BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03639.x

Pharmacological approaches to methamphetamine dependence: a focused review

Laurent Karila,[1] Aviv Weinstein,[2] Henri-Jean Aubin,[3] Amine Benyamina,[3] Michel Reynaud[3]* & Steven L. Batki[4]*

[1]Addiction Research and Treatment Center, Paul Brousse Hospital, Paris XI University, AP-HP, CEA-INSERM U1000, Villejuif, France, [2]Department of Medical Biophysics and Nuclear Medicine, Hadassah Hospital Ein Kerem, Jerusalem, Israel, [3]Addiction Research and Treatment Center, Paul Brousse Hospital, Paris XI University, AP-HP, INSERM U669, Villejuif, France and [4]Department of Psychiatry, University of California, San Francisco and San Francisco VA Medical Center, San Francisco, California, USA

Correspondence
Dr Laurent Karila MD, Hôpital Universitaire Paul Brousse, C.E.R.T.A (Centre d'Enseignement, de Recherche, de Traitement des Addictions), 12 Avenue Paul Vaillant-Couturier, Villejuif 94800, France.
Tel.: + 33 1 4559 6513 or + 33 1 4559 6923
Fax: + 33 1 4559 3863
E-mail: laurent.karila@pbr.aphp.fr

*The authors contributed equally to this article.

Keywords
addiction, amphetamine, clinical trials, dependence, medication, methamphetamine, treatment

Received
2 September 2009

Accepted
8 December 2009

Methamphetamine dependence is a serious worldwide public health problem with major medical, psychiatric, socioeconomic and legal consequences. Various neuronal mechanisms implicated in methamphetamine dependence have suggested several pharmacological approaches. A literature search from a range of electronic databases (PubMed, EMBASE, PsycInfo, the NIDA research monograph index and the reference list of clinicaltrials.gov) was conducted for the period from January 1985 to October 2009. There were no restrictions on the identification or inclusion of studies in terms of publication status, language and design type. A variety of medications have failed to show efficacy in clinical trials, including a dopamine partial agonist (aripiprazole), GABAergic agents (gabapentin) and serotonergic agents (SSRI, ondansetron, mirtazapine). Three double-blind placebo-controlled trials using modafinil, bupropion and naltrexone have shown positive results in reducing amphetamine or methamphetamine use. Two studies employing agonist replacement medications, one with d-amphetamine and the other with methylphenidate, have also shown promise. Despite the lack of success in most studies to date, increasing efforts are being made to develop medications for the treatment of methamphetamine dependence and several promising agents are targets of further research.

Introduction

Methamphetamine, already a significant drug problem in East and Southeast Asia and in North America in the past decade, has become a more prominent part of the European drug scene, especially in East European countries (Czech Republic, Slovakia). While the prevalence of methamphetamine use in the general population is low, rates in some social groups in younger age groups are significantly higher [1, 2].

Methamphetamine is available in different forms such as a pure crystalline hydrochloride salt or as formulated tablets. Routes of administration are intranasal sniffing, pulmonary inhalation, injection and oral ingestion [3]. The effects of methamphetamine use include euphoria and many of the same stimulant effects seen with cocaine, but these effects may last much longer [3].

Methamphetamine exerts multiple effects in the central nervous system and acts as a highly potent releaser of monoamines by increasing cytoplasmic concentrations of dopamine and serotonin and also norepinephrine, adrenaline and histamine [4] i) by blocking the activity of the intracellular vesicular monoamine transporter 2 (VMAT2) [5, 6], ii) by decreasing the expression of the dopamine transporter (DAT) at the cell surface [7] and iii) by inhibiting the activity of monoamine oxidase and increasing the activity and the expression of tyrosine hydroxylase [8]. Brain imaging studies of methamphetamine dependent patients have demonstrated brain structural abnormalities (severe grey-matter deficits in the cingulate, limbic and paralimbic cortices, smaller hippocampal volumes, significant white-matter hypertrophy, medial temporal lobe damage and striatal enlargement) [9, 10] and neurochemical and metabolite changes particularly prominent in the ventral striatum [11, 12]. Prolonged use leads to down-regulation of dopamine D_2-receptors and uptake sites [13]. A state of hypodopaminergic activity is reported as in other addictions [14, 15].

© 2010 The Authors
Journal compilation © 2010 The British Pharmacological Society

There is also evidence for disturbances of mood and anxiety and regional cerebral metabolic abnormalities in recently abstinent methamphetamine dependent patients [16].

Methamphetamine dependence is a serious worldwide public health problem with major medical [17–21], psychiatric [22–25], cognitive [26–29], socioeconomic and legal consequences [18].

Currently, there is no pharmacological therapy with established efficacy for the treatment of this addictive disorder, nor is there any medication approved by the regulatory authorities for such treatment [30]. The need to find effective treatments for methamphetamine dependence has been identified as a priority by the United States National Institute on Drug Abuse (NIDA) and by European investigators. Various neuronal mechanisms implicated in methamphetamine dependence have suggested several pharmacological approaches. Recent reviews on pharmacotherapy for methamphetamine dependence have been published [30–34], but this is a quickly evolving area with preclinical findings and clinical trials reported frequently. Although there is not much substantial evidence in terms of proof of concept studies and randomized clinical trials, this review will bring to light some of the newer pharmacological targets. We will focus on agents affecting the biogenic amine transporters mentioned above and other neurotransmitter systems (acetylcholine, GABA, endogenous opioids, endocannabinoids). We will also discuss pharmacological candidates in the pipeline such as immunotherapies (vaccine, anti-methamphetamine monoclonal antibodies) and other approaches based on preclinical data. We will not discuss the management of acute methamphetamine intoxication or the treatment of methamphetamine dependence in patients with comorbid psychiatric disorders.

Literature searches were conducted for the period from 1985 to October 2009, using PubMed, EMBASE, PsycInfo, the NIDA research monograph index and the reference list of clinicaltrials.gov, the main electronic sources of ongoing trials, using the following key words alone or in combination: methamphetamine, amphetamine, dependence, addiction, pharmacotherapy, immunotherapy, clinical trials.

References in empirical articles and narrative and meta-analytic reviews were used for further potential sources of articles. There were no restrictions on the identification or inclusion of studies in terms of publication status, language and design type.

Tables are included to summarize the salient details of some studies. The tables include clinical trials for those medications that appear to have shown the greatest promise at the time of this review (e.g. dopamine agonists and one antagonist, GABAergic agents and an opioid antagonist).

Human laboratory studies are not included in the tables, nor are studies involving compounds that have not yielded positive results (e.g. dopamine partial agonists, cholinesterase inhibitors, serotonergic agents).

Dopaminergic agents

Dopamine agonists

Modafinil Modafinil is a non-amphetamine stimulant that is approved for managing symptoms of narcolepsy with or without cataplexy, obstructive sleep apnoea/hypopnoea syndrome or idiopathic hypersomnia [35–38]. The precise neurobiological mechanism of action of this medication is complex and includes dopaminergic and glutamatergic effects [39]. A recent brain imaging study showed that modafinil binds to the DAT, and thus shares some properties with methylphenidate [40].

Clinical studies suggest that modafinil may be effective in treating cocaine dependence [41–43], and might also be effective for methamphetamine dependence. Modafinil stimulant-like activity has been proposed as a potential treatment to decrease the symptoms of cocaine withdrawal [43]. No evidence of significant abuse liability has been reported [44]. Modafinil can produce cognitive benefits [45], affecting memory [46] as well as motor, attention and executive functions in healthy adults [47], in attention-deficit/hyperactivity disorder (ADHD) and schizophrenia patients [48, 49]. Modafinil may be a cognitive enhancer [50] in methamphetamine-dependent patients [51] and may therefore have the potential to improve the response to behavioural therapies. Because of its weak stimulant properties, modafinil has been cited as a putative treatment to decrease stimulant drug seeking and craving.

