine drug screens and motivational incentives for providing methamphetamine- free urine sample.	**Measures** Methamphetamine use self-reported for the last 30 days of the 10-week active treatment phase using Addiction Severity Index Lite (ASI), and assessed by twice weekly urine drug screen. Other drug use measured by ASI self-report and urine screen. Level of methamphetamine craving measured by Visual Analog Craving Scale (VAS) and the Craving Questionnaire–Now (CQ-Now) Treatment retention and compliance measured via a log of dose and dose taken and log of CBT and MI. Adverse events were collected at each clinical visit and treatment satisfaction questions asked at treatment end. **Summary** No difference was found between treatment groups in self-reported days of MA use during the last 30 days of the active phase (P = 0.22), however the MPH group reduced their use from	Level II — double-blind, placebo-controlled RCT

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				baseline to end of the active phase significantly more than the placebo group (6.5 vs 3.5 days, P = 0.05). The reductions were most notable among users with baseline moderate- to severe-level use. The MPH group also had lower craving scores and fewer positive screens for cannabis in the last 30 days of the active phase. Treatment retention, other drug use, adverse events and treatment satisfaction were similar for the two groups with no serious adverse events reported and 52.7% of the MPH group and 57.4% of the placebo group completed week 10.	
Solhi et al. (2014). Methylphenidate vs. risperidone in treatment of methamphetamine dependence: A clinical trial. *Saudi Pharm J.*, 22(3):191-4. Iran	Methylphenidate, Risperidone	86 methamphetamine dependent users enrolled in the study, 100% smokers; 73 completed the study and are included in reporting. Males n = 64 (87.7%) Mean age: *group M* 34.12 years, *group R* 30.35 years Mean years of methamphetamine use: not reported Mean use in last month: not reported Mean daily dose used (grams): *group M* = 1.27 *group R* = 1.24 Randomized to Methylphenidate (n = 35) and Risperidone (n = 35).	Risperidone 1 mg daily for 1 week, then 2 mg daily in a divided dose for 3 weeks (orally). Or methylphenidate 10 mg orally, daily for 2 weeks, 7.5 mg daily for 1 week, then 5 mg daily for 1 week.	**Measures** Drug cravings were evaluated by a physician and reported as number of craving per week. Psychological, neurologic, cardiac and somatic symptoms were assessed by a physician, with the presence and severity of different symptoms within each category scored from 0-5. **Summary** Both risperidone and methylphenidate showed effect in lowering drug craving at end of treatment (4 weeks), with risperidone found to be significantly more effective (average of 6.31 cravings per week vs 19.6 in the methylphenidate group at end treatment). Both groups showed reductions in psychiatric, neurologic, cardiac and somatic symptoms after discontinuation of MA abuse, however risperidone was shown to achieve significantly greater effect.	Level II – randomized trial with two active medications (no placebo control)
Miles et al. (2013). Extended release methylphenidate for treatment of amphetamine/ methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. *Addiction*, 108(7): 1279–1286. New Zealand and Finland	Methylphenidate	79 dependent amphetamine/ methamphetamine users n = 41 from New Zealand (mainly smokers of methamphetamine) and n = 38 from Finland (mainly injectors of amphetamine) Males n = 48 (61%) Mean age: 37.5 years for Finland; 35.3 years for New Zealand Mean years of methamphetamine use: 21.5 years All participants returned methamphetamine positive urine screens at baseline. Randomized to methylphenidate n = 40 or placebo n = 38 Participants had high scores on severity of dependence (SDS) at baseline (mean 10.5 for methylphenidate group and 10 for placebo)	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 supervised dosing.	**Measures** Urine drug screens for methamphetamine; previous and current substance use (Pompidou questionnaire); severity of dependence (SDS); methamphetamine craving (visual analogue scale); alcohol use (Alcohol Use Disorders Identification Test — AUDIT); record of attendance and medication consumption- acceptable adherence measure of 60% or more of doses; and adverse medication effects. **Summary** Methylphenidate was no more effective than placebo in reducing the number of methamphetamine-positive urines returned by participants or decreasing scores on the craving scale or SDS. Very low adherence and high attrition rate from the study — only 21% overall met adherence measure, 34.2% completed 22 weeks, with the placebo group having a significantly lower retention rate than the methylphenidate group. There was a decrease in mean SDS scores (–3.7 for methylphenidate vs –1.6 for placebo) and craving scores (–21.2 for methylphenidate vs –13.3 for placebo) but neither reached statistical significance. Authors suggest high attrition could be due in part to the requirement for daily clinic visits for dosing.	Level II- double-blind placebo-controlled RCT
Tiihonen et al. (2007). A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *American Journal of Psychiatry*, 164(1): 160–162. Finland	Aripiprazole, methylphenidate	53 dependent amphetamine users Males n = 36 (68%) Mean age: 32.2 years Mean years of methamphetamine use: approx. 14 years Randomized to aripiprazole (n = 19), methylphenidate (n = 17) or placebo (n = 17)	Daily supervised dispensing. Aripiprazole 15 mg/day Methylphenidate 18 mg/day for the first week, 36 mg/day for the second week, and 54 mg/day thereafter Equivalent gel capsule placebo All patients received un-structured psychosocial treatment	**Measures** The primary outcome measure was the proportion of amphetamine-positive urine samples during pharmacological treatment. **Summary** Patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than did the placebo group. Those who received methylphenidate had significantly fewer amphetamine-positive urine samples than did the placebo group.	Level II — double-blind placebo-controlled randomized trial

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				The trial was ceased after initial analysis reported aripiprazole significantly worsened symptoms.	
Anderson et al. (2012). Modafinil for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence*, 120(1–3): 135–141. United States of America	Modafinil	210 dependent methamphetamine users 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 Randomized 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 standardized 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 Behavior Scale; pill count, self-report and urinalysis of medication adherence. **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. Low medication adherence shown by urine screen: 25% (n = 36) of active group showed > 85% of urines positive for modafinil. 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 between groups differences for ASI, CGI, craving, or HIV risk-taking behaviors. 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 randomized trial
Heinzerling 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	Modafinil	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 Randomized to modafinil n = 34 or placebo n = 37	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).	**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. Rates of treatment completion were 41% modafinil and 35% placebo. Available pill count data found treatment group took average of 91% of dispensed study medication compared to 83% in the placebo group. 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).	Level II — double-blind, placebo-controlled RCT
McElhiney et al. (2009). Provigil (modafinil) plus cognitive	Modafinil	13 gay men n = 11 (85%) HIV + n = 7 with DSM–IV stimulant abuse (54%) and n = 6 DSM–IV stimulant dependence	Twelve weeks of modafinil followed by four weeks of placebo. Starting modafinil dose was 50 mg/day for those taking HIV antiretroviral	**Measures** Urine drug screen; methamphetamine use self-report; Hamilton Rating Scale for Depression (HAM–D); University of Minnesota	Level III–3 — single blind within subjects' pilot

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
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		(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	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.	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, no medication adherence measure reported.	
McGaugh et al. (2009). Open-label pilot study of modafinil for methamphetamine dependence. *Journal of Clinical Psychopharmacology*, 29(5): 488–491. United States of America	Modafinil	Seven dependent methamphetamine users Males n = 3 (43%) Mean age: 45.3 years Mean years of methamphetamine use: not reported Mean use in last 30 days: 20.1 (8.25) days	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, individualized 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 behavior therapy sessions.	**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; pill count for adherence. **Summary** Study showed the tolerability and safety of modafinil 400 mg/day among a sample of eight methamphetamine-dependent outpatients. Although anxiety is a potential side effect of modafinil, ratings on both the Hamilton anxiety and depression scales decreased over the course of the study. The study was not designed to test the efficacy of modafinil for methamphetamine dependence, nor did it report medication compliance, however self-reported methamphetamine use decreased but amphetamine-positive urine screens did not change. Scores on both the HAM–D and HAM–A decreased significantly.	Level IV — open-label clinical trial without a control group
Shearer et al. (2009). A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. *Addiction*, 104(2): 224–233. Australia	Modafinil	80 dependent methamphetamine users Males n = 50 (62.5%) Mean age: 35.9 years Mean years of methamphetamine use: 7 years Mean use in last 28 days: 19.4 days Randomized to modafinil n = 38 or placebo n = 42	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 behavioral intervention developed specifically for methamphetamine users.	**Measures** Self-reported ATS use: The Opiate Treatment Index (OTI) and 28-day drug use diaries; weekly urine drug screen; Brief Symptom Inventory (BSI); Severity of Dependence Scale (SDS); methamphetamine craving in the past week on a100-mm visual analogue scale (VAS); weekly urine specimens during treatment; medication adherence via event monitoring system (MEMS) cap bottles and urine screen; and adverse events. **Summary** There were no differences in methamphetamine abstinence, craving, severity of dependence, treatment retention or medication adherence. There was a non-significant trend for medication-compliant participants to provide more methamphetamine-negative urine samples. Outcomes were better for methamphetamine-dependent participants with no other substance dependence and those who accessed counselling. Treatment retention was very low (32.5% completed treatment). Among small sample retained, the medication was well tolerated and daily medication adherence was 78%. Regardless of group allocation, each session of counselling attended during the 10-week treatment period reduced 28-day stimulant self-report by one day (95% CI: –1.7, –0.3) at post-treatment follow-up. Simply attending any form of counselling reduced 28-day self-report by six days (95% CI: –10.8, –1.8). HIV-positive participants who were over-represented in the modafinil group had poorer methamphetamine use outcomes.	Level II — double-blind placebo-controlled RCT (pilot)

