Journal of Substance Use, 2011; Early Online:1–21

informa
healthcare

REVIEW

A review of psychological and pharmacological treatment options for methamphetamine dependence

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Abstract
Methamphetamine (MA) is a public health problem both in Australia and internationally and very little is known about the most cost-effective treatment options. This study is a review of recent studies and an assessment of current treatment options for MA dependence. Treatment options for MA dependence can be divided into outpatient and inpatient modality settings according to the level of drug use. Moderate improvements through higher rates of retention in treatment (especially residential rehabilitation) have been found in individuals who completed either cognitive-behavioural therapy or counselling as a form of outpatient treatment and in those users who completed a residential rehabilitation treatment programme at an inpatient treatment modality. There remains a need for further research to investigate the efficacy of existing treatment options in individuals with MA use problems and to address the economic impact of those interventions in terms of cost-effectiveness/cost utility.

Keywords: *Methamphetamine, review, treatment*

Introduction

Methamphetamine (MA) use problems have created the need for relevant treatment services and this study comprises an overview of the most recent evidence-based options for treatment. Existing knowledge of the treatment options for MA dependence and abuse is scattered and limited due to the fact that MA use has increased recently in a number of countries. This review seeks to identify and classify possible treatment options for future economic evaluations, that is, cost-effectiveness/cost utility analysis of interventions, to reduce harm for MA abuse and dependence. The study will review international experiences and where appropriate focus on Australian circumstances.

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ISSN 1465-9891 print/ISSN 1475-9942 online
DOI: 10.3109/14659891.2011.592900

The prevalence of MA use and abuse worldwide has been estimated to be at 35 million users (United Nations Office for Drug Control and Crime Prevention, 2000). However, new estimates show that the prevalence of amphetamine-type substances worldwide may be in the order of between 16 and 51 million people (annual prevalence 0.4–1.2%) aged 15–64 years. After cannabis, MA is the most widely used and abused illicit drug in the world (United Nations Office on Drugs and Crime, 2009).

MA has also become a major public health and public safety problem in the USA and worldwide (Cho & Melega, 2002; Rawson et al., 2002a, b; Roehr, 2005). Rates of MA use somewhat stabilised in the USA since 2002, but rates of dependence increased from 10.6% of users in 2002 to 22.3% in 2004 (US Department of Health and Human Services, 2005). Recent estimates suggest that there are about 3.7 million (annual prevalence 0.9–1.0%) individuals in the USA who have used amphetamines at least once in the past year (United Nations Office on Drugs and Crime, 2009).

Australia has one of the highest rates of MA use in the world and high rates of injecting MA which led to greater morbidity among the drug-using population (Lee & Rawson, 2008). The use of MA has risen in the past decade in Australia among the general population, especially among the sentinel drug-using population (Cogger et al., 2008). MA features among the most problematic drugs in Australia with over 100,000 regular users, of which there are about 73,000 dependent individuals. Most current users take MAs infrequently (McKetin et al., 2005b). This figure is almost double that of the estimated 45,000 regular heroin users in Australia (Degenhardt et al., 2004). With regard to treatment episodes, there were 15,935 drug treatment episodes in the financial year 2005/2006 in Australia where MA was the primary drug of concern (Australian Institute of Health and Welfare, 2007; Cogger et al., 2008).

Frequent use of MA may lead to psychosocial and physical health problems. Major harms of regular or heavy MA use include toxicity and mortality, cardiovascular/cerebrovascular pathology, dependence and blood-borne virus transmissions, MA psychosis, depression, suicide, anxiety and violent behaviour (Darke et al., 2008).

Treatment options for MA dependence and abuse are primarily psychosocial (Shearer, 2007). In spite of the potential harm associated with MA disorder, evidence about the efficacy of current treatment options is sparse. The majority of studies addressing treatment available to MA users do not distinguish the treatment options that are available for MA users due to high heterogeneity of treatment modalities and their duration.

A number of reviews have been conducted in recent years (Baker & Lee, 2003; Knapp et al., 2007; Shearer, 2007; Lee & Rawson, 2008) and these reviews concluded that psychological interventions are effective for stimulant users (Lee & Rawson, 2008). However, there are few studies up to date of treatment options for MA only as a psychostimulant drug.

This article will provide an overview of the current state of treatment options for MA dependence including recent studies conducted in 2007, 2008 and 2009. Very few studies are available that merge the existing evidence on psychosocial and pharmacological treatment options for MA abuse. The evidence concerning psychosocial and pharmacological treatments is merged in this study with the addition of nine new studies to the existing evidence on MA treatment options. This study will provide a starting point to assess the effectiveness and cost-effectiveness of possible available interventions for MA abuse and dependence.

