Amphetamines for schizophrenia (Review)

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[Intervention Review]

Amphetamines for schizophrenia

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ABSTRACT

Background

It is estimated that between 10% and 65% of people with schizophrenia use illicit drugs such as amphetamines. This group have an increased rate of hospitalisation, homelessness, unemployment and suicide compared with those with schizophrenia who do not abuse drugs.

Objectives

To evaluate the effects of amphetamines for people with schizophrenia in terms of clinically meaningful outcomes, cognitive functioning and physiological tests.

Search methods

We searched the Cochrane Schizophrenia Group's Register (February 2002).

Selection criteria

We included all randomised controlled trials investigating the effects of amphetamines on people with schizophrenia, compared with a placebo intervention.

Data collection and analysis

Working independently, we selected and critically appraised studies, extracted data and analysed on an intention-to-treat basis. Where possible and appropriate we calculated risk ratios (RR) and their 95% confidence intervals (CI), with the number needed to treat (NNT). For continuous data we calculated Weighted Mean Differences (WMD).

Main results

We included four short studies with a total of 83 participants. Data were few and poorly reported. The results indicated a reduction of negative symptoms for people allocated to amphetamines (n = 16, 1 RCT, WMD -3 CI -5.02 to -0.98). No such effect was found for positive symptom change (n = 16, 1 RCT, WMD 0 CI -4.46 to 4.46). Compared with placebo, amphetamines significantly increased metabolism in the left and right cerebellum (n = 23, 1 RCT, WMD 0.12 CI 0.06 to 0.18; n = 23 1 RCT, WMD 0.12 CI 0.06 to 0.18) and left striatum (n = 23, 1 RCT, WMD 0.14 CI 0.00 to 0.28) and also significantly decreased metabolism in the left dorsolateral prefrontal cortex (n = 23, 1 RCT, WMD -0.09 CI -0.17 to -0.01).

Authors' conclusions

Understandably amphetamines are rarely formally evaluated in randomised studies and therefore unpublished work in this area is likely to exist. Addition of more studies may clarify reasons why people with schizophrenia persist in taking these harmful stimulants.

PLAIN LANGUAGE SUMMARY

Amphetamines for schizophrenia

We undertook this review with an aim to summarise randomised experimental research findings concerning the effects of amphetamines on people with schizophrenia. Most of the potentially relevant data were unusable hence it is impossible to draw firm conclusions. The findings of one small short study suggested that amphetamines may cause a reduction of the apathy and lack of energy which is often associated with schizophrenia, and this could explain why those with schizophrenia persist in taking these potentially damaging drugs.

BACKGROUND

Substance abuse among people with psychiatric difficulties is becoming a widely recognised problem (Drake 1989; Reiger 1990). Blanchard 2000 reported that approximately 40% to 50% of people with schizophrenia have lifetime substance use disorder, but estimates can range between 10% and 65% (Mueser 1992). This range is likely to be a reflection of different methodologies across studies, such as differing populations, assessment techniques and demographic characteristics (Mueser 1992).

People with schizophrenia who abuse drugs have an increased risk of hospitalisation compared to those with this condition who dont (Lieberman 1989; Cleghorn 1991; Drake 1990). They have a higher risk of suicide (Cohen 1990), higher rates of homelessness (Drake 1990) and more unemployment (Seibyl 1993). Consequently, it is apparent that drug abuse has implications in both the course and treatment of schizophrenia (Blanchard 2000). It is likely that the poor outcome of those with schizophrenia who abuse substances is due to a combination of reduced compliance with treatment and the effects of the drugs being abused (Drake 1991).

There are three types of models that have been proposed to account for the high incidence of drug use in people with schizophrenia (Blanchard 2000). The first proposes that schizophrenia causes substance abuse which results in self-medication of the illegal drug. The second suggests that substance abuse disorders cause schizophrenia, and the third points towards substance abuse disorders and schizophrenia sharing a common genetic origin.

Whatever the relationship between substance use and schizophrenia, clinicians actively discourage psychotic people from experimenting with stimulants. Strong clinical impression would suggest that using stimulants such as amphetamines is detrimental to the mental state and functioning of a person with schizophrenia. Objective quantification of the effects of amphetamines on people with schizophrenia is rare, however, and this review attempts to synthesise all relevant studies.

OBJECTIVES

Our objective was to quantify the effects of amphetamines on people with schizophrenia in terms of clinically meaningful outcomes, cognitive functioning and physiological tests.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials were included (RCTs). Where a trial was described as 'double-blind', but it was only implied that the study was randomised, we included them in a sensitivity analysis. If there was no substantive difference within primary outcomes (see types of outcome measures) when these 'implied randomisation' studies were added, then we also included them in the final analysis. If there was a substantive difference within the primary outcomes, we used only the clearly randomised trials and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

Adults (18+ years) with schizophrenia. To account for changing definitions in diagnostic criteria, when study participants were described as suffering from 'severe/chronic mental illness/disorder' they met the inclusion criteria. We did not include studies involving individuals with bipolar disorder in the review.

Types of interventions

1. d-amphetamine/l-amphetamine/d/l-amphetamine/methamphetamine instigation of any sort, dose, and mode of administration.
2. d-amphetamine/l-amphetamine/d/l-amphetamine/methamphetamine maintained use of any sort, dose, mode of administration.
3. d-amphetamine/l-amphetamine/d/l amphetamine/methamphetamine withdrawal of any sort, dose, and mode of administration.
4. Placebo.

Types of outcome measures

All outcomes were reported for the immediate term (within 24 hours) short term (up to one week), medium term (eight days to one month), and long term (more than one month).

Primary outcomes

1. Primary clinical outcomes, selected before data were inspected
1.1 Clinical
1.1.1 Clinically significant response in global state - as defined by each of the studies
1.2 Behaviour
1.2.1 Clinically significant response in general behaviour - as defined by each of the studies
1.3 Service utilisation outcomes
1.3.1Hospital admission/relapse
2. Primary outcomes for neuropsychological measures, selected before data were inspected
2.1 Cognitive function
2.1.1 Clinically significant change in composite functioning - as defined by each of the studies
2.1.2 Clinically significant change in attention/concentration/tracking - as defined by each of the studies
2.1.3 Clinically significant change in memory - as defined by each of the studies
2.1.4 Clinically significant change in executive function

Secondary outcomes

1. Death, suicide or natural causes
2. Leaving the study early
3. Clinical response
3.1 Any response in global state
3.2 Average score/change in global state
3.3 Clinically significant response on psychotic symptoms - as defined by each of the studies
3.4 Any response in psychotic symptoms
3.5 Average score/change on psychotic symptoms
3.6 Clinically significant response in positive symptoms - as defined by each of the studies
3.7 Any response in positive symptoms
3.8 Average score/change in positive symptoms
3.9 Clinically significant response in negative symptoms - as defined by each of the studies
3.10 Any response in negative symptoms
3.11 Average score/change in negative symptoms
4. Physiological effects
4.1 Central nervous system, for example, clinically relevant and any change in tremor, etc
4.2 Cardiovascular system, for example, clinically relevant and any change in heart rate, blood pressure, blood flow etc
4.3 Gastro-intestinal system, for example, clinically relevant and any change in nausea, vomiting, etc
4.4 Respiratory system, for example, clinically relevant and any change in respiratory rate, etc
4.5 Genitourinary system, for example, clinically relevant and any change in urinary output, etc
4.6 Others
5. Behaviour
5.1 Any response in general behaviour
5.2 Average score/change in general behaviour
5.3 Clinically significant response in specific behaviour - as defined by each of the studies
5.4 Any response in specific behaviour
5.5 Average score/change in specific behaviour
6. Mood
6.1 Clinically significant change in mood - as defined by each of the studies
6.2 Any change in mood
6.3 Average change/score in mood
7. Cognitive function
7.1 Any change in composite cognitive functioning
7.2 Average score/change in composite cognitive functioning
7.3 Clinically significant change in orientation - as defined by each of the studies
7.4 Any change in orientation
7.5 Average score/change in orientation
7.6 Any change in attention/concentration/tracking
7.7 Average score/change in attention/concentration/tracking
7.8 Clinically significant change in perception - as defined by each of the studies
7.9 Any change in perception
7.10 Average score/change in perception

7.11 Any change in memory
7.12 Average score/change memory
7.13 Clinically significant change in verbal function/language skills
7.14 Any change in verbal function/language skills
7.15 Average score/change in verbal function/language skills
7.16 Clinically significant change in construction
7.17 Any change in construction
7.18 Average score/change in construction
7.19 Clinically significant change in concept formation/reasoning
7.20 Any change in concept formation/reasoning
7.21 Average score/change in concept formation/reasoning
7.22 Any change in executive function
7.23 Average score/change in executive function
7.24 Clinically significant change in motor performance
7.25 Any change in motor performance
7.26 Average score/change in motor performance
8. Personality
8.1 Clinically significant change in personality
8.2 Any change in personality
8.3 Average score/change personality
9. Satisfaction with intervention/quality of life
9.1 Significant change in satisfaction/quality of life - as defined by each of the studies
9.2 Any change in satisfaction/quality of life
9.3 Average score/change in satisfaction/quality of life
10. Extrapyramidal side effects
10.1Incidence of use of antiparkinson drugs
10.2 Clinically significant extrapyramidal side effects - as defined by each of the studies
10.3 Any extrapyramidal side effects
10.4 Average score/change in extrapyramidal side effects
11. Other adverse effects, general and specific
12. Service utilisation outcomes
12.1 Days in hospital
13. Economic outcomes
14. Miscellaneous outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Schizophrenia Group's Register (February 2002) using the phrase:
[methylph* or amphetamine* in title, or *methylph* or *amphetamine* in title, abstract or index terms of REFERENCE] or [amphetamine in interventions of STUDY]} This register is compiled by methodical searches of BIOSIS CINAHL, Dissertation abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED, Sociofile, supplemented with hand searching of relevant journals and numerous conference proceedings (see Group Module).

Searching other resources

We searched all reference lists of included studies for additional citations to relevant trials.