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
Anderson et al. (2015) Bupropion for the treatment of methamphetamine dependence in non-daily users: a randomized, double-blind, placebo-controlled trial. Drug and Alcohol Dependence 50:170-4 United States of America	Bupropion	204 methamphetamine dependent users reporting less-than-daily use. Males n = 132 (65%) Mean age: 39.3 years Mean years of use: **not reported** Use in last month > 19 days in past 30: 35% bupropion participants, 27%. placebo. Randomized to bupropion (n = 100) or placebo (n = 104)	Bupropion, sustained release, 150 mg twice daily or matched placebo All participants received 90-minute cognitive-behavioral, relapse-prevention, manual-driven group psychotherapy three times a week.	**Measures** Abstinence during last two weeks of treatment, measured by at least two urine drug tests in each of treatment weeks 11 and 12. Negative MA = negative results or result < 300 ng/ml. Positive test results were confirmed by gas chromatography/ mass spectrometry, quantification limit of 78 ng/mL for MA. Participant drop out prior to last two weeks of treatment scored as a failure on the primary outcome. Urine screening three times a week- medication adherence assessed as detectable bupropion, > 5 ng/mL, in at least 50% of urine samples in weeks 1 to 10, and at least 66% of samples during weeks 11 and 12. **Summary** There was no significant difference between groups in the proportion achieving abstinence during final 2 weeks of treatment. Subgroup analysis of participants with less frequent use at baseline (≤18 days of past 30) did not support previous study findings, as it showed no difference in success between groups. No significant difference in abstinence (past 2 weeks) between treatment and placebo groups was evident among sub-groups of participants who were male, more depressed or had adult ADHD. Overall lower frequency users in both treatment groups did better. Subgroup analysis also showed no significant difference in last-two-weeks abstinence, between bupropion and placebo treatments for: males, participants with higher level of depression or participants with adult ADHD. Moderate treatment completion (57%) and low medication adherence (47%). Authors noted that due to a higher than expected placebo success rate (19% compared to 14% bupropion) and poor medication adherence, the statistical power of the study was weakened; hence while the study does not support bupropion effectiveness, the authors cannot strongly conclude against it.	Level II — double-blind placebo-controlled RCT
Heinzerling et al. (2014). Randomized, placebo-controlled trial of bupropion in methamphetamine-dependent participants with less than daily methamphetamine use. *Addiction* 109(11): 1878-1886. United States of America	Bupropion	84 methamphetamine-dependent adult treatment-seekers, used < 30 days past month. Males n = 68 (81%) Mean age: approx. 38 years Mean years of methamphetamine use: Mean use in last month: 10.3days -bupropion; 9.9 days placebo Randomized to bupropion (n = 41) and placebo (n = 43).	Bupropion sustained release 150 mg twice daily and matched placebo twice daily Weekly individual CBT sessions during the medication phase Study dosing was twice daily except for single doses given on first three days and final three days of 12-week trial.	**Measures** Urine drug screens conducted three times per week. End of treatment abstinence from MA defined/assessed as- urine drug screens for weeks 11 and 12 being negative for MA and > = 2 screens available each week. Treatment retention (number of days attended) and treatment effectiveness measured by group's mean number of methamphetamine negative urine drug screens. Medication adherence assessed post-hoc via bupropion/hydroxy bupropion levels found in blood plasma samples taken week 6 of trial. **Summary** No significant difference was found in the end of treatment abstinence for the bupropion group (29%, 12/41) and placebo participants (14%, 6/43; p = 0.087). The mean number of methamphetamine-negative urine drug screens (treatment effectiveness score) was significantly higher for bupropion than for placebo but there was no significant difference in treatment retention. Medication adherence assessed by blood plasma samples was low (32%). End of treatment abstinence was significantly higher among bupropion recipients assessed as medication adherent (54%, 7/13) compared to non-adherent participants (18%, 5/28; p = 0.018), and this group showed greater treatment retention and treatment effectiveness. No	Level II — Randomized, double-blind, placebo-controlled clinical trial

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				serious adverse events were deemed to be due to study medication, though more than half participants reported at least one adverse event generally of mild to moderate severity (71% bupropion; 51% placebo). Authors report results suggest efficacy of bupropion in methamphetamine dependence, but only in a subgroup of medication adherent participants with less than daily use at baseline.	
McCann and Li (2012). A novel, nonbinary evaluation of success and failure reveals bupropion efficacy versus methamphetamine dependence: reanalysis of a multisite trial. *CNS Neuroscience and Therapeutics*, 18(5): 414–418. [Also see Elkashef et al. (2008) for original data analysis] United States of America	Bupropion	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 Randomized to bupropion (n = 79) or placebo (n = 72)	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. All participants received 90 min. of manualized, group-based CBT three times a week (Matrix Model) for 12 weeks.	**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); adherence was assessed by weekly tablet count. **Summary** This study re-analyzed 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. However, the previously reported high rate of medication adherence was not corroborated in this analysis. 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 end of study abstinence. 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).	Level II — double-blind, placebo-controlled RCT
Das 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	Bupropion	30 men dependent methamphetamine users who had anal sex with men in the past three months while using methamphetamine (43% HIV+) Males n = 30 (100%) Mean age: 35.7 years Mean years of use: not reported Mean use in last month: less than 3 days a week n = 14 (42.5%); 3–7 days a week n = 16 (57.5%) Randomized to bupropion (n = 20) or placebo (n = 10)	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)	**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 behavior; 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	Level II – double-blind placebo-controlled RCT (feasibility pilot)

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				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 behaviors, 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. Good study completion rates, but low to moderate medication adherence. Low phone pre-screen to randomization rate (9%), but 56% for those assessed in person. No serious adverse events occurred and there were no significant differences in adverse events by treatment assignment.	
Elkashef et al. (2008) Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology*, 33(5): 1162–1170. United States of America	Bupropion	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 > 18 days n = 80 (53%) Randomized to bupropion n = 79 or placebo n = 72	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 All participants received 90 min. of manualized, group-based CBT three times a week (Matrix Model) for 12 weeks.	**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 assessed by weekly tablet count. **Summary** 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. Overall treatment completion rate of 51%. Medication compliance was reported as high for both groups (average 1.73 tablets taken daily). The authors concluded that bupropion, in combination with behavioral group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence in male patients.	Level II –double-blind multi-site placebo-controlled RCT
Shoptaw et al. (2008). Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence*, 96(3): 222–232. United States of America	Bupropion	73 dependent methamphetamine users recruited from 3 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 Randomized to bupropion (n = 36) or placebo (n = 37)	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)	**Measures** Methamphetamine use as assessed via urine drug screens; treatment retention; depressive symptoms (Beck Depression Inventory — BDI); methamphetamine-cravings (visual analogue scale); pill count and self-report of medication adherence; 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	Level II — double-blind placebo-controlled RCT