The findings of an open-label study of modafinil to treat methamphetamine withdrawal symptoms in an inpatient setting [53] indicated possible amelioration of these symptoms. In a small 16-week single-blind trial, modafinil was combined with cognitive behavioural therapy (CBT) for treatment of methamphetamine dependence among HIV+ gay men. Primary outcome measures were self-reported use of drugs per week plus urine toxicology assays. Sixty percent of those who completed the study reduced their methamphetamine use by over 50% [51]. More recently, 80 methamphetamine dependent patients were randomly assigned to modafinil (200 mg day^{-1}) or placebo under double-blind conditions for 10 weeks plus 12 weeks post-treatment follow-up. There were no differences in treatment retention, medication adherence, methamphetamine abstinence, craving or severity of dependence. Of possible clinical significance, there was a statistically significant reduction in systolic blood pressure in the modafinil group [54]. Modafinil therefore may have some beneficial effects in methamphetamine-dependent patients, although there is no clear evidence of its efficacy in reducing methamphetamine use.

Bupropion Bupropion is an antidepressant that is also approved as treatment for smoking cessation [55]. It is a monoamine uptake inhibitor with stimulant-like effects in animals. It inhibits re-uptake of dopamine and norepinephrine, increases dopamine in the synaptic cleft after

blocking the presynaptic DAT, and targets the norepinephrine transporter (NET) and nicotinic receptors. By restoring depleted concentrations of monoamines [56, 57], bupropion could be effective in ameliorating withdrawal symptoms and cognitive deficits in early methamphetamine abstinence, thereby reducing methamphetamine use.

A phase I clinical trial evaluating interactions between intravenous methamphetamine and sustained-release (SR) bupropion (300 mg day^{-1}) did not show any exacerbation of methamphetamine-induced cardiovascular effects [58]. Euphoria and craving were significantly reduced by bupropion in a randomized single-blind placebo-controlled trial [59]. Two recent controlled trials have been conducted [60, 61]. In a 12-week multi-site double-blind placebo-controlled study, the administration of SR bupropion 300 mg day^{-1} combined with CBT showed promising results [60]. The intent-to-treat analysis found a trend toward less methamphetamine use in the bupropion group. Subgroup analysis indicated significantly less use in male subjects who had low to moderate baseline use (less or equal to 18 days $month^{-1}$). In the other randomized controlled trial, SR bupropion 300 mg day^{-1} was compared with placebo, with both groups receiving contingency management and weekly CBT sessions for 12 weeks. Bupropion was no more effective than placebo in reducing methamphetamine use verified by urine drug screens, or in reducing the severity of depressive symptoms. However, as in the first study, bupropion was again found to reduce significantly methamphetamine use among baseline light, but not heavy, methamphetamine users in a *posthoc* analysis [61]. It may therefore be important to focus further evaluation of bupropion on its efficacy in light users.

Methylphenidate Methylphenidate is the most commonly prescribed medication for childhood ADHD worldwide. It has binding affinity for both the dopamine and norepinephrine transporter but not to the serotonin transporter. The functional effect is to block catecholamine re-uptake from and increase catecholamine release into the synapse. It has pharmacological effects similar to cocaine and amphetamine, but may produce less neuroadaptation and have less abuse liability (for review, see [62]). Reports suggest that immediate-release oral methylphenidate has more potential for abuse [63, 64] than SR methylphenidate [65, 66]. A 20 week randomized study of SR methylphenidate (54 mg day^{-1}), aripiprazole (15 mg day^{-1}), and placebo for intravenous amphetamine dependence revealed promising results. Interim analysis showed that methylphenidate was an effective treatment reducing intravenous stimulant use in patients with severe dependence, in contrast to aripiprazole and to placebo. The primary outcome measure was the proportion of amphetamine-positive urine samples [67]. Further studies with methylphenidate are planned by the NIDA.

Dextroamphetamine (d-amphetamine) Dextroamphetamine promotes release of dopamine, norepinephrine and serotonin. Despite the fact that this compound has a high potential for abuse, maintenance programs using d-amphetamine have reported positive outcomes, such as decrease in amphetamine use and injecting [68]. A double-blind, controlled clinical trial indicated that d-amphetamine may be effective for the treatment of cocaine dependence [69] and a small pilot open trial suggested that d-amphetamine may increase treatment engagement in patients with methamphetamine dependence [70]. Preliminary results of an Australian double-blind placebo-controlled trial with sustained release (SR) d-amphetamine (from 20 to 110 mg day^{-1}) demonstrated increased retention and a lower level of dependence in the SR d-amphetamine group. This study provides preliminary evidence that SR d-amphetamine may be an efficacious treatment option for methamphetamine dependence [71].

Dopamine D_2 partial agonists

Dopamine D_2-receptor partial agonists have also been proposed as possible treatments for stimulant dependence [72]. Aripiprazole, a second generation antipsychotic, acts as a partial agonist at both the dopamine D_2 and 5-HT_{1A} receptors [73]. Two human laboratory studies showed that aripiprazole (10 or 20 mg) significantly attenuated the discriminative stimulus and subjective rated effects of orally administrated d-amphetamine [74, 75]. However, in a more recent study [76], aripiprazole treatment increased some of the rewarding and stimulatory effects produced by acute methamphetamine, suggesting that 15 mg aripiprazole is unlikely to be efficacious for the treatment of methamphetamine dependence. Supporting these findings, a recent controlled trial comparing aripiprazole, methylphenidate and placebo had to be terminated prematurely. An interim analysis showed that aripiprazole-treated subjects had significantly more amphetamine-positive urines than those treated with placebo [67].

Dopamine antagonists

Conventional (first generation) antipsychotics act chiefly as dopamine D_2-receptor antagonists. Newer second generation antipsychotics also act on serotonin receptors. These medications have also been proposed as potential treatments for stimulant dependence.

Risperidone (3, 6 mg day^{-1}) was evaluated in a 4 week open-label study in veterans seeking methamphetamine dependence treatment. Outcome measures were self-reports of substance use, urine drug tests and adverse effects. Methamphetamine use decreased in association with risperidone treatment and the medication was well tolerated [77]. An open trial evaluating long-acting injectable risperidone in methamphetamine dependence has recently been completed (see http://clinicaltrials.gov,

identifier NCT00284206) but no results are yet available (Table 1).

GABA agents

By decreasing transmission in the mesolimbic dopamine system, the gamma-aminobutyric acid (GABA) agonists may reduce the reinforcing effects of stimulants [78, 79]. For this reason, GABA agonists have been proposed as potential therapeutic agents for treating methamphetamine dependence.

Clinical trials with baclofen ($GABA_B$ receptor agonist) [80], gabapentin (nonselective GABA agonist) [80, 81] and gamma-vinyl-GABA (Vigabatrin) (GABA transaminase inhibitor) [82, 83] in methamphetamine dependent patients are summarized in Table 2.

Urschel and colleagues reported favourable results for an open trial of a proprietary mixture of flumazenil, gabapentin and hydroxyzine in reducing methamphetamine use [81]. A subsequent controlled trial, however, failed to find any significant advantage for the medication combination over placebo [84].A recent human laboratory study indicated that gamma-vinyl-GABA treatment was well tolerated but not efficacious in attenuating the positive subjective effects of methamphetamine [85]. As yet, there have been no reports of randomized controlled trials to determine whether gamma-vinyl-GABA is effective as a treatment for methamphetamine dependence.

Topiramate has also been evaluated in methamphetamine dependence. It has several neuro-pharmacological actions: blockade of voltage-dependent sodium channels, enhancement of GABA neurotransmission at $GABA_A$ receptors, blockade of glutamate receptors (AMPA/kainate subtype), and inhibition of carbonic anhydrase.

In a double-blind study of topiramate (100 or 200 mg) compared with placebo, in subjects receiving low or high dose (15 or 30 mg) intravenous methamphetamine, acute dosing of topiramate appeared to enhance the positive effects of methamphetamine and to act as an anticraving agent [86]. The effects of topiramate on cognitive performance were also evaluated in both the presence and absence of low and high dose intravenous methamphetamine. Cognitive effects were mixed, with a trend for improvement in attention while there was worsening psychomotor retardation [87]. One possible explanation may be that topiramate could increase plasma methamphetamine concentrations [88]. As of yet, there have been no reports of clinical trials to determine whether topiramate is effective as a treatment for methamphetamine dependence.