Method

A systematic review was conducted using the Medline, Web of Science (including Social Science Citation Index), PsycInfo and Cochrane Collaboration databases. The following treatments were researched to identify studies most relevant to MA treatment: "intervention", "treatment", "cognitive behavioural", "residential", "counselling", "residential rehabilitation" and "cognitive-behavioural therapy (CBT)". The results were then combined and research added for "amphetamine" or "MA" to include studies involving this class of drugs. Studies were then limited to the following: those published between years 1990 and 2009, human studies published in peer-reviewed journals in English including clinical, randomised controlled trials (RCTs), controlled trials, systematic reviews and reviews (see Table I).

For the purpose of this review, studies (including reviews), which were published recently, were selected from 236 identified articles which were considered relevant. Articles were manually searched via abstract for relevance and the results are presented in Table II.

Results

Treatment options and level of evidence from published studies and RCTs on the effects of different treatment modalities

Psychosocial interventions such as CBT, counselling, residential rehabilitation and contingency management (CM) show promise and effectiveness in the treatment of individuals. Other forms of psychosocial treatment options include motivational interviewing (MI), relapse prevention (RP) and other behavioural therapies. The findings in relation to pharmacologic treatments show that some chemical agents do reduce MA use while other agents do not have any effect at all, or have perhaps a negative effect on the treatment group in comparison with the control group (non-treatment group). The findings from the studies on pharmacological treatments are generally limited due to small sample sizes.

Psychosocial treatments

Consistent findings across several studies (Baker et al., 2001; Baker & Lee, 2003; Rawson et al., 2004, 2006; Yen et al., 2004; Baker et al., 2005, 2006; Petry et al., 2005; Shoptaw et al., 2005; Feeney et al., 2006; Ling et al., 2006; Roll et al., 2006; Knapp et al., 2007; Shearer, 2007; Cogger et al., 2008; Lee & Rawson, 2008; Cleary et al., 2009) indicate that CBT (or a modality thereof as described in Table II) is effective in reducing MA use and effective in increasing abstinence rates while in treatment (more urine-free samples obtained

Table I. Review results

Source	Total citations (combined for search terms above)	Limited according to search criteria	Selected studies (recently published studies)
Cochrane Library	5676	10	1
Medline	218	54	7
Web of Science	796	65	8
PsycInfo	18	14	4

Table II. Summary of the selected studies

Study	Participants	Methods	Intervention	Main outcomes
Baker & Lee (2003)	n/a	Review of psychosocial interventions for amphetamine use	Inpatient and outpatient treatment, residential treatment, RP, CBT Matrix Model programme and alternative and complementary therapies	RP and CBT, the most effective treatment for amphetamine users; CBT with MI appears to present the best treatment practice
Baker et al. (2001)	$n = 64$ regular amphetamine users (32 in the intervention group and 32 in the control group)	Randomised controlled single-blind trial	Two (MI and discussion of skills) and four sessions of CBT (MI, skill training, coping with craving and RP vs. self-help control group)	Significant reduction in amphetamine use group but no differences between subgroups
Baker et al. (2005)	$n = 214$ (regular amphetamine users)	RCT	Two or four sessions of CBT versus self-help control group	Significant reduction in amphetamine use and reduction in depression levels but difference was lost at 6-month follow-up
Baker et al. (2006)	$n = 130$ ($n = 65$ in the intervention group and $n = 65$ in the control group)	RCT	10 sessions of CBT MI versus TAU	MI and CBT only modestly associated with improvements in comparison with TAU
Cleary et al. (2009)	n/a	Meta-analysis of 54 studies (30 randomised trials and 23 non-experimental studies)	CBT, MI, MI plus CBT, group approaches, CM, integrated assertive community treatment, intensive case management, residential programmes	MI can assist in reduction of substance use at least in the short term; long-term residential rehabilitation is effective but the quality of evidence is less supportive; CM is gaining more support but more research is needed for CM interventions

(*Continued*)

Table II. (Continued)

Study	Participants	Methods	Intervention	Main outcomes
Elkashef et al. (2008)	$n = 30$ amphetamine users (10 in the intervention group and 20 in the control/placebo group)	RCT and review of studies on pharmacotherapy for MA dependence	3 months, daily dose of dexamphetamine versus placebo	Decreased MA use and higher rates of retention but the sample size is too small to show significant statistical differences
Feeney et al. (2006)	$n = 507$	Longitudinal study	4 weeks of CBT hourly therapy session (no control group)	Significant changes in general health, anxiety, depression and social dysfunction
Knapp et al. (2007)	n/a	Systematic review of 27 RCT studies	CBT, RP, RP plus coping skills training plus cognitive therapy, CBT plus CM, community reinforcement approach plus CM, CM, CM plus counselling, reinforcement therapy plus coping skills training	Effects of different interventions found were mostly analysed for cocaine and resulted generally in different findings; groups that received CBT or drug counselling or CM or RP versus usual care were found to have lower rates of use; comparison between different interventions yielded inconclusive results in most cases as treatment intensity varied across different treatments
Lee & Rawson (2008)	n/a	Review of 12 RCT studies of cognitive behavioural and behavioural interventions	Cognitive and behavioural therapies, CM	Overall conclusion is that MA use appears reactive to interventions; good outcomes with CBT (with or without MI) and CM; broad approach of either CM or CBT or MI appears useful in the treatment of amphetamine dependence

