WHO/MSD/MSB/01.5

Management of substance dependence review series

Systematic review of treatment for amphetamine-related disorders

Department of Mental Health
and Substance Dependence

World Health Organization
Geneva

WHO/MSD/MSB/01.5
Original: English
Distr.: General

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This work was funded by the UNDCP and by the Ministry of Health and Welfare of Japan.

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ABSTRACT

The ease of synthesis from inexpensive and readily available chemicals makes possible the wide spread of amphetamine dependence and abuse. During the phase of chronic, high-dose consumption of amphetamines, many amphetamine users may have the experience of paranoia and hallucination. In addition, amphetamine withdrawal has been less studied although it is a common problem with a prevalent rate of 87% among amphetamine users. The objective of this review is to search and determine risks, benefits and costs of a variety treatments for amphetamine dependence or abuse, psychosis and withdrawal. Electronic searches of MEDLINE (1966 - December 2000), EMBASE (1980 - February 2001), CINAHL (1982 - January 2001) and Cochrane Controlled Trials Register (Cochrane Library 2000 issue 4) were undertaken. References to the articles obtained by any means were searched. All relevant randomised controlled trials (RCTs) and clinical controlled trials (CCTs) were included. Participants were people with amphetamine dependence or abuse, amphetamine psychosis and amphetamine withdrawal diagnosed by any set of criteria. Any kinds of biological and psychological treatment both alone and combined were examined. A variety of outcomes, for example, number of treatment responders, score changes, were considered. Two reviewers evaluated and extracted the data independently. The dichotomous data were extracted on an intention-to-treat basis in which the dropouts were assigned as participants with the worst outcomes. For amphetamine dependence or abuse, short-term treatment of fluoxetine significantly decreased craving. Medium-term treatment of imipramine significantly increased the duration of adherence to treatment. No treatment for amphetamine dependence or abuse had benefits on a variety of outcomes, including amphetamine use. The comprehensive searches found no controlled trials of treatment for amphetamine psychosis meeting the criteria for considering studies. For amphetamine withdrawal, amineptine had some benefits in the respects of discontinuation rate and global state. However, no direct benefit of amineptine on amphetamine withdrawal symptoms or craving was shown. The evidence about the treatment for amphetamine dependence and abuse, amphetamine psychosis and amphetamine withdrawal is very limited. At present, no available treatment has been demonstrated to be effective in the treatment of amphetamine dependence or abuse, psychosis and withdrawal.

ACKNOWLEDGEMENTS

This work was prepared by Dr. Manit Srisurapanont (Department of Psychiatry, Chiang Mai University, Chiang Mai, Thailand), Dr. Ngamwong Jarusuraisin (Department of Psychiatry, Chiang Mai University, Chiang Mai, Thailand) and Dr. Phunnapa Kittirattanapaiboon (Suanprung Hospital, Chiang Mai, Thailand). Technical revision was provided by Dr. Walter Ling (Department of Psychiatry, University of California, Los Angeles, U.S.A.), Dr. Maristela Monteiro (WHO/MSD/MSB), Dr. Marina Davoli (Cochrane Alcohol and Drugs Collaborative Review Group, Department of Epidemiology, Osservatorio Epidemiologico Regione Lasio, Rome, Italy). Dr. Steven L. Batki (Department of Psychiatry, State University of New York, New York, U.S.A.) generously gave us some data of his studies. We wish to thank Ms Vanna Pistotti (Head of the Library, Mario Negri Institute for Pharmacological Research, Milano, Italy) and Dr. Linda Gowing (Drug and Alcohol Services Council, Adelaide, South Australia, Australia) for database-search assistance and Ms Marica Ferri (Cochrane Alcohol and Drugs Collaborative Review Group, Department of Epidemiology, Osservatorio Epidemiologico Regione Lasio, Rome, Italy) for her co-ordination assistance. Many referees of Cochrane Drug and Alcohol Group generously gave invaluable comments on the protocol and review.

This work was funded by the UNDCP and by the Ministry of Health and Welfare of Japan.

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INTRODUCTION

Rationale for this series of systematic reviews on the treatment of amphetamine-related disorders.

Healthcare providers, consumers, researchers, and policy makers are inundated with unmanageable amounts of information. We need systematic reviews to efficiently integrate valid information and provide a basis for rational decision making. Systematic reviews establish where the effects of healthcare are consistent and research results can be applied across populations, settings, and differences in treatment (e.g. dose); and where effects may vary significantly. The use of explicit, systematic methods in reviews limits bias (systematic errors) and reduces chance effects, thus providing more reliable results upon which to draw conclusions and make decisions. Meta-analysis, the use of statistical methods to summarise the results of independent studies, can provide more precise estimates of the effects of healthcare than those derived from the individual studies included in a review.

Wider recognition of the key role of reviews in synthesising and disseminating the results of research has prompted people to consider the validity of reviews. In the 1970s and early 1980s, psychologists and social scientists drew attention to the systematic steps needed to minimise bias and random errors in reviews of research. It was not until the late 1980s that people drew attention to the poor scientific quality of healthcare review articles. However, recognition of the need for systematic reviews of healthcare has grown rapidly and continues to grow, as reflected by the number of articles about review methods and empirical studies of the methods used in reviews the number of systematic reviews published in healthcare journals, and the rapid growth of the Cochrane Collaboration.

The ease of synthesis from inexpensive and readily available chemicals makes possible the wide spread of amphetamine dependence and abuse. During the phase of chronic, high-dose consumption of amphetamines, many amphetamine users may have the experience of paranoia and hallucination. In addition, amphetamine withdrawal has been less studied although it is a common problem with a prevalent rate of 87% among amphetamine users. A systematic review relevant to the treatment of amphetamine dependence or abuse, psychosis and withdrawal, therefore, would of helpful in providing evidence-based medical services for people with amphetamine-related disorders.

This review was conducted using the Cochrane Collaboration standards for preparing systematic reviews. An electronic version of this report will be published as a Cochrane Review, and will be updated to include new evidence as it emerges.

BACKGROUND

The evidence from both in vivo and in vitro studies has shown that amphetamine administration increases concentration of monoamines in the synapse by inducing their release, blocking their uptake, or both (Seiden et al, 1993). They are toxic to dopamine and/or 5-hydroxytryptamine neurons (Seiden & Sabol, 1996). The duration and magnitude of these effects are dose dependent and are accompanied by different degrees of recovery. The results of a recent study show that methamphetamine users have dopamine transporters reduction in the striatum associated with motor slowing and memory impairment (Volkow et al, 2001).