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				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). Available pill count data indicated high medication adherence (> 85%), overall low completion rates (around 35%). No treatment-related serious adverse effects.	
Mooney et al. (2016). Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder. *Journal of Addiction Medicine* 10(4): 236-243. United States of America	Naltrexone and bupropion	49 high-severity methamphetamine users (DSM-5 severe stimulant use disorder) seeking treatment at three sites. Male n = 26 (53%) Mean age: 39.9 years Mean years of methamphetamine use: not reported Mean use in last 30 days: 27	Pharmacotherapy provided for 8 weeks and combined extended release injectable naltrexone (as Vivitrol 380 mg) in weeks 1 and 5, with extended-release oral bupropion (as Wellbutrin XL 450 mg/d). Bupropion dosing titrated as: 150 mg days 1 and 2, 300 mg days 3 and 4, and 450 mg daily from day 5. A reduction to 300 mg was permitted to alleviate any treatment related adverse effects. Dose tapered in week 9, 300 mg days 57, 58 and to 150 mg days 59, 60. Participants were provided a smartphone-assisted medication adherence platform.	**Measures** Methamphetamine use measured using urine drug screens collected twice weekly; quality of life measured with the Treatment Effectiveness Assessment; craving for MA measured using visual analog 1-100 scale (VAS); self-reports of treatment-emergent adverse events. Medication adherence measured via: blood samples taken weeks 5 & 8 (bupropion/hydroxy bupropion levels); observation of oral medication dosing on clinic days; participants using study-provided smartphones to video record oral dosing on non-clinic days. **Summary** The pilot study found the pharmacotherapy to have a 24% response rate, identifying 11 'responders'- participants who provided at least 6 of 8 MA-negative urine drug screens during weeks 5 to 8 of treatment. 84% of participants received the second naltrexone injection and oral medication adherence was also high (93.6% self-report; 86.6% in-person/video observation). High rates of retention indicated by 89.4% clinic visit attendance rate (of visits required twice weekly). Methamphetamine craving scores decreased for both groups, but significantly more reduced for the responder group than non-responders each week (weeks 2-8; $P < 0.05$). Responders showed significantly greater quality of life scores at treatment end ($P < 0.001$). Medications were generally well tolerated (79% of adverse events were mild) and did not typically lead to discontinuation; seizure reported for 1 participant.	Level— IV single-arm, open-label pilot study
Pal et al. (2015) Impact of Prospectively Determined A118 G Polymorphism on Treatment Response to Injectable Naltrexone Among Methamphetamine-Dependent Patients: An Open-Label, Pilot Study. *Journal of Addiction Medicine,* 9(2):130-135. United States of America	Naltrexone	22 methamphetamine dependent users; equal ratio of participants with A118 A and A118 G genotypes. Predominantly smokers of methamphetamine (68%, n = 15) Males n = 15 (68%) Mean age: A118 G group 39.5 years; A118 A group 40.7 years Mean years of methamphetamine use: not reported Mean use in last 30 days: A118 G group 17.4 days; A118 A group 21.2 days. Both genotype groups received sustained release intramuscular naltrexone	All participants received a one-off injection of 380 mg naltrexone and weekly, individual psychosocial therapy for 4 weeks. Participants with the A118 A genotype were compared with those in the A118 G single nucleotide polymorphism (SNP) group.	**Measures** Methamphetamine use assessed weekly via self-report and urine screens. Weekly assessment of adverse events using a checklist of 34 possible events. **Summary** Although previous trials have indicated A118 G alcohol-dependent patients showed a better response to naltrexone treatment, in this study there was no significant difference in methamphetamine use (days abstinent or negative urine screens) between A118 G and A118 A methamphetamine-dependent participants. There were no serious adverse events and the treatment was generally well tolerated.	Level III-3 open-label pharmacogenetic efficacy trial.
Kelty et al. (2013). A retrospective assessment of the use of naltrexone implants for the treatment of	Naltrexone implants	41 problematic amphetamine users. Males n = 27 (61%) Mean age:31.4 ± 7.3years Mean years of methamphetamine use: 10 years	Participants received an O'Neil Long Acting Naltrexone Implant (OLANI), implanted into the subcutaneous tissue of the abdomen. Procedures were conducted under local anesthetic, each underwent a	**Measures** Amphetamine abstinence following treatment measured via self-report, non-systematic urine screens (17 participants, total of 403 samples). Blood tests for concentrations of naltrexone and 6-beta-naltrexol	IV – Open cohort study

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
problematic amphetamine use. *The American Journal on Addictions,* 22(1):1-6. Australia		Mean use in last month: approx. 15 days Predominately methamphetamine use by injection (77.5%) and smoking (20.0%) All patients were treated with a sustained release naltrexone implant	minimum of one implant procedure, with each procedure involving two to three implants.	tested opportunistically (11 participants, total of 47 samples) with limits of detection and quantification of .1 and .5 ng/ml, respectively. Self-reported changes in non-amphetamine drug use following treatment. **Summary** Participants reported a median abstinence period of 2.5 months following treatment with naltrexone implant; 66% (n = 29) reported no amphetamine use for at least 1-month post-treatment, 32% reported being still abstinent at 6 months. Higher blood naltrexone levels were associated with higher rates of abstinence; participants with levels above 2 ng/ml were 2.27 times more likely to be abstinent than those with lower levels. 44% (n = 19) of participants self-reported some level of decrease in use of other AOD. Implant was generally well tolerated, ten people reported low-moderate transient adverse events following treatment. Provides preliminary data supporting the use of implant naltrexone, particularly at levels above 2 ng/ml.	
Grant 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	N-acetyl cysteine (NAC) plus naltrexone	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 Randomized to NAC + naltrexone (n = 14) or placebo (n = 17)	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	**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 (QoLI). **Summary** There were no differences between groups on any measures. The authors concluded that naltrexone plus NAC did not significantly reduce craving among non-treatment-seeking methamphetamine-dependent individuals. Authors noted limitations of small sample size. Medication adherence not reported and moderate retention (64.3% active medication group completed, 47.1% placebo).	Level II — double-blind, placebo-controlled RCT (pilot)
Jayaram-Lindström 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 Randomized to naltrexone n = 40, placebo n = 40	50 mg naltrexone daily for 12 weeks and matching placebo, plus 60 min. of individual manualized CBT-based relapse prevention weekly	**Measures** Urine drug screens; Addiction Severity Index (ASI); self-reported amphetamine use (TLFB); Craving Visual Analog Scale (VAS); pill count and weekly urinary analysis for medication adherence; and medication adverse events. **Summary** Naltrexone resulted in higher negative urine screens and self-reported amphetamine use, better retention in treatment and reduced craving. Moderate treatment retention (68.6% completed) and medication adherence (62.5% adherence among active medication group). There was an effect for time in treatment with an increase in mean amphetamine-negative urine screens among both groups over 12 weeks. Higher adherence (based on urine analysis) correlated with higher rates of abstinence. Treatment was well tolerated.	Level II — double-blind, placebo-controlled RCT
Jayaram-Lindström et al. (2005). An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. *Nordic Journal of Psychiatry*,	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 min. weekly of manual-driven individualized 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. **Summary** Eleven participants (55%) completed the 12-week study. The	Level IV – open-label clinical trial without control group (feasibility)