(*Continued*)

Table II. (Continued)

Study	Participants	Methods	Intervention	Main outcomes
Ling et al. (2006)	n/a	Review of literature on MA abuse	Behavioural treatments for MA dependence and abuse (CBT, CM); pharmacologic treatments (bupropion, modafinil, baclofen); future approaches (vaccine against MA abuse and guided CBT training)	Reductions in MA use from Matrix and other treatment conditions were substantial at 6- and 12-month follow-up. At 6- and 12-month follow-up CM produced significant treatment effects, fewer positive urine samples and longer periods of abstinence; bupropion reduced subjective effects of MA and cue-induced cravings, modafinil may replace MA while not posing same abuse potential, baclofen produced significant effect of treatment when compared with placebo; CBT training recommended to better regulate the regions of the brain damaged by MA use
Maglione et al. (2000a)	$n = 2570$	Longitudinal study	Residential rehabilitation over a 90-day period	Retention in treatment was measured against a 90-day threshold mark and it was found that less than one-third of MA users completed the critical threshold of 90 days
McElhiney et al. (2009)	$n = 13$ MA (HIV + gay men)	Single-blind trial	12 weeks of modafinil plus 4 weeks of placebo plus 18 sessions of CBT over 16 weeks (no control group)	Modafinil appeared to be more useful to those diagnosed with abuse rather than dependence; most effective in patients who taper or start to discontinue MA use; modafinil and CBT showed high rates of retention

(*Continued*)

Table II. (Continued)

Study	Participants	Methods	Intervention	Main outcomes
Rawson et al. (2004)	$n = 978$ MA users	RCT	TAU (outpatient treatment model) 4–16 weeks vs. 16 weeks treatment (Matrix model CBT that incorporates family education groups, social support groups combined with weekly breath alcohol testing and urine testing)	Both groups showed improvements from baseline to post-treatment and 6-month follow-up. Matrix treatment resulted in increased retention, more urine-free samples and longer periods of abstinence. The effect was lost at follow-up
Rawson et al. (2006)	$n = 177$ ($n = 160$ cocaine users and $n = 17$ MA-dependent users)	RCT	CM versus CBT versus combined CM/CBT	Significant increased retention and treatment completion in CM/CBT and CM groups as compared with CBT only
Roll et al. (2006)	$n = 113$ MA users or dependent users	RCT	12 weeks of TAU versus 12 weeks of TAU plus CM	CM treatment as adjunct to psychosocial treatment only (counselling)

(*Continued*)

Table II. (Continued)

Study	Participants	Methods	Intervention	Main outcomes
Rose & Grant (2008)	n/a	Review of pharmacotherapies for MA dependence	Monoamine agonists (sertraline, paroxetine, fluoxetine, imipramine, methylphenidate); mixed monoamine agonist/antagonists (mirtazepine); dopamine antagonists (haloperidol and risperidone, quetiapine, baclofen and gabapentin, gamma-vynil GABA, topiramate)	Determining the most effective pharmacological treatment is complicated as each group of users is distinguished by special needs; bupropion and mirtazepine appear useful in managing some of the symptoms of MA abstinence; topiramate and baclofen show promise in improving treatment engagement and drug use outcomes
Shearer (2007)	n/a	Systematic review of 43 RCTs of psychosocial approaches for psychostimulant dependence	Community reinforcement approach, incentive-based programmes, cue exposure, MI, RP, CBT, detoxification, residential rehabilitation, 12-step programmes	Different findings in relation to different treatment approaches; behavioural and cognitive interventions are generally effective in lower disadvantaged groups of users but not effective in heavy users; more intensive treatments such as Matrix programme are generally more utilised by more users with a greater social disadvantage and heavier use of amphetamines; early attrition in most studies is high

(*Continued*)

Table II. (Continued)

Study	Participants	Methods	Intervention	Main outcomes
Shoptaw et al. (2005)	$n = 162$ MA-dependent gay/bisexual men	RCT	16 weeks of CBT versus CM versus CBT plus CM, culturally tailored CBT	Significant increase in retention, longest period of consecutive negative urine tests for MA, effectiveness score showed better results in CM and CBT plus CM than standard CBT, CM and CBT plus CM showed significant decrease in unprotected sexual activities than standard CBT
Shoptaw et al. (2006a)	$n = 229$ MA-dependent users	RCT	Sertraline versus sertraline plus CM versus placebo plus CM versus placebo only	No significant effects for sertraline or CM in reducing MA use, lower retention rates in sertraline only in comparison with other groups, sertraline groups produced significantly more adverse effects than placebo group, CM groups had higher abstinence rates at 3weeks than in the non-CM groups
Yen et al. (2004)	$n = 145$ ($n = 70$ in the intervention group, 40 heroin and 30 MA users; $n = 75$ in the control group, 38 heroin and 37 MA users)	RCT	Five-session CBT versus control group (no intervention)	Significant improvement to manage self-confidence in the intervention group