Although amphetamines are classified as stimulants, their pharmacological actions appear to be different from those of other stimulants, including cocaine. While dopamine re uptake blockade, in particular in the nucleus accumbens, is generally believed to be the most important action of cocaine, it is generally agreed that enhancing the release of dopamine in the nucleus accumbens is of major importance in mediating amphetamines reinforcing and psychomotor stimulant effects (Altman et al, 1996). While other types of stimulants such as cocaine, which act through storage pools of catecholamines, amphetamines increase the release of newly synthesized norepinephrine and dopamine (Ellinwood & Petrie, 1977). The pharmacological effects of amphetamines also last longer than cocaine.

Because amphetamine dependence or abuse, psychosis and withdrawal are prevalent amphetamine-related disorders, only the treatment for these conditions are included in this review. Although there are a variety of amphetamines and amphetamine derivatives, the word "amphetamines" in this review stands for amphetamine, dextroamphetamine and methamphetamine only.

AMPHETAMINE DEPENDENCE OR ABUSE

Amphetamines produce feelings of euphoria and relief from fatigue, may improve performance on some simple tasks, increase activity levels, and produce anorexia. The abuse liability of the amphetamines is thought to be primarily related to their euphorigenic effects (King & Ellinwood, 1997). However, their dependence and abuse are viewed as resulting from a process in which multiple interacting factors (social, psychological, cultural, and biological) influence drug-using behaviour (Jaffe, 2000).

Amphetamines have been abused almost since their introduction. Taken intravenously, the abuse potential of amphetamines is comparable to that of heroin or cocaine (Kramer et al, 1967). The ease of synthesis from inexpensive and readily available chemicals makes possible the wide spread of amphetamine dependence and abuse. Two major epidemics of amphetamine dependence and abuse were widely recognized in 1960s and 1990s. These epidemics, in particular the recent one, affect many developed and developing countries around the world, in particular North America, Europe, Far East Asia, and Australia. Of 180 million people worldwide consuming drugs in the late 1990s, 29 million people of them were taking amphetamine-type stimulants (United Nations Office for Drug Control and Crime Prevention, 2000). This figure was larger than the number of people consuming cocaine and opiates combined.

Routes of amphetamine administration and patterns of amphetamine use are complex, not stable and various among different individuals or cultural groups. While smoking, injecting and oral taking are prevalent routes of administration, there have been some reports of amphetamine sniffing or snorting. The patterns of amphetamine use may be classified as follows (World Health Organization, 1997):

1. Instrumental use: amphetamines are exploited by the users to achieve desired goals, such as improve concentration and ward off fatigue.
2. Subcultural/recreational use: amphetamine stimulant properties are exploited to allow the user to remain active for longer periods in social/recreational settings, such as at music and dance events.
3. Chronic use: for several reasons, such as craving, tolerance and withdrawal, some amphetamine users turn to be chronic users to relieve unwanted effects of abstinence.

Amphetamine use is of concern because it causes a variety of devastating health consequences. These can be classified as follows:

1. Physical and neurological disorders due to amphetamines (World Health Organization, 1997), e. g.,
   - excitation syndrome: hyperthermia and tachycardia followed by circulatory collapse with eventually fatal outcome,
   - vascular accidents: due to increased blood pressure, cerebral hemorrhage may occur, but also myocardial infarction, both with an increased mortality risk,
   - cerebral convulsions and coma, followed by cardiovascular shock, an eventually fatal

outcome, and

- stereotype movements and choreic syndrome.

2. Amphetamine-induced mental disorders (American Psychiatric Association, 2000), including
    - dependence and abuse
    - intoxication
    - withdrawal
    - intoxication delirium
    - psychotic disorders
    - mood disorders
    - anxiety disorders
    - sexual dysfunctions
    - sleep disorders
3. Health consequences of amphetamine use (World Health Organization, 1997), e.g.,
    - human immunodeficiency virus infection
    - hepatitis
    - other sexually transmitted diseases
    - tuberculosis
    - other bacterial, fungal, and viral infections
4. Social consequences of amphetamine use (World Health Organization, 1997), e.g.,
    - violence
    - crime
    - accidents

Although a great deal has been learned about the neurobiological mechanisms underlying amphetamine use, the development of rational treatment strategies has lagged behind.

AMPHETAMINE PSYCHOSIS

During the phase of chronic, high-dose consumption of amphetamines, many amphetamine users may have the experience of paranoia and hallucination (Hall et al, 1996). This conclusion has been supported by at least two experiments, which found that most amphetamine users became psychotic within a week after a continuous administration of amphetamines (Griffith et al, 1972; Bell, 1973). The main characteristics of this psychosis are delusion of persecution, delusion of reference, auditory hallucination, and visual hallucination (Ellinwood, 1967). With further consumption, the individual becomes increasingly exhausted, loses insight into his or her actions, and may become violent and increasingly psychotic (King & Ellinwood, 1997). Although amphetamine psychosis may last longer than cocaine psychosis, it usually abate rapidly (within days) with the cessation of amphetamine intake and the excretion of amphetamines (Jonsson & Sjostrom, 1970). However, about 5-15% of the users who develop an amphetamine psychosis fail to recover completely (Hofmann, 1983). Psychiatrists in Japan have also presented data showing that amphetamine psychosis may persist for several years (Sato et al, 1992).

There is very little evidence about the risk factors of amphetamine psychosis. However, the results of a recent study found that mental health problems, including hallucinations and paranoia, significantly correlated with 4 factors (Vincent et al, 1998). Those are: i) increasing severity of dependence on amphetamines, ii) a larger number of mental health symptoms experienced before starting to use amphetamines, iii) a larger average quantity of amphetamine used in a day of use, and iv) a greater number of days on which benzodiazepines had been used in the previous 6 months.

It has long been believed that dopamine antagonists, such as chlorpromazine, haloperidol, and thioridazine, are effective for the treatment of this psychosis (Angrist et al, 1974; Tinklenberg, 1976). In addition, the use of ascorbic acid can accelerate the renal elimination of amphetamines (Beckett et al, 1965). However, there has been some advancement in the treatment of schizophrenia, e.g., the availability of newer antipsychotics, in the past decade. Because of the new epidemic of amphetamine use in 1990s, it is timely to search and determine the treatment available for amphetamine psychosis.