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
59(3): 167–171. Sweden				frequency and amount of amphetamine used were significantly lower during treatment compared with pre-treatment consumption, and craving scores also decreased among completers. There was a significantly higher proportion of positive tests of 6-beta-naltrexol in urine among patients completing 12 weeks of treatment compared to those who did not (77% vs 22%); 90% of participants tolerated naltrexone, even when all but two continued to use amphetamines.	
Colfax et al. (2011). Mirtazapine to reduce methamphetamine use: a randomized controlled trial. *Archives of General Psychiatry*, 68(11): 1168–1175. United States of America	Mirtazapine	60 dependent methamphetamine users -all 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) Randomized to mirtazapine (n = 30) or placebo (n = 30)	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.	**Measures** Urine drug screen for methamphetamine metabolite; medication adherence measured by MEMS capped bottles and self-report; Depressive symptoms - Center for Epidemiologic Studies–Depression Scale (CES-D); and sexual risk behavior. **Summary** Mirtazapine group significantly decreased methamphetamine use and sexual risk-taking behaviors. The number needed to treat to achieve a negative weekly urine test result was 3.1. Participants receiving mirtazapine showed a 40% reduction in positive urine test results from baseline the final visit, compared to a 6% reduction for the placebo group. Majority participants (93%) completed the trial, 85% of follow-up visits were completed, medication adherence was 48.5% by medication event monitoring systems and 74.7% by self-report; completion and adherence were not significantly different between arms. Sexual risk behaviors 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.	Level II – double-blind placebo-controlled RCT
Zorick et al. (2011). Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine. *Drug and Alcohol Dependence*, 118(2–3): 500–503. United States of America	Sertraline	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 Randomized to sertraline plus CM (n = 61), sertraline-only (n = 59), placebo plus CM (n = 54), or placebo-only (n = 55)	Sertraline or placebo at 50 mg/day at randomization. On the eighth day following randomization, 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 a week.	**Measures** Re-analysis of data from Shoptaw et al. (2006) included measures: urine drug screen to identify sample with increase in methamphetamine use > 15% during the last month of trial. Characteristics of this sample and measure of craving - Visual Analogue Scale. **Summary** More participants in the sertraline condition increased methamphetamine use more than 15% during treatment (n = 13) than in the placebo condition (n = 5; p = 0.03). No difference between groups on the number of participants who decreased their use. 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 characterized participants in the sertraline group who increased their methamphetamine use.	Level II — double-blind placebo-controlled RCT
Shoptaw et al. (2006). Randomized, placebo-controlled trial of sertraline and contingency management for the	Sertraline	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	Sertraline or placebo at 50 mg/day at randomization. On the eighth day following randomization, dose was increased to 50 mg twice daily maintained for the 12-week duration of the trial. Contingency management participants observed	**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**	Level II — double-blind placebo-controlled RCT

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
treatment of methamphetamine dependence. *Drug and Alcohol Dependence*, 85(1): 12–18. United States of America		years Mean use in last 30 days: approx. 13 days Randomized to sertraline plus CM (n = 61), sertraline-only (n = 59), placebo plus CM (n = 54), or placebo-only (n = 55)	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$10 bonus voucher each third metabolite-free urine sample. Plus, all participants received 90-min. Matrix Model relapse prevention groups three times per week.	No statistically significant main or interaction effects for sertraline or CM in reducing methamphetamine use were observed using a generalized estimating equation (GEE), although post hoc analyses showed the sertraline-only condition had significantly poorer retention than other conditions ($\chi 2(3) = 8.40$, $p < 0.05$). 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. High medication adherence- between 78%-91% of each group reported at least 80% adherence to study medication. Low completion rates- drop-outs in sertraline plus CM (30/61), sertraline-only (35/59), 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 ($\chi 2(3) = 8.40$, $p < 0.05$).	
Batki et al. (1999). Fluoxetine in methamphetamine dependence — a-controlled trial: a preliminary analysis. Paper presented at the Annual Meeting of the College on Problems of Drug Dependence, Acapulco, Mexico. United States of America	Fluoxetine	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 Randomized to fluoxetine (n = 30) daily or placebo (n = 30)	One week single-blind placebo lead-in followed by seven weeks of double-blind fluoxetine 40 mg daily or placebo	**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.	Level II — double-blind placebo-controlled pilot RCT
Ling et al. (2012). Double-blind placebo-controlled evaluation of the PROMETA™ protocol for methamphetamine dependence. *Addiction*, 107(2): 361–369. United States of America	Prometa™ protocol (flumazenil and gabapentin)	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 Randomized to flumazenil/gabapentin/hydroxyzine (n = 60) or placebo (with hydroxyzine) (n = 60)	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).	**Measures** 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. Pill counts and self-report of take-home medicine adherence **Summary** No effect of the protocol over placebo on measures of methamphetamine use, craving or retention in treatment. Less than 70% of the sample received all five infusions (58.9% experimental group, 69.1% placebo) and adherence to take home medications appeared low. 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	Level II — double-blind, placebo-controlled RCT

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				findings may have been influenced by a strong placebo effect due to considerable publicity about the protocol.	
Urschel et al. (2011). A controlled trial of flumazenil and gabapentin for initial treatment of methylamphetamine dependence. *Journal of Psychopharmacology*, 25(2): 254–262. United States of America	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
Urschel et al. (2007). Open-label study of a proprietary treatment program targeting type A γ-aminobutyric acid receptor dysregulation in methamphetamine dependence. *Mayo Clinic Proceedings*, 82(10): 1170–1178. United States of America	Flumazenil and gabapentin	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	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	**Measures** Methamphetamine craving (visual analogue scale); urine drug screens; self-report methamphetamine use (TLFB); adherence to treatment (number infusions, pill count). **Summary** 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.	Level IV – open-label trial
Rezaei et al. (2016). Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial. *Fundamental & Clinical Pharmacology* 30, 282–289 Iran	Topiramate	62 dependent methamphetamine adults; n = 57 completed trial, all provided at least one MA-positive urine sample during screening, 100% were receiving methadone maintenance therapy. Males n = 57 (100%) Mean age: 29 years Mean years of methamphetamine use: not reported Mean use in last month: not reported Randomized to topiramate (n = 29) and placebo (n = 28).	Daily oral topiramate, or placebo, for 10 weeks. Topiramate initiated at 50 mg/day week 1, increased by 50 mg/day every week, until 200 mg/day. After week 10, dose was tapered, 3 days of 100 mg/day f and 50 mg/day for 2 days.	**Measures** Methamphetamine severity and craving, measured by weekly Addiction Severity Index (AS) and Brief Substance Craving Scale (BSCS). Fortnightly Beck Depression Rating Scale and urine drug screens. Medication adherence assessed by capsule count. **Summary** The topiramate group had significantly lower ASI domain scores for 'drug use severity' ($P < 0.001$) and 'drug need' ($P < 0.001$) at treatment end and showed greater improvement in legal status, and employment. Both groups showed reductions in psychostimulant-positive urine samples over the course of the trial, with the topiramate group providing significantly lower proportion of positive tests than the placebo group, only at week 6. There were no differences between topiramate and placebo groups in depression scores or methamphetamine craving (intensity and frequency), though craving (duration) was significantly lower for the treatment group, and no significant differences on ASI scores for medical status, family/social relationship and psychiatric	Level II — randomized double-blind placebo-controlled trial

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Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
				domains. Topiramate was concluded to show promise in reducing drug use, severity of dependence and craving duration.	
Elkashef et al. (2012). Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction*, 107(7): 1297–1306. United States of America	Topiramate	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 Randomized to topiramate (n = 69) or placebo (n = 71)	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 > 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. All participants received weekly brief behavioral compliance enhancement treatment (BBCET), a manualized, low-intensity supportive program to promote medication adherence and retention.	**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 (compliance rate = total mg dose dispensed minus total dose returned divided by recommended dose, multiplied by 100). **Summary** Participants who contributed > 6 usable urine samples and took > 50 mg/day of topiramate (or placebo) for 21 days were included in the analysis (n = 111, 79.3%, were evaluated: 58 topiramate; 53 placebo). ITT analysis showed similar results to completer-only analysis. Study showed no effect for topiramate in increasing abstinence, but there were significant reductions in reducing use, severity of dependence and improving general functioning compared to placebo. Abstinence at entry was related to abstinence in weeks 6–12. Topiramate recipients experienced significant improvement in observer-rated global severity of dependence, measured by CGI–O, a non-significant trend toward decreasing craving over time. Topiramate was safe and well tolerated. Mean adherence rate was 69.8% for topiramate and 67.4% for placebo. No significant difference between groups in drop-out rate.	Level II – double-blind multi-site placebo-controlled RCT
Heinzerling 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	Baclofen and gabapentin	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 Randomized to baclofen (n = 25), gabapentin (n = 26) and placebo (n = 37)	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.	**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 and self-report 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.	Level II — double-blind, placebo-controlled RCT
Brodie et al. (2005). Safety and efficacy of gamma vinyl GABA (GVG) for	Vigabatrin (Gamma Vinyl GABA (GVG))	30 participants: n = 27 methamphetamine-dependent entered and 18 completed the study; 17 participants	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,	**Measures** Urine samples twice a week; daily vital signs. **Summary**	Level IV — open-label safety trial

