Cognitive-behavioural treatment for amphetamine-type stimulants (ATS) use disorders

Protocol information

Review type: Intervention

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What's new

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History

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Abstract

Background
Objectives
Search methods
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Data collection and analysis
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Plain language summary

[Summary title]
[Summary text]
Background

Description of the condition
Amphetamine-type stimulants (ATS) refer to a group of synthetic stimulants including amphetamine, methamphetamine and phenethylamines such as MDMA (3,4-methylenedioxy-methamphetamine) and its analogues. These substances have marked central and peripheral stimulant effects upon people and prolonged use results in series of mental and physical symptoms including anxiety, confusion, insomnia, mood disturbances, cognitive impairments, paranoia, hallucinations and delusion (Barr 2006; Baylen 2006; Greene 2008; Montoya 2002; Morgan 2000).

Since the 1990s, ATS use has been widespread globally and it is now the second most popular illicit drug in the world after cannabis. ATS use is of serious concern in East Asia, Southeast Asia, North America, Europe and Oceania. Statistics from the United Nations Office on Drugs and Crime (UNODC) indicate that approximately 25 million to 80 million people regularly use ATS worldwide (UNODC 2012). In recent years, several new synthetic drugs have been gaining popularity, including MDMA and related amphetamines. These drugs are known as substituted amphetamines and they are characterised by enhanced hallucinogenic properties (Greene 2008).

Amphetamines are highly addictive substances and produce euphoria and elevated mood. The short-term adverse effects of amphetamines include high body temperature, cardiovascular system failure, hostility, irregular or increased heart rate, increased diastolic/systolic blood pressure, increased activity/talkativeness, euphoria, heightened sense of well-being, decreased fatigue/drowsiness, decreased appetite, dry mouth, dilated pupils, increased respiration, heightened alertness/energy, nausea, headache, palpitations, altered sexual behaviour, tremor/twitching of small muscles, release of social inhibitions and unrealistic feelings of cleverness, great competence and power (Barr 2006; Lee 2008).

Amphetamines can be ingested, injected, smoked and snorted. Prolonged amphetamines use may result in more severe and devastating consequences. These include a series of mental and physical symptoms such as dizziness, mood or mental changes, chronic tiredness or weakness, physiological and behavioural disorders, flush or pale skin, malnutrition, ulcers, repetitive motor activity, loss of coordination and physical collapse, anxiety, confusion, insomnia, mood disturbances, cognitive impairments, paranoia, cardiac arrhythmias, toxic psychosis, amphetamine induced psychosis, convulsions, coma and death (Baylen 2006; Greene 2008; Montoya 2002).

ATS use is also related to infections of HIV/AIDS and other sexually transmitted diseases. The stimulating effects of ATS can impair judgment and inhibition, and lead people to engage in risky sexual behaviours. Moreover, sharing of injecting paraphernalia is common among people who inject drugs and such practice puts them at elevated risk of blood-borne infectious diseases such as HIV, AIDS and hepatitis C (Degenhardt 2010; Ellickson 2009; King 2012; Strathdee 2010).

The use of MDMA and its analogues is particularly prevalent among young people (UNODC 2012). These drugs are usually taken orally as a tablet or capsule. Their pattern of use is different from that of "traditional drugs". Among young MDMA users, occasional use is most common, typically related to social events and involves the use of a relatively small amount of the drug. They are likely to use multiple substances at the same time and MDMA tablets frequently contain other substances. Due to the combination of these substances, the consequences of MDMA use are unpredictable (Rogers 2009).

MDMA and related substances have both stimulant and hallucinogenic effects. Therefore, the short-term effects of these substances include increased heart rate and blood pressure, hyperactivity, euphoria, a heightened sense of well-being, decreased fatigue/drowsiness and decreased appetite. In addition, distorted time and exaggerated sensory perception are frequently experienced. On the other hand, long-term consequences are not well known because abuse of these substances is relatively recent (Rogers 2009). Young MDMA users frequently use drugs in club or all-night dance parties, known as "raves". They tend to take drugs with alcohol and dance for a long time, and this may result in hyperthermia, dehydration, hypertension, and even kidney failure and death (NIDA 2006).