Data collection and analysis

1. Selection of trials
The two reviewers (Sue Nolte - SN, Gary Latchford - GL) independently performed the inspection of the citations identified in the search outlined above. Potentially relevant abstracts were identified and full papers ordered and reassessed for inclusion and methodological quality. Any disagreement was discussed and reported.
2. Assessment of quality
SN, GL and DW, working independently, allocated trials to three quality categories based on allocation concealment, as suggested in the Cochrane Collaboration Handbook (Clarke 2003). When disputes arose as to which category a trial was allocated, again, we attempted resolution by discussion. When this was not possible, and further information was necessary, we did not enter data into the analyses and assigned the study to the list of those awaiting assessment. We only included trials in Category A or B in the review.
We appraised methodological quality by examining the description of randomisation, blinding and participants leaving early as each of these factors reduces the risk of bias (Jadad 1996).
3. Data management
3.1 Data extraction
We independently extracted data from included studies and entered details as to why we chose not to put outcomes from included studies in the review in the 'included studies table.
3.2 Intention to treat analysis
We excluded data on outcomes where more than 50% of participants in any group were lost to follow up. In studies with less than 50% dropout rate, people leaving early were considered to have had the negative outcome, except for the event of death or unless other reasons unrelated to interventions were clearly reported. The influence of including studies with high attrition rates (25-50%) was analysed in a sensitivity analysis. If inclusion of data from this latter group did result in a substantive change in the estimate of effect, we did not add their data to trials with fewer dropouts, but presented them separately
4. Data analysis
4.1 Binary data
We calculated a standard fixed effect risk ratio (RR) and its 95% confidence interval (CI) for binary outcomes. Where possible we calculated the number needed to treat/harm statistic (NNT/H).

If we found heterogeneity (see section 5) we employed a random effects model.

4.2 Continuous data

4.2.1 Skewed data

Continuous data on mental health outcomes are often skewed and not normally distributed. Review Manager (RevMan) analyses of continuous data are based on the assumption that the data are, at least to a reasonable extent, normally distributed. It would be inappropriate to apply parametric tests to non-parametric data. Consequently to identify non-parametric data and avoid this pitfall, we applied the following standards to all data before inclusion:

(a) Standard deviations and means were reported in the paper or were obtainable from the authors

(b) When a scale started from a finite number (such as zero), the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution - Altman 1996). Endpoint scores on scales often have a finite start and end point and this rule can be applied to them.

Change data (endpoint minus baseline) is problematic. With no individual patient data it is impossible, even after applying the above test, to know if change data are skewed. After consulting the ALLSTAT electronic statistics mailing list, we decided that change data could be entered into RevMan. However, in doing this it is assumed that either that data were not skewed or that the analyses could cope with the unknown degree of skew. Unfortunately, with no individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category, only endpoint data are presented as it was believed that this type of data was less open to bias and closer to being interpreted clinically.

4.2.2 Summary statistic

For continuous outcomes we estimated a weighted mean difference (WMD) between groups. Again, if heterogeneity was found we used a random effects model.

4.2.3 Valid scales

A wide range of rating scales is available to measure outcomes in drug trials and these measures differ in validity. It is commonly acknowledged that measuring instruments should be both reliable and valid. Therefore, we included continuous data from rating scales only if the measuring instrument had (a) been described in a peer-reviewed journal (Marshall 2000) and (b) the instrument was either a self-report or completed by an independent rater or relative (not the researcher).

4.2.3.1 Publication

Before publication of an instrument, most scientific journals insist that reliability and validity are demonstrated to the satisfaction of referees. We decided, therefore, as a minimum standard, not to include any data from a measure in this review unless its properties had been published in a peer-reviewed journal (Marshall 2000).

4.2.3.2 Psychometric assessments

A wide range of psychometric assessments is also available. Again, these measures vary in quality and many are questionably validated, or even ad hoc. We evaluated the quality of psychometric tests included in this review using the 1997 revision of the Dutch Rating System for Test Quality employed by the Committee of Test Affairs of the Dutch Association of Psychologists (COTAN) (Evers 2001). This rating system evaluates the quality of a test on seven criteria:

1. Theoretical basis and the soundness of the test development procedure
2. Quality of the testing materials
3. Comprehensiveness of the manual
4. Norms
5. Reliability
6. Construct validity
7. Criterion validity.

Several items are included for each criterion. Some of these items are termed as 'key questions'(*), which ensure minimum conditions of quality are met. Consequently, should a key question be rated negative, the rating criterion will be 'insufficient'. Once all items have been rated, the final grades ('insufficient', 'sufficient' or 'good') for each of the criteria can be determined. For the purposes of this study only tests with a grading of either 'sufficient' or 'good' for all criterion will be included in the review.

4.2.3.3 Subscale versus total scores

To be considered as above.

4.2.4 Endpoint versus change data

For change data (endpoint minus baseline), the situation is even more problematic than endpoint data. In the absence of individual patient data it is impossible to know if data are skewed, though this is likely. After consulting the ALLSTAT electronic statistics mailing list, we hoped to present change data in Metaview to summarise available information. In doing this, it is assumed either that data were not skewed or that the analyses could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category we presented endpoint data only. We acknowledge that by doing this, much of the published change data were excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data it would be given undeserved equal prominence. Authors of studies reporting only change data were contacted for endpoint figures. We reported non-normally distributed data in the 'Other data types' tables

4.2.5 Cluster trials

Studies are increasingly employing 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby p values are spuriously low, confidence intervals excessively narrow and statistical significance overestimated, thus causing type I errors (Bland 1997;

Gulliford 1999). Secondly, RevMan does not currently support meta-analytic pooling of clustered dichotomous data, even when these are correctly analysed by the authors of primary studies, since the 'design effect' (a statistical correction for clustering) cannot be incorporated.

Where trialists had not accounted for clustering in primary studies, data were presented in a table, with a '*' symbol to indicate the presence of a probable unit of analysis error. Any subsequent versions of this review should seek to contact first authors of studies, to seek intra-class correlation co-efficients of their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

If clustering had been incorporated into the analysis of primary studies, then we would have presented data in a table. No further secondary analysis (including meta-analytic pooling) will be attempted until there is consensus on the best methods of doing so, and until RevMan, or any other software, allows this. A Cochrane Statistical Methods Workgroup is currently addressing this issue. In the interim, individual studies will be very crudely classified as positive or negative, according to whether a statistically significant result ($p<0.05$) was obtained for the outcome in question, using an analytic method that allowed for clustering.

5. Investigation for heterogeneity

Firstly, in any meta-analysis we were to have considered all the included studies within any comparison to judge clinical heterogeneity. Subsequently we would have made a visual inspection of graphs to investigate the possibility of statistical heterogeneity. This would have been supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Should the I-squared estimate have been greater than or equal to 75%, we would have interpreted this as indicating the presence of high levels of heterogeneity If inconsistency had been high, data would not have been summated, but we would have presented them separately and investigated reasons for heterogeneity.

6. Addressing publication bias

Should there have been enough studies we would have entered data from all included studies into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

7. Sensitivity analyses

It was our intention to investigate the effect of including studies with implied randomisation and high attrition rates by sensitivity analyses. In addition, as the separate forms of amphetamine may have differential effects both centrally and peripherally, we would have also explored potential differences using sensitivity analyses. If there had been no substantive difference within primary outcomes (see types of outcome measures) we would have grouped all included data together in the final analyses. However, if there had been substantive differences, we would have considered groups separately.

8. General

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for amphetamine.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 85 citations by the initial search, all of which were selected for further inspection. These citations yielded 73 studies. We excluded 54 studies as they did not meet the inclusion criteria. A further 11 that met the inclusion criteria had to be excluded because of poor data reporting. Four studies, randomising a total of 83 people, are included in this review. Another four await assessment. Three of the included studies report outcomes assessed less than three and a half hours following intervention. Modell 1965, however, presented data for an outcome assessed 4 weeks after the trial.

Included studies

4. Included studies

Four studies are included (Mathew 1989; Modell 1965; Wolkin 1987; Wolkin 1994). These are referred to in four citations from the original search and two citations identified through manual reference searching. These studies included a total of 83 people.

4.1 Length of studies

Three of the four included studies reported data for the immediate effects (within 24 hours) with duration ranging between one and 3.5 hours. Modell 1965 was the only trial to report medium term data, with a duration of four weeks. No studies reported data for the short term (up to one week) or long term (more than one month).

4.2 Participants

All studies included people with schizophrenia. Mathew 1989 and Wolkin 1994 included people diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, Revised (APA 1987). Wolkin 1987 utilised Diagnostic and Statistical Manual of Mental Disorders, third edition (APA 1980) as well as Research Diagnostic Criteria (Spitzer 1978). Modell 1965 did not report using any standardised criteria for diagnosis.

Most participants were inpatients. Mathew 1989 and Wolkin 1994 included only inpatients. Four participants in Wolkin 1987 were outpatients admitted for the duration of the study. It was unclear as to whether the participants included in Modell 1965

were inpatients or outpatients. Mathew 1989 and Modell 1965 gave no details of the history of participant's mental illness. For Wolkin 1987 and Wolkin 1994, the mean duration of illness was approximately 12 years. Only Wolkin 1994 reported the range of duration of illness, which was three-24 years.

Modell 1965; Wolkin 1987 and Wolkin 1994 included only male participants. Mathew 1989 included both males and females. In the current version of this review approximately 80% of participants were male. The mean age was about 37 years with Modell 1965; Wolkin 1987 and Wolkin 1994 all reporting age ranges of between 24 and 54 years of age.

4.3 Setting

All studies took place in a hospital setting.

4.4 Study size

Study size was small with the largest trial (Mathew 1989) randomising 24 people, and the smallest (Wolkin 1987) only 16.

4.5 Interventions

All participants received d-amphetamine, with no-one receiving amphetamine, l-amphetamine or methamphetamine. Dose and method of administration, however, was variable. Modell 1965; Wolkin 1987 and Wolkin 1994 all used oral administration with doses of 5 mg, 0.5 mg/kg and 0.25 mg/kg respectively. Mathew 1989 administered a fixed dose of intravenous d-amphetamine sulphate (15 mg). All studies used placebo as a control.

Participants in Wolkin 1987 and Wolkin 1994 were not taking any antipsychotic medication during the study, but in Mathew 1989 and Modell 1965 people were also taking neuroleptic medication.

4.6 Outcomes

4.6.1 Missing outcomes

No data were available for the following outcome measures: death, behaviour, other adverse effects, quality of life/satisfaction, cognitive function, service utilisation outcomes and economic outcomes. None of the studies explicitly reported numbers leaving early so we assumed that this was not a factor.

4.6.2 Scales

Trials used six scales to collect data. Only three scales were reported in such a way that we could utilise their data and details of these scales are provided below. Data from three scales (CGI, WCST, WAIS-R), however, were unusable. The WCST used was a modified version and data from such scales cannot be used in this review (see Methods 4.2.3). The other two scales could not be used as no data were reported.

4.6.2.1 Abnormal Involuntary Movement Scale - AIMS (Guy 1976)

The AIMS is a 12-item scale. It consists of a standardised examination followed by questions rating the orofacial, extremity and trunk movements; and 3 global measurements. Each of these ten items can be scored from 0 (none) to 4 (severe). Two additional items assess the dental status. The AIMS score ranges from 0-40. Higher scores indicate greater severity.