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
the treatment of methamphetamine and/or cocaine addiction. *Synapse*, 55(2): 122–125. United States of America		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	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).	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.	
Meredith et al. (2009). Open trial of injectable risperidone for methamphetamine dependence. *Journal of Addiction Medicine*, 3(2): 55–65. United States of America	Risperidone	34 dependent methamphetamine users entered the study, 22 received injectable risperidone Males n = 19 (86.4%) Mean age: 38 years Mean years of methamphetamine use: 12.2 years Mean use in last 30 days: 17.1 days	Participants entered a seven-day open-label run-in with oral risperidone. Those who tolerated oral risperidone (n = 22) were started on long-acting injectable risperidone 25 mg intramuscular medication with subsequent injections every two weeks to a total of four injections. Participants remained on oral risperidone during the first three weeks after initial injection. Participants were offered eight weekly individual sessions of relapse prevention counselling.	**Measures** 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. Risperidone and 9-hydroxy-risperidone plasma levels were obtained at weeks 3, 6, and 8. **Summary** No serious adverse events occurred. Methamphetamine used was significantly reduced among those who received injections. Improvements were seen in verbal memory and psychiatric symptoms.	Level IV — open-label clinical trial without a control group
Meredith et al. (2007). An open-label pilot study of risperidone in the treatment of methamphetamine dependence. *Journal of Psychoactive Drugs*, 39(2): 167–172. United States of America	Risperidone	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	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.	**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).	Level IV — open-label clinical trial without a control group
Coffin et al. (2013). Aripiprazole for the treatment of methamphetamine dependence: a	Aripiprazole	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	5 mg daily of Aripiprazole (or placebo) for one week, 10 mg daily for the next week, then 20 mg daily for the remainder of the 12-week study Weekly 30-minute CBT and MI substance abuse counselling	**Measures** Urine drug screens for methamphetamine; medication adherence (self-report and medication event monitoring system -MEMS); sexual risk-taking behavior; methamphetamine craving; severity of dependence (SDS).	Level II — double-blind placebo-controlled randomized trial

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
randomized, double-blind, placebo-controlled trial. *Addiction*, 108(4): 751–761. United States of America		n = 43 (47.8%); 2 days or less n = 28 (31.1%) Mean years of methamphetamine use: not reported Major depression, history of psychiatric medication within the past four weeks and a CD4 cell count below 200 cells/μl were exclusion criteria. Randomized to aripiprazole (n = 45) or placebo (n = 45)		**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).	
Salehi et al. (2015). The effect of buprenorphine on methamphetamine cravings. *Journal of Clinical Psychopharmacology* 35(6): 724-727. Iran	Buprenorphine	40 methamphetamine dependent users referred to treatment Male n = 40 (100%) Mean age: 31.8 years (medication group), 29.6 years (placebo) Mean years of methamphetamine use: not reported Mean use in last 30 days: not reported	16 weeks of Matrix model program and either daily buprenorphine or matched placebo. Sublingual buprenorphine initial dose of 2 mg/d, increased to 6 mg within 7 days (3 sublingual tablets). After 16 weeks, doses tapered and stopped in 10 days, both groups followed for 28 weeks.	**Measures** Measures of methamphetamine craving (Cocaine craving questionnaire-brief) and use (urine drug test), and assessment of drug side effects conducted every 2 weeks. **Summary** The study found that during the treatment period, buprenorphine augmentation with the Matrix program significantly reduced methamphetamine craving compared with placebo ($P < 0.001$). After treatment (weeks 17-28) both groups showed increase in meth cravings but the medication group showed less increases and average CCQ scores remained significantly lower than placebo group ($P < 0.05$). The medication group reported less positive urine tests than the placebo group at each observation, showing a statistically significant difference at all weeks ($P < 0.05$), excluding weeks 3 and 28. No prominent side effects were observed in the placebo group. Some limitations in quality/level of reporting and medication adherence not directly reported.	Level II — double-blind placebo-controlled randomized trial
Mousavi et al. (2015). The Efficacy of N-Acetylcysteine in the Treatment of Methamphetamine Dependence: A Double-blind Controlled, Crossover Study. *Archives of Iranian medicine,* 18(1):28-33. Iran	N-Acetylcysteine (NAC)	23 treatment-seeking, dependent methamphetamine users; 23 people completed the study and are included in reporting. Males n = 19 (82.6%) Mean age: 29.21 years Mean years of methamphetamine dependency: 4.1 years Mean use in past month: not reported Crossover design: first randomized to N-Acetylcysteine (n = 11) and placebo (n = 12).	Two four-week interventions: 600 mg/day NAC effervescent tablets for one week, then three weeks 1200 mg/day NAC with a matched placebo, followed by three days 'washout period' for both group- no medication. After this, each group received the crossover intervention for another four weeks. During the 8 weeks, all participants received weekly, standardized, one-hour group sessions (Matrix Model).	**Measures** Symptoms of methamphetamine craving measured by the Cocaine Craving Questionnaire-Brief (CCQ-Brief). Pill counts for medication adherence and self-reported medication side effects. Self-reported methamphetamine use and urine screening were completed weekly but not reported. **Summary** NAC was shown to have a significant effect in reducing levels of methamphetamine craving, as compared to placebo, among the predominantly male participants. Mean CCQ-Brief craving scores at end of first intervention were 3.38 for NAC group vs 5.96 for placebo, at end of second intervention scores were 3.2 vs 4.57 respectively. The medication was well tolerated with no unexpected side effects or related study drop-out reported. Authors noted that increases in craving score for the NAC to placebo crossover group may indicate NAC has a limited, shorter-term effect. Findings suggest lower doses of NAC may also be effective and the Matrix model psychotherapy may have increased effectiveness of NAC treatment.	Level II – randomized, double-blind controlled crossover trial
Johnson et al. (2008). A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine	Ondansetron	150 dependent methamphetamine users Males n = 96 (64%) Mean age: 36 years Mean years of methamphetamine use: 18.4 years Mean use in last month: 11.7 days Randomized to ondansetron 0.25 mg (n = 37), 1 mg (n = 29), or 4 mg (n = 38)	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	**Measures** 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. **Summary**	Level II — double-blind, placebo-controlled RCT

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Table 1 (*continued*)

Reference	Medicine	Number and description of participants	Intervention and comparison if relevant	Primary outcomes including measures used	Level of evidence
dependence. *International Journal of Neuropsychopharmacology*, 11(1): 1–14. United States of America		orally twice daily and matched placebo (n = 46)		There were no significant differences in drug use measures, urine methamphetamine level, self-reported non-methamphetamine-use days, or rates of success vs failure in self-reported achievement of at least three consecutive weeks of abstinence. No statistically significant differences among the study groups in the scales of clinical severity of methamphetamine dependence or withdrawal (MAWQ) or in the rate of change in craving. No differences in retention rates, and relatively high dropout rates overall (32.3%). The average decline in the drug score was significantly less negative for the ondansetron (0.25 mg b.i.d.) group compared with placebo (p = 0.04) but after correction for multiple comparisons, it was NS. Ondansetron was well tolerated, and adverse events were more likely to be reported in the placebo group compared with two of the three ondansetron treatment groups.	
Swanson 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	Varenicline	20 dependent methamphetamine users No other participant level data were reported in this conference abstract.	Varenicline 1 mg twice daily or placebo for eight weeks Weekly individual counselling using cognitive behavior therapy	**Measures** Urine screens for methamphetamine metabolites; adverse events of medication. **Summary:** 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 (3.7 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.	Level II —double-blind placebo-controlled trial (pilot)
Batki 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	Amlodipine	77 dependent methamphetamine users Males n = 59 (77%) Mean age: 35.6 years Mean years of methamphetamine use: 8 years Mean use in last 30 days: 1.5 g approx. Randomly assigned to PLA (n = 26), AML 5 mg/day (n = 25), and AML 10 mg/day (n = 26)	Parallel outpatient groups were given Amlodipine 5 mg, or Amlodipine 10 mg per day, or placebo	**Measures** Depression (BDI); retention; methamphetamine use in grams; craving. **Summary** 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.	Level II — randomized double-blind placebo-controlled trial

Level of evidence was rated according to the National Health and Medical Research Council guidelines (2009) (I = A systematic review of level II studies; II = A randomized controlled trial; III-1 = pseudorandomized controlled trial; III-2 = A comparative study with concurrent controls, a retrospective cohort study; III-3 = A comparative study without concurrent controls, a case control study; IV = Case series with either post-test or pre-test/post-test outcomes, A cross-sectional study or case series.

Table 2
Synthesis of studies reviewed for the treatment of amphetamine-type stimulant dependence.