Notes: This table was reproduced in parts with permission from the *Drug and Alcohol Review* journal. *Source*:: Lee and Rawson (2008). n/a, not applicable; MA, methamphetamine; CBT, cognitive-behavioural therapy; CM, contingency management; MI, motivational interviewing; TAU, treatment as usual; RCT, randomised controlled trial; RP, relapse prevention; GABA, gamma aminobutyric acid.

from in-treatment participants). For example, Rawson et al. (2004) reviewed the treatment effectiveness of Matrix treatment (a form of CBT) and these authors report that participants were 38% more likely to stay in treatment (odds ratio = 1.384) and 31% more likely to have urine-free MA test results (odds ratio = 1.311) in comparison with treatment-as-usual (TAU) participants.

Cognitive-behavioural therapy

Abstinence-oriented outcomes of CBT were compared among 64 MA-using participants (Baker et al., 2001). This study compared two and four sessions of MI plus CBT with a self-help booklet control group. The findings of the study show a decrease in MA use across the groups and a significant increase in abstinence in the treatment groups compared with the control group. The findings of this study indicate that the Opiate Treatment Index scores showed a significant reduction in mean daily amphetamine use among the intervention versus control groups (1.02 vs. 0.44). This study was replicated by Baker et al. (2005) and similar results were obtained, that is, the mean Opiate Treatment Index score at 6-month follow-up was 0.78 for the control group compared with the average of all treatment groups of 0.62. In addition, it was found that the four-session group also showed a significant decrease in depression post-treatment, although the effect was lost by the 6-month follow-up. But both studies described above suggested a significantly higher rate of abstinence among the CBT group of participants compared with the control group of participants at the 6-month follow-up (Lee & Rawson, 2008). In support of the finding of increased abstinence, Feeney et al. (2006) examined the outpatient abstinence based on CBT for a duration of 4 weeks ($N = 507$ amphetamine users) and found increased abstinence in 168 individuals who completed the programme.

Retention-related outcomes of the CBT intervention were examined for 2337 MA users in California, USA (Maglione et al., 2000b). These authors report that, overall, only 23% of the participants completed treatment and males were 1.35 times more likely to drop out of treatment than females. Furthermore, it was also found that being referred from criminal justice system was a strong predictor of treatment non-retention, that is, the coerced clients were 0.7 times more likely to drop out of treatment. Another finding in this study indicated that injecting drug users were 1.5 times more likely to drop out of treatment than those who smoked or snorted the drug (Baker & Lee, 2003). Rawson et al. (2004) in a multi-site study using the Matrix Model compared TAU with the multi-component treatment (which includes CBT, group family education, group social support and individual counselling over 16 weeks). Both groups showed similar outcomes; though the Matrix treatment resulted in increased attendance (odds ratio = 1.38), more drug-free urine samples and longer periods of abstinence during treatment, the difference was lost at follow-up (Lee & Rawson, 2008).

Studies on 67 MA, 78 heroin and 507 amphetamine users in Taiwan looking at outcomes of self-efficacy (Yen et al., 2004) and refusal of self-efficacy (Feeney et al., 2006) showed improved outcomes among MA users in the intervention groups compared with the control group. The interventions that were compared were five sessions of MI and RP versus the control group (which was not specifically stated in the study) (Yen et al., 2004) and 4 weeks of CBT with no control group (Feeney et al., 2006).

CBT for specific groups of MA users

Using data from drug abuse treatment programs in California, USA, a few researchers compared the effectiveness of four types of treatment modalities of CBT and CM (including

gay-specific CBT), CBT alone, CM alone, CBT + CM and gay-specific CBT alone intervention among homosexual and bisexual men who were MA dependent (Peck et al., 2005; Shoptaw et al., 2005; Jaffe et al., 2007). They found that all interventions were associated with reductions in self-reported MA use up to 1-year post-treatment (Lee & Rawson, 2008). For example, Shoptaw et al. (2005) found increases in treatment retention in the longest period of consecutive MA-negative urine test and increases in treatment effectiveness score of the Addiction Severity Index in the groups that included CM (CM only and CBT + CM). They also recorded fewer missing urine screen tests. The participants in the CBT + CM group were rewarded with more incentive payouts than those in the CM-only group and attended significantly more sessions than those in the CBT-only group (Lee & Rawson, 2008). These findings were supported by another study (Peck et al., 2005) which reported that depression improved post-treatment across the groups and that there was no influence of HIV status on these results. Furthermore, the CBT-only group showed higher levels of depression after 1-year post-treatment, but had higher premorbid rates of major depressive disorders (Lee & Rawson, 2008).