AMPHETAMINE WITHDRAWAL

Prolonged amphetamine abuse can lead to physiological changes when the drugs are discontinued,

spontaneously or in detoxification procedures. Amphetamine withdrawal has been less studied although it is a common problem with a prevalent rate of 87% among amphetamine users (Cantwell & McBride, 1998; Schuckit et al, 1999). This prevalence is as high as those of opiate withdrawal (91%) and cocaine withdrawal (86%). Although the duration of amphetamine withdrawal tends to be much longer than cocaine withdrawal, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for amphetamine withdrawal are the same as those for cocaine withdrawal (American Psychiatric Association, 2000). The findings of a factor analysis of amphetamine withdrawal symptoms suggest that this clinical condition may be comprised of three factors (Srisurapanont et al, 1999a). The hyperarousal factor comprises drug craving, agitation, and vivid or unpleasant dreams. The reversed vegetative factor comprises decreased energy, increased appetite, and craving for sleep. The anxiety factor comprises loss of interest or pleasure, anxiety and slowing of movement. Depressive mood is a prevalent symptom and should be considered as a symptom incorporated in more than one factor or more. Although the symptoms occurring during amphetamine withdrawal may be over in four or five days, some of the symptoms may continue for weeks or months (Watson et al, 1972; Hofmann, 1983). As amphetamine users are usually required to stop their amphetamine use before receiving any treatment, amphetamine withdrawal should be considered as a common problem for health professionals providing treatment for amphetamine abusers.

Although amphetamine withdrawal is generally not deemed as aversive as opiate withdrawal, its symptoms, in particular intense craving, may be a critical factor leading to relapse to amphetamine use (King & Ellinwood, 1997). In clinical practice, treatment for cocaine withdrawal has been recommended to be applied for amphetamine withdrawal although their pharmacodynamic and pharmacokinetic properties are not the same. The use of antidepressants for a period of 3-4 weeks during this state has been suggested by some experts (Ellinwood, 1976). In addition, acupuncture and herbal preparations have been use in several countries (World Health Organization, 1997).

Objectives

A systematic review relevant to the treatment of amphetamine dependence and abuse, psychosis and withdrawal, would be helpful for those providing evidence-based medical services for people with amphetamine dependence or abuse, psychosis and withdrawal. We, therefore, proposed to search and determine risks, benefits and costs of a variety treatments for amphetamine dependence or abuse, psychosis and withdrawal.

METHODS

Search strategy for identification of studies

Electronic Searches

1. MEDLINE (1966 - December 2000)

1 randomized controlled trial.pt.
2 controlled trial.pt.
3 randomized controlled trials/
4 controlled clinical trials/
5 random$.ti,ab.
6 Double-blind method/ or Random allocation/
7 single blind method/
8 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$).mp.[mp=title, abstract, registry number word, mesh subject heading]
9 clinical trial.pt.
10 clinical trials/
11 (clinical adj trial$).ti,ab.
12 placebos/
13 placebo$,ti,ab.
14 research design/
15 exp evaluation studies/
16 follow-up studies/
17 follow up.ti,ab.
18 prospective studies/
19 (control$ or prospectiv$ or volunteer$).ti,ab.
20 or/1-19
21 amphetamine/ or dextroamphetamine/ or methamphetamine/
22 (amphetamine or methamphetamine or dextroamphetamine).ti,ab.
23 21 or 22
24 exp substance-related disorders/dt,px,rh,th [Drug Therapy, Psychology, Rehabilitation, Therapy]
25 20 and 23 and 24
26 limit 25 to human

2. EMBASE (1980 - February 2001)

1 Clinical Trial/
2 Clinical Study/
3 Longitudinal Study/
4 Major Clinical Study/
5 Prospective Study/
6 Controlled Study/
7 Follow Up/
8 random$ trial$.ti,ab.
9 controlled trial$.ti,ab.
10 Crossover Procedure/
11 Drug Comparison/
12 Double Blind Procedure/
13 Single Blind Procedure/ or Human Experiment/
14 Randomized Controlled Trial/
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 amphetamine.ti,ab.
17 chloramphetamine.ti,ab.
18 methamphetamine.ti,ab.
19 AMPHETAMINE/ct, dt, pd, to [Clinical Trial, Drug Therapy, Pharmacology, Drug Toxicity]

20 Dexamphetamine/ct, ad, dt, pd, to [Clinical Trial, Drug Administration, Drug Therapy, Pharmacology, Drug Toxicity]
21 METHAMPHETAMINE/ct, dt, pd, to [Clinical Trial, Drug Therapy, Pharmacology, Drug Toxicity]
22 16 or 17 or 18 or 19 or 20 or 21
23 Substance Abuse/ or Drug Abuse/ or Drug Dependence Treatment/
24 Withdrawal Syndrome/co, pc, dm, rh, dt, th [Complication, Prevention, Disease Management, Rehabilitation, Drug Therapy, Therapy]
25 exp psychosis/
26 23 or 24 or 25
27 22 and 26
28 15 and 27
29 limit 28 to human

3. CINAHL (1982 - January 2001)

1 amphetamines/
2 amphetamine/
3 dextroamphetamine/
4 methamphetamine/
5 or/1-2
6 dependence/
7 abuse/
8 psychosis
9 withdrawal
10 or/6-9
11 5 and 10

4. Cochrane Controlled Trials Register issue 4, 2000

The Cochrane Controlled Trials Register was searched by using the words: (amphetamines or dextroamphetamine or methamphetamine) and (dependence or abuse or psychosis or withdrawal).

Additional search

5. Citation search: references of the articles obtained by any means were searched.

The specialised register of trials of the Drugs and Alcohol Cochrane group is regularly searched for trials or other types of relevant information.

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs) and clinical controlled trials (CCTs) were included.

Types of participants

AMPHETAMINE DEPENDENCE OR ABUSE

People with amphetamine dependence or abuse, diagnosed by any set of criteria. For the study carried out in amphetamine dependent/abuse people with comorbidity, a sensitivity analysis was conducted to determine the appropriateness of including the study data. The study carried out in both amphetamine dependent/abuse people and other substance dependent/abuse people would be included only if:

1. The data of people with amphetamine dependence or abuse were reported separately, or
2. More than half of the participants were amphetamine dependent/abuse people. However, a sensitivity analysis was conducted to determine the appropriateness of including the data obtained from a study in which most (50%-75%) participants were amphetamine dependent/abuse people (see Methods of the review). For a study in which almost all (more than 75%) participants were amphetamine dependent/abuse people, its data were included as those of study in which all participants were amphetamine dependent/abuse people.

AMPHETAMINE PSYCHOSIS

People with amphetamine psychosis, diagnosed by any set of criteria. The study carried out in both amphetamine psychotic patients and other substance-induced psychotic patients would be included only if:

1. The data of amphetamine psychotic patients were reported separately, or
2. More than half of the participants were amphetamine psychotic patients. However, a sensitivity analysis was conducted to determine the appropriateness of including the data obtained from a study in which most (50%-75%) participants were amphetamine psychotic patients (see Methods of the review). For a study in which almost all (more than 75%) participants were amphetamine psychotic patients, its data were included as those of study in which all participants were amphetamine psychotic patients.