	Dexamphetamine	Methylphenidate	Modafinil	Bupropion	Naltrexone	Antidepressants			Flumazenil and gabapentin combination	Anticonvulsants			Antipsychotics		Buprenorphine	N-acetyl cysteine	Baclofen	Ondansetron	Varenicline	Amlodipine
						Mirtazapine	Sertraline	Fluoxetine		Topiramate	Gabapentin	Vigabatrin	Risperidone	Aripiprazole						
Number of studies	7	6	5	7	6	1	2	1	3	2	1	1	3	2	1	2	1	1	1	1
Number of RCTs	4	5	3	5	2	1	1	1	2	2	1	0	1	2	1	2	1	1	1 pilot	1
ATS use reduced?	Yes, but not more than placebo	Yes, may reduce use	Yes, if compliant with medicine	Yes, but evidence equivocal	Yes, but evidence equivocal	Possibly but limited evidence	Appears to increase use	No more than placebo but limited evidence	May increase use or have no effect	Yes, but limited evidence	No	Possibly but evidence limited (no RCTs)	Possibly but evidence limited	May increase use or have no effect	Yes, but limited evidence	Combined with Naltrexone may reduce use, but no more than placebo	Reductions when medication compliant	No	Possibly but evidence limited	No
Other effects	Appears to reduce severity of dependence	Appears to reduce craving, though possibly not to the same extent as risperidone	No effect on craving or treatment retention	Reduces tobacco smoking	May improve retention, reduce craving	Sexual risk-taking reduced among men who have sex with men	Poorer retention and more adverse events	May reduce craving	Increased frequency of use in one study, but less than placebo	May reduce severity of dependence and improve general functioning	No effect on craving or retention	May result in weight gain	Improvements in craving, verbal memory and psychiatric symptoms	Increased use in one study and adverse events in both	May reduce craving	May reduce craving	Medication adherence related to outcome, short half-life limits its utility	No effect on craving or severity of dependence	May improve retention and duration of abstinence	No
Safety	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Potentially increases adverse events	Safe and well tolerated	Very high rates of mild adverse events	Safe and well tolerated	Safe and well tolerated	May cause visual field defects	Safe and well tolerated	May have unsafe side effects	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Safe and well tolerated	Not reported	Not reported
Comments	Studies had a high drop-out rate	Studies had a high drop-out rate	Studies had a high drop-out rate	Some studies had low medication adherence	Most studies had a high drop-out rate	Study had low medication adherence	Studies had a high drop-out rate	Small pilot RCT	Studies had a high drop-out rate	One study had high drop out rate	Study had a very high drop-out rate	Open-label study only	No RCT reporting ATS use; studies had a high drop-out rate	One RCT had to be abandoned for safety reasons	Single study	One RCT not reporting drug use outcomes	Study had a high drop-out rate	Study had a high drop-out rate	A large-scale trial is now underway	Single study abstract only
Evidence of benefit rating	**	**	**	**	**	*	×	*	×	*	—	×	*	×	*	—	—	—	*	—
Key points	Shows some benefits in reducing severity of dependence, but not use	Shows some benefits in reducing use and symptoms of craving.	Shows some benefits in reducing use if medication-compliant	Shows some benefits in reducing use.	Shows some benefits reducing use and may improve retention and lower craving	Shows indications of benefit but evidence is very limited; some reduction in sexual risk-taking in MSM	May increase use	Shows indications of reducing craving, but not use, but evidence is limited	Complicated protocol and may increase use	Shows some benefits in reducing use and severity of dependence, evidence is limited.	Little or no evidence of potential effectiveness	Evidence is limited, but concerns over serious visual field deficits suggest caution	Shows indications of benefit but evidence is limited	May increase use and there are concerns over adverse side effects	Limited evidence shows some benefits as adjunct to Matrix model.	Little or no evidence of effectiveness	Little or no evidence of potential effectiveness	Little or no evidence of potential effectiveness	Indication that it may reduce use, and increase retention and duration of abstinence but evidence is limited	Little or no evidence of potential effectiveness

Legend- Evidence of: **some benefit; *potential benefit but current evidence is limited; —little or no evidence of benefit; ×evidence of harm.

reported more favorable outcomes were achieved among regular, low dose intravenous methamphetamine users (Minarik et al., 2016).

3.2.3. Modafinil

Modafinil belongs to a relatively new class of wakefulness-promoting agents known as eugeroics and is approved for the treatment of narcolepsy, sleep disorder associated with shift work, and excessive daytime sleepiness associated with obstructive sleep apnea. The pharmacology of modafinil is complex and involves dopaminergic effects and modulation of glutamate, GABA, histamine, and hypocretin, although the exact mechanism of action is not yet known (Ballon and Feifel, 2006).

Five studies of modafinil for treatment of amphetamine dependence were found, including two non-controlled studies that alternately reported modafinil was beneficial (McEihiney et al., 2009) and not beneficial (McGaugh et al., 2009) for reducing methamphetamine use.

Three double-blind placebo-controlled RCT trials (quality level II) compared modafinil at daily doses ranging from 200 mg to 400 mg daily; two studies showed that those who were compliant with taking medicine were more likely to reduce drug use (Anderson et al., 2012; Shearer et al., 2009) and one RCT reported no benefits above placebo for reducing use (Heinzerling et al., 2010).

3.2.4. Bupropion

Bupropion is an atypical, non-tricyclic antidepressant and smoking cessation aid thought to act through noradrenaline–dopamine reuptake inhibition and also acts as a nicotinic acetylcholine receptor antagonist. Bupropion has a mild stimulant effect, and antidepressant properties probably brought about by restoring depleted levels of dopamine (Brensilver et al., 2013). Seven studies of bupropion pharmacotherapy for methamphetamine dependence were reviewed.

A two-stage pilot study (Mooney et al., 2016) of bupropion plus naltrexone utilized additional strategies for medication monitoring and adherence, and suggests it has potential as a combination pharmacotherapy for methamphetamine dependence, requiring further investigation.

As detailed in Table 1, six studies of five RCTs examining treatment for amphetamine dependence, involved bupropion trialed at tapered doses from 150 to 300 mg daily. Analysis of findings from three of the trials variously report bupropion as: associated with reduced methamphetamine use (McCann and Li, 2012), reduced use among men but not women (Elkashef et al., 2008) and reduced among subgroups of medication compliant users with 'lighter' use patterns of less than 18 days in a month (Elkashef et al., 2008; Shoptaw et al., 2008) or less than daily use (Heinzerling et al., 2014). Two RCTs showed no support for its benefits (Anderson et al., 2015; Das et al., 2010).

In contrast to previous studies, Anderson et al.'s (2015) multi-site RCT found no difference between a bupropion and placebo group in achieving abstinence during the final 2-weeks of treatment, including among subgroups of male participants and less frequent methamphetamine users.

3.2.5. Naltrexone

Naltrexone is an opioid receptor antagonist that has been used in the

management of opioid dependence and alcohol dependence (Brensilver et al., 2013). The opioid receptors partially modulate dopaminergic effects and may act as a relevant pharmacological target for the positive reinforcing effects of methamphetamine (Karila et al., 2010). Six studies of naltrexone for amphetamine dependence were reviewed and are summarized in Table 1.

Three clinically relevant though non-placebo-controlled studies provided preliminary support of naltrexone for reducing methamphetamine use in the form of oral naltrexone (Jayaram-Lindstrom et al., 2005), implant naltrexone (Kelty et al., 2013) and extended-release injectable naltrexone in combination with oral bupropion (Mooney et al., 2016). A fourth, exploratory open-label study (Pal et al., 2015) examined responsivity to treatment based on genotype but found no difference in efficacy.

Equivocal evidence was demonstrated by two level II quality, double-blind, placebo-controlled randomized trials. One RCT study (Jayaram-Lindstrom et al., 2008) found lower amphetamine use, reduced craving and better retention among the naltrexone group compared to placebo, and that higher medication adherence was associated with higher rates of abstinence. A smaller, pilot RCT (Grant et al., 2010) found no differences in outcomes between dependent methamphetamine users receiving Naltrexone plus N-acetyl cysteine (NAC) and those receiving NAC plus placebo.

3.2.6. Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant used primarily in the treatment of major depressive disorders and thought to work by enhancing the release of noradrenaline and serotonin (Anttila and Leinonen, 2001).

Mirtazapine to treat amphetamine dependence has been the subject of only one published study, a double-blind placebo-controlled RCT among a sample of men who have sex with men (Colfax et al., 2011). The study found the mirtazapine group significantly decreased their methamphetamine use and sexual risk-taking behaviors. Over 90% of participants completed the 12-week trial, with no difference found between treatment groups.