Contingency management

The aim of the CM is to use positive reinforcement to reward achievement of goals in treatment, most commonly abstinence. The incentives include vouchers exchangeable for goods or privileges and cash rewards. For example, attendance at treatment sessions or a drug-negative urine specimen is rewarded with cash. Generally, studies on CM interventions have shown strong evidence of efficacy across drug types, although long-term follow-ups are uncommon and there is some reduction in the treatment benefits at post-treatment follow-up once the contingencies have been removed (Lee & Rawson, 2008). CM has been used in the USA but it is not widely used in Australia. For example, Rawson et al. (2006) compared CM with CBT using a combined CM + CBT treatment in a sample of stimulant users and the sample included both MA and cocaine users. The study results demonstrated a reduction in stimulant use for all groups whereby CM produced increased retention and reduced stimulant use during the treatment period, although there was no difference between groups at follow-up (Lee & Rawson, 2008).

Another study involved 388 MA users enrolled in methadone maintenance treatment with or without incentives for 12 weeks. The results showed that stimulant-free urine test results were twice as likely to occur in the CM group as in the usual care group. It was also found that continuous abstinence for 4, 8 and 12 weeks was more likely to occur in the incentive group (Peirce et al., 2006). Roll et al. (2006) had randomised 113 MA-using participants to 12 weeks of TAU or TAU + CM. They found that participants in CM showed a significantly greater increase in MA-free urine samples and were abstinent for longer periods, but there was no difference in treatment retention between the groups.

Shoptaw et al. (2006a) compared sertraline (antidepressant) or placebo with and without CM. These authors found no main effects of sertraline or of CM, but the sertraline-only group showed fewer weeks of abstinence, poorer retention rates and attended fewer RP groups.

Relapse prevention

RP is a treatment modality in which responding behaviour is controlled by preceding stimuli rather than the consequent stimuli reinforcing operant behaviour (Shearer, 2007). Marlatt and Gordon (1985) developed a CBT model of RP in which patients were taught (1) skills

to cope with drug craving; (2) drug refusal skills and assertiveness; (3) how to recognise seemingly irrelevant decisions; (4) general problem-solving skills; and (5) how to cope with drug use lapses. There are no such studies that have been conducted among amphetamine users (Shearer, 2007). Comparable studies on other psychostimulants report different findings in relation to effectiveness, that is, Carroll (1996) found in his review of 24 RCTs among cocaine users that RP was more effective than no treatment but equally effective as other treatment approaches, whereas other findings indicate that RP was less effective than other approaches in the treatment of cocaine dependence ($r = -0.03$; 95% CI = -0.17 to 0.11).

Motivational interviewing

Miller and Rollnick (2002) describe MI as a treatment modality with the following components: (1) expressing empathy through techniques such as reflective listening; (2) developing a discrepancy between the patient's self-image as a drug user and other preferred non-drug using images; (3) rolling with resistance and avoiding argumentation; and (4) supporting self-efficacy or the patient's personal sense of ability to change. Carroll et al. (2006) describe a large multi-site RCT that examined the effectiveness of integrating MI into the intake procedures of community drug treatment programmes. These authors found that MI significantly improved retention rates in treatment 1-month post-enrolment, that is, treatment retentions were 84% for MI versus 75% for standard counselling therapy (with a mean number of sessions of 5.0 completed for MI compared with 4.0 for standard counselling). However, there were no differences in drug use across conditions and outcomes after 3 months of treatment. Zweben and Zuckoff (2002) found, in their review of 21 studies of MI treatment adherence, that there were significant adherence effects in 12 studies (ranging from 47% to 100% treatment retention) comparable with effects to other standard interventions in five studies and no incremental benefit in four studies.

Pharmacological treatments

Rose and Grant (2008) reviewed the effectiveness of several agents considered to be useful for pharmacotherapy treatment of MA dependence: monoamine agonists (sertraline, paroxetine, fluoxetine and imipramine), dopamine agonists (bupropion, methylphenidate), mixed monoamine agonists (mirtazepine) and monoamine antagonists [haloperidol and risperidone, quetiapine, baclofen and gabapentin, gamma-vynil gamma aminobutyric acid (GABA), topiramate]. Each of these pharmacological agents is discussed briefly below.

Monoamine agonists

Sertraline. Shoptaw et al. (2006a) compared the effects of serotonergic agent, sertraline, in a placebo RCT among 229 MA-dependent outpatients. The patients were randomised to one of four conditions for 12 weeks: (1) sertraline plus CM; (2) placebo plus CM; (3) sertraline only; and (4) placebo only. Despite a very high percentage of study adherence (>80%), individuals in the sertraline group did not show improvement in depressive symptoms or cravings and actually had worse outcomes than patients receiving the CM or placebo.