4.6.2.2 Abrams and Taylor Scale of Emotional Blunting - ATS (Abrams 1978): The ATS was used to measure negative symptoms in Wolkin 1987. It was originally constructed to assess affective blunting in schizophrenia and includes three subscores: lack of pleasure seeking behaviour, affective blunting, and cognitive blunting.

4.6.2.3 Brief Psychiatric rating scale - BPRS (Overall 1962)

This is used to evaluate the degree of abnormal mental state. The original scale has 16 items. However, a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from 0-6 or 1-7. Scores can range from 0-126, with high scores indicating more severe symptoms.

Excluded studies

1. Excluded studies

A total of 65 studies are entered into the excluded studies table. Eight were not randomised, 21 did not involve adults with schizophrenia and 21 were not studies of amphetamine, l-amphetamine, d-amphetamine or methamphetamine. We excluded four studies because in three of these all participants received amphetamine, and one study administered amphetamine only in combination with another drug.

A further 11studies met the inclusion criteria but were excluded due to poor data reporting. Eight of these were a crossover design that did not report pre-crossover findings (see discussion, section 2.1). Two other studies did not report data separately and one study reported incomplete data with unclear initial numbers.

2. Awaiting assessment.

Four studies are awaiting assessment. Two require translation (Filipova 1978; Os'makova 1972). Barch 1997 has been completed but is in the process of being written up for publication (personal communication with D. Barch). The data for Casey 1961 is being sought as it is presented in a separate article.

3. Ongoing

As far as we are aware, there are no ongoing studies relevant to this review.

Risk of bias in included studies

Allocation

Only Modell 1965 was described as 'randomised'. The other three studies implied randomisation from either the text or similar baseline characteristics. None of the studies described adequate concealment of randomisation. We categorised all studies B - moderate risk of bias (see Methods 2. Assessment of a trials methodological quality).

Blinding

Wolkin 1987 and Wolkin 1994 were described as double blind. Only Wolkin 1994, however, provided details concerning how participants and researchers were blinded (matched capsules). Modell 1965 did not state that blindness was double, however, this was implied in the text. Mathew 1989 stated that participants had been blinded to interventions but gave no details regarding blindness of the researchers. No study tested whether blinding had been successful.

Incomplete outcome data

No study reported data on: behaviour, other adverse effects, quality of life/satisfaction, cognitive function, service utilisation or economic outcomes.

Selective reporting

Data reporting was poor. Fifteen trials meet the inclusion criteria for this review but only four could be included as data were impossible to use in the other 11 (see 'excluded studies' table for details). Data reporting in cross-over trials was a particular problem, with eight trials not reporting data from the first arm of the study. Other areas of concern were that data were not reported at all or were presented in such an unclear fashion as to render them useless. One trial used a modified scale and as such the data from this scale could not be used in this review (see Methods 4.2.3)

Other potential sources of bias

1. Publication bias
A limitation common to all meta-analyses concerns the availability of unpublished data. Publication bias can be defined as "...the greater likelihood that studies with positive results will be published" (Olson 2002). It is likely that there are a large number of unpublished studies but we chose not to invest time studying unpublished work.
2. Leaving the study early
No study explicitly reported the number of people who did not complete the study so we assumed no loss for all studies.
3. Jadad quality score
Only one study stated methods of randomisation and no study provided an adequate description of people leaving early. Therefore, according to the quality criteria used, all data can be considered as at least at moderate risk of bias (Juni 2001).

Effects of interventions

1. COMPARISON: AMPHETAMINE versus PLACEBO
1.1 Mental state
Wolkin 1987 provided data concerning clinical response using the ATS and BPRS (modified to measure positive symptoms). Data from the ATS indicated a favourable outcome for amphetamine, with a reduction of negative symptoms (n = 16, 1 RCT, WMD -3 CI -5.02 to -0.98). Data from the BPRS found no significant difference for average positive symptom change between groups (n = 16, 1 RCT, WMD 0 CI -4.46 to 4.46).
1.2 Leaving the study early
Nobody left the study early from either the placebo or amphetamine groups, so it is impossible to estimate the relative risk. None of the studies explicitly stated the number of people who withdrew. We assumed that the initial number of participants minus the number of participants included in data analysis provided an indication of the number of people who completed the whole study.
1.3 Adverse effects
One study, Wolkin 1987, measured extrapyramidal side effects using the AIMS. Mean difference could not be estimated, however, because of odd data in the placebo group. The authors report that this result was not significant, t(14) = 1.94, p = 0.07. It is possible that the average change of zero reported for placebo was a typographical error.
1.4 Physiological
Most studies were not clinical investigations but were designed to investigate physiological changes. This is evident in the number of measures of cerebral function, blood flow and arousal.
1.4.1 Cerebral function
1.4.1.1 Percent change in local cerebral metabolic rate
Data from Wolkin 1987, suggests that amphetamine significantly decreases local cerebral metabolic rate in the right temporal lobe as compared with placebo (n = 23, 1 RCT, WMD -12.30 CI -23.16 to -1.44). This study also found non-statistically significant reductions in metabolic rate in the left and right frontal lobes(n = 23, 1 RCT, WMD -4.00 CI -16.36 to 8.36; n=23, 1 RCT, WMD -8.40 CI -16.82 to 0.02), left and right striatum (n = 23, 1 RCT, WMD -10.80 CI -23.93 to 2.33; n = 23, 1 RCT, WMD -13.40 CI -26.94 to 0.14) and left temporal lobe (n = 23, 1 RCT, WMD -9.60 CI -23.28 to 4.08).
1.4.1.2 Average change in absolute cerebral metabolic rate
Findings, again from Wolkin 1994, indicate that compared with placebo, amphetamine does not significantly alter absolute cerebral metabolic rate in the left and right cerebellum (n = 23, 1 RCT, WMD -0.03 CI -3.09 to 2.49; n = 23, 1 RCT, WMD 0.00 CI -2.88 to 2.88) mesial temporal lobes (n = 23, 1 RCT, WMD -2.00 CI -4.67 to 0.67; n = 23, 1 RCT, WMD -2.30 CI -5.64 to 1.04) orbital medial temporal cortices (n = 23, 1 RCT, WMD -2.90 CI -6.43 to 0.63; n =23, 1 RCT, WMD -1.30 CI -5.56 to 2.96) striatum (n = 23, 1 RCT, WMD 0.30 CI -4.54 to 5.14; n = 23, 1 RCT, WMD 1.10 CI -5.04 to 7.24) and thalamus (n = 23, 1 RCT, WMD -3.40 CI -7.35 to 0.55; n = 23, 1 RCT, WMD -4.30 CI -8.99 to 0.39) Despite this, data indicated that amphetamine significantly reduced metabolism in the left and right temporal (n =23, 1 RCT, WMD -6.90 CI -10.41 to -3.39; n = 23, 1 RCT, WMD -6.80 CI -10.48 to -3.12) and dorsolateral prefrontal (n

= 23, 1 RCT, WMD -7.90 CI -11.15 to -4.65; n = 23, 1 RCT, WMD -6.20 CI -10.53 to -1.87) cortices.

1.4.1.3 Ratio of regional to whole brain cerebral metabolic rate

Wolkin 1994 also examined the effects of amphetamine on regional compared with whole brain cerebral metabolic rate. Data indicates that compared with placebo, amphetamine significantly increases metabolism in the left and right cerebellum (n = 23, 1 RCT, WMD 0.12 CI 0.06 to 0.18; n = 23 1 RCT, WMD 0.12 CI 0.06 to 0.18) and left striatum (n = 23, 1 RCT, WMD 0.14 CI 0.00 to 0.28) and also significantly decreases metabolism in the left dorsolateral prefrontal cortex (n = 23, 1 RCT, WMD -0.09 CI -0.17 to -0.01). No significant regional compared with whole brain metabolic change was indicated in the left and right mesial temporal lobes (n = 23, 1 RCT, WMD 0.05 CI -0.02 to 0.12; n = 23, 1 RCT, WMD 0.04 CI -0.02 to 0.10), left and right orbital medial temporal cortex (n = 23, 1 RCT, WMD 0.04 CI -0.05 to 0.13; n = 23, 1 RCT, WMD 0.07 CI -0.04 to 0.18) right striatum (n = 23, 1 RCT, WMD 0.15 CI -0.01 to 0.31), left and right thalamus (n = 23, 1 RCT, WMD 0.04 CI -0.05 to 0.13; n = 23, 1 RCT, WMD 0.01 CI -0.07 to 0.09), left and right temporal cortices (n = 23, 1 RCT, WMD -0.05 CI -0.13 to 0.03; n = 23, 1 RCT, WMD -0.04 CI -0.11 to 0.03) and right dorsolateral prefrontal cortex (n = 23, 1 RCT, WMD -0.04 CI -0.12 to 0.04).

1.4.2 Cerebral blood flow

Mathew 1989 examined the effects of amphetamine compared with placebo on cerebral blood flow. The results of this study suggest that amphetamine significantly decreases blood flow in the left and right hemispheres (n = 12, 1 RCT, WMD -13.6 CI -18.56 to -8.64; n = 12, 1 RCT, WMD -7 CI -12.6 to -1.4).

1.4.3 Cardio respiratory

Only Mathew 1989 examined the effects of amphetamine compared with placebo on cardio respiratory functioning.

1.4.3.1 Pulse rate

This small trial found no significant change in pulse rate in either the immediate term (n = 12, 1 RCT, WMD 4.30 CI -6.03 to 14.63) or medium term (n = 20, 1 RCT, WMD 5.00 CI -2.31 to 12.31).

1.4.3.1 Respiration

Mathew 1989 found no significant change in respiratory rate in the immediate term (n = 12, 1 RCT, WMD 0.9 CI -4.23 to 6.03).

1.4.3.3 Systolic blood pressure

Data reported in Mathew 1989 suggest that amphetamine significantly increases systolic blood pressure compared with placebo in the immediate term (n = 12, 1 RCT, WMD 14 CI 1.02 to 26.98). The findings of Modell 1965 indicate no significant difference in the medium term, although the systolic pressure was also raised (n = 20, 1 RCT WMD 7.00 CI -0.45 to 14.45).

1.4.3.4 Diastolic blood pressure

No significant difference between amphetamine and placebo for the change diastolic blood pressure was indicated either for the immediate term (n = 12, 1 RCT, WMD -3.10 CI -10.45 to 4.25) or the medium term (n = 20, 1 RCT, WMD 5.00 CI -0.67 to 10.67).

1.4.3.5 PECO2

In the immediate term, Mathew 1989 found no significant difference between the change in PECO2 for amphetamine and placebo (n = 12, 1 RCT, WMD -1.30 CI -4.19 to 1.59).