3.2.7. Sertraline

Sertraline is an antidepressant of the selective serotonin reuptake inhibitor class. Sertraline and other medications which increase serotonin at the synaptic cleft have been considered valid targets of investigation based on preclinical studies showing that blocking serotonergic transmission increases amphetamine consumption, as well as a range of methamphetamine withdrawal symptoms which appear similar to that of depression (Rose and Grant, 2008)

There were two level II, double-blind placebo-controlled RCT studies (Shoptaw et al., 2006; Zorick et al., 2011) with outcomes of sertraline (different analyses of the same dataset). The studies showed increases in use during the trial period, and one of these analyses also showed poorer retention and more adverse events than placebo.

3.2.8. Fluoxetine

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class (Rose and Grant, 2008).

A single study was identified reporting outcomes of fluoxetine treatment. Preliminary data of a double-blind RCT (Batki et al., 1999), reported only in conference proceedings, found fluoxetine was not superior to placebo in reducing both self-reported and urinalysis-confirmed methamphetamine use, but the craving was lower in the fluoxetine group compared to the placebo group.

3.2.9. Flumazenil and gabapentin combination

The gamma-aminobutyric acid (GABA) system has been found to play a key role in inhibiting synaptic transmission in the brain. A possible mechanism to reduce the reinforcing and rewarding effects of amphetamines and craving is through GABA agonists mediating transmission along the mesolimbic dopamine system (Rose and Grant, 2008). Hence a number of GABAergic medicines have been investigated for their potential role in treating amphetamine dependence.

Flumazenil is a GABA antagonist available for injection only and used as an antidote in the treatment of benzodiazepine overdose. Gabapentin is a GABA agonist and anticonvulsant that increases GABA concentrations in the central nervous system, possibly via inhibition of GABA-transaminase (Cai et al., 2012). This medication combination was investigated as a treatment for methamphetamine dependence in three studies.

A pilot, open-label study of combination flumazenil and gabapentin (Urschel et al., 2007) reported a significant reduction in methamphetamine cravings and self-reported methamphetamine use. This was followed by a double-blind, placebo-controlled RCT (Urschel et al., 2011) in which 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 and frequency of use was lower among the treatment group than placebo at each assessment (Urschel et al., 2011). The placebo group also showed a similar level of reduction suggesting the initial decrease may have been a response to entering treatment. A second RCT (Ling et al., 2012) found no effect of the protocol over placebo on measures of methamphetamine use, craving or retention in treatment.

3.2.10. Topiramate

Topiramate is an anticonvulsant (anti-epilepsy) drug, known to facilitate GABAergic transmission througha non-benzodiazepine site on the GABAA receptor, and which has shown promise in the treatment of alcohol and cocaine use (Olive et al., 2012).

Two clinical trials of the medication to treat methamphetamine dependence are published, both of which administered escalating doses of topiramate (up to 200 mg per day). One large, double-blind, multisite 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. The overall retention rate was 55%, with no significant difference between groups in the drop-out rate. More recently one smaller sample RCT (Rezaei et al., 2016) reported significant reductions in methamphetamine use at week 6 of topiramate treatment, as compared to placebo, and reduction in dependence severity and drug need.

3.2.11. Gabapentin

Gabapentin is a GABA agonist and anticonvulsant that increases GABA concentrations in the central nervous system, possibly via inhibition of GABA-transaminase (Cai et al., 2012).

While more commonly trialed in combination with flumazenil, as described above, one double-blind RCT (Heinzerling et al., 2006) examined gabapentin as an individual medication in a study using three-treatment groups. The trial found no effect for gabapentin in reducing methamphetamine use, craving or retention when compared to both baclofen and placebo, and reported lower rates of treatment retention (35% gabapentin group completion, 40% placebo and 60% completion for baclofen group).

3.2.12. Vigabatrin

Vigabatrin (Gamma Vinyl GABA or GVG) is an analog of GABA (but not a receptor agonist) that has been shown to minimize the rapid rise of dopamine, and associated behaviors (Gerasimov et al., 1999). Vigabatrin has been reported to cause visual field defects following prolonged use (Brodie et al., 2005).

One open-label, non-controlled safety and efficacy trial (quality level IV) of Vigabatrin for treatment of methamphetamine and/or cocaine dependence (Brodie et al., 2005) found it may facilitate abstinence and did not produce serious adverse effects, particularly visual field defects, over the nine weeks of use.

3.2.13. Risperidone

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 stabilizers for treating acute mania associated with bipolar 1 disorder (Salwan et al., 2013).

There are three studies of risperidone for the treatment of amphetamine dependence. Two small sample, open-label uncontrolled trials by the same research group (Meredith et al., 2009, 2007) found in favor of oral and injectable risperidone on measures of methamphetamine use, craving, verbal memory and psychiatric symptoms. One randomized trial (Solhi et al., 2014) found risperidone superior to methylphenidate in its effect on reducing craving and decreasing psychiatric, neurologic, cardiac and somatic symptoms, however, methamphetamine use or abstinence outcomes were not reported.

3.2.14. Aripiprazole

Aripiprazole is a partial dopamine agonist and atypical antipsychotic with additional antidepressant properties used in the treatment of schizophrenia, bipolar disorder and clinical depression (Tadori et al., 2008).

It was the subject of two double-blind placebo-controlled randomized trials. One RCT (Coffin et al., 2013) found that Aripiprazole was not superior to placebo in reducing methamphetamine use or any of the other measures. One smaller trial with three treatment arms (Tiihonen et al., 2007) was discontinued as participants in the aripiprazole group produced significantly more positive ATS urine samples as compared to a placebo and methylphenidate group, and showed a worsening of symptoms.

3.2.15. Buprenorphine

Buprenorphine is a partial mu opioid receptor agonist approved for treatment of opioid dependence, which causes morphine-like subjective effects and produces tolerance to other opioids (Mattick et al., 2014). It has been subjected to pre-clinical testing for cocaine dependence treatment (Grabowski et al., 2004) and trialed as a treatment for concurrent opiate and cocaine dependence (Montoya et al., 2004).

One RCT study (Salehi et al., 2015) examined 16 weeks of daily buprenorphine with Matrix model program. The study of forty participants found adjunct buprenorphine achieved greater reductions in methamphetamine use and cravings than a matched placebo group.

3.2.16. N-acetyl cysteine

N-acetyl cysteine (NAC) is an amino acid which reduces the release of glutamate from the synapsis by stimulating inhibitory metabotropic glutamate receptors (Olive et al., 2012). There is some evidence that restoring extracellular glutamate concentration in the nucleus accumbens may block the reinstitution of compulsive behaviors (Olive et al., 2012).

Two RCT studies of NAC were identified. One trial (Grant et al., 2010) found that NAC plus naltrexone was not superior to placebo on measures of craving or methamphetamine use. An RCT crossover trial (Mousavi et al., 2015) found NAC had a superior, likely short-term effect on craving, as compared with placebo, but did not report on methamphetamine use outcomes.

3.2.17. Baclofen

Baclofen is a derivative of GABA and an agonist for $GABA_B$ receptors and was the subject of one RCT (Heinzerling et al., 2006). The study found baclofen was not superior to placebo overall on measures of methamphetamine use, craving or treatment retention. However, post hoc analyses found that participants with greater medication adherence, based on pill count and self-report, showed a significant reduction in methamphetamine use when compared with placebo. Despite some treatment effect relative to placebo, authors suggest the short half-life of baclofen compared to the long half-life of ATS may limit its use.

3.2.18. Ondansetron

Ondansetron is a serotonin receptor antagonist and modulator of cortico-mesolimbic dopamine function (Johnson et al., 2008).

One multi-site 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, at the doses provided (up to 4 mg twice daily). The treatment groups showed poorer outcomes (non- significant) than the placebo group. A potential limitation of the study for demonstrating efficacy was reported to be the high-intensity level of the adjunct psychosocial intervention.

3.2.19. Varenicline

Varenicline is a selective α4β2 nicotinic acetylcholine receptor partial agonist, which stimulates nicotine receptors more weakly than nicotine (Rollema et al., 2007).