Paroxetine. The study by Piasecki et al. (2002) randomised 20 individuals to either placebo or paroxetine for 8 weeks. However, the attrition in the study was substantial with only

15% completing the study protocol. Overall, the study reported only one individual, who remained abstinent from MA during the 8 weeks. It was also acknowledged that weight gain, sexual side effects and sedation induced by paroxetine are the opposite desired effects of MA that are sought by users of the drug therefore presenting serious difficulties with acceptance of the medication.

Fluoxetine. The findings of a study conducted among 60 MA-dependent subjects in an 8-week trial of fluoxetine versus a placebo indicated that craving was less in the groups receiving the medication and MA use declined in both groups. No significant differences were found between the two groups on measures of self-report or urine toxicology screening to detect MA use (Batki et al., 2000).

Imipramine. Galloway et al. (1996) examined the efficacy of the serotonergic/noradrenergic tricyclic antidepressant, imipramine, in a RCT of 32 MA-dependent outpatients by comparing two different dosage scenarios, one being a very low dose in comparison with the second group. It was found that although patients who received the higher dose remained in treatment longer, there were no differences in craving, depression, percentage of MA-positive urine, days since last MA use and study visit attendance.

Dopamine agonists

Bupropion. Bupropion was examined in a RCT of 26 non-treatment-seeking subjects in a placebo versus medication setting with extended release for 6 days and then administration of a MA placebo or MA as an intravenous drug. Compared with the placebo group, the bupropion group indicated reduced drug effects and desire to use, as well as reduced cue-elicited cravings (Newton et al., 2006). Newton et al. (2006) summarised that although the sample was small and the results probably needed replication in another study, bupropion may play a role in reducing craving for MA in early abstinence. The findings also indicated diminished relapse severity by limiting the reinforcing effects of MA.

Methylphenidate (dextroamphetamine). Shearer et al. (2002) suggested an approach for prescribing methylphenidate to patients addicted to MA. This approach is similar to the replacement therapies for opiate addiction, such as methadone substitution therapy. Limited experimental findings from a low-power statistical study on the parent drug of MA, amphetamine, indicate that using methylphenidate to treat withdrawal symptoms in long-term amphetamine abusers appears a promising approach in delivering positive treatment outcomes associated with amphetamine abuse and dependence (Laqueille et al., 2005).

Mixed monoamine agonists/antagonists

Mirtazepine. Kongsakon et al. (2005) examined the impact of mirtazepine on amphetamine withdrawal in a RCT among 20 amphetamine-dependent subjects, that is, placebo versus mirtazepine. The medication and placebo were administered for 2 weeks. While the active treatment individuals exhibited lower levels of withdrawal symptoms, there were no differences in depressive symptoms between the two groups.

Monoamine antagonists

Haloperidol and risperidone. A study examining the effects of haloperidol and risperidone conducted among 17 and 18 non-addicted individuals in a placebo-controlled trial showed no success in blocking the desired effects of use of MA among MA users (Wachtel et al., 2002).

Quetiapine. This medication has been examined for its effects in nine users who received quetiapine for non-psychotic anxiety (Sattar et al., 2004). Two patients were diagnosed with MA dependence and all patients were alcohol dependent. Although the authors discovered lower self-reported craving scores in those individuals who were administered the medication, due to the small sample size and lack of blinding procedures the results of the study do not allow conclusive findings in relation to the effect of the medication on MA users.

GABA receptor agonists

Baclofen and gabapentin. In a study by Heinzerling et al. (2006) baclofen and gabapentin were administered to 88 MA-dependent outpatients in a double-blind, randomised placebo-controlled trial of 16 weeks duration. The protocol completion rates in the treatment groups in the trial were 60% for baclofen, 34.6% for gabapentin and 40.5% for the placebo. The study found that there were no statistically significant differences between the groups with no reduction in depressive symptoms, craving for MA or reduction in MA-positive urine samples. However, it was observed among high protocol adherent patients that baclofen recipients returned greater numbers of MA-negative urine samples relative to the gabapentin and placebo subjects, which suggests a small but positive effect of baclofen in reducing MA use. Furthermore, it was also found that greater attendance of psychosocial therapy groups, in addition to the medications provided, was associated with decreased MA use across all the three groups showing the importance of psychosocial therapy augmentation of pharmacotherapy for MA dependence.

Gamma-vynil GABA. Gamma-vynil GABA was evaluated in a 9-week open-label pilot study involving 10 MA-dependent individuals, 17 MA- and cocaine-dependent individuals and three cocaine-dependent individuals (Brodie et al., 2005). Overall, 18 participants continued to be administered the medication beyond the initial dose on day 15 and administration continued over the next 4 weeks with a decreased dosage regime over the following 3 weeks. Overall, a total of 18/30 study participants completed the trial with 16/18 subjects testing negative for MA and cocaine during the last 6 weeks with a median of 42 days being drug free during the 63-day study period. Although the study delivered promising findings a weakness was the lack of a control group. Another study that examined the same 18 participants for their safety outcomes did not find changes in the visual field or abnormalities in visual acuity or ocular adverse effects (Fechtner et al., 2006).