1.5 Body weight and appetite

Only Modell 1965 reported body weight and the skewed data, presented in a table rather than a graph, do not indicate any difference between groups. The same applies to a scoring of appetite.

1.6 Arousal

Modell 1965 recorded awakenings and naps taken by all participants. They found no differences for those allocated amphetamine compared with people on placebo.

DISCUSSION

1. Overall

Only four of the studies identified met inclusion criteria. There are too few data to present clear findings about the effects of amphetamine for people with schizophrenia. Systematic reviews aim to summarise large amounts of information in a critical, transparent and reproducible manner. Synthesising data using meta-analytic techniques increases power to identify differences in effects, and combining data from several studies increases the accuracy of estimates (Gilbody 1999). In this review only a single outcome, leaving the study early, included more than one trial and for this outcome calculation of relative risk was not possible. Consequently, no meta-analyses could be performed and the results from each study stand alone. The lack of included studies and information available sheds very little light on the effects of amphetamines on people with schizophrenia. A further 11 studies that met inclusion criteria were excluded either because reported data was unusable or because they were crossover design and did not report pre-crossover findings. Had data from these studies been useful it would have more than doubled the size of this review.

2. Methodological quality and quality of data reporting

We measured methodological quality by evaluating allocation concealment (Schulz 1995). Furthermore, included studies had to be randomised and the descriptions of blinding and people leaving early were examined as each of these factors reduces risk of bias (Jadad 1996).

Allocation concealment protects against selection bias and safeguards the randomisation sequence until interventions are implemented (Jadad 1998) and can always be put into practice (Schulz 1995). Blinding can be more difficult to implement successfully, but is useful as it protects randomisation after interventions are administered. It also reduces the risk of ascertainment bias, i.e. distortion of the results or conclusions of a study due to investiga-

tors or participants having knowledge of the interventions being received (Jadad 1998).

In an ideal world all participants randomised to receive an intervention would complete the study or trial, and all expected data for every participant would be collected. Unfortunately this is often the exception rather than the rule. Missing data can arise for a variety of reasons, ranging from participant withdrawal and technical difficulties to mistakes made by investigators. Irrespective of cause, inappropriate management of missing data can lead to bias. Managing missing data can be problematic, particularly if the investigators do not know why a participant has dropped out of the protocol. However, statistical techniques are available to manage missing data (Jadad 1998).

Based on the above criteria, the overall methodological quality of included studies was poor (see Methods). This indicates that all data are prone to at least a moderate degree of bias. We recognise, however, that the criteria used to measure quality have been conventionally employed to measure quality for clinical trials and thus these criteria may, or may not be as suitable for other types of studies. For example, a researcher administering a single dose of amphetamine to examine its effects on cerebral blood flow may not consider clear reporting of why people dropped out as relevant to the overall findings, as these types of studies tend to be of a shorter duration than clinical trials and attrition is less likely. Since assessment of quality relies upon information contained in the written report, this presents a difficulty in accurate quality assessment, because authors writing-up these studies may not include information that is considered less relevant.

The Jadad Scale (Jadad 1996) does use non-clinical, purely methodological parameters to rate the quality of studies and there is no clear reason why these criteria should not be used to quality rate non-clinical investigations. It is, however, feasible that using a scale validated on clinical trials could result in an inherent 'quality bias' towards clinical studies. Nevertheless, it is our belief that all research studies concerning the effects of amphetamines are of importance if the effects of these drugs are to be summarised. If we had concentrated on only clinical trials, a large amount of valuable data could have been ignored.

Findings are made more difficult to interpret by poor description of participants involved. Despite the fact that most studies assessed prior and current substance abuse disorder and some tested for recent use using urine screening, only a single study presented further details regarding participants' current or prior history of recreational drug use. Consequently, in order to include studies in the review it has to be assumed that any current or previous drug use was not sufficient to affect the data. In addition, data concerning participants' age and gender were inconsistent. Finally, only one included study reported any information about participants' cognitive functioning. This information would have been useful should data from cognitive assessments have been included.

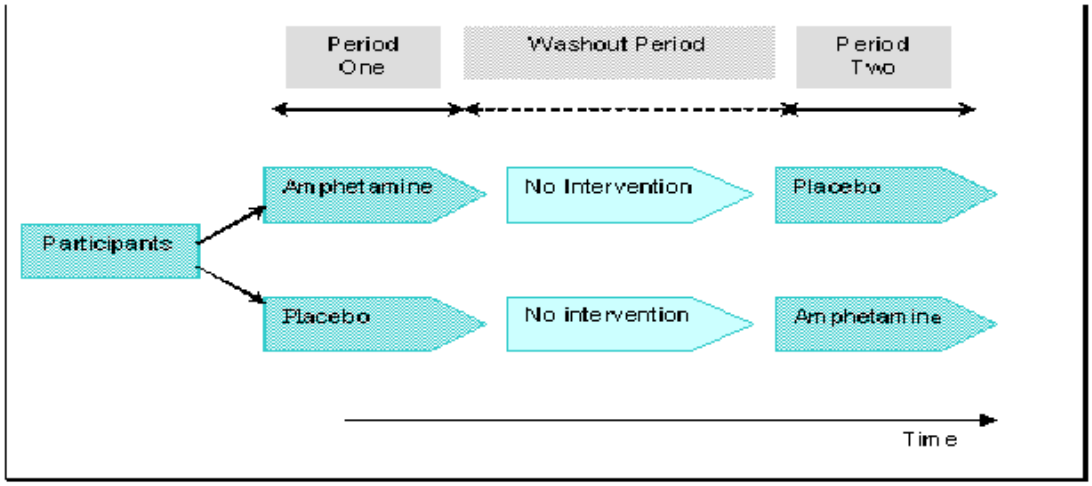
One of the criticisms of using such strict inclusion criteria in systematic reviews and meta-analysis is that the results obtained may not be applicable to the 'real world'. Evidence suggests that individuals consenting to be randomised may be different from the average person seen in everyday practice (Bowen 1994; Bowen 1992). Furthermore, by utilising restricted inclusion criteria, such as the requirement of an operational diagnosis with no co-morbid disorders, a large group of individuals will be overlooked. Thus, using limiting criteria for homogeneity may result in limited generalisability (Britton 1999).

Better reporting would have allowed more information to become available. Compliance with CONSORT (Moher 2001) is recommended in the future. However, again, we recognise that CONSORT was only introduced relatively recently (Begg 1996), and was drawn up to encourage good reporting in clinical trials. It may be helpful for researchers and editors to construct and implement similar universal standard for reporting of investigative randomised experiments (i.e. non-clinical studies).

2.1. Crossover studies

A crossover trial "is one in which subjects are given sequences of treatments with the object of studying differences between individual treatments (or sub-sequences of treatments)" (Senn 1993). Figure 1 is illustrated. In contrast to parallel design, crossover trials have two main advantages (Senn 1993). As each participant contributes to data for more than one treatment, fewer participants have to be recruited. Furthermore, each participant can be used as his or her own control, and therefore individual reaction to treatments can be studied and variations between participants are eliminated.

Figure 1. Crossover design.Example of an AB/BA crossover design with washout period



Example of an AB/BA crossover design with washout period

2.1.1 The use of crossover designs for people with schizophrenia

It is a necessary requirement when using a crossover design that the condition being investigated is stable (Richens 2001; Senn 1999). This is to ensure that when one intervention ceases, the condition will return to its baseline state before the next intervention begins. This requirement cannot definitely be met when participants are those with schizophrenia. Schizophrenia is a variable illness and it cannot be ensured that all participants will be experiencing the same symptoms during the different crossover periods. Given that crossover trials are designed to compare paired data from each participant, this would introduce unacceptable bias in the results. We felt, therefore, that this design may not be suitable for investigating this population.

2.1.2 Carryover effects

Another reason for the exclusion of crossover data relates to carryover effects. Carryover effects are frequently considered to be the outstanding difficulty in crossover trials (Senn 1993). Carryover takes place when the treatment given during the first intervention period has an effect that continues into the second period. The effects of carryover can be reduced by the introduction of an appropriate washout period, where no intervention is given. This provides time for the effects of the first intervention to dissipate.

Consider the example of a crossover design in the figure (Figure 1). Here participants are randomly allocated to receive amphetamine and then placebo, or placebo and then amphetamine. For participants receiving amphetamine and then placebo, if the period of washout is too short, the effects produced by amphetamine could directly influence the subsequent effects of the placebo. The difficulty arises therefore when deciding on the length of washout. In the majority of studies this appears to be calculated on the estimated half-life of amphetamine and detection of amphetamine or its metabolites in body fluids. However, this does not necessarily mean that the effects of amphetamine are no longer present. For example, many of these drugs will result in changes at the receptor level, such as receptor up/down regulation. It is likely that these changes will take longer to return to baseline than the excretion of the drug from the system, and therefore these drugs are likely to alter the effects of the post crossover intervention.

Carryover effects can be psychological as well as physiological (Cleophas 1993). In several of the crossover studies that were identified, authors reported that participants were told the classes of drugs they might receive e.g. stimulants, sedatives, inactive drugs etc. Consequently, it is likely that participants after receiving the interventions(s) would have reached some conclusion regarding the drug they had received and the drug(s) they were to receive. These expectations pose a threat to blinding, especially in studies where subjective effects of an active intervention are being sought as compared with placebo (Mazzacato 2001).

Other treatment by period interactions that can also bias results of crossover trials include participants becoming increasing familiar with procedures. This can result in improved performance, or conversely participants becoming bored in later experimental sessions, hence losing motivation and completing measures/tasks in a more haphazard manner.

2.1.3 Statistical Methods

As far as we are aware, at the present time no agreed statistical method exists to correctly include post crossover data in meta-analyses. The current method of data analysis using weighted mean difference is based upon the assumption that each piece of data arises from a single participant, i.e. it is independent. Data in crossover trials does not meet this assumption, as each participant contributes to both drug and placebo data. Therefore, entering post crossover data in the analyses would have resulted in biased results heavily weighted towards the crossover data.

A significant amount of time was taken considering other methods by which crossover data could have been included in the review. These alternative options are discussed below.

One option would have been to include data from the first arm of the crossover only, thereby treating pre crossover data as if it were from a parallel design. We discarded this idea for two reasons. Firstly, this is not practical as none of the crossover trials reported pre crossover data. Secondly, and perhaps more importantly, should only a proportion of crossover trials have been included, this could well represent a biased subset of all crossover studies (Curtin 2002a). A second option would have been to perform the analyses of the post crossover data separately from that obtained from the parallel studies. This situation is not satisfactory as it results in two separate reviews (Curtin 2002b). However, in addition, difficulties with statistical assumptions and potential carryover effects remain.