Cholinesterase inhibitors

Acetylcholine has been implicated in the reinforcing and locomotor activating effects produced by methamphetamine. Acetylcholinesterase inhibitors may play a role in reducing methamphetamine seeking behaviour in animals. For example, donepezil attenuated the reinstatement of methamphetamine-seeking behaviour induced by exposure to cues and self administration in rats. This effect could possibly be due to activation of nicotinic, but not of muscarinic, cholinergic receptors in the nucleus accumbens core, prelimbic cortex, amygdala and hippocampus [89].

Rivastigmine equally inhibits both butyrylcholinesterase and acetylcholinesterase and has selectivity for central nervous system activity [90]. It has no affinity for dopaminergic, adrenergic, muscarinic or opioid receptors [91]. In a 2 week double-blind placebo-controlled human laboratory study, cardiovascular and subjective effects of rivastigmine (1.5 or 3 mg) in combination with intravenous methamphetamine (30 mg) were evaluated in dependent patients. The 3 mg dosage significantly reduced methamphetamine-induced increases in diastolic blood pressure and self-reports of craving and anxiety [92]. Another controlled study found that the same dosage may reduce positive subjective effects in an experimental model of intravenous self-administration in human volunteers [93]. At this time, there are no reports of clinical trials of rivastigmine in methamphetamine dependence.

Serotonergic agents

Selective serotonin re-uptake inhibitors (SSRI)

Methamphetamine affects neural networks associated with depression [94]. Inhibited serotonergic signals lead to increased amphetamine self-administration in animals [95], while serotonin transporter inhibition decreases the rewarding effects of psychostimulants [96]. For example, pre-treatment with fluoxetine had inhibitory effects on methamphetamine-induced locomotor sensitization in mice [97]. Evidence exists for a modulatory role of the serotonin system in the discriminative stimulus effects of methamphetamine [98]. However, controlled clinical trials of fluoxetine [99, 100] and paroxetine [101] have shown no efficacy for reducing methamphetamine use. Moreover, in a large randomized, placebo-controlled trial using a counselling platform of Matrix Model relapse prevention groups [102], sertraline (100 mg day^{-1}) failed to improve methamphetamine use outcomes and actually worsened retention. Taken together, these results suggest that sertraline and possibly the entire class of SSRIs are ineffective and may be contra-indicated for methamphetamine dependence [103].

Ondansetron

Ondansetron, an anti-emetic agent, is a serotonin $5\text{-}HT_3$ receptor antagonist. $5\text{-}HT_3$ receptor activation increases dopamine activity in the nucleus accumbens [104], making blockade of these receptors a potential treatment

Table 1

Dopamine agonists and antagonists

Pharmacological agents	Study design Sample characteristics	Outcomes	Results	Main limitations	References
Modafinil (400 mg day^{-1})	10-day open-label study 14 methamphetamine dependent patients seeking treatment Amphetamine use for at least 3 days a week over the previous month Amphetamine use within the previous 96 h	**Primary outcomes** Withdrawal syndrome Sleep disturbance **Secondary outcomes** Tolerance Adverse effects or events	Milder withdrawal syndrome Less sleep disturbance Safe and well tolerated	Patients and clinicians aware of study group allocation Small sample size Study outcomes were assessed against a historical comparison group enrolled in a separate study	[53]
Modafinil (50 to 200 mg day^{-1}) and HIV medications **Modafinil (100 to 400 mg day^{-1}) (not on HIV medications)**	16-week pilot study: 12-week single blind trial + 4-week placebo phase 13 patients seeking to reduce or stop methamphetamine use Seven of 13 met DSM-IV criteria for stimulant abuse and 6 for dependence Mean duration for abuse or dependence: 43 months Mean reported days of use/week: 4 Primary route of use: smoking (9 patients) HIV+ (11/13 men)	**Primary outcomes** Self-reported use of days per week (urine toxicology assays) **Secondary outcomes** Craving (Methamphetamine Craving Scale; Obsessive/Compulsive Methamphetamine Use Scale) Depression (Beck Depression Inventory II) Side effects or adverse events	Decrease of methamphetamine use by >50% Decreased craving No side effects except in 2 patients	Difficulty in recruitment Low number of responders High attrition rates	[51]
Modafinil (200 mg day^{-1})	10-week randomized, double-blind, placebo-controlled clinical trial + 12-week post-treatment follow-up 80 methamphetamine-dependent subjects seeking treatment 2–3 days of methamphetamine use per week or more Most subjects injected methamphetamine on a daily basis, with a third who preferred to smoke it	**Primary outcome** Self-reported use of days per week (urine toxicology assays) **Secondary outcomes** Treatment retention Medication adherence Craving Severity of dependence Other substance dependence Adverse events	No differences in treatment retention, medication adherence, methamphetamine abstinence, craving or severity of dependence. More methamphetamine-negative urine samples in the modafinil group Significant reductions in systolic blood pressure and weight gain No medication-related serious adverse events	Absence of an objective quantitative measure, reliance on self-reported outcomes A sample size too small to detect reliably the small differences between modafinil and placebo	[54]
SR bupropion (300 mg day^{-1})	12-week double-blind placebo-controlled study and a 30-day follow-up 151 methamphetamine dependent patients seeking treatment Primary route of administration: smoking Days of methamphetamine use in last 30 days (less or equal to 18 days or superior to 18 days)	**Primary outcome** Change in proportion of participants having a methamphetamine -free week. **Secondary outcomes** Urine for quantitative methamphetamine Self-report of methamphetamine use Subgroup analyses of balancing factors and comorbid conditions Addiction severity, craving Risk behaviours for HIV Use of other substances	Decrease of methamphetamine use (intent-to-treat analysis) Decreased use in male subjects who had low to moderate baseline use (less or equal to 18 days per month) (Subgroup analysis)	Poor therapeutic response in female patients Imbalance between groupson the presence of ADHD (15% of participants) Lack of training for inter-rater reliability between raters using DSM-IV checklist	[60]

SR bupropion (300 mg day^{-1})	12-week randomized, double-blind, placebo-controlled clinical trial 73 methamphetamine dependent patients	**Primary outcome** Methamphetamine use (as assessed via urine drug screens) **Secondary outcomes** Treatment retention Severity of depressive symptoms Methamphetamine craving Adverse effects Cigarette smoking among methamphetamine dependent patients	Significant decrease of methamphetamine use among light users (*post hoc* analysis) Decrease of self-reported cigarette use	Small sample size Lowered power of the study Attrition of the participants	[61]
SR methylphenidate (54 mg day^{-1})	20-week randomized placebo controlled trial With 3 arms including aripirazole and placebo as well as methylphenidate 17 amphetamine or methamphetamine dependent patients 5 women, HIV infection (n = 4), hepatitis B or C infection (n = 13) Duration of use: 15 years	**Primary outcome** Proportion of amphetamine-positive urine samples **Secondary outcomes** Adverse effects	Decrease of amphetamine intravenous use in the SR methylphenidate group reaching significance after 18 weeks (intention-to-treat analysis) No adverse effects	Small sample size Long period of time to achieve full benefit from this treatment	[67]
d-amphetamine (from 20 to 60 mg day^{-1})	12-week open, two-group pre-post randomized controlled trial 41 amphetamine dependent patients seeking treatment d-amphetamine group (n = 20) and control group (counselling (n = 21))	**Primary outcome** Amphetamine and methamphetamine use (urine toxicology assays). **Secondary outcomes** Adverse events Psychotic symptoms	Reduced amphetamine use and severity of dependence in both group d-amphetamine group significantly more likely to attend counselling and receiving twice as many sessions as the control group. No adverse events or psychotic symptoms	Small sample size Study group restricted to subjects who were able to attend an inner-city clinic on a daily basis Possible selective attrition bias	[70]
SR d-amphetamine (from 20 to 110 mg day^{-1})	16-week randomized double blind, placebo-controlled clinical trial 49 methamphetamine dependent patients Positive urine sample and use of methamphetamine on 3 or more days per week over the previous 12 months Sufficient hair length for hair analysis	**Primary outcomes** Methamphetamine use and degree of dependence over time, and treatment retention. **Secondary outcomes** Adverse effects	Better retention in treatment in the SR d-amphetamine group Lower degree of methamphetamine dependence Trend to a greater reduction in self-reported methamphetamine use No serious adverse events	High attrition rates in the placebo group Number of subjects in each group	[71]
Risperidone (3.6 mg day^{-1})	4-week open-label study 11 veteran methamphetamine dependent patients seeking treatment	**Primary outcome** Self-reports of substance use (urine drug tests) **Secondary outcomes** Adverse effects	Decrease of methamphetamine use	Small sample size No placebo group	[77]