ATS use disorder can be diagnosed by several set of criteria. For example, according to the ICD-10 (International Classification of Diseases-10th Revision), substance dependence syndrome is characterized by "a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value." Major diagnostic criteria include a strong desire to use, difficulties in controlling drug use, existence of withdrawal symptoms, evidence of tolerance, progressive neglect of alternative pleasures and persisting with substance use despite clear evidence of harmful consequences (WHO 2004).

Description of the intervention
Currently there is no widely accepted treatment for ATS use disorder. This is especially the case for newly-emerged ATS. However, cognitive-behavioural treatment (CBT) is the first choice of treatment in order to prevent relapse (Lee 2008). The effectiveness of CBT for other substance use disorders (e.g. alcohol, opioid and cocaine use disorders) has been well documented and as such this basic treatment approach has been applied to the ATS use disorder. The treatment of MDMA use and the use of other new ATS drugs has not been extensively studied and the lack of evidence makes it difficult to treat people who use new ATS drugs (Rogers 2009).

CBT for a substance use disorder can be defined as a structured approach to help clients reduce substance use behaviour by modifying their thoughts and behaviours. There are a number of therapies that are under the broad category of CBT, including behavioural therapy, cognitive therapy, cognitive–behavioural therapy and the “third-wave” CBT. CBT usually employs a set of structured techniques such as motivational enhancement, relapse prevention, skills training, cognitive restructuring, stress management, emotional control and contingency management.
How the intervention might work
CBT for a substance use disorder is based on the assumption that drug use is learned behaviour and it emphasizes individual commitment for recovery in order to learn new adaptive behaviours and ways of thinking. From the cognitive-behavioural perspective, substance use is considered as the result of coping deficits, or maladaptive cognitions, or both. For example, if individuals do not have an appropriate coping repertoire or have positive outcome expectations towards substance use, or both, they are likely to use drugs in high-risk situations (Marlatt 2005; Thombs 2005). Therefore, coping skills training is considered an essential treatment component in CBT and emerging data suggested that acquisition and performance of skilful coping may account for CBT's effects on substance use disorders (Kiluk 2010; Litt 2003). CBT for substance use disorders is mainly designed to identify drug using triggers and provides people who use drugs with cognitive and behavioral skills to cope with these triggers to achieve and sustain abstinence from drugs. It also addresses thoughts, emotions, outcome expectations and lifestyles associated with drug use in order to address these multiple problem areas.

Why it is important to do this review
ATS use is increasing worldwide, especially in East Asia, Southeast Asia, North America, Western Europe and Oceania (Farrell 2002; UNODC 2012). Given this widespread ATS use, a comprehensive review of the effectiveness of treatment targeting ATS users is required to inform future research, clinical practice and policy making. Moreover, this review places a focus on CBT because CBT has multiple strengths over pharmacological treatment. For example, CBT is not associated with side effects and tends to have long-lasting effects. Several studies indicate that ATS users who receive CBT reduce their ATS use even after treatment is terminated (Carroll 2000; Rawson 2002).

Objectives
To investigate the efficacy of cognitive-behavioural treatment for people with ATS use disorder for reducing amphetamine-type stimulants use compared to other types of psychotherapy, pharmacotherapy, 12-step facilitation, no intervention or treatment as usual.

Methods
Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs) and quasi-RCTs. This includes designs that either randomly assign participants to the cognitive-behavioral treatment or comparator condition, or designs that use a quasi-random allocation mechanism, such as alternating assignment, next available treatment slot or wait-list controls. We will exclude all other trial designs.