Recent medical statistical research is beginning to suggest that there could be techniques that account for both data that are not independent and carryover effects**.** Preceding this research, inappropriate, ill considered summation was possible, but results were meaningless and impossible to interpret. With the pioneering work of highly specialised medical statistical researchers, we do have the possibility of being able to appropriately summate 'lost' data from crossover studies in the future. Currently, this work is in the realms of statistical and meta-analytic research and is not generally accepted or applied. Unfortunately, even if acceptable techniques become available, reporting in the studies identified for this review is poor and predates the recent stipulations by the statisticians for estimates of carryover, normal continuous data and paired data from each patient (Elbourne 2002).

Elbourne 2002 does recognise the practical difficulties of undertaking such work. Whilst stipulating the need for reporting such things as paired data from each patient, they do also state "poor reporting of crossover trials will often impede attempts to perform meta-analysis using available methods". In addition to poor reporting, the majority of crossover trials in this review involved more than two intervention periods. Consequently, even with the future introduction of the new statistical methods for two period crossover studies, the data from studies with more than two intervention periods would still be outstanding.

In summary, at the present time there appears to be no consensus regarding the inclusion of crossover data in meta-analyses. We did not take the decision to exclude crossover data lightly. However, because of the risk of carryover and statistical limitations we felt that exclusion was the most appropriate judgment. We acknowledge that by doing this a substantial proportion of data were lost.

3. Effects of amphetamine on people with schizophrenia

3.1. Outcomes

Data were available for a total of four outcomes; mental state, leaving the study early, adverse extapyramidal effects and physiological effects. No data were available for death, behaviour, mood, cognitive effects, personality, satisfaction, other adverse effects, service utilisation outcomes and economic outcomes.

3.2. Mental state

Results from Wolkin 1987 suggest that when compared with placebo, in the immediate term, administration of amphetamine significantly reduces negative symptoms such as apathy and lack of energy, but has no significant effect on positive symptoms of delusions and hallucinations. The clinical meaning of a three point change in the ATS is not clear, but this is an interesting, hypothesis-generating result. Very few interventions have been found to have any affect on the insidious and often intractable negative symptoms of schizophrenia. Claims are often made for new drugs that are unsubstantiated by evidence (Duggan 2003; Hunter 2003) and older non-drug interventions may be as good, if not better (McMonagle 2003).

Evidence suggests that the negative symptoms of schizophrenia are related to dopaminergic hypoactivity in the frontal lobes (Andreasson 1987). It would therefore follow, that administration of a drug that increased dopaminergic activity would result in a decrease of negative symptoms. Furthermore, this finding may be seen to lend some support to the self-medication hypothesis of drug abuse (Khantzian 1987; Khantzian 1985), as it has been proposed that people with schizophrenia are more inclined to abuse stimulant drugs such as amphetamine to alleviate their apathy (Schneier 1987).

3.3. Leaving the study early

Not one of the studies explicitly reported the number of people who did not complete the study, but the low loss may have been a reflection of the time limitation of these studies. It could also indicate that doses of amphetamine administered were acceptable to participants, or at least do not cause such immediate difficulties that lead to dropout.

3.4. Adverse effects

Only one study measured extrapyramidal adverse effects using the AIMS (Guy 1976). Mean difference could not be estimated due to lack of data. The authors, however, reported in the text no significant difference between amphetamine and placebo for the change in extrapyramidal effects, and as mentioned in the results, we think the lack of data may be a typographical error.

3.5. Physiological effects

Wolkin 1994 and Wolkin 1987 reported cerebral metabolic rate. Unfortunately data were presented in varying formats so the results of these studies could not be added together. Limited data

from Wolkin 1987 suggests that amphetamine significantly decreases percent change in local cerebral metabolic rate in the right temporal lobe compared with placebo. Again, limited data from Wolkin 1994 indicates that amphetamine significantly reduces average change in absolute cerebral metabolism in the left and right temporal and dorsolateral prefrontal cortices. This study also found, by comparing regional or whole brain cerebral metabolic rate (ratio data), that compared with placebo, amphetamine significantly increases metabolism in the left and right cerebellum and left striatum. It does, however, significantly decrease metabolism in the left dorsolateral prefrontal cortex.

Other results suggest that amphetamines have no significant effect on pulse rate, respiration, systolic blood pressure, diastolic blood pressure, or PECO2. However, these findings were based on a single study (Mathew 1989) involving 12 participants. In the same vein, the equivocal findings for body weight change, appetite and arousal are all based on one small, short study and do not mean that amphetamines have no such effects.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with serious mental illnesses and their family

Amphetamines are known to be bad for people with schizophrenia. The small, short very unusual studies in this review hint at some effects of which the clinical meaning is unclear. Because all studies are so short and small the other equivocal findings could nevertheless belie dangerous and damaging effects of these powerful illicit drugs.

2. For clinicians

Clinical experience and data from other types of studies bears testament to the detrimental effects of stimulant drugs for people with schizophrenia. This review attempted to summarise some data from randomised experiments. Even the poor data in this review hints at the reasons why people with schizophrenia may be attracted to these drugs. Negative symptoms caused by the illness, not offset by antipsychotic treatment, may be affected by amphetamines. It is, however, impossible to say this with certainty.

Implications for research

1. General

Should more data from unidentified existing studies be acquired, we would probably know much more about the effects of amphetamine on schizophrenia. Much important data within the included studies were not reported clearly and therefore clinicians, funders and recipients of care may feel that they have been let down by the research community. If the CONSORT recommendations (Begg 1996; Moher 2001) were to be followed in reporting of future studies, this would greatly assist synthesis of data in reviews.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Mathew 1989

Methods	Allocation: unclear - implied randomisation.* Blindness: single.** Duration: 1 hour.
Participants	Diagnosis: schizophrenia (DSM-IIIR). N = 24. Age: mean ~ 34 years. Sex: 9M, 15F. History: no details. Setting: hospital.
Interventions	1. d-Amphetamine sulphate: dose 15mg IV. N = 12. 2. Placebo. N = 12. All participants taking medication (no further details).
Outcomes	Leaving the study early. *** Physiological: CBF, pulse rate, respiritory rate, blood pressure, PECO2 Unable to use - Mental state: BPRS (no data for placebo). Physiological: blood Hb levels (no data, used to calculate CBF only)
Notes	* baseline demographics similar. ** participants blind, no details about researchers. *** assumed from text.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Modell 1965

Methods	Allocation: randomised (table of random numbers). Blindness: double - implied.* Duration: 4 weeks.
Participants	Diagnosis: schizophrenia (diagnosis previously made by psychiatric servcie). N = 20. Age: 32-63 years, mean ~ 43 years. Sex: all male. History : all participants obese, mean weight ~ 92 kg. Setting: hospital.

Modell 1965 (*Continued*)

Interventions	1. Dextroamphetamine: dose 5mg orally 4x day. N = 10. 2. Placebo. N = 10. All participants taking neuroleptic medication.
Outcomes	Leaving the study early. ** Physiological: pulse rate, blood pressure. Unable to use - Physiological: weight, appetite, sleep (data skewed).
Notes	* similar tablets, coded bottles of medication. ** assumed from text.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Wolkin 1987

Methods	Allocation: unclear - implied randomisation.* Blindness: double (matching capsules). Duration: three hours.
Participants	Diagnosis: schizophrenia (DSM-III, RDC). N = 16. Age: 24-52 years, mean ~ 35 years. Sex: all male. History: duration of illness amphetamine group (mean ~ 13 years), placebo group (mean ~ 8 years). Setting: hospital.
Interventions	1. d-Amphetamine: dose 0.25 mg/kg orally. N = 10. 2. Placebo. N = 6. Following placebo administration, no participannts taking neuroleptic medication
Outcomes	Mental state: BPRS, ATS. Leaving the study early. ** Adverse effects: AIMS. Physiological: PET scan Unable to use - Physiological: vital signs (no data).
Notes	* baseline demographics and clinical data similar. ** assumed from text.

Risk of bias

Wolkin 1987 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Wolkin 1994

Methods	Allocation: unclear - implied randomisation.* Blindness: double (no further details). Duration: 3.5 hours.
Participants	Diagnosis: schizophrenia, chronic (DSM-IIIR). N = 23. Age: 26-44 years, mean ~ 35 years. Sex: all male. History : duration of illness 3-24 years, mean ~ 14 years, no drug abuse within preceeding month. Setting: veterans hospital.
Interventions	1. d-Amphetamine: dose 0.5mg/kg orally. N = 17. 2. Placebo. N = 6. Following placebo administration, no participants taking neuroleptic medication
Outcomes	Leaving the study early. ** Physiological: PET scan Unable to use - Mental state: BPRS, ATS, CGI (no data reported for placebo). Adverse effects: AIMS (no data reported for placebo). Cognitive function: WCST (modified version used), WAIS-R vocabulary subtest (pre-study data only)
Notes	* baseline and demographic details similar. ** assumed from text.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

AIMS = Abnormal Involuntary Movements Scale
APA = American Psychiatric Association
ATS = Abrams and Taylor Scale for Emotional Blunting
BAR = version of a simple sensorimotor control task
BPRS = Brief Psyciatric Rating Scale
BPRS (SZ) = Brief Psychiatric Rating Scale schizophrenia
BPRS (W-R) = Brief Psychiatric Rating Scale withdrawal-retardation
CPT = Continuous Performance Test
DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-IIIR = Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised

DSST = Digit Symbol Substitution Test
IMPS = Inpatient Mulidimentional Psychiatric Scale
POMS = Profile of Mood States
PRP = Psychotic Reaction Profile
PR = Pursuit Rotor
PSAS = Psychiatric Symptom Assessment Scale
RCD = Research Diagnostic Criteria
RFT = Rod and Frame Test
RFTs = Rod and Frame Test serial version
RT = Simple recation time without warning
RTW = Simple recation time with warning
SD = standard deviation
WCST = Modified Wisconsin Card Sorting Task
YMRS = Young Mania Rating Scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aman 1985	Allocation: randomised. Participants: adults and adolescents with severe learning diffciulties, not people with schizophrenia
Angrist 1971	Allocation: unclear. Participants: healthy people, not people with schizophrenia.
Angrist 1974	Allocation: not randomised.
Angrist 1980	Allocation: not randomised.
Angrist 1982	Allocation: not randomised.
Baker 2002	Allocation: randomised. Participants: people with comorbid psychiatric and substance abuse disorders. Interventions: individual motivational interview versus self-help booklet, not amphetamine
Bilder 1992	Study 1 Allocation: randomised. Participants: people with schizophrenia and people with schizoaffective disorder. Interventions: methylphenidate + chlorpromazine (or equivalent) versus placebo + chlorpromazine (or equivalent), not amphetamine Study 2 Allocation: unclear. Interventions: methamphetamine versus apomorphine, not amphetamine
Broadhurst 1958	Study 1 Allocation: not randomised. Study 2 Allocation: not randomised.