Table 2

GABA agents

Pharmacological agents	Study design Sample characteristics	Outcomes	Results	Main limitations	References
Baclofen (60 mg day^{-1})	16-week, randomized, placebo-controlled, double-blind trial with 3 arms including gabapentin and placebo as well as baclofen 25 methamphetamine dependent patients Primary route of use: smoking	**Primary outcome** Methamphetamine use (urine drug tests) **Secondary outcomes** Treatment retention, depressive symptoms, methamphetamine cravings, adverse events	Not effective in reducing methamphetamine use Small treatment effect relative to placebo among participants who reported taking a higher percentage of study medication (post hoc analyses)	Small sample size Increasing attrition of the participants biological measures of medication adherence not performed	[80]
Gabapentin (2400 mg day^{-1})	16-week, randomized, placebo-controlled, double-blind trial with 3 arms including baclofen and placebo as well as gabapentin 26 methamphetamine dependent patients Primary route of use: smoking	**Primary outcome** Methamphetamine use (urine drug tests) **Secondary outcomes** Treatment retention, depressive symptoms, methamphetamine cravings, adverse events	Not effective in reducing methamphetamine use	Small sample size Increasing attrition of the participants biological measures of medication adherence not performed	[80]
Vigabatrin (from 1 to 3 g day^{-1})	9-week open-label safety study 28 methamphetamine and/or cocaine dependent patients	**Primary outcomes** Change of visual fields, visual acuity, ocular adverse effects **Secondary outcomes** Methamphetamine use	No ophthalmologic adverse effects Decrease of methamphetamine use	Small sample size Open label design No control group High drop-out rate (approximately 50%)	[83]
Vigabatrin (from 1.5 to 3 g day^{-1})	9-week open-label safety study 30 methamphetamine and/or cocaine dependent patients	**Primary outcomes** Change of visual fields, visual acuity, ocular adverse effects **Secondary outcomes** Methamphetamine use	No ophthalmologic adverse effects Decrease of methamphetamine use	Small sample size Open label design No control group High drop-out rate (approximately 50%)	[83]

approach. In a preliminary, multi-site, randomized, double-blind, 8 week controlled trial, ondansetron (0.25, 1 or 4 mg twice daily) combined with CBT was not superior to placebo at decreasing methamphetamine use, craving, withdrawal and clinical severity of dependence [105].

Mirtazapine

Mirtazapine is a serotonin ($5HT_{2A}$ and $5HT_3$ receptors), histamine H_1 and adrenergic α_2 antagonist [106]. A preclinical study demonstrated that mirtazapine reversed methamphetamine-induced behavioural sensitization, condition preference place and motor sensitization [107]. As an antidepressant with anxiolytic and sedative properties, mirtazapine has been evaluated in the treatment of methamphetamine withdrawal in an outpatient setting. An open trial of mirtazapine compared with modafinil in inpatients showed inferiority to modafinil in countering methamphetamine withdrawal symptoms [53]. A small double-blind placebo-controlled trial of mirtazapine (15 mg for 2 days and 30 mg for 12 days) with drug counselling also failed to find a significant treatment effect [108].

Opioid antagonist: naltrexone

There is evidence that the endogenous opioid system plays a role in the reinstatement of methamphetamine seeking behaviour and behavioural sensitization [109] in methamphetamine self-administering animals. Naltrexone, an opioid antagonist, attenuated cue- but not drug-induced methamphetamine in animals [110]. In humans, naltrexone may reduce the reinforcing effects of amphetamine via modulation of the opioid system [111]. Naltrexone 50 mg along with CBT was evaluated in a 12 week open clinical trial for amphetamine dependence. This medication was well tolerated with moderate rates of compliance [112]. In a double-blind placebo-controlled design, naltrexone 50 mg significantly attenuated the subjective effects produced by dexamphetamine in dependent patients. Craving was also significantly blocked [113]. Moreover, it also was effective in reducing amphetamine use in a recent double-blind, placebo-controlled outpatient clinical trial [114]. Naltrexone therefore appears to be a highly promising medication for amphetamine dependence (Table 3).

Calcium channel blockers

Calcium-channel blockers (CCBs) have been proposed as a treatment for methamphetamine dependence because of their modulating effects on dopaminergic tone [115]. Human laboratory studies with selective dihydropyridine CCBs isradipine [115] and amlodipine [116] found reduced subjective and physiological responses to methamphetamine. However, a controlled outpatient clinical trial of amlodipine failed to show any efficacy in reducing methamphetamine use [117].

Pharmacological candidates in the pipeline

Immunotherapies

Immunotherapies, either active immunization (vaccines) or passive administration of anti-methamphetamine monoclonal antibodies (AMMA), are an innovative treatment strategy for drug addiction. Vaccines may be effective in blocking the effects of drugs of abuse [118] and have advantages over conventional medications in that they would have no direct psychoactive effects and no abuse liability. Their effects may persist for months, improving patient adherence to treatment [119]. Nicotine and cocaine vaccines have advanced to the level of clinical trials [120, 121], whereas a new generation of active immunization therapies for methamphetamine is at an advanced stage of preclinical development [122]. A methamphetamine vaccine has been shown to produce antibodies in rats but did not attenuate their locomotor activity in response to the drug [123].

Preclinical studies have also shown the therapeutic potential of the AMMA approach [124–126]. Reduction of methamphetamine self-administration, locomotor activity and inhibition of discriminative stimulus effects of methamphetamine was shown in rats and pigeons [127–129]. The two primary indications for the use of AMMA in the treatment of human methamphetamine dependence would be overdose and relapse prevention [33, 122].

Endocannabinoid system

Cannabinoid CB_1 receptors modulate the dopamine-releasing effects of drugs of abuse and are involved in relapse to drug seeking for many addictive drugs [130]. The endocannabinoid system may serve as a modulator of the reinstating effects of methamphetamine-priming and cues [131]. In a recent study, pre-treatment with methanandamide, a CB_1 agonist, elicited cross-sensitization to methamphetamine effects in mice, whereas pre-treatment with JWH 015, a CB_2 agonist, did not. Combined pre-treatment with methamphetamine and the cannabinoid antagonist AM 251 suppressed sensitization to methamphetamine [132]. No human studies are available as of yet.

Nicotinic agents

Lobeline, an alkaloid constituent of Lobelia, is used as a respiratory stimulant for tobacco smoking cessation. As a partial agonist at nicotinic receptors, it interacts with the DAT and VMAT2 proteins involved in dopamine storage and release [133, 134]. It alters dopamine function by inhibition of dopamine uptake and promotion of dopamine release from storage vesicles within the pre-synaptic ter-

Table 3

Opioid antagonist

Pharmacological agents	Study design Sample characteristics	Outcomes	Results	Main limitations	References
Naltrexone (50 mg day^{-1})	12-week open clinical trial 20 amphetamine-dependent patients	**Primary outcomes** Adverse events Compliance to medication (assessed by by the presence of naltrexone's metabolite, 6-beta-naltrexol in urine) Tolerability: patient's self-report and observed adverse effects along with plasma markers of hepatotoxicity.	No serious adverse events Moderate rates of compliance Decrease of amphetamine use	Small sample size Open label design High attrition rate	[112]
Naltrexone (50 mg day^{-1})	Randomized double-blind placebo-controlled design. 20 abstinent amphetamine-dependent patients DSM-IV criteria for ADHD Drug-free from amphetamine for a minimum of 30 days Residence in Stockholm county.	**Primary outcome** Difference in subjective measures of amphetamine effects (use of a Visual Analog Scale). **Secondary outcomes** Effects of naltrexone on physiological and biochemical responses to amphetamine, as measured by changes in blood pressure, heart rate, skin conductance and cortisol.	Significant decrease of the subjective effects produced by dexamphetamine Reduction in dexamphetamine craving No difference between the groups on the physiological measures.	Study was conducted in a small homogenous population of male amphetamine-dependent individuals. Small dexamphetamine dose	[113]
Naltrexone (50 mg day^{-1})	12-week double-blind, placebo-controlled clinical trial 80 treatment-seeking amphetamine-dependent individuals Amphetamine use on at least 12 days in the past 12 weeks.	**Primary outcome** Number of negative amphetamine urine samples during 12 weeks of treatment (of a total of 24 samples) **Secondary outcomes** Treatment retention Medication adherence Craving Pill count Adverse events	Decrease in amphetamine use High treatment retention and medication adherence Significant reduction in craving No serious adverse events	Sample selected for the study did not achieve an equal representation of the genders. Treatment outcomes assessed for 3 months Long-term effects in this population are unknown.	[114]

minal on the VMAT2 [135]. Lobeline or its analogues act as a methamphetamine antagonist, in that they decrease self-administration [136], attenuate stereotypy and antagonize discrimination of the subjective effects (for review, see [137]). Two ongoing double-blind placebo-controlled studies are underway at the time of writing: one assessing intravenous methamphetamine and sublingual lobeline interactions and the other tolerability, safety and pharmacokinetics of multiple dosages of lobeline (see http://clinicaltrials.gov identifiers NCT00100074 and NCT00519259).