Since acute and chronic amphetamine psychoses may be different from each other in the respects of pathophysiology, clinical features, response to treatment, course of illness, and prognosis.

People with amphetamine psychosis were divided into: i) acute psychotic patients - their psychotic symptoms persist for 4 weeks (or 1 month) or less, and ii) chronic psychotic patients - their psychotic symptoms persist for more than 4 weeks (or 1 month).

AMPHETAMINE WITHDRAWAL

People with amphetamine withdrawal, diagnosed by any set of criteria. The study carried out in combined participants of amphetamine withdrawal patients with people with other substance withdrawal would be included only if:

1. The data of amphetamine withdrawal patients were reported separately, or
2. More than half of the participants were amphetamine withdrawal patients. However, a sensitivity analysis was conducted to determine the appropriateness of including the data obtained from a study

in which most (50%-75%) participants were amphetamine withdrawal patients (see Methods of the review). For a study in which almost all (more than 75%) participants were amphetamine withdrawal patients, its data were included as those of study in which all participants were amphetamine withdrawal patients.

Types of interventions

1. Placebo
2. Any kind of pharmacological treatment,
3. Any kind of psychosocial treatment, and
4. Any kind of combined pharmacological and psychosocial treatment.

Types of outcome measures

All outcomes were reported for the short term (4 weeks or 1 month), medium term (more than 4 weeks or 1 month to 12 weeks or 3 months), and long term (more than 3 months). If any outcome was assessed more than once in a particular term, only the results of the longest duration in that term were considered.

AMPHETAMINE DEPENDENCE OR ABUSE

The outcomes of interest were classified as proximal and distal ones. Proximal outcomes are those directly relevant to amphetamine use. Distal outcomes are those not directly relevant to amphetamine use.

1. Dichotomous data (proximal outcomes)
    - 1.1 Number of people who relapse to amphetamine dependence or abuse (as priori criteria),
    - 1.2 Number of people who return to amphetamine use (but not meet the priori criteria for amphetamine dependence or abuse),
2. Dichotomous data (distal outcomes)
    - 2.1 Discontinuation rate, and
    - 2.2 Death
3. Continuous data (proximal outcomes)
    - 3.1 Number or percentage of abstinent days prior to the recommencement of amphetamine use,
    - 3.2 Number or percentage of amphetamine positive urines
    - 3.3 Number or percentage of amphetamine-use days,
    - 3.4 Frequency of amphetamine use,
    - 3.5 Amount of amphetamine consumed (as measured by any kind of unit, e.g., milligrams, tablets),
4. Continuous data (distal outcomes)
    - 4.1 Craving,
    - 4.2 Severity of dependence, abuse, or addiction (as measured by any published rating scale, e.g., Addiction Severity Index, Severity of Amphetamine Dependence, etc),
    - 4.3 Days of adherence to treatment,
    - 4.4 Patient satisfaction,
    - 4.5 Functioning,
    - 4.6 Health status or health-related quality of life, and
    - 4.7 Economic outcomes.

AMPHETAMINE PSYCHOSIS

The outcomes of interest were:

1. Dichotomous data
    - 1.1 Number of people who response to treatment (as priori criteria),
    - 1.2 Incidence of extrapyramidal side effects (EPSs), including acute dystonia, parkinsonism, and akathisia,
    - 1.3 Incidence of use of antiparkinson drugs for treating EPSs
    - 1.4 Discontinuation rate, and
    - 1.5 Death
2. Continuous data (proximal outcomes)
    - 2.1 Average score/change in global state (as measured by global psychiatric rating scales, e.g.,

Clinical Global Impression),
2.2 Average score/change on psychotic symptoms (as measured by psychotic rating scales, e.g., Brief Psychiatric Rating Scale),
2.3 Average score/change in positive symptoms (as measured by rating scales for positive symptoms, e.g. Positive Subscale of Positive and Negative Syndrome Scale)
2.4 Average score/change in negative symptoms as measured by rating scales for negative symptoms, e.g. Negative Subscale of Positive and Negative Syndrome Scale).
2.5 Average score/change in extrapyramidal side effects (as measured by rating scales for extrapyramidal side effects, e.g. Simpson-Angus Scale).
2.6 Duration of adherence to treatment,
3. Continuous data (distal outcomes)
3.1 Patient satisfaction,
3.2 Functioning,
3.3 Health status or health-related quality of life, and
3.4 Economic outcomes.

AMPHETAMINE WITHDRAWAL

The outcomes of interest were:
1. Dichotomous data
1.1 Number of people who response to treatment (as priori criteria),
1.2 Discontinuation rate, and
1.3 Death
2. Continuous data (proximal outcomes)
2.1 Average score/change in global state (as measured by global psychiatric rating scales, e.g Clinical Global Impression),
2.2 Average score/change in withdrawal symptoms,
2.3 Average score/change in craving,
2.4 Duration of adherence to treatment,
3. Continuous data (distal outcomes)
3.1 Patient satisfaction,
3.2 Economic outcomes.

Methods of the review

SELECTION OF TRIALS

Reports identified by the electronic searches were assessed for relevance. Two reviewers (MS & NJ) independently inspected all study citations identified by the electronic searches and full reports of the studies of agreed relevance were obtained. Where disputes arose the full report were acquired for more detailed scrutiny. The reviewers (MS & NJ) then independently inspected all these full study reports.

QUALITY ASSESSMENT

The quality of methodology of each selected study was independently rated (MS & NJ) using the Cochrane Collaboration Handbook (Clarke & Oxman, 1999). The trial quality was based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment (Schulz et al, 1995) and was defined as below:

A. Low risk of bias (adequate allocation concealment),
B. Moderate risk of bias (unclear allocation concealment),
C. High risk of bias (inadequate allocation concealment), and
D. No allocation concealment used.

DATA COLLECTION

Data were extracted independently by MS and NJ onto data extraction forms. Again, if the disputes arose these were resolved either by discussion between the two reviewers or the correspondence author of the paper.

DATA SYNTHESIS

In conducting a meta-analysis, a fixed effect model, an analysis that ignores the between-study variation, can give a narrower confidence interval than a random effect model. It is generally agreed that the fixed effect model is valid as a test of significance of the overall null hypothesis (i.e. 'no effect in all studies'). A statistically significant result obtained by the use of this model indicated that there is an effect in at least one of the studies. Because of these advantages, the fixed effect model was used for the synthesis of a group of data with homogeneity. Although a random effect model can be applied for the synthesis of a group of data with significant heterogeneity, the results obtained by the synthesis of this group of data have to be interpreted with great caution. The reviewers, therefore, decided to disregard the groups of data with significant heterogeneity.