(*Continued*)

Brown 2002	Allocation: randomised. Participants: people with schizophrenia, bipolar disorder, schizoaffective disorder or major depressive disorder with cocaine/amphetamine related disorders. Interventions: continuation of neuroleptic medication + quetiapine versus discontinuation of neuroleptic medication + quetiapine versus contuniation of neuroleptic medication versus discontinuation of neuroleptic medication, not amphetamine
Buchanan 1995	Allocation: unclear, "double blind. Participants: people with schizophrenia. Interventions: mazindol, not amphetamine.
Campbell 1972	Allocation: unclear, "double blind". Participants: children with schizophrenia, not adults.
Campbell 1976	Allocation: unclear, "double blind". Participants: children with schizophrenia, not adults.
Campbell 1982	Allocation: randomised. Participants: children, not adults.
Carpenter 1992	Allocation: randomised. Participants: people with schizophrenia or schizoafective disorder with a history of childhood hyperactivity. Interventions: methylphenidate + neuroleptic medication versus placebo + neuroleptic medication, not amphetamine
Cassady 1998	Allocation: randomised. Participants: people with schizophrenia spectrum personality disorders and healthy people, not people with schizophrenia
Cesarec 1974	Allocation: unclear, possibly randomised. Participants: people with schizophrenia. Interventions: fluphenazine, pimozide and flupenthixol, not amphetamine
Chouinard 1978	Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus tryptophan-benserazide, not amphetamine
Clausen 1973	Allocation: randomised. Participants: healthy people, not people with schizophrenia.
Corr 2000	Allocation: unclear, "double blind". Participants: healthy people, not people with schizophrenia.
Costello 1964	Allocation: randomised. Participants: healthy people, not people with schizophrenia.

(*Continued*)

Daniel 1991	Allocation: unclear, "double blind, counter-balanced", crossover design. Participants: people with schizophrenia. Interventions: d-amphetamine versus placebo, all participants taking haloperidol. Outcomes: Unable to use - leaving the study early, clinical response, behaviour, physiological effects, adverse side effects, cognitive function (no data reported pre crossover)
Fann 1973	Allocation: randomised. Participants: people with tardive dyskinesia. Interventions: methyphenidate + chlorpromazine (or equivalent) versus placebo + chlorpromazine (or equivalent), not amphetamine
Fish 1966	Allocation: unknown. Participants: children, not adults.
Forrest 1967	Allocation: randomised. Particpants: healthy people, not people with schizophrenia.
Gefvert 2002	Study 1 Allocation: randomised. Participants: people with schizophrenia. Interventions: OSU6162 100mg versus placebo, not amphetamine Study 2 Allocation: not randomised, all participants receiced OSU6162
Gillin 1978	Allocation: randomised. Participants: unclear. Intervention: pimozide pretreatment or placebo, all participants recieved amphetamine
Gray 1996	Allocation: unclear. Participants: healthy people, not people with schizophrenia.
Gross 1998	Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: LU 111995 up to 350 mg versus placebo, not amphetamine
Honigfeld 1984	Study 1 Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: clozapine versus chlorpromazine, not amphetamine Study 2 Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: clozapine versus chlorpromazine, not amphetamine Study 3 Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: clozapine versus chlorpromazine versus placebo, not amphetamine Study 4

(*Continued*)

	Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: clozapine versus haloperidol, not amphetamine
Janowsky 1973	Allocation: randomised. Participants: people with schizophrenia or manic depressive illness, depression or healthy people. Interventions: methylphenidate versus placebo, not amphetamine
Janowsky 1974	Allocation: randomised, crossover. Participants: people with schizophrenia, not all participants received all drugs for ethical reasons. Interventions: d-amphetamine versus l-amphetamine versus methylphenidate versus placebo. Outcomes: unable to use - leaving the study early, clinical response, behaviour, physiological effects, mood (no data reported pre-crossover)
Janowsky 1978	Allocation: randomised. Participants: people with schizophrenia, manic depression, depressive neurosis, drug dependence or antisocial personality disorder. Interventions: methylphenidate versus placebo, not amphetamine
Jauhar 2001	Allocation: not randomised, survey.
Kopell 1968	Allocation: unclear, crossover. Participants: people with schizophrenia, neuroses, or personality disorders. Interventions: chlorpromazine versus methamphetamine versus placebo. Outcomes: unable to use - leaving the study early, cognitive effects (no reported data pre-crossover)
Kornetsky 1976	Study 1 Allocation: unclear, "double blind, latin square", crossover. Participants: people with schizophrenia. Interventions: dextroamphetamine versus iproniazid versus placebo. Outcomes: unable to use - leaving the study early, physiological effects, cognitive function (no data reported pre-crossover) Study 2 Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: dextroamphetamine versus placebo. Outcomes: unable to use - leaving the study early, behaviour (no data reported pre crossover/incomplete data) Study 3 Allocation: not randomised, case series.
Kroner 1999	Allocation: unclear, "double blind, counterbalanced". Participants: healthy people, not people with schizophrenia.
Krystal 2000	Allocation: unclear. Participants: healthy people, not people with schizophrenia.
Kumari 1997	Allocation: randomised. Participants: healthy people, not people with schizophrenia.

(*Continued*)

Lahti 2001	Allocation: randomised. Participants: people with schizophrenia or healthy people. Interventions: ketamine versus placebo, not amphetamine.
Laurelle 1996	Allocation: not randomised.
Leszak 1991	Allocation: unclear. Participants: people with schizophrenia. Interventions: human leukocyte interferon versus placebo, not amphetamine
Levy 1993	Allocation: unclear. Participants: people with schizophrenia, schizoaffective disorder, schizotypal personality disorder or healthy people. Interventions: methylphenidate versus apomorphine, not amphetamine
Lieberman 1984	Allocation: randomised. Participants: people with subacute, subchronic or chronic schizophrenia or schizoaffective disorder. Interventions: methylphenidate versus placebo, not amphetamine
Malaspina 1994	Allocation: unclear, "double blind". Participants: healthy people, not people with schizophrenia.
McCartan 2001	Study 1 Allocation: randomised. Participants: healthy people, not people with schizophrenia. Study 2 Allocation: randomised. Participants: healthy people, not people with schizophrenia.
Overall 1961	Allocation: randomised. Participants: people with neurotic depressive reactions, psychotic depression, manic depressive reactions, involutional reactions, or depressed schizoaffective reactions. Interventions: dextroamphetamine + amobarbital versus isocarboxazide versus imipramine versus placebo, not amphetamine alone
Pandurangi 1989	Allocation: randomised, crossover. Participants: people with schizophrenia or schizoaffective disorder. Interventions: dextroamphetamine versus placebo. Outcomes: unable to use - leaving the study early, clinical response, physiological effects (no data reported pre crossover)
Perry 1995	Allocation: unclear, "counterbalanced". Participants: healthy people, not people with schizophrenia.
Pfeiffer 1965	Study 1 Allocation: unclear. Participants: people with schizophrenia or healthy people. Interventions: pentobarbital versus caffeine versus d-amphetamine versus d-LSD-25.

(*Continued*)

	Outcomes: unable to use - leaving the study early, physiological effects (incomplete data, no N values) Study 2 Allocation: unclear, "double blind". Participants: people with schizophrenia and healthy people. Interventions: deanol versus chlorpromazine versus perphenazine versus placebo (various combinations), not amphetamine Study 3 Allocation: unclear. Participants: people with schizophrenia or healthy people. Interventions: meprobamate versus chlordiazeproxide versus orphenadrine versus placebo, not amphetamine
Rappaport 1968	Study 1 Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus perphenazine versus dextroamphetamine versus methylphenidate. Outcomes: unable to use - leaving the study early, cognitive function (data for dextroamphetamine not presented separately) Sub-study Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: chlorpromazine versus perphenazine, not amphetamine
Robinson 1991	Allocation: randomised. Participants: people with schizophrenia or schizoaffective disorder. Interventions: methylphenidate versus placebo, not amphetamine
Schulz 1982	Allocation: randomised, crossover. Participants: people with schizophrenia or schizoaffective disorder. Interventions: d-amphetamine versus placebo. Outcomes: unable to use - leaving the study early, physiological effects, beta endorphin levels (no data reported pre crossover)
Sharma 1990	Allocation: randomised. Participants: people with schizophrenia, schizoaffective dsiorder and people with major affective disorder (N= 9). Interventions: methylphenidate 0.5mg/kg versus placebo, not amphetamine
Sherr 1999	Allocation: randomised. Participants: people with schizophrenia spectrum personality disorder and healthy people, not people with schizophrenia
Smith 1977	Allocation: unclear, "double blind". Participants: people with schizophrenia or schizoaffective psychosis. Interventions: apomorphine + neuroleptic medication versus apomorphine - neuroleptic medication versus placebo, not amphetamine
Soederholm 1976	Allocation: randomised. Participants: adolescents with drug induced withdrawal symptoms, irritability and dysphoria, not adults with schizophrenia

(*Continued*)

St Jean 1967	Nine studies. Study 1-5, 8-9 not randomised. Study 6 Allocation: randomised. Participants: people with chronic psychosis, mental deficiency and epilepsy. Interventions: chlorpromazine versus propericiazine, not amphetamine Study 7 Allocation: randomised. Participants: people with schizophrenia. Interventions: chlorpromazine versus propericiazine, not amphetamine
Strakowski 1997	Allocation: randomised, crossover. Participants: people with schizophrenia, schizophreniform disorder or bipolar disorder. Interventions: amphetamine versus placebo. Outcomes: unable to use - leaving the study early, clinical response, behaviour, physiological effects, mood, cognitive function (pre crossover data reported, but data not reported separately for participants with schizophrenia/schizophreniform disorder and biploar disorder)
van Kammen 1982	Allocation: unclear "partly randomised", "double blind", crossover. Participants: people with schizophrenia or schizoaffective disorder. Interventions: d-amphetamine versus d-amphetamine + lithium carbonate pre treatment versus d-amphetamine + pimozide pre treatment versus placebo. Outcomes: unable to use - leaving the study early, clinical response, physiological effects (no reported data pre crossover)
van Kammen 1985	Allocation: randomised. Participants: unclear. Interventions: lithium, placebo, all participants received amphetamine
van Kammen 1988	Allocation: randomised, crossover. Participants: people with schizophrenia or schizoaffective disorder. Interventions: dextroamphetamine versus dextoamphetamine + pimozide versus pimozide versus placebo. Outcomes: unable to use - leaving the study early, clinical response (no data reported pre crossover)
Witton 1960	Allocation: not randomised.
Zahn 1981	Allocation: randomised. Participants: healthy people, not people with schizophrenia.
Zemishlany 1998	Study 1 Allocation: unclear. Participants: people with schizophrenia. Interventions: amantadine + neuroleptic versus placebo, not amphetamine Study 2 Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: L-deprenyl + neuroleptic versus placebo, not amphetamine

(*Continued*)

Zylberman 1995	Reports a study to be conducted. Allocation: unclear, "double blind". Participants: people with schizophrenia. Interventions: oral glycine, not amphetamine.