Benzoquinolizine derivatives

Evidence exists that VMAT2 plays a crucial role in psychostimulant pharmacology. Benzoquinolizine derivatives, such as tetrabenazine, have high affinity for VMAT2. Tetrabenazine is approved, in some countries, with license applications pending in several European countries and the United States, for the treatment of hyperkinetic movement disorders. This pharmacological agent decreases locomotor activity and aggressiveness in monkeys and decreases methamphetamine-induced hyperactivity in rodent animal models [138, 139]. The NIDA is currently conducting an animal study.

Conclusion

Methamphetamine dependence is a growing problem in various areas of the world. The development of effective treatments for methamphetamine dependence has become a pressing concern. Recent improvements in the understanding of the underlying neurobiology of methamphetamine dependence have led to a number of potentially useful pharmacological agents. The general research strategy adopted has to a large extent resembled the approach to research on cocaine dependence pharmacotherapy, and has aimed at similar pharmacological targets and employed similar preclinical and clinical methods.

The development of methamphetamine pharmacotherapies is at an early stage. No substantial evidence for efficacious treatment has yet emerged. Clinical trials using aripiprazole, GABA agents (gabapentin, baclofen, vigabatrin), SSRIs, ondansetron and mirtazapine have failed to show efficacy.

Only three double-blind placebo-controlled trials have shown positive results in reducing methamphetamine or amphetamine use. One clinical trial of naltrexone has shown evidence of efficacy for treatment for amphetamine dependence, and trials involving bupropion and modafinil have demonstrated possible benefit in treating methamphetamine use in selected methamphetamine-dependent patients. The use of agonist replacement medications such as d-amphetnaine and modafinil may also hold promise in the treatment of methamphetamine dependence. Despite the lack of clear and robust success to date, increasing efforts are being made to develop medications for the treatment of methamphetamine dependence.

Competing interests

Dr Batki: Alkermes, Inc. (research grant). Dr Aubin has received sponsorship to attend scientific meetings, speaker honorariums and consultancy fees from Pfizer, McNeil, GlaxoSmithKline, Pierre-Fabre Sante, Sanofi-Aventis and Merck-Lipha. Dr Laurent Karila, Dr Amine Benyamina and Professor Michel Reynaud have no competing interests.

Dr Karila (France) received support from the MILDT (Mission Interministérielle de Lutte contre les Drogues et la Toxicomanie) INSERM and Assistance Publique-Hôpitaux de Paris. Dr Weinstein (Israel) is supported by the National Institute for Psychobiology (Israel). Dr Batki (USA) received support from National Institute of Health, National Institute on Drug Abuse (NIDA) Grants N°. 5R01 DA016764-05 and U10 DA015815, National Institute on Alcohol Abuse and Alcoholism and a Department of Veterans Affairs Grant for the VISN 2 Center for Integrated Healthcare.

REFERENCES

1 EMCDDA: European Monitoring Center for Drugs and Drug Abuse. Annual report 2008: The state of the drug problem in Europe. 2009. Available at http://www.emcdda.europa.eu (last accessed November 2009).

2 Barr A, Panenka W, MacEwan W, Thornton A, Lang D, Honer W, Lecomte T. The need for speed: an update on methamphetamine addiction. J Psychiatry Neurosci 2006; 31: 301–13.

3 Rawson RA, Gonzales R, Marinelli-Casey P, Ang A. Methamphetamine dependence: a closer look at treatment response and clinical characteristics associated with route of administration in outpatient treatment. Am J Addict 2007; 16: 291–9.

4 Nakagawa T, Kaneko S. Neuropsychotoxicity of abused drugs: molecular and neural mechanisms of neuropsychotoxicity induced by methamphetamine, 3,4-methylenedioxymethamphetamine (ecstasy), and 5-methoxy-N,N-diisopropyltryptamine (foxy). J Pharmacol Sci 2008; 106: 2–8.

5 Vergo S, Johansen JL, Leist M, Lotharius J. Vesicular monoamine transporter 2 regulates the sensitivity of rat dopaminergic neurons to disturbed cytosolic dopamine levels. Brain Res 2007; 1185: 18–32.

6 Volz TJ, Hanson GR, Fleckenstein AE. The role of the plasmalemmal dopamine and vesicular monoamine transporters in methamphetamine-induced dopaminergic deficits. J Neurochem 2007; 101: 883–8.

7 McCann UD, Kuwabara H, Kumar A, Palermo M, Abbey R, Brasic J, Ye W, Alexander M, Dannals RF, Wong DF,

Ricaurte GA. Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. Synapse 2008; 62: 91–100.

8 Pereira FC, Lourenco ES, Borges F, Morgadinho T, Ribeiro CF, Macedo TR, Ali SF. Single or multiple injections of methamphetamine increased dopamine turnover but did not decrease tyrosine hydroxylase levels or cleave caspase-3 in caudate-putamen. Synapse 2006; 60: 185–93.

9 Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. Biol Psychiatry 2005; 57: 967–74.

10 Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, Lee JY, Toga AW, Ling W, London ED. Structural abnormalities in the brains of human subjects who use methamphetamine. J Neurosci 2004; 24: 6028–36.

11 Baicy K, London ED. Corticolimbic dysregulation and chronic methamphetamine abuse. Addiction 2007; 102 (Suppl. 1): 5–15.

12 Aron JL, Paulus MP. Location, location: using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. Addiction 2007; 102 (Suppl. 1): 33–43.

13 Volkow ND, Wang GJ, Fowler JS, Thanos PP, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas N. Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. Synapse 2002; 46: 79–82.

14 Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. Nat Rev Neurosci 2004; 5: 963–70.

15 Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 2002; 159: 1642–52.

16 London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, Shinn AK, Miotto K, Learn J, Dong Y, Matochik JA, Kurian V, Newton T, Woods R, Rawson R, Ling W. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. Arch Gen Psychiatry 2004; 61: 73–84.

17 Rawson RA, Gonzales R, Pearce V, Ang A, Marinelli-Casey P, Brummer J, Methamphetamine Treatment Project Corporate Authors. Methamphetamine dependence and human immunodeficiency virus risk behavior. J Subst Abuse Treat 2008; 35: 279–84.

18 Shoptaw S, Peck J, Reback CJ, Rotheram-Fuller E. Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment. J Psychoactive Drugs 2003; 35 (Suppl. 1): 161–8.

19 Vigil O, Woods SP, Moran LM, Letendre SL, Young-Casey C, Grant I, Atkinson JH. Is hepatitis C infection associated with increased risk of depression in persons with methamphetamine dependence? Am J Addict 2007; 16: 418–23.

20 Haning W, Goebert D. Electrocardiographic abnormalities in methamphetamine abusers. Addiction 2007; 102 (Suppl. 1): 70–5.

21 Maxwell JC. Emerging research on methamphetamine. Curr Opin Psychiatry 2005; 18: 235–42.

22 Dore G, Sweeting M. Drug-induced psychosis associated with crystalline methamphetamine. Australas Psychiatry 2006; 14: 86–9.