As high attrition rate would affect the study results, the studies with the attrition rate of 50% or higher of the total participants will be excluded.

Other than raw data (e.g. death), the outcomes derived from only valid scales will be included in the reviews. In this review, a valid scale means a scale that has been published in a scientific journal.

Dichotomous data: The Relative Risk (RR) with the 95% confidence interval (95% CI) was used. RR is the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk of one indicates no difference between comparison groups. For undesirable outcomes an RR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

In addition, as a measure of efficacy, the number needed to treat (NNT) was also calculated. The reviewers extracted the dichotomous data on an intention-to-treat basis by applying the following guidelines to analyse data from included studies: (i) the analysis included all those who entered the trial; and (ii) the analysis maintained the study groups according to the original randomisation procedure. The reviewers assigned people lost to follow-up to the worst outcome.

Continuous data: The Weighted Mean Difference (WMD) with 95% CI was used. WMD is a method of meta-analysis used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The weight given to each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect and, in the statistical software in RevMan and CDSR, is equal to the inverse of the variance. This method assumes that all of the trials have measured the outcome on the same scale.

For the studies that the treatment and/or controlled groups were divided into subgroups because of the differences of concurrent treatment, the continuous data of the subgroups receiving more rigorous treatment, e.g., higher doses of drug treatment, more intensive psychotherapy, would be extracted.

SENSITIVITY ANALYSIS

Sensitivity analysis is an analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

The reviewers examined whether the decision to include the data obtained from studies in which participants were amphetamine dependent or abuse with comorbidity affected the results of review. In addition, the effects of including the data obtained from studies in which most (50%-75%) participants were amphetamine dependence or abuse were examined. The sensitivity analyses were done by the inclusion and exclusion of the data obtained from these studies. If both analyses point to the same conclusion in the respect of significant heterogeneity of data, the meta-analyses including the data obtained from these studies were taken into consideration. Otherwise,

the meta-analyses conducted by the exclusion of the data obtained from these studies were considered.

TEST FOR HETEROGENEITY

The test of heterogeneity is important to check whether the results of studies are similar within each comparison. The reviewers checked whether differences between the results of trials were greater than could be expected by chance alone. This was done by looking at the graphical display of the results but also by using Chi square tests of heterogeneity. A p-value being less than 0.05 of a Chi-square test was indicated the significant heterogeneity of a data set. The statistical methods for dealing with a data set with significant and nonsignificant heterogeneity were described in 'Data synthesis'. In addition, the causes possibly leading to the significant heterogeneity of a data set were discussed.

REVIEW 1: AMPHETAMINE DEPENDENCE OR ABUSE

Description of studies

"Table1: Characteristics of included studies on treatment for amphetamine dependence or abuse" is the summary of the main characteristics of included studies given by the author of each study.

This review included the results of four studies (Batki et al, 2000; Batki et al, 2001; Galloway et al, 1996; Tennant et al, 1986). While two studies compared fluoxetine 40 mg/day (Batki et al, 2000), amlodipine 10 and 5 mg/day (Batki et al, 2001) and desipramine 100-150 mg/day (Tennant et al, 1986) with placebo, the other compared imipramine 150 mg/day with imipramine 10 mg/day (Galloway et al, 1996). Three included studies (Batki et al, 2000; Batki et al, 2001; Tennant et al, 1986), therefore, should be considered as placebo, randomised, double-blind controlled studies. The other study should be considered as a randomised, double-blind controlled study of imipramine 150 mg/day and imipramine 10 mg/day although the investigators considered that imipramine 10 mg/day was a placebo.

Short-term, proximal outcomes presented in three studies were: i) number or percentage of amphetamine positive urines (Batki et al, 2000; Galloway et al, 1996); ii) number or percentage of amphetamine-use days (Batki et al, 2000; Galloway et al, 1996); iii) frequency of amphetamine use (Batki et al, 2000) and iv) amount of amphetamine consumed (Batki et al, 2001).

Short-term, distal outcomes presented in four studies were: i) craving (Batki et al, 2000; Batki et al, 2001; Galloway et al, 1996); ii) severity of dependence, abuse or addiction as measured by Addiction Severity Index (ASI) (Batki et al, 2001); iii) discontinuation rate (Batki et al, 2000) and iv) days of adherence to treatment (Batki et al, 2000; Batki et al, 2001; Tennant 1986).

Medium-term, proximal outcomes presented in one study (Galloway et al, 1996) were: i) number or percentage of amphetamine positive urines and ii) number or percentage of amphetamine-use days.

Medium-term, distal outcomes presented in one study (Galloway et al, 1996) were: i) craving and ii) days of adherence to treatment.

Methodological quality of included studies

The techniques of randomization and double-blindness were applied in all studies. No study stated the method used for randomization. The duration of studies were 6 weeks (Tennant et al, 1986), 8 weeks (Batki et al, 2000; Batki et al, 2001) and 6 months (Galloway et al, 1996). Note that a medium-term, 6-month study also presented its short-term data. Therefore all studies presented short-term data, but only one study presented medium-term data (Galloway et al, 1996).

Table 1: Characteristics of included studies on treatment for amphetamine dependence or abuse

Author	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Tennant et al 1986	randomised, double-blind, 6-week study	persons dependent upon amphetamines (no criteria specified), 23-30 years of age	desipramine 100-150 mg/day (n = 2) vs placebo (n = 2)	days of adherence to treatment, conversion of the urine containing amphetamines on admission to negative later in the study, mean withdrawal score for the first four days of drug administration and the self-reports of subjects relative to drug effectiveness to reduce drug craving, provide sleep assistance and prevent anergy and depression	only the outcome relevant to days of adherence to treatment fully presented in figure	B
Gallaway et al 1996	randomised, double-blind, 6-month study	methamphetamine dependence (DSM-III-R), 18-65 years of age	imipramine 150 mg/day (n = 22) vs imipramine 10 mg/day (n = 10), all participants received standard clinical care (i.e. group counselling and psychiatric and medical care	days of adherence to treatment, craving, depressive symptoms, percentage of methamphetamine positive urines, days since last use and study visit attendance	No outcome fully presented in figure	B
Batki et al 2000	randomised, double-blind, 8-week study	methamphetamine dependence (no criteria specified), mean age of 35 years old	fluoxetine 40 mg/day (n = 32) vs placebo (n = 28)	days of adherence to treatment, number of amphetamine-use day, frequency of amphetamine use, craving, Number or percentage of amphetamine positive urines	No outcome fully presented in figure	B
Batki et al 2001	randomised, double-blind, 8-week study	methamphetamine dependence (no criteria specified), mean age of 35.6 years old	amlodipine 10 mg/day (n = 26) vs amlodipine 5 mg/day (n = 25) vs placebo (n = 26)	days of adherence to treatment, amount of amphetamine consumed, craving, Severity of dependence, abuse, or addiction		B

The reviewers decided to present the results only in text. The data synthesis was not done because of a few reasons. Firstly, the data of two studies (Batki et al, 2000; Galloway et al, 1996) did not present data in figures. In addition, a study presented only one of many outcomes in figures (Tennant et al, 1986). Secondly, the drugs investigated in all four studies are not the same.