DATA AND ANALYSES

Comparison 1. AMPHETAMINES vs PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: Average change in symptoms - by <3 hours (decline = good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 positive symptoms (BPRS)	1	16	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 negative symptoms (ATS)	1	16	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-5.02, -0.98]
2 Leaving the study early	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 <3.5 hours	3	63	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 by 4 weeks	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Adverse effects: 1. Average change in movement disorders - by <3 hours (AIMS, decline = good)	1	16	Mean Difference (IV, Random, 95% CI)	Not estimable
4 Physiological: 1a. Cerebral function - local cerebral metabolic rate (percentage change <3 hours)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 frontal - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-16.36, 8.36]
4.2 frontal - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-8.4 [-16.82, 0.02]
4.3 striatum - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-10.8 [-23.93, 2.33]
4.4 striatum - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-13.40 [-26.94, 0.14]
4.5 temporal - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-9.6 [-23.28, 4.08]
4.6 temporal - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-12.30 [-23.16, -1.44]
5 Physiological: 1b. Cerebral function - cerebral metabolic rate <3.5 hours (µm/100g/min)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 cerebellum - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-3.09, 2.49]
5.2 cerebellum - right	1	23	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.3 mesial temporal lobe - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-2.00 [-4.67, 0.67]
5.4 mesial temporal lobe - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-5.64, 1.04]
5.5 orbito medial frontal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-6.43, 0.63]
5.6 orbito medial frontal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-5.56, 2.96]
5.7 striatum - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.30 [-4.54, 5.14]
5.8 striatum - right	1	23	Mean Difference (IV, Fixed, 95% CI)	1.10 [-5.04, 7.24]
5.9 thalamus - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-7.35, 0.55]
5.10 thalamus - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-4.30 [-8.99, 0.39]
5.11 temporal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-6.90 [-10.41, -3.39]
5.12 temporal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-6.80 [-10.48, -3.12]

5.13 dorsolateral prefrontal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-7.90 [-11.15, -4.65]
5.14 dorsolateral prefrontal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-6.20 [-10.53, -1.87]
6 Physiological: 1c. Cerebral function - ratio of regional to whole brain metabolic rate <3.5hours	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 cerebellum - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.06, 0.18]
6.2 cerebellum - right	1	23	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.06, 0.18]
6.3 mesial temporal lobe - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.02, 0.12]
6.4 mesial temporal lobe - right	1	23	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.02, 0.10]
6.5 orbito medial frontal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.05, 0.13]
6.6 orbito medial frontal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.04, 0.18]
6.7 striatum - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.00, 0.28]
6.8 striatum - right	1	23	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.01, 0.31]
6.9 thalamus - left	1	23	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.05, 0.13]
6.10 thalamus - right	1	23	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.07, 0.09]
6.11 temporal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.13, 0.03]
6.12 temporal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.11, 0.03]
6.13 dorsolateral prefrontal cortex - left	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.17, -0.01]
6.14 dorsolateral prefrontal cortex - right	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.12, 0.04]
7 Physiological: 2. Cerebral blood flow change <3 hours (ml/100 g/min)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 hemisphere - left	1	24	Mean Difference (IV, Fixed, 95% CI)	-13.60 [-18.56, -8.64]
7.2 hemisphere - right	1	24	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-12.60, -1.40]
8 Physiological: 3a. Cardio-respiratory function by <1 hour	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 pulse/min2	1	24	Mean Difference (IV, Fixed, 95% CI)	4.30 [-6.03, 14.63]
8.2 respiration/min	1	24	Mean Difference (IV, Fixed, 95% CI)	0.90 [-4.23, 6.03]
8.3 systolic blood pressure, mm Hg3	1	24	Mean Difference (IV, Fixed, 95% CI)	14.0 [1.02, 26.98]
8.4 diastolic blood pressure, mm Hg4	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-10.45, 4.25]
8.5 PECO2, mm Hg5	1	24	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-4.19, 1.59]
9 Physiological: 3b. Cardio-respiratory function by 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 pulse (beats/min)	1	20	Mean Difference (IV, Fixed, 95% CI)	5.0 [-2.31, 12.31]
9.2 systolic blood pressure, mm Hg3	1	20	Mean Difference (IV, Fixed, 95% CI)	7.0 [-0.45, 14.45]
9.3 diastolic blood pressure, mm Hg4	1	20	Mean Difference (IV, Fixed, 95% CI)	5.00 [-0.67, 10.67]

10 Physiological: 4. Body weight & appetite by 4 weeks (data skewed)	Other data	No numeric data
10.1 appetite score (increase = decline in appetite)	Other data	No numeric data
10.2 weight change	Other data	No numeric data
11 Physiological: 5. Arousal by 4 weeks (data skewed)	Other data	No numeric data
11.1 awakenings during night	Other data	No numeric data
11.2 naps during day	Other data	No numeric data

Analysis 1.1. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 1 Mental state: Average change in symptoms - by <3 hours (decline = good).

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 1 Mental state: Average change in symptoms - by <3 hours (decline = good)

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 positive symptoms (BPRS)							
Wolkin 1987	10	2 (5)	6	2 (4)		100.0 %	0.0 [-4.46, 4.46]
Subtotal (95% CI)	**10**		**6**			**100.0 %**	**0.0 [-4.46, 4.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 negative symptoms (ATS)							
Wolkin 1987	10	-2 (3)	6	1 (1)		100.0 %	-3.00 [-5.02, -0.98]
Subtotal (95% CI)	**10**		**6**			**100.0 %**	**-3.00 [-5.02, -0.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.90 (P = 0.0037)							
Test for subgroup differences: Chi² = 1.44, df = 1 (P = 0.23), I² =31%							

Analysis 1.2. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 2 Leaving the study early.

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 2 Leaving the study early

Study or subgroup	Amphetamine n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 <3.5 hours				
Mathew 1989	0/12	0/12		0.0 [0.0, 0.0]
Wolkin 1987	0/10	0/6		0.0 [0.0, 0.0]
Wolkin 1994	0/17	0/6		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**24**		**0.0 [0.0, 0.0]**
Total events: 0 (Amphetamine), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 by 4 weeks				
Modell 1965	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Amphetamine), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.3. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 3 Adverse effects: 1. Average change in movement disorders - by <3 hours (AIMS, decline = good).

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 3 Adverse effects: 1. Average change in movement disorders - by <3 hours (AIMS, decline = good)

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Wolkin 1987	10	1 (0.4)	6	0 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**10**		**6**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						

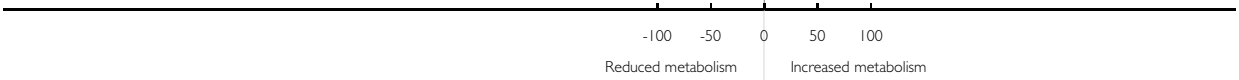
Analysis 1.4. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 4 Physiological: 1a. Cerebral function - local cerebral metabolic rate (percentage change <3 hours).

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 4 Physiological: 1a. Cerebral function - local cerebral metabolic rate (percentage change <3 hours)

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 frontal - left							
Wolkin 1987	17	-2.6 (12)	6	1.4 (13.7)		100.0 %	-4.00 [-16.36, 8.36]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-4.00 [-16.36, 8.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
2 frontal - right							
Wolkin 1987	17	-2.7 (11.1)	6	5.7 (8.2)		100.0 %	-8.40 [-16.82, 0.02]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-8.40 [-16.82, 0.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.96 (P = 0.051)							
3 striatum - left							
Wolkin 1987	17	-3 (10.8)	6	7.8 (15.1)		100.0 %	-10.80 [-23.93, 2.33]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-10.80 [-23.93, 2.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.61 (P = 0.11)							
4 striatum - right							
Wolkin 1987	17	-4 (16)	6	9.4 (14)		100.0 %	-13.40 [-26.94, 0.14]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-13.40 [-26.94, 0.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.94 (P = 0.052)							
5 temporal - left							
Wolkin 1987	17	-4.5 (11.4)	6	5.1 (15.7)		100.0 %	-9.60 [-23.28, 4.08]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-9.60 [-23.28, 4.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							
6 temporal - right							
Wolkin 1987	17	-3.1 (7.6)	6	9.2 (12.8)		100.0 %	-12.30 [-23.16, -1.44]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-12.30 [-23.16, -1.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.22 (P = 0.026)							
Test for subgroup differences: Chi^2 = 1.44, df = 5 (P = 0.92), I^2 =0.0%							



Analysis 1.5. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 5 Physiological: 1b. Cerebral function - cerebral metabolic rate <3.5 hours (µm/100g/min).