23 Harris D, Batki SL. Stimulant psychosis: symptom profile and clinical course. Am J Addict 2000; 9: 28–37.

24 McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. Addiction 2006; 101: 1473–8.

25 Lapworth K, Dawe S, Davis P, Kavanagh D, Young R, Saunders J. Impulsivity and positive psychotic symptoms influence hostility in methamphetamine users. Addict Behav 2009; 34: 380–5.

26 Moon M, Do KS, Park J, Kim D. Memory impairment in methamphetamine dependent patients. Int J Neurosci 2007; 117: 1–9.

27 Scott JC, Woods SP, Matt GE, Meyer RA, Heaton RK, Atkinson JH, Grant I. Neurocognitive effects of methamphetamine: a critical review and meta-analysis. Neuropsychol Rev 2007; 17: 275–97.

28 Rendell PG, Mazur M, Henry JD. Prospective memory impairment in former users of methamphetamine. Psychopharmacology 2009; 203: 609–16.

29 van der Plas EA, Crone EA, van den Wildenberg WP, Tranel D, Bechara A. Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. J Clin Exp Neuropsychol 2008; 1–14.

30 Vocci FJ, Appel NM. Approaches to the development of medications for the treatment of methamphetamine dependence. Addiction 2007; 102 (Suppl. 1): 96–106.

31 Elkashef A, Vocci F, Hanson G, White J, Wickes W, Tiihonen J. Pharmacotherapy of methamphetamine addiction: an update. Subst Abus 2008; 29: 31–49.

32 Srisurapanont M, Jarusuraisin N, Kittirattanapaiboon P. Treatment for amphetamine withdrawal. Cochrane Database Syst Rev 2001; (4): CD003021.

33 Elkashef A, Biswas J, Acri JB, Vocci F. Biotechnology and the treatment of addictive disorders: new opportunities. BioDrugs 2007; 21: 259–67.

34 Ling W, Rawson R, Shoptaw S, Ling W. Management of methamphetamine abuse and dependence. Curr Psychiatry Rep 2006; 8: 345–54.

35 Arnulf I, Derenne JP. [Modafinil (Midiodal): wakefulness stimulant in narcoleptic patients]. Presse Med 2000; 29: 1131–2.

36 Billiard M, Besset A, Montplaisir J, Laffont F, Goldenberg F, Weill JS, Lubin S. Modafinil: a double-blind multicentric study. Sleep 1994; 8 (Suppl.): S107–12.

37 Laffont F, Mayer G, Minz M. Modafinil in diurnal sleepiness. A study of 123 patients. Sleep 1994; 17 (8 Suppl.): S113–5.

38 Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. Prog Neuropsychopharmacol Biol Psychiatry 1988; 12: 695–700.

39 Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 2006; 67: 554–66.

40 Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang GJ, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 2009; 301: 1148–54.

41 Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L, Slee A, Smith EV, Kahn R, Chiang N, Vocci F, Ciraulo D, Dackis C, Roache JD, Salloum IM, Somoza E, Urschel HC 3rd, Elkashef AM. Modafinil for the treatment of cocaine dependence. Drug Alcohol Depend 2009; 104: 133–9.

42 Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology 2005; 30: 205–11.

43 Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend 2003; 70: 29–37.

44 Myrick H, Malcolm R, Taylor B, LaRowe S. Modafinil: preclinical, clinical, and post-marketing surveillance – a review of abuse liability issues. Ann Clin Psychiatry 2004; 16: 101–9.

45 Randall DC, Viswanath A, Bharania P, Elsabagh SM, Hartley DE, Shneerson JM, File SE. Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? J Clin Psychopharmacol 2005; 25: 175–9.

46 Muller U, Steffenhagen N, Regenthal R, Bublak P. Effects of modafinil on working memory processes in humans. Psychopharmacology 2004; 177: 161–9.

47 Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ. Cognitive enhancing effects of modafinil in healthy volunteers. Psychopharmacology (Berl) 2003; 165: 260–9.

48 Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 2004; 55: 1031–40.

49 Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. Neuropsychopharmacology 2004; 29: 1363–73.

50 Gerrard P, Malcolm R. Mechanisms of modafinil: a review of current research. Neuropsychiatr Dis Treat 2007; 3: 349–64.

51 McElhiney MC, Rabkin JG, Rabkin R, Nunes EV. Provigil (modafinil) plus cognitive behavioral therapy for methamphetamine use in HIV+ gay men: a pilot study. Am J Drug Alcohol Abuse 2009; 35: 34–7.

52 Castells X, Casas M, Vidal X, Bosch R, Roncero C, Ramos-Quiroga JA, Capella D. Efficacy of central nervous system stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials. Addiction 2007; 102: 1871–87.

53 McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. J Subst Abuse Treat 2008; 35: 334–42.

54 Shearer J, Darke S, Rodgers C, Slade T, van Beek I, Lewis J, Brady D, McKetin R, Mattick RP, Wodak A. A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. Addiction 2009; 104: 224–33.

55 Garrett BE, Rose CA, Henningfield JE. Tobacco addiction and pharmacological interventions. Expert Opin Pharmacother 2001; 2: 1545–55.

56 Rothman RB. High affinity dopamine reuptake inhibitors as potential cocaine antagonists: a strategy for drug development. Life Sci 1990; 46: PL17–21.

57 Rau KS, Birdsall E, Hanson JE, Johnson-Davis KL, Carroll FI, Wilkins DG, Gibb JW, Hanson GR, Fleckenstein AE. Bupropion increases striatal vesicular monoamine transport. Neuropharmacology 2005; 49: 820–30.

58 Newton TF, Roache JD, De La Garza R II, Fong T, Wallace CL, Li SH, Elkashef A, Chiang N, Kahn R. Safety of intravenous methamphetamine administration during treatment with bupropion. Psychopharmacology (Berl) 2005; 182: 426–35.

59 Newton TF, Roache JD, De La Garza R II, Fong T, Wallace CL, Li SH, Elkashef A, Chiang N, Kahn R. Bupropion reduces methamphetamine-induced subjective effects and cue-induced craving. Neuropsychopharmacology 2006; 31: 1537–44.

60 Elkashef AM, Rawson RA, Anderson AL, Li SH, Holmes T, Smith EV, Chiang N, Kahn R, Vocci F, Ling W, Pearce VJ, McCann M, Campbell J, Gorodetzky C, Haning W, Carlton B, Mawhinney J, Weis D. Bupropion for the treatment of methamphetamine dependence. Neuropsychopharmacology 2008; 33: 1162–70.

61 Shoptaw S, Heinzerling KG, Rotheram-Fuller E, Steward T, Wang J, Swanson AN, De La Garza R, Newton T, Ling W. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. Drug Alcohol Depend 2008; 96: 222–32.

62 Yano M, Steiner H. Methylphenidate and cocaine: the same effects on gene regulation? Trends Pharmacol Sci 2007; 28: 588–96.

63 White BP, Becker-Blease KA, Grace-Bishop K. Stimulant medication use, misuse, and abuse in an undergraduate and graduate student sample. J Am Coll Health 2006; 54: 261–8.

64 Arria AM, Wish ED. Nonmedical use of prescription stimulants among students. Pediatr Ann 2006; 35: 565–71.

65 Castaneda R, Levy R, Hardy M, Trujillo M. Long-acting stimulants for the treatment of attention-deficit disorder in cocaine-dependent adults. Psychiatr Serv 2000; 51: 169–71.

66 Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend 2007; 87: 20–9.

67 Tiihonen J, Kuoppasalmi K, Fohr J, Tuomola P, Kuikanmaki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry 2007; 164: 160–2.

68 Klee H, Wright S, Carnwath T, Merrill J. Role of substitute therapy in the treatment of problem amphetamine use. Drug Alcohol Rev 2001; 20: 417–29.

69 Grabowski J, Rhoades H, Schmitz J, Stotts A, Daruzska LA, Creson D, Moeller FG. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. J Clin Psychopharmacol 2001; 21: 522–6.

70 Shearer J, Wodak A, Mattick RP, Van Beek I, Lewis J, Hall W, Dolan K. Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. Addiction 2001; 96: 1289–96.

71 Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. Addiction 2010; 105: 146–54.