Results

The participants in imipramine study met the DSM-III-R diagnosis of methamphetamine dependence (Galloway et al, 1996). The participants in the other three studies (Batki et al, 2000; Batki et al, 2001; Tennant et al, 1986) were also amphetamine or methamphetamine dependence but had no detail about the criteria for diagnosis. Their ages were between 18-65 years old. The total number of participants included in this review is 173. The number of participants allocated to each treatment is as follows:

1. Fluoxetine 40 mg/day (n = 32) vs placebo (n = 28) (Batki et al, 2000)
2. Amlodipine 10 mg/day (n = 26) vs amlodipine (n = 25) vs placebo (n = 26) (Batki et al, 2001)
3. Imipramine 150 mg/day (n = 22) vs imipramine 10 mg/day (n = 10) (all participants received standard clinical care, i.e., group counselling and psychiatric and medical care) (Galloway et al, 1996)
4. Desipramine 100-150 mg/day (n = 2) vs placebo (n = 2) (Tennant et al, 1986)

SHORT-TERM, PROXIMAL OUTCOMES

Number or percentage of amphetamine positive urine tests and number or percentage of amphetamine-use days: Fluoxetine 40 mg/day and imipramine 150 mg/day did not significantly different from placebo and imipramine 10 mg/day, respectively.

Frequency of amphetamine use: Fluoxetine 40 mg/day did not significantly differ from placebo.

Amount of amphetamine consumed: Amlodipine 5-10 mg/day did not significantly differ from placebo.

SHORT-TERM, DISTAL OUTCOMES

Craving: In comparison to placebo, fluoxetine 40 mg/day but not amlodipine 5-10 mg/day and desipramine 100-150 mg/day significantly decreased craving.

Severity of dependence, abuse or addiction: Amlodipine 5-10 mg/day did not significantly different from placebo.

Discontinuation rate: Fluoxetine 40 mg/day did not significantly different from placebo.

Days of adherence to treatment: Fluoxetine 40 mg/day, amlodipine 5-10 mg/day and desipramine 100-150 mg/day did not significantly differ from placebo.

MEDIUM-TERM, PROXIMAL OUTCOMES

number or percentage of amphetamine positive urine tests and number or percentage of amphetamine-use days: Imipramine 150 mg/day was not significantly different from imipramine 10 mg/day.

Craving: Imipramine 150 mg/day was not significantly different from imipramine 10 mg/day.

Days of adherence to treatment: In comparison to imipramine 10 mg/day, imipramine 150 mg/day significantly

increased days of adherence to treatment.

Discussion

The evidence about the treatment for amphetamine dependence and abuse is very limited. Only four drugs have been investigated in 4 studies with small sample sizes. This review finds no controlled trials of a psychosocial intervention for amphetamine dependence and abuse. The small number of treatment studies may reflect the fact that this issue has been received less attention than the treatment for other substances, e.g., alcohol, heroin, or cocaine. In addition, any conclusion of this review should be considered as tentative.

The evidence shows that fluoxetine, amlodipine, imipramine and desipramine have very limited benefits for amphetamine dependence and abuse. Fluoxetine may decrease craving in short-term treatment. Imipramine may increase duration of adherence to treatment in medium-term treatment. Apart from these distal benefits, no other benefits, in particular the proximal ones, can be found. This limited evidence suggests that no treatment has been demonstrated to be effective for the treatment of amphetamine dependence and abuse.

Although there is a large number of people with amphetamine dependence and abuse worldwide, very few controlled trials in this issue have been conducted. As the previous treatment trials show no promising results, other treatments, both biological and psychosocial, should be further investigated. However, the results of neurotoxic studies of amphetamines are also crucial for the study designs appropriate for further treatment studies for amphetamine dependence and abuse.

Conclusions

IMPLICATIONS FOR PRACTICE

The evidence about the treatment for amphetamine dependence and abuse is very limited. It shows that fluoxetine, amlodipine, imipramine and desipramine have very limited benefits for amphetamine dependence and abuse. Fluoxetine may decrease craving in short-term treatment. Imipramine may increase duration of adherence to treatment in medium-term treatment. Apart from these, no other benefits, in particular proximal benefits, can be found. This limited evidence suggests that no treatment has been demonstrated to be effective for the treatment of amphetamine dependence and abuse.

IMPLICATIONS FOR RESEARCH

Although there is a large number of people with amphetamine dependence and abuse worldwide, very few controlled trials in this issue have been conducted. As the previous treatment trials show no promising results, other treatments, both biological and psychosocial, should be further investigated. However, the results of neurotoxic studies of amphetamines are also crucial for the study designs appropriate for further treatment studies for amphetamine dependence and abuse.

REVIEW 2: AMPHETAMINE PSYCHOSIS

Description of studies

By the use of above-mentioned search strategies, no controlled trials of treatment for amphetamine psychosis met the criteria for considering studies.

Methodological quality of included studies

By the use of above-mentioned search strategies, no controlled trials of treatment for amphetamine psychosis met the criteria for considering studies.

Results

By the use of above-mentioned search strategies, no controlled trial of treatment for amphetamine psychosis met the criteria for considering studies.

Discussion

The evidence about the treatment for amphetamine psychosis is very limited. To our knowledge, there are no controlled trials of treatment for amphetamine psychosis. However, the results of two studies should be mentioned although they do not meet the criteria for considering studies. The results of an open study including eight amphetamine psychotic patients show that the symptoms of excitement and paranoid ideation are significantly decreased within 60 minutes of haloperidol intramuscular administration (Angrist et al, 1974). The results of a randomized-controlled trial in 146 acutely agitated methamphetamine users show that droperidol, a butyrophenone, can sedate the patients significantly faster than lorezepam at 10, 15, 30 and 60 minutes after the intravenous administration (Richards et al, 1997).

Because an antipsychotic injection demonstrated its effectiveness for agitation and some psychotic symptoms occurring in amphetamine users, its risks and benefits should be further investigated in amphetamine psychotic patients. Medications that have been used for the treatment of acute exacerbation of schizophrenia should be studied in amphetamine psychotic patients. The medications that may be of interest are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine psychosis.