Topiramate. Johnson et al. (2007a) examined the effects of topiramate in a randomised, placebo-controlled, cross-over factorial-designed pilot study among 10 MA-dependent patients. Subjects in this study received either low-dose MA or high-dose MA and low-dose topiramate or high-dose topiramate. When topiramate alone was administered, it showed a trend towards reductions in positive mood and reinforcement. However, administered with MA, it was found that subjects experienced enhancement in "positive" MA effects of

simulation and euphoria but not for craving and reinforcement. In another study Johnson et al. (2007b) examined the effects of topiramate on attention span and concentration among 10 MA-dependent inpatients and found that there was no evidence of worsening of cognitive function after administration of topiramate. The authors concluded that the effects of topiramate on cognitive performance do not present an obstacle to adherence and compliance and may even improve cognitive functions of those in treatment with this pharmacotherapy.

New directions in pharmacological treatment options

More recent studies support the finding that the provision of provigil (modafinil) as a conjunct therapy to cognitive-behavioural treatment for specific subgroups of MA users to be more than 50% effective in reducing MA use. These authors found that bupropion and baclofen are effective in managing abstinence and drug use outcomes while modafinil may be useful in situations when participants start to decrease their use (McElhiney et al., 2009). They conclude that MA users do not respond so well to pharmacotherapy but with some success in reduced craving seen in studies utilising buproprion in outpatient setting. Elkashef et al. (2008) demonstrated decreased rates of MA use and higher rates of retention over 3 months of dexamphetamine treatment in comparison with the control group. The findings of this study are promising but they are limited due to the small sample size (30 MA-dependent individuals).

Shearer (2007) also suggests that the current research of pharmacological treatment modalities for MA dependence that may be available within the next 5 years includes agents used for other psychostimulants: diversive agent disulfiram (Carroll et al., 2004), amphetamine/MA substitution with dexamphetamine (Shearer et al., 2002; Grabowski et al., 2004), therapeutic vaccines (Kosten et al., 2002), central nervous system (CNS) stimulant modafinil (Dackis et al., 2004) and the GABA agonist baclofen (Shoptaw et al., 2003).

The delivery of treatment for MA use in practice

In general, there are two types of treatment provided for MA abuse and dependence: inpatient and outpatient treatment settings. Outpatient treatment in most studies is associated with CBT and/or counselling forms of treatment, whereas inpatient treatment involves referral to residential rehabilitation treatment and/or short-term detoxification (Australian Institute of Health and Welfare, 2007). The main goals of psychosocial interventions are the following: (1) to engage dependent users in the treatment process; (2) to work to retain them in treatment; (3) to encourage treatment compliance; and (4) to provide RP support (Shearer, 2007). Treatment approaches can further be subdivided into treatment intensity (duration and frequency) and also whether treatments are delivered to individuals, groups or through other channels (Baker & Lee, 2003).

It is also acknowledged in studies that perhaps a more specific user-targeted approach needs to be introduced in order for treatment modalities to show better cost-effectiveness (Schumacher et al., 2002), treatment retention (or attrition) (Simpson et al., 1999; Maglione et al., 2000a, b; Simpson et al., 2002; Hubbard et al., 2003), related reduction in consumption of the drug and drug abstinence after treatment (Shearer, 2007). In comparison, the findings from studies on psychostimulant drugs other than MA indicate that behavioural and cognitive interventions have not been generally effective in retaining acutely disadvantaged groups in treatment such as homeless, the poor and populations with

unmet complex health and welfare needs (Kirby et al., 1998; Maude-Griffin et al., 1998; Milby et al., 2000; Donovan et al., 2001; Marlowe et al., 2003; Aharonovich et al., 2006). Inpatient-based treatment modalities, therefore, offer a better option to these groups (Lam et al., 1995; Milby et al., 2000; Donovan et al., 2001; Marlowe et al., 2003; Milby et al., 2003; Williamson et al., 2006).

Overall, outpatient and inpatient treatment modalities to treat MA dependence are widely used with different aims of either harm minimisation or reduction in drug use (more likely outpatient modalities) or abstinence-based approaches (more likely residential inpatient treatment modalities).