Types of participants
Participants with ATS dependence or abuse diagnosed by any set of criteria. This includes both the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) and ICD 10 criteria as well as any other explicit ATS dependence or abuse diagnostic system. We will excluded studies that rely solely on client self-reporting of an ATS dependence or abuse disorder without formal clinical assessment. We will only include trials recruiting adults (i.e. aged 18 years or above). Participants may have comorbid conditions.

Types of interventions
We will include any CBT interventions in either individual or group therapy formats, in any treatment settings and any treatment modalities (e.g. face-to-face treatment, telephone treatment, computer-based treatment). CBT interventions include behavioural therapy, cognitive therapy, cognitive-behavioural therapy, "third-wave" CBT and any combinations of these therapies. However, we will exclude any studies where CBT is delivered in conjunction with other types of psychotherapy and pharmacotherapy.

Comparison: other types of psychotherapy, pharmacotherapy, 12-step facilitation, no intervention or treatment as usual.

Types of outcome measures
Primary outcomes
Abstinence rate measured by urine samples, or self-reported drug use, or both. Drug use may include amount of drug use, frequency of drug use, continuous using days or other indicators of actual drug-using behaviour. We will only use measures of drug use behaviour within the past 30-days or less.

Secondary outcomes
Secondary outcomes will include treatment drop-out rate, death, psychological variables such as self-esteem and coping skills measured by standardised questionnaires (i.e. we will only include psychological outcomes if they are based on a published measure that has been standardized or has known psychometric properties).

We will note any adverse outcomes reported in a trial.

Search methods for identification of studies
Electronic searches
We will search for relevant trials in the following sources:
- Cochrane Drugs and Alcohol Group Specialised Register;
Cognitive-behavioural treatment for amphetamine-type stimulants (ATS) use disorders

- The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, latest Issue);
- MEDLINE (PubMed) (1966 - to present);
- EMBASE (EMBASE.com) (1974 - to present);
- CINAHL (EBSCO Host) (1982 - to present);
- WEB OF SCIENCE (1991-to present);
- PsycINFO (1985 - to present).

We will search databases using MeSH and free-text terms relating to CBT and ATS use disorder as shown in Appendix 1. We will combine the PubMed search with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity-maximising version (2008 revision; Lefebvre 2011). We will revise this strategy appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

We will search for ongoing clinical trials and unpublished trials via Internet searches on the following sites:
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

**Searching other resources**

We will contact trial authors for additional trials and data. We will also examine the reference lists of eligible studies and other systematic reviews for trials that may have otherwise been missed.

We will not apply any language or publication restrictions.

**Data collection and analysis**

**Selection of studies**

Two review authors will independently screen the abstracts of all studies obtained through the search process. Any disagreement will be resolved by discussion. Subsequently, we will retrieve full-text copies of all potentially relevant studies and two review authors will independently assess the eligibility for inclusion. We will resolve any disagreement by discussion and when necessary, with the third author.

**Data extraction and management**

For eligible trials, at least two review authors will extract the data using a pre-designed data extraction form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. We will enter data into RevMan 2011 and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact trial authors to provide further details.

**Assessment of risk of bias in included studies**

Two review authors will independently assess risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreement by discussion or by involving a third review author. The recommended approach for assessing risk of bias in studies included in a Cochrane Review is a two-part tool, addressing seven specific domains namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The first part of the tool involves describing what was reported to have happened in the trial. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments we will use the criteria indicated by Higgins 2011 but adapt them to the addiction field. See Appendix 2 for details.

**Measures of treatment effect**

**Dichotomous data**

For dichotomous data, we will present results as summary risk ratio with 95% confidence interval (CI).

**Continuous data**

For continuous data we will use the standardized mean difference effect size (Hedges' g). Ideally, these effect sizes will be based on means, standard deviations and sample sizes for each condition. However, this effect size can be computed from a range of reported statistical information such as from a t-test, a P value from a t-test, an F-test, regression coefficients, etc. Using this effect size index enables the combination of effect sizes across trials that examine a common construct but measure that construct differently.