72 Lile JA, Stoops WW, Vansickel AR, Glaser PE, Hays LR, Rush CR. Aripiprazole attenuates the discriminative-stimulus and subject-rated effects of d-amphetamine in humans. Neuropsychopharmacology 2005; 30: 2103–14.

73 El-Sayeh HG, Morganti C, Adams CE. Aripiprazole for schizophrenia: systematic review. Br J Psychiatry 2006; 189: 102–8.

74 Stoops WW, Lile JA, Glaser PE, Rush CR. A low dose of aripiprazole attenuates the subject-rated effects of d-amphetamine. Drug Alcohol Depend 2006; 84: 206–9.

75 Stoops WW. Aripiprazole as a potential pharmacotherapy for stimulant dependence: human laboratory studies with d-amphetamine. Exp Clin Psychopharmacol 2006; 14: 413–21.

76 Newton TF, Reid MS, De La Garza R, Mahoney JJ, Abad A, Condos R, Palamar J, Halkitis PN, Mojisak J, Anderson A, Li SH, Elkashef A. Evaluation of subjective effects of aripiprazole and methamphetamine in methamphetamine-dependent volunteers. Int J Neuropsychopharmacol 2008; 11: 1037–45.

77 Meredith CW, Jaffe C, Yanasak E, Cherrier M, Saxon AJ. An open-label pilot study of risperidone in the treatment of methamphetamine dependence. J Psychoactive Drugs 2007; 39: 167–72.

78 Dewey SL, Morgan AE, Ashby CR Jr, Horan B, Kushner SA, Logan J, Volkow ND, Fowler JS, Gardner EL, Brodie JD. A novel strategy for the treatment of cocaine addiction. Synapse 1998; 30: 119–29.

79 Cousins MS, Roberts DC, de Wit H. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. Drug Alcohol Depend 2002; 65: 209–20.

80 Heinzerling KG, Shoptaw S, Peck JA, Yang X, Liu J, Roll J, Ling W. Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. Drug Alcohol Depend 2006; 85: 177–84.

81 Urschel HC III, Hanselka LL, Gromov I, White L, Baron M. Open-label study of a proprietary treatment program targeting type A gamma-aminobutyric acid receptor dysregulation in methamphetamine dependence. Mayo Clin Proc 2007; 82: 1170–8.

82 Fechtner RD, Khouri AS, Figueroa E, Ramirez M, Federico M, Dewey SL, Brodie JD. Short-term treatment of cocaine and/or methamphetamine abuse with vigabatrin: ocular safety pilot results. Arch Ophthalmol 2006; 124: 1257–62.

83 Brodie JD, Figueroa E, Laska EM, Dewey SL. Safety and efficacy of gamma-vinyl GABA (GVG) for the treatment of methamphetamine and/or cocaine addiction. Synapse 2005; 55: 122–5.

84 Urschel HC, Hanselka LL, Baron M. A controlled trial of flumazenil, gabapentin and hydroxyzine in treatment of methamphetamine dependence. CPDD 70th annual scientific meeting June 2008. Puerto Rico 2008; 56.

85 De La Garza R II, Zorick T, Heinzerling KG, Nusinowitz S, London ED, Shoptaw S, Moody DE, Newton TF. The cardiovascular and subjective effects of methamphetamine combined with gamma-vinyl-gamma-aminobutyric acid (GVG) in non-treatment seeking methamphetamine-dependent volunteers. Pharmacol Biochem Behav 2009; 94: 186–93.

86 Johnson BA, Roache JD, Ait-Daoud N, Wells LT, Wallace CL, Dawes MA, Liu L, Wang XQ. Effects of acute topiramate dosing on methamphetamine-induced subjective mood. Int J Neuropsychopharmacol 2007; 10: 85–98.

87 Johnson BA, Roache JD, Ait-Daoud N, Wells LT, Wallace CL, Dawes MA, Liu L, Wang XQ. Effects of topiramate on methamphetamine-induced changes in attentional and perceptual-motor skills of cognition in recently abstinent methamphetamine-dependent individuals. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31: 123–30.

88 Johnson BA, Wells LT, Roache JD, Wallace CL, Ait-Daoud N, Dawes MA, Liu L, Wang XQ, Javors MA. Kinetic and cardiovascular effects of acute topiramate dosing among non-treatment-seeking, methamphetamine-dependent individuals. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31: 455–61.

89 Hiranita T, Nawata Y, Sakimura K, Anggadiredja K, Yamamoto T. Suppression of methamphetamine-seeking behavior by nicotinic agonists. Proc Natl Acad Sci USA 2006; 103: 8523–7.

90 Williams BR, Nazarians A, Gill MA. A review of rivastigmine: a reversible cholinesterase inhibitor. Clin Ther 2003; 25: 1634–53.

91 Bentue-Ferrer D, Tribut O, Polard E, Allain H. Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. CNS Drugs 2003; 17: 947–63.

92 De La Garza R, Shoptaw S, Newton TF. Evaluation of the cardiovascular and subjective effects of rivastigmine in combination with methamphetamine in methamphetamine-dependent human volunteers. Int J Neuropsychopharmacol 2008; 11: 729–41.

93 De La Garza R II, Mahoney JJ III, Culbertson C, Shoptaw S, Newton TF. The acetylcholinesterase inhibitor rivastigmine does not alter total choices for methamphetamine, but may reduce positive subjective effects, in a laboratory model of intravenous self-administration in human volunteers. Pharmacol Biochem Behav 2008; 89: 200–8.

94 Gibb JW, Stone DM, Stahl DC, Hanson GR. The effects of amphetamine-like designer drugs on monoaminergic systems in rat brain. NIDA Res Monogr 1987; 76: 316–21.

95 Yoo JH, Cho JH, Yu HS, Lee KW, Lee BH, Jeong SM, Nah SY, Kim HC, Lee SY, Jang CG. Involvement of 5-HT receptors in the development and expression of methamphetamine-induced behavioral sensitization: 5-HT receptor channel and binding study. J Neurochem 2006; 99: 976–88.

96 Fleckenstein AE, Haughey HM, Metzger RR, Kokoshka JM, Riddle EL, Hanson JE, Gibb JW, Hanson GR. Differential effects of psychostimulants and related agents on dopaminergic and serotonergic transporter function. Eur J Pharmacol 1999; 382: 45–9.

97 Takamatsu Y, Yamamoto H, Ogai Y, Hagino Y, Markou A, Ikeda K. Fluoxetine as a potential pharmacotherapy for methamphetamine dependence: studies in mice. Ann N Y Acad Sci 2006; 1074: 295–302.

98 Munzar P, Baumann MH, Shoaib M, Goldberg SR. Effects of dopamine and serotonin-releasing agents on methamphetamine discrimination and self-administration in rats. Psychopharmacology (Berl) 1999; 141: 287–96.

99 Batki SL, Moon J, Bradley M, Hersh D, Smolar S, Mengis M, Delucchi K, Sexe D, Bennett S, Lefkowitz E, Chu W, Morello L, Jacob P III, Jones RT. Fluoxetine in methamphetamine dependence. A controlled trial: a preliminary analysis. CPDD 61st Annual Scientific Meeting. June 1999; Acapulco 1999; 235.

100 Batki SL, Moon J, Delucchi K, Bradley M, Hersh D, Smolar S, Mengis M, Lefkowitz E, Sexe D, Morello L, Everhart T, Jones RT, Jacob P 3rd. Methamphetamine quantitative urine concentrations during a controlled trial of fluoxetine treatment. Preliminary analysis. Ann N Y Acad Sci 2000; 909: 260–3.

101 Piasecki MP, Steinagel GM, Thienhaus OJ, Kohlenberg BS. An exploratory study: the use of paroxetine for methamphetamine craving. J Psychoactive Drugs 2002; 34: 301–4.

102 Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, Galloway GP, Herrell J, Huber A, McCann MJ, Obert J, Pennell S, Reiber C, Vandersloot D, Zweben J, Methamphetamine Treatment Project Corporate Authors. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction 2004; 99: 708–17.

103 Shoptaw S, Huber A, Peck J, Yang X, Liu J, Jeff D, Roll J, Shapiro B, Rotheram-Fuller E, Ling W. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. Drug Alcohol Depend 2006; 85: 12–8.