Conclusions

IMPLICATIONS FOR PRACTICE

The evidence of the treatment for amphetamine psychosis is very limited. To our knowledge, no controlled trials of treatment for amphetamine psychosis have been carried out. The results of two studies in amphetamine users shows that agitation and some psychotic symptoms may be abated within an hour after antipsychotic injection. Whether this limited evidence can be applied for amphetamine psychotic patients is not yet known.

IMPLICATIONS FOR RESEARCH

Because an antipsychotic injection demonstrated its effectiveness for some psychotic symptoms and agitation occurring in amphetamine users, its risks and benefits should be further investigated in amphetamine psychotic patients. Medications that have been used for the treatment of acute exacerbation of schizophrenia should be studied in amphetamine psychotic patients. The medications that may be of interest are conventional antipsychotics, newer antipsychotics and benzodiazepines. However, naturalistic studies of amphetamine psychotic symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine psychosis.

REVIEW 3: AMPHETAMINE WITHDRAWAL

Description of studies

"Table 2: Characteristics of included studies on treatment for amphetamine withdrawal" is the summary of the main characteristics of included studies given by the author of each study.

Only 2 studies (Jittiwutikan et al, 1997; Srisurapanont et al, 1999b) met the criteria for considering studies. Both of them compared amineptine and placebo in the treatment of amphetamine withdrawal. Lorazepam was occasionally used during the treatment. The total number of participants in the two included studies was 73. All of them were adults with amphetamine withdrawal (DSM-IV). The outcomes of interest in both studies were:

1. Discontinuation rate in both studies
2. Average score in global state, as measured by Clinical Global Impression or CGI (Guy, 1976) in both studies
3. Average score in withdrawal symptoms, as measured by Amphetamine Withdrawal Questionnaire or AWQ (Srisurapanont et al, 1999a) in one study (Srisurapanont et al, 1999b)
4. Average score in craving, as measure by craving score of Questionnaire for Evaluating Cocaine Craving and Related Responses or QECCRR (Voris et al, 1991) in one study (Jittiwutikan et al, 1997)

Methodological quality of included studies

The techniques of randomisation and double-blindness were applied in both studies. The method of randomisation was stated in one study (Srisurapanont 1999b). The duration of both studies were 14 days.

About the measures called CGI and AWQ, the higher the score, the more severity of clinical features. For QECCRR, the higher the score, the less severity of clinical features. It is of interest to note that the QECCRR was developed to separately measure four respects of cocaine withdrawal, including craving, depressed mood, no energy and sick feeling. Therefore, the craving score of QEECCRR was considered in this review.

Results

The participants in both studies met the DSM-IV diagnosis of amphetamine withdrawal with the mean age of 18-20 years old. While a study (Jittiwutikan et al, 1997) did not define the severity of withdrawal symptoms, the other study included only those who had the AWQ score of 10 or more (Srisurapanont et al, 1999b). The doses of amineptine in both studies were 300 mg/day. The total number of participants included in this review is 74 and is equally divided into amineptine and placebo groups. In addition to the investigated medications, lorazepam was occasionally used in these studies.

Table 2: Characteristics of included studies on treatment for amphetamine withdrawal

Author	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Jittiwutikan et al 1997	randomised, double-blind, 14-day study	amphetamine withdrawal (DSM-IV), mean = 18.5 years of age	amineptine 300 mg/day (n = 15) vs placebo (n = 15); occasional use of lorazepam	discontinuation rate; QECCRR score; CGI score		B
Srisurapanont et al 1999b	randomised, double-blind, 14-day study	amphetamine withdrawal (DSM-IV), AWQ score = 10 or more; mean = 19.6 years of age	amineptine 300 mg/day (n = 22) vs placebo (n = 22); occasional use of lorazepam	discontinuation rate, AWQ score; CGI score		A

The results of both studies have been shown some benefits of amineptine in the treatment of amphetamine withdrawal. Those benefits can be seen in the respects of discontinuation rate [RR (95% CI) = 0.22 (0.07 to 0.70), chi-square = 0.36, df = 1, p = 0.55] (see figure 1) and global state, as measured by CGI [WMD (95% CI) = -0.54 (-0.82 to -0.26), chi-square = 0.06, df = 1, p = 0.81] (see figure 2). However, no direct benefit of amineptine on amphetamine withdrawal symptoms [WMD (95% CI) = -1.40 (-4.55 to 1.75), chi-square = 0.00, df = 0] (see figure 3) or craving [WMD (95% CI) = 0.43 (-1.23 to 2.08), chi-square = 0.00, df = 0] (see figure 4) was shown. It should be reiterated that the results on amphetamine withdrawal symptoms and craving came only from one study each.

Discussion

The evidence about the treatment for amphetamine withdrawal is very limited. Only amineptine has been studied for treating this condition. Amineptine is a central stimulant with dopamine re uptake inhibitory effect. Its biochemical and pharmacological effects are similar to those of amphetamine (Samanin et al, 1977). It was an antidepressant originally launched by Servier Company in France and available only in some countries. After more than 10 years of its availability, the drug company voluntarily withdrew this drug from the market in 1999 because of some reports of amineptine abuse.

The results of this review suggest that amineptine has some limited benefits in increasing the adherence to treatment and improving general condition. However, it has no direct benefit on amphetamine withdrawal or craving. As amineptine has been withdrawn from the market, no further risk-benefit study of this drug can be done.

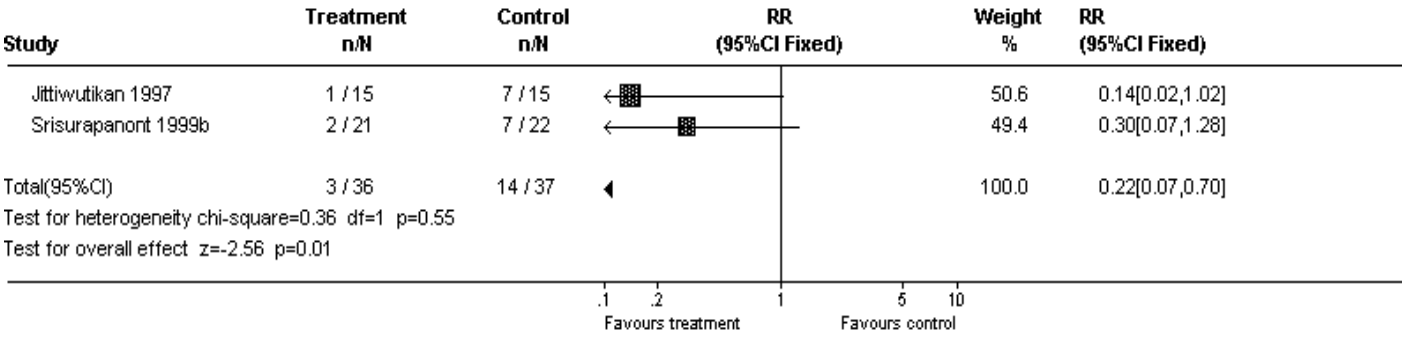

Figure 1: Comparison the discontinuation rates between amineptine- and placebo-treatment groups