Treatment access is poor for MA dependence in Australia and as a consequence it is estimated that approximately less than one-third of dependent MA users receive treatment (McKetin & Kelly, 2007). One study (Kelly et al., 2005) shows that only 10% of regular amphetamine users receive treatment in any given year whereas more than one-half of regular opiate users receive treatment for their condition. Taking into account the fact that most disadvantaged users inject drugs and therefore suffer more from associated harms of abuse of amphetamine/MA, residential treatment intervention may well be the best avenue for treatment for this group of users. MA accounts for one-third of all injecting drug users in Australia (National Centre in HIV Epidemiology and Clinical Research, 2005). In comparison, users who do not use the drug intravenously and use infrequently respond better to counselling and CBT treatment approaches. However, findings from the Australian Institute of Health and Welfare (2007) indicate that within Australian settings and circumstances counselling was the most common form of treatment provided (39%) followed by residential rehabilitation (14%) and withdrawal management (13%). McKetin et al. (2005a) find that counselling and residential rehabilitation are the main treatment services provided for MA use. In support of this finding, current evidence also suggests that the best way to treat MA dependence is by using CBT or CM (i.e. provision of monetary or other incentives for abstinence) (Baker et al., 2004; Shoptaw et al., 2006b). Brief CBT-based psychosocial interventions have been trialled in Australia and significantly reduce levels of MA use, increase abstinence rates and alleviate MA-related harms (Baker et al., 2005). The findings from Feeney et al. (2006) indicate that there is a significant improvement among amphetamine-dependent users in levels of general health, anxiety, depression and social dysfunction after provision of a 4-week 1-h session of CBT.

Pharmacotherapies for the treatment of MA dependence do not have a supportive evidence base although dexamphetamine substitution therapy is the most widely implemented and evaluated pharmacotherapy for MA dependence (Mattick & Darke, 1995). Trials of dexamphetamine are still underway in Australia. Evaluation studies from the United Kingdom show that modest post-treatment improvement was offset by the increased risk of psychosis, continued illicit use of the drug and diversion of prescribed dexamphetamine (Shearer & Gowing, 2004). Antidepressant medication (e.g. selective serotonin re-uptake inhibitors) has also been used to treat MA dependence but the evidence in favour of this approach is poor (Galloway et al., 1996; Shearer & Gowing, 2004).

Remarks on costing of MA treatment options

In order to conduct a full economic evaluation for the future, in addition to the effects of treatment outcomes described above, we also need to be educated about the costs of available treatment options provided in practice. While some costs are easy to assess, such as the cost of rapid detoxification in an inpatient detoxification facility, the cost of, for example,

counselling therapy or behavioural therapy may not be as straightforward to calculate or not calculable at all in some circumstances.

For example, the Drug Abuse Treatment Cost Analysis Program is a data collection instrument and interview guide designed to estimate the costs of a substance abuse treatment for opiate dependence in the USA (French et al., 1997). Another protocol for costing can be found in Australia, the National Evaluation of Pharmacotherapies for Opiate Dependence. However, this programme also assesses cost in relation to opiate dependence to be used in conventional inpatient and outpatient detoxification programmes (Mattick et al., 2001). Although for a different class of drugs, these costing guidelines can be used for costing MA interventions as well, that is, on admission to residential rehabilitation as a psychosocial treatment modality, patients are most likely detoxified first in order to commence treatment. Only a few sources from abroad (Montana Department of Justice, 2009; Nicosia et al., 2009) have attempted to thoroughly cost the treatment and consequences of MA use in their societies.

Overall, the process of obtaining costs may also be more difficult as there are no clear treatment protocols for psychosocial treatment modalities in organisations that provide treatment such as non-government organisations. Non-government organisations are inclined to treat the majority of individuals with MA problems. Frequently, treatment modalities differ in duration and level of contact with the MA users, making costing of these treatments difficult. This article aimed to classify and identify approaches to treatment modalities and identify costs in relation to treatment options sought and consequently used and the economic evaluation of the selected interventions.

Discussion

Knapp et al. (2007) came to the conclusion that due to the heterogeneity of treatment options provided within different countries it is almost impossible to estimate a cost or to summarise the effects of the different intervention modalities for MA disorder on another very closely related parent psychostimulant drug, amphetamine. More generally, the evidence base for psychosocial interventions from international studies for psychostimulant-related disorders is not strong as there are insufficient controlled trials to support one intervention over another (Shearer, 2007). However, the overall impression is that psychosocial interventions are moderately effective in reducing drug use and associated problems (Carroll, 1996; Crits-Christoph et al., 1999; Gowing et al., 2001; Burke et al., 2003; Baker et al., 2005).

A good treatment constitutes a reduction in MA use aimed at abstinence. This is mostly implemented through either CBT as a form of counselling therapy or residential rehabilitation treatment. It has been found that treatment effectiveness of psychosocial interventions ranges between 30% and 40% but different treatment modalities of psychosocial interventions make this interpretation more difficult. While there remains a need for further research on outcomes of MA treatments in the future, it merits the case to conduct an economic evaluation of the effectiveness of treatment modalities in terms of both health outcomes and costs as these are provided in communities.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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