One study was identified, a pilot RCT with results only found published as a brief conference abstract (Swanson et al., 2011) which reported greater retention rates and trends in favor of varenicline over placebo in reducing methamphetamine use and increasing duration of abstinence compared with placebo.

3.2.20. Amlodipine

Amlodipine is a long-acting calcium ion antagonist used as an antihypertensive and in the treatment of angina pectoris (Derosa and Maffioli, 2011). Calcium-channel blockers have been proposed as a treatment for methamphetamine dependence because of their observed ability to reduce subjective effects of methamphetamine, by antagonizing the effect of dopamine in central dopaminergic pathways (Johnson et al., 2008).

Amlodipine is the subject of one RCT (Batki et al., 2001) which found no effect for the medication at daily doses of 5 mg or 10 mg on any measures, including treatment retention, amount of methamphetamine use and level of craving. This report was a conference abstract with little detail about the direction of any changes.

4. Discussion

In this study, we examined 49 peer-reviewed journal articles and abstracts covering 20 different pharmacotherapies for amphetamine dependence.

Although a wide variety of medications have been trialled, most individual medicines have been the subject of only one or two studies. Many of the studies are typical of early pharmacotherapy research; that is, they are case studies, open-label trials or feasibility RCTs, and do not commonly have a very large sample size.

Five medications were found to have more than four published reports and included two or more controlled trials each, offering somewhat more confidence in the results. Among these, investigation of agonist pharmacotherapy approaches was most common. The five medicines are dexamphetamine (n = 7 studies), bupropion (n = 7), methylphenidate (n = 6), naltrexone (n = 6) and modafinil (n = 5). These medications were found to be generally safe and well tolerated. Bupropion and methylphenidate are the subjects of the most controlled trials (n = 5 each) followed by dexamphetamine (n = 4 RCTs).

All five of these medicines showed some benefit for amphetamine dependence treatment outcomes in one or more of the studies reviewed, but study results are not unequivocal. As with previous reviews (Brensilver et al., 2013; Perez-Mana et al., 2013; Stoops and Rush, 2013), this review identified no broadly effective pharmacotherapy, despite the inclusion of eight new RCT level studies. Overall, many trials showed variable outcomes and some conflicting results, and promising findings of these medications are presented in this context.

Bupropion showed some potential for reducing amphetamine use among subgroups of people with amphetamine dependence in three trials. Dexamphetamine showed some benefits in reducing the severity

of dependence and withdrawal symptoms (two studies) and improving treatment retention (also shown in two trials), however, it did not reduce amphetamine use more than placebo. The majority of studies (including two RCTs) trialed shorter acting dexamphetamine, and further investigation of longer acting preparations may yield different results. Methylphenidate was reported in three studies to reduce the use of amphetamines and appeared to reduce craving. Two trials of modafinil also showed some limited evidence for the reduced use of amphetamines among medicine compliant study participants.

Among the five medications with the most available evidence, Naltrexone is the only medication with no psychostimulant effect and had fewer controlled trials (n = 2), of which one supported its potential benefit for reducing use and craving and improving retention.

Six other medicines showed some potential benefit for the treatment of amphetamine dependence but had an insufficient number of studies (most with only one controlled trial) upon which to draw firm conclusions. These medications included mirtazapine, topiramate, fluoxetine, risperidone, buprenorphine, and varenicline. A clinical trial of mirtazapine was underway at the time of review, which aims to expand on the promising results demonstrated by an RCT among a sample of men who have sex with men (Colfax et al., 2011).

Also identified were a number of medicines not recommended for use or as a high priority for further study. Baclofen, gabapentin ondansetron, and amlodipine showed limited evidence of benefit; and an unacceptable adverse effect profile was demonstrated by aripiprazole, vigabatrin, sertraline and the Prometa™ protocol of combination flumazenil and gabapentin.

The complex action of methamphetamine in the brain (Herin et al., 2010; Scott et al., 2007), which affects multiple systems, means a single medicine may not meet the needs of this group. It is still largely unclear who benefits from which treatments, and what is considered optimal dosing, to match medicines to individuals. There is a need for studies of medicines showing the most potential for reducing amphetamine use or preventing relapse, to be able to examine who most benefits.

Pharmacotherapy potency and dose, and people's level of baseline amphetamine use, appear to be useful considerations for future trials aiming to improve treatment matching, at least in studies of agonist pharmacotherapies. One study (Ling et al., 2014) found methylphenidate to be particularly of benefit for reducing amphetamine use among people with higher use at treatment entry. Methylphenidate has also demonstrated some benefit in people with ADHD and amphetamine dependence (studies excluded from this review), improving treatment retention and resulting in reduced ADHD symptoms and drug use (Konstenius et al., 2013), though only when administered at greater than routine doses (Konstenius et al., 2010), suggesting higher doses may be optimal for some groups of amphetamine dependent people. Subgroup analysis in two trials of the milder stimulant bupropion showed benefit only for people with 'lighter' patterns of use (Elkashef et al., 2008; Shoptaw et al., 2008), though this finding was not consistent across all studies reviewed. Dean et al. (2009) showed that lower baseline amphetamine use was strongly related to benefit from treatment with bupropion. While results of some bupropion studies varied (Anderson et al., 2015; Elkashef et al., 2008) these RCTs do demonstrate sufficient homogeneity for meaningful comparison, an important feature, as variation in outcomes reporting across trials of pharmacotherapy studies for amphetamine dependence (see Table 1) is an acknowledged issue of concern (Kiluk et al., 2016; Perez-Mana et al., 2013). More consistent approaches to outcomes measurement and reporting across trials, as well as larger sample studies, may enable more robust investigation of any differential benefit of trialed medicines for subgroups of dependent users.

All five of the most trialed medications had many studies with high dropout rates (commonly ranging from 40 to 50 %) and/or low medication adherence. Clearly, this has implications for the veracity of the results of the studies. These issues also raise significant clinical and research design questions about how to improve treatment engagement and medication adherence among a group of people whose drug use can result in a chaotic lifestyle.

Assessing and improving medication compliance is a key challenge for developing an effective pharmacotherapy for amphetamine dependence. Methamphetamine use is associated with reduced medication adherence (Hermanstyne et al., 2014). A number of the reviewed studies reported that benefits of treatment were selective for medication-adherent participants. Yet, treatment compliance was not commonly well assessed, with few trials applying robust, objective measures of medication adherence (only nine of the 35 RCTs used biomarkers, seven used supervised daily dosing- see Table 1). Trials which integrate strategies to promote medication adherence and which use objective measures to monitor compliance are needed.

From the limited evidence, contingency management has shown promise in supporting adherence to the pharmaceutical protocol (Heinzerling et al., 2010; Shoptaw et al., 2008, 2006). Daily supervised dosing is a strategy with the potential to improve compliance and minimize diversion; however, Miles et al. (2013) suggest the high attrition in their study (34.2% completed) may be in part due to the requirement for daily clinic visits. In their study of twice daily dosing of sustained-release bupropion (Heinzerling et al., 2014), authors suggested that once-daily extended release bupropion may have helped to improve poor medication adherence. Mooney et al. (2016) showed preliminary support for the acceptability of implementing novel smartphone-based adherence procedures and long-action medication preparations with severe methamphetamine users that may assist with adherence to treatment. Where feasible, more flexible dosing regimens and extended delivery formulations of medications could be considered for future trials.

5. Summary and conclusion

No medicines demonstrated strong enough evidence of effectiveness in reducing amphetamine use or preventing relapse among dependent methamphetamine users to recommend its use.

Medications such as dexamphetamine, methylphenidate, bupropion, modafinil, and naltrexone are potentially beneficial for some participants in improving treatment outcomes, but none has sufficient consistent evidence to support its use in routine treatment. Meta-analysis may be useful in further assessing the viability of medicines, though sample sizes in many studies were low, and more consistent and standardized outcomes measurement would assist future research and reporting across studies.

Behavioral therapies have been shown to be effective in reducing amphetamine use (Lee and Rawson, 2008), and remain the treatment of choice. Medication has been posited as a valuable tool for encouraging people who use amphetamines to enter treatment (Kenny et al., 2011), and evidence suggests some potential for medications to support treatment retention. However, high drop out and poor medication adherence raises important clinical questions about how to ensure people who may benefit from these treatments can be encouraged to engage with, and remain in treatment, to gain some benefit.

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Contributors

Lee, Jenner, Harney and Cameron completed the review and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

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Appendix A. Supplementary data

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