**Unit of analysis issues**

The unit of analysis will be an individual patient. We will consider cluster-RCTs if identified but we will compute effect sizes at the individual patient level.

**Cluster-RCTs**

We will include cluster-RCTs in the analyses along with individually-RCTs. We will adjust their sample sizes using the methods described in Higgins 2011 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-RCTs and individually-RCTs, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both unless...
there is non-negligible heterogeneity between the trial designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be likely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

**Dealing with missing data**

For included trials, we will note levels of attrition. We will explore the impact of including trials with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and we will analyse all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**

We will assess statistical heterogeneity in each meta-analysis using the $T^2$, $I^2$ and $\chi^2$ statistics. We will regard heterogeneity as substantial if the $I^2$ is greater than 30% and or if the $P$ value for the $\chi^2$ test for heterogeneity is less than 0.10.

**Assessment of reporting biases**

If there are 10 or more included trials in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots and the trim-and-fill method. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform explanatory analysis to investigate it.

**Data synthesis**

We will carry out statistical analysis using *RevMan 2011*. We will use a random-effects model for combining data as the assumptions of the fixed-effects model are unreasonable for this literature. Trials are likely to differ in numerous ways that may affect the underlying treatment effect being estimated such as the specifics of the CBT being implements, the context of the treatment and the unique characteristics of the population. The random-effects model converges on the fixed-effects model as the data becomes homogeneous, so this approach is reasonable and consistent with recommended practice within the meta-analysis literature. We will present the results as the average treatment effect with its 95% CI, and also calculate the estimates of $T^2$ and $I^2$.

**Quality of the evidence**

We will assess the overall quality of the evidence for the primary outcome and for adverse effect will be assessed using the GRADE system ([Atkins 2004](#)). The GRADE system uses the following criteria for assigning grade of evidence:

- High: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low: any estimate of effect is very uncertain.

The grade of evidence is decreased if there is:

- Serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

Also, the grade of evidence can be increased if there is:

- Strong evidence of association - significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1);
- Very strong evidence of association - significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- Evidence of a dose response gradient (+1);
- All plausible confounders would have reduced the effect (+1).

**Subgroup analysis and investigation of heterogeneity**

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses:

- Gender;
- Age;
- Treatment duration;
- Treatment setting;
Characteristics of the CBT treatment, such as presence or absence of the following treatment component: relapse prevention, motivational component, contingency management, cognitive restructuring and social skills training.

- Characteristics of treatment providers such as inhouse therapists or outside contractors;
- Characteristics of CBT therapists such as length of training.

We will use the following outcomes in subgroup analysis:

- Abstinence rate measured by urine samples, or self-report, or both.

We will perform these moderator analyses using random effects meta-analytic regression methods or analog-to-the ANOVA, depending on the nature of the moderator variable. These analyses will be performed in Stata using macros developed by David Wilson and available at http://mason.gmu.edu/~dwilsonb/ma.html

**Sensitivity analysis**

We plan to carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other risk of bias components, by omitting trials at high risk of bias for these components. We will restrict sensitivity analysis to the primary outcome.

**Results**

Description of studies

Results of the search

Included studies

Excluded studies

Risk of bias in included studies

Allocation (selection bias)

Blinding (performance bias and detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other potential sources of bias

Effects of interventions

Discussion

Summary of main results

Overall completeness and applicability of evidence

Quality of the evidence

Potential biases in the review process

Agreements and disagreements with other studies or reviews

Authors' conclusions

Implications for practice

Implications for research

Acknowledgements

Contributions of authors

Takayuki Harada - protocol development

Hiroshi Tsutomi - protocol development

Rintaro Mori - protocol development

David Wilson - protocol development

Declarations of interest

We have no known conflicts of interest.