104 Dremencov E, Weizmann Y, Kinor N, Gispan-Herman I, Yadid G. Modulation of dopamine transmission by 5HT2C and 5HT3 receptors: a role in the antidepressant response. Curr Drug Targets 2006; 7: 165–75.

105 Johnson BA, Ait-Daoud N, Elkashef AM, Smith EV, Kahn R, Vocci F, Li SH, Bloch DA. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. Int J Neuropsychopharmacol 2008; 11: 1–14.

106 de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996; 57: 19–25.

107 Harper L, Napler T. Treatment with the antidepressant mirtazapine negates conditioned place preference and motor sensitization established by methamphetamine. 2005. Available at http://sfn.scholarone.com/itn2005/Index.html (last accessed 22 January 2007).

108 Cruickshank C, Montebello M, Dyer K, Quigley A, Blaszcyk J, Tomkins S, Shand D. A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. Drug Alcohol Rev 2008; 27: 326–33.

109 Chiu CT, Ma T, Ho IK. Attenuation of methamphetamine-induced behavioral sensitization in mice by systemic administration of naltrexone. Brain Res Bull 2005; 67: 100–9.

110 Anggadiredja K, Sakimura K, Hiranita T, Yamamoto T. Naltrexone attenuates cue- but not drug-induced methamphetamine drug-seeking: a possible mechanism for dissociation of primary and secondary reward. Brain Res 2004; 1021: 272–6.

111 Jayaram-Lindstrom N, Wennberg P, Hurd YL, Franck J. Effects of naltrexone on the subjective response to amphetamine in healthy volunteers. J Clin Psychopharmacol 2004; 24: 665–9.

112 Jayaram-Lindstrom N, Wennberg P, Beck O, Franck J. An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. Nord J Psychiatry 2005; 59: 167–71.

113 Jayaram-Lindstrom N, Konstenius M, Eksborg S, Beck O, Hammarberg A, Franck J. Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. Neuropsychopharmacology 2008; 33: 1856–63.

114 Jayaram-Lindstrom N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized placebo-controlled trial. Am J Psychiatry 2008; 165: 1442–8.

115 Johnson B, Roache J, Bordnick P, Ait-Daoud N. Isradipine, a dihydropyridine-class calcium channel antagonist, attenuates some of d-methamphetamine's positive subjective effects: a preliminary study. Psychopharmacology (Berl) 1999; 144: 295–300.

116 Batki SL, Bui L, Mendelson J, Benowitz N, Moon Bradley J, Jones RT, Delucchi K, Jacob P III. Methamphetamine-amlodipine interactions: preliminary analysis (abstract). Drug Alcohol Depend 2002; 66: S12.

117 Batki SL, Moon J, Delucchi K, Hersh D, Bradley C, Aguillon-Doms C, Mendelson J, Jones RT, Pnganiban T, Everhart T, Mengis M, Smola S, Helmke H, Jacob P III. Amlodipine treatment of methamphetamine dependence, a controlled outpatient trial: preliminary analysis. Drug Alcohol Depend 2001; 63 (Suppl. 1): 12.

118 Meijler MM, Matsushita M, Wirsching P, Janda KD. Development of immunopharmacotherapy against drugs of abuse. Curr Drug Discov Technol 2004; 1: 77–89.

119 Orson FM, Kinsey BM, Singh RA, Wu Y, Gardner T, Kosten TR. The future of vaccines in the management of addictive disorders. Curr Psychiatry Rep 2007; 9: 381–7.

120 Maurer P, Bachmann MF. Vaccination against nicotine: an emerging therapy for tobacco dependence. Expert Opin Investig Drugs 2007; 16: 1775–83.

121 Martell B, Mitchell E, Poling J, Gonsai K, Kosten T. Vaccine pharmacotherapy for the treatment of cocaine dependence. Biol Psychiatry 2005; 158–64.

122 Gentry WB, Ruedi-Bettschen D, Owens SM. Development of active and passive human vaccines to treat methamphetamine addiction. Hum Vaccin 2009; 5: 206–13.

123 Byrnes-Blake KA, Carroll FI, Abraham P, Owens SM. Generation of anti-(+)methamphetamine antibodies is not impeded by (+)methamphetamine administration during active immunization of rats. Int Immunopharmacol 2001; 1: 329–38.

124 Danger Y, Gadjou C, Devys A, Galons H, Blanchard D, Follea G. Development of murine monoclonal antibodies to methamphetamine and methamphetamine analogues. J Immunol Methods 2006; 309: 1–10.

125 Gentry WB, Laurenzana EM, Williams DK, West JR, Berg RJ, Terlea T, Owens SM. Safety and efficiency of an anti-(+)-methamphetamine monoclonal antibody in the protection against cardiovascular and central nervous system effects of (+)-methamphetamine in rats. Int Immunopharmacol 2006; 6: 968–77.

126 Byrnes-Blake KA, Laurenzana EM, Carroll FI, Abraham P, Gentry WB, Landes RD, Owens SM. Pharmacodynamic mechanisms of monoclonal antibody-based antagonism of (+)-methamphetamine in rats. Eur J Pharmacol 2003; 461: 119–28.

127 McMillan DE, Hardwick WC, Li M, Gunnell MG, Carroll FI, Abraham P, Owens SM. Effects of murine-derived anti-methamphetamine monoclonal antibodies on (+)-methamphetamine self-administration in the rat. J Pharmacol Exp Ther 2004; 309: 1248–55.

128 Byrnes-Blake KA, Laurenzana EM, Landes RD, Gentry WB, Owens SM. Monoclonal IgG affinity and treatment time alters antagonism of (+)-methamphetamine effects in rats. Eur J Pharmacol 2005; 521: 86–94.

129 Daniels JR, Wessinger WD, Hardwick WC, Li M, Gunnell MG, Hall CJ, Owens SM, McMillan DE. Effects of anti-phencyclidine and anti-(+)-methamphetamine monoclonal antibodies alone and in combination on the discrimination of phencyclidine and (+)-methamphetamine by pigeons. Psychopharmacology (Berl) 2006; 185: 36–44.

130 Maldonado R, Valverde O, Berrendero F. Involvement of the endocannabinoid system in drug addiction. Trends Neurosci 2006; 29: 225–32.

131 Anggadiredja K, Nakamichi M, Hiranita T, Tanaka H, Shoyama Y, Watanabe S, Yamamoto T. Endocannabinoid system modulates relapse to methamphetamine seeking: possible mediation by the arachidonic acid cascade. Neuropsychopharmacology 2004; 29: 1470–8.

132 Landa L, Sulcova A, Slais K. Involvement of cannabinoid CB1 and CB2 receptor activity in the development of behavioural sensitization to methamphetamine effects in mice. Neuro Endocrinol Lett 2006; 27: 63–9.

133 Miller DK, Crooks PA, Zheng G, Grinevich VP, Norrholm SD, Dwoskin LP. Lobeline analogs with enhanced affinity and selectivity for plasmalemma and vesicular monoamine transporters. J Pharmacol Exp Ther 2004; 310: 1035–45.

134 Wilhelm CJ, Johnson RA, Lysko PG, Eshleman AJ, Janowsky A. Effects of methamphetamine and lobeline on vesicular monoamine and dopamine transporter-mediated dopamine release in a cotransfected model system. J Pharmacol Exp Ther 2004; 310: 1142–51.

135 Wilhelm CJ, Johnson RA, Eshleman AJ, Janowsky A. Lobeline effects on tonic and methamphetamine-induced dopamine release. Biochem Pharmacol 2008; 75: 1411–5.

136 Neugebauer NM, Harrod SB, Stairs DJ, Crooks PA, Dwoskin LP, Bardo MT. Lobeline decreases methamphetamine self-administration in rats. Eur J Pharmacol 2007; 571: 33–8.

137 Dwoskin LP, Crooks PA. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem Pharmacol 2002; 63: 89–98.

138 Kuribara H. Effects of tetrabenazine on methamphetamine-induced hyperactivity in mice are dependent on order and time-course of administration. Pharmacol Biochem Behav 1997; 56: 9–14.

139 Frey K, Kilbourn M, Robinson T. Reduced striatal vesicular monoamine transporters after neurotoxic but not after behaviorally-sensitizing doses of methamphetamine. Eur J Pharmacol 1997; 334: 273–9.