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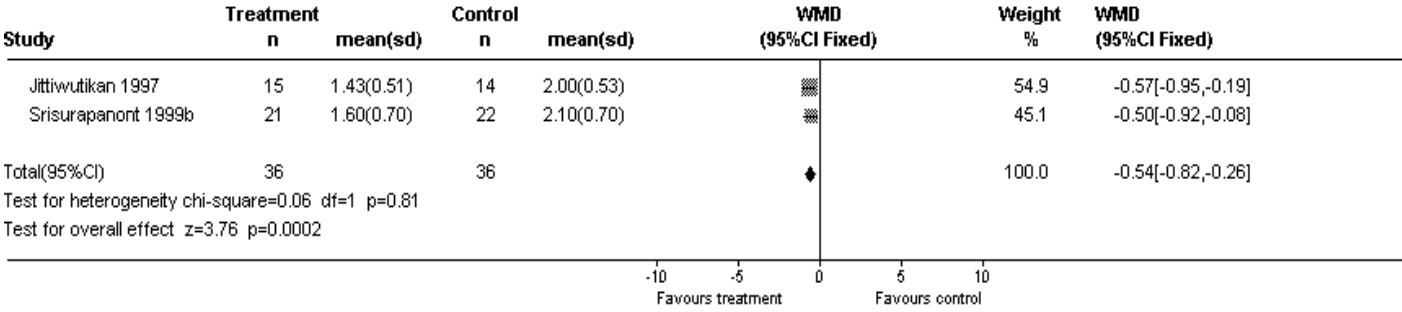

Figure 2: Comparison the average score of global improvement, as measured by Clinical Global Impression, between amineptine- and placebo-treated groups

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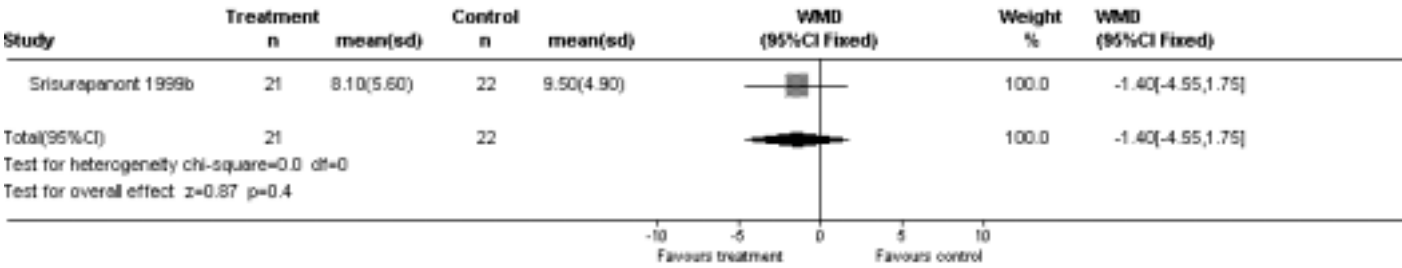

Figure 3: Comparison the average score of amphetamine withdrawal, as measured by Amphetamine Withdrawal Questionnaire, between amineptine- and placebo-treated group

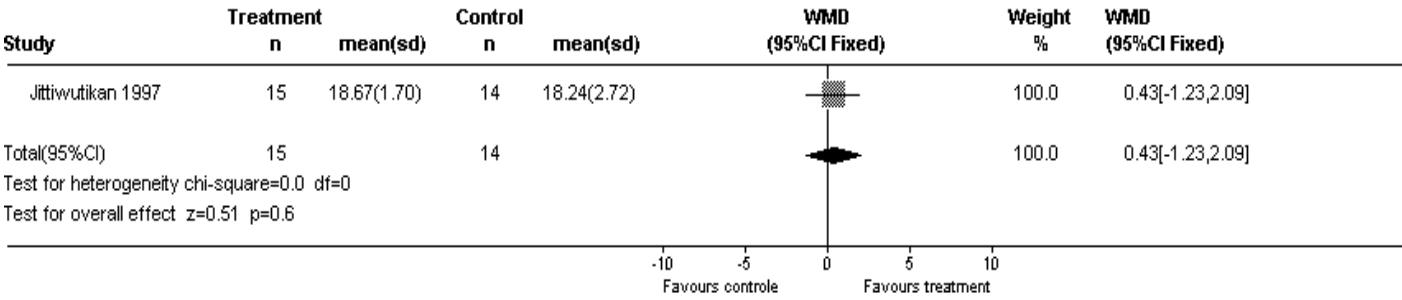

Figure 4: Comparison the average score of craving, as measured by Questionnaire for Evaluating Cocaine Craving and Related Responses, between amineptine- and placebo-treated group

At present, no available treatment has been demonstrated to be effective in the treatment of amphetamine withdrawal.

Not only the number of treatment studies but also the total number of clinical studies of amphetamine withdrawal are very small. As we have known very little about this condition, the evidence to support any practice relevant to this condition is very limited. This may reflect the fact that amphetamine withdrawal has not been an issue of concern in the management of amphetamine-related disorders. The reports of high prevalence (about 87%) of amphetamine withdrawal in amphetamine users (Cantwell & McBride 1998; Schuckit et al, 1999) should be good evidence to support that amphetamine withdrawal is an existing problem and needs attention.

The medications that should be considered for further treatment studies may be those with the propensities to increase dopamine, norepinephrine and/or serotonin acitivities of the brain. Naturalistic studies of amphetamine withdrawal symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine withdrawal.

Conclusions

IMPLICATIONS FOR PRACTICE

The evidence about the treatment for amphetamine withdrawal is very limited. Although amineptine has limited benefits for amphetamine withdrawal, this drug has been withdrawn from the market. At present, no available treatment has been demonstrated to be effective in the treatment of amphetamine withdrawal.

IMPLICATIONS FOR RESEARCH

The medications that should be considered for further treatment studies may be those with the propensities to increase dopamine, norepinephrine and/or serotonin acitivities of the brain. Naturalistic studies of amphetamine withdrawal symptoms and course are also crucial for the development of study designs appropriate for further treatment studies of amphetamine withdrawal.

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