Differences between protocol and review

Published notes

Characteristics of studies
Characteristics of included studies

Characteristics of excluded studies

Characteristics of studies awaiting classification

Characteristics of ongoing studies

Summary of findings tables

Additional tables

References to studies

Included studies

Excluded studies

Studies awaiting classification

Ongoing studies

Other references

Additional references

Atkins 2004

Barr 2006

Baylen 2006

Carroll 2000

Degenhardt 2010

DSM-IV

Ellickson 2009

Farrell 2002

Greene 2008

Higgins 2011

Kiluk 2010
Kiluk BD, Nich C, Babuschio T, Carroll KM. Quality versus quantity: acquisition of coping skills following computerized

King 2012

Lee 2008

Litt 2003

Marlatt 2005

Montoya 2002

Morgan 2000

NIDA 2006

Rawson 2002

RevMan 2011

Rogers 2009

Strathdee 2010

Thombs 2005

UNODC 2012

WHO 2004

Other published versions of this review
Classification pending references

Data and analyses

Figures

Sources of support

Internal sources
- No sources of support provided
External sources
• Health Labour and Sciences Research Grant, Ministry of Health, Labour and Sciences, Japan

Feedback

Appendices

1 PubMed search strategy
1. Substance-Related Disorders [MeSH]
3. #1 OR #2
4. Amphetamines[MeSH]
6. #4 OR #5
7. cognitive therapy[MeSH]
8. CBT[tiab]
9. (cogniti*[tiab] AND (behavio*[tiab] OR therap*[tiab]))
10. (cogniti*[tiab] AND (technique* [tiab] OR restructur*[tiab] OR challeng*[tiab]))
11. #7 OR #8 OR #9 OR #10
12. randomized controlled trial [pt]
13. controlled clinical trial [pt]
14. placebo [tiab]
15. drug therapy [sh]
16. randomly [tiab]
17. trial [tiab]
18. groups [tiab]
19. #12 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
20. animals [mh] NOT humans [mh]
21. #19 NOT #20
22. #3 AND #6 AND #11 AND #21

2 Assessment of risk of bias in included studies

1. Sequence generation (checking for possible selection bias)
We will describe for each included trial the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:
• low risk of bias (any truly random process, e.g. random number table; computer random number generator);
• high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
• unclear risk of bias (insufficient information to permit judgement).

2. Allocation concealment (checking for possible selection bias)
We will describe for each included trial the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:
• low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
• high risk of bias (e.g. open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
• unclear risk of bias (insufficient information to permit judgement).

3.1 Blinding of participants and personnel (checking for possible performance bias)
Blinding of personnel delivering the intervention and participants is not feasible. It is not desirable to blind participants to the knowledge of which condition they are in. Knowledge that you are participating in a cognitive-behavioral program is part of the intervention (this knowledge is often categorised along with other non-specific intervention factors). For this reason we will not assess the risk of bias of this item.

3.2 Blinding of outcome assessment (checking for possible detection bias)
For each included trial we will describe the methods used, if any, to blind outcome assessors from the knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. Outcomes will be grouped into subjective (drug use measured by urine analysis, dropout rate, death) and objective (self-reported drug use, psychological outcomes).
We will assess methods used to blind outcome assessment as:

Objective outcomes:
• low risk of bias: no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured and unlikely that the blinding could have been broken;
4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included trial, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses we undertake. We will assess methods as:

- low risk of bias: e.g. less than 20% missing outcome data; missing outcome data balanced across groups;
- high risk of bias: e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation; or
- unclear risk of bias: insufficient information to permit judgement.

5. Selective reporting bias

For each included trial we will describe how we investigated the possibility of selective outcome reporting bias and our findings. We will assess the methods as:

- low risk of bias: where it is clear that all of the trial's pre-specified outcomes and all expected outcomes of interest to the review have been reported;
- high risk of bias: where not all the trial's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; trial fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk of bias: insufficient information to permit judgement.

6. Other sources of bias

We will describe any important concerns we have about other possible sources of bias for each included trial. We will assess whether each trial was free of other problems that could have put it at risk of bias by stating:

- low risk of other bias;
- high or unclear risk of other bias.

Graphs