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 5 Physiological: 1b. Cerebral function - cerebral metabolic rate <3.5 hours (m/100g/min)

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 cerebellum - left							
Wolkin 1994	17	38.4 (3)	6	38.7 (3)		100.0 %	-0.30 [-3.09, 2.49]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-0.30 [-3.09, 2.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 cerebellum - right							
Wolkin 1994	17	39 (3.8)	6	39 (2.8)		100.0 %	0.0 [-2.88, 2.88]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.0 [-2.88, 2.88]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 mesial temporal lobe - left							
Wolkin 1994	17	31.7 (3.9)	6	33.7 (2.4)		100.0 %	-2.00 [-4.67, 0.67]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-2.00 [-4.67, 0.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							
4 mesial temporal lobe - right							
Wolkin 1994	17	31.1 (5.2)	6	33.4 (2.8)		100.0 %	-2.30 [-5.64, 1.04]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-2.30 [-5.64, 1.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.35 (P = 0.18)							
5 orbito medial frontal cortex - left							
Wolkin 1994	17	40.9 (6.7)	6	43.8 (1.9)		100.0 %	-2.90 [-6.43, 0.63]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-2.90 [-6.43, 0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.61 (P = 0.11)							
6 orbito medial frontal cortex - right							
Wolkin 1994	17	39.4 (6.1)	6	40.7 (3.9)		100.0 %	-1.30 [-5.56, 2.96]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-1.30 [-5.56, 2.96]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
7 striatum - left							
Wolkin 1994	17	45.8 (6.4)	6	45.5 (4.7)		100.0 %	0.30 [-4.54, 5.14]

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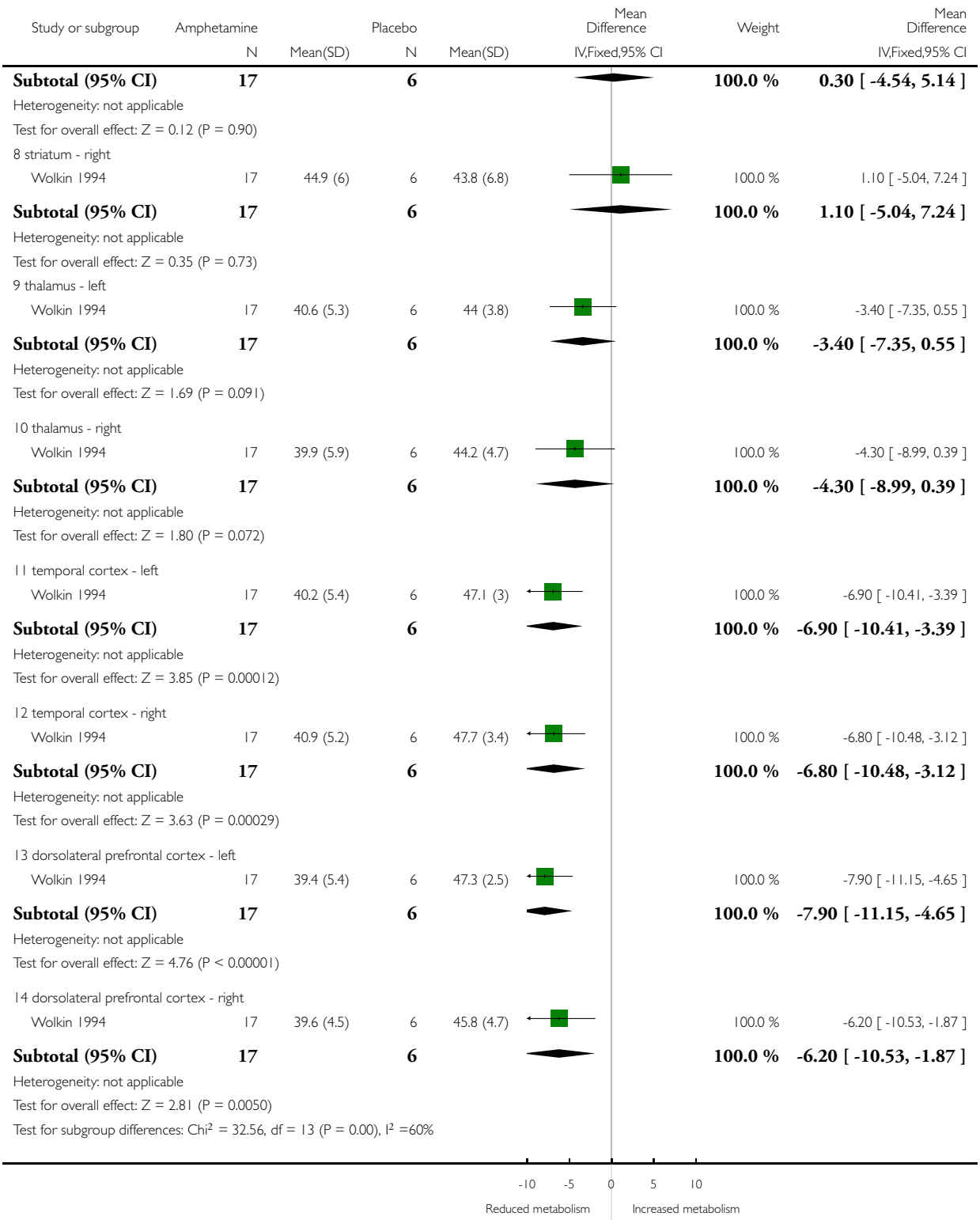

Analysis 1.6. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 6 Physiological: 1c. Cerebral function - ratio of regional to whole brain metabolic rate <3.5hours.

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 6 Physiological: 1c. Cerebral function - ratio of regional to whole brain metabolic rate <3.5hours

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 cerebellum - left							
Wolkin 1994	17	1.05 (0.09)	6	0.93 (0.05)		100.0 %	0.12 [0.06, 0.18]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.12 [0.06, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.02 (P = 0.000059)							
2 cerebellum - right							
Wolkin 1994	17	1.06 (0.09)	6	0.94 (0.05)		100.0 %	0.12 [0.06, 0.18]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.12 [0.06, 0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.02 (P = 0.000059)							
3 mesial temporal lobe - left							
Wolkin 1994	17	0.86 (0.08)	6	0.81 (0.08)		100.0 %	0.05 [-0.02, 0.12]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.05 [-0.02, 0.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							
4 mesial temporal lobe - right							
Wolkin 1994	17	0.84 (0.1)	6	0.8 (0.05)		100.0 %	0.04 [-0.02, 0.10]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.04 [-0.02, 0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.26 (P = 0.21)							
5 orbito medial frontal cortex - left							
Wolkin 1994	17	1.1 (0.1)	6	1.06 (0.09)		100.0 %	0.04 [-0.05, 0.13]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**0.04 [-0.05, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							
6 orbito medial frontal cortex - right							

(*Continued . . .*)

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Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
14 dorsolateral prefrontal cortex - right							
Wolkin 1994	17	1.07 (0.07)	6	1.11 (0.09)		100.0 %	-0.04 [-0.12, 0.04]
Subtotal (95% CI)	**17**		**6**			**100.0 %**	**-0.04 [-0.12, 0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							
Test for subgroup differences: Chi² = 43.93, df = 13 (P = 0.00), I² =70%							

Analysis 1.7. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 7 Physiological: 2. Cerebral blood flow change <3 hours (ml/100 g/min).

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 7 Physiological: 2. Cerebral blood flow change <3 hours (ml/100 g/min)

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 hemisphere - left							
Mathew 1989	12	-9.6 (6.4)	12	4 (6)		100.0 %	-13.60 [-18.56, -8.64]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**-13.60 [-18.56, -8.64]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.37 (P < 0.00001)							
2 hemisphere - right							
Mathew 1989	12	-10 (7)	12	-3 (7)		100.0 %	-7.00 [-12.60, -1.40]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**-7.00 [-12.60, -1.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.45 (P = 0.014)							
Test for subgroup differences: Chi² = 2.99, df = 1 (P = 0.08), I² =67%							

Analysis 1.8. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 8 Physiological: 3a. Cardio-respiratory function by <1 hour.

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 8 Physiological: 3a. Cardio-respiratory function by <1 hour

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 pulse/min2							
Mathew 1989	12	85.7 (14.8)	12	81.4 (10.7)		100.0 %	4.30 [-6.03, 14.63]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**4.30 [-6.03, 14.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 respiration/min							
Mathew 1989	12	16 (6.8)	12	15.1 (6)		100.0 %	0.90 [-4.23, 6.03]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**0.90 [-4.23, 6.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
3 systolic blood pressure, mm Hg3							
Mathew 1989	12	136.5 (18.1)	12	122.5 (14.1)		100.0 %	14.00 [1.02, 26.98]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**14.00 [1.02, 26.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.11 (P = 0.035)							
4 diastolic blood pressure, mm Hg4							
Mathew 1989	12	76.4 (9.9)	12	79.5 (8.4)		100.0 %	-3.10 [-10.45, 4.25]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**-3.10 [-10.45, 4.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.83 (P = 0.41)							
5 PECO2, mm Hg5							
Mathew 1989	12	34.3 (3.3)	12	35.6 (3.9)		100.0 %	-1.30 [-4.19, 1.59]
Subtotal (95% CI)	**12**		**12**			**100.0 %**	**-1.30 [-4.19, 1.59]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.88 (P = 0.38)							
Test for subgroup differences: Chi^2 = 6.65, df = 4 (P = 0.16), I^2 =40%							

Analysis 1.9. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 9 Physiological: 3b. Cardio-respiratory function by 4 weeks.

Review: Amphetamines for schizophrenia

Comparison: 1 AMPHETAMINES vs PLACEBO

Outcome: 9 Physiological: 3b. Cardio-respiratory function by 4 weeks

Study or subgroup	Amphetamine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 pulse (beats/min)							
Modell 1965	10	99 (9.02)	10	94 (7.6)		100.0 %	5.00 [-2.31, 12.31]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**5.00 [-2.31, 12.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.34 (P = 0.18)							
2 systolic blood pressure, mm Hg3							
Modell 1965	10	125 (8.62)	10	118 (8.38)		100.0 %	7.00 [-0.45, 14.45]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**7.00 [-0.45, 14.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.84 (P = 0.066)							
3 diastolic blood pressure, mm Hg4							
Modell 1965	10	79 (6.97)	10	74 (5.93)		100.0 %	5.00 [-0.67, 10.67]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**5.00 [-0.67, 10.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.73 (P = 0.084)							
Test for subgroup differences: Chi^2 = 0.20, df = 2 (P = 0.90), I^2 =0.0%							

Analysis 1.10. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 10 Physiological: 4. Body weight & appetite by 4 weeks (data skewed).

Physiological: 4. Body weight & appetite by 4 weeks (data skewed)

Study	Interventions	N	Mean	SD	Notes
appetite score (increase = decline in appetite)					
Modell 1965	Amphetamine	10	1.90	1.45	No significant difference in food consumption.
Modell 1965	Placebo	10	2.10	2.96	
weight change					

Physiological: 4. Body weight & appetite by 4 weeks (data skewed) (*Continued*)

Modell 1965	Amphetamine	10	1.36	4.80	
Modell 1965	Placebo	10	0.09	2.35	

Analysis 1.11. Comparison 1 AMPHETAMINES vs PLACEBO, Outcome 11 Physiological: 5. Arousal by 4 weeks (data skewed).

Physiological: 5. Arousal by 4 weeks (data skewed)

Study	**Interventons**	**N**	**Mean**	**SD**	**Reported results**
awakenings during night					
Modell 1965	Amphetamine	10	29.70	21.32	Participants on amphetamine “slept a bit less”. Possible error - should have been a ’bit more’.
Modell 1965	Placebo	10	38.6	18.44	No details re: statistical significance.
naps during day					
Modell 1965	Amphetamine	10	43.70	50.63	Particpants taking amphetamine napped “bit less”.
Modell 1965	Placebo	10	44.60	33.82	No details re: statistical significance.

WHAT'S NEW

Last assessed as up-to-date: 25 April 2004.

Date	**Event**	**Description**
10 November 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 4, 2004

Date	Event	Description
4 August 2010	Amended	Contact details updated.
11 November 2009	Amended	Contact details updated.
4 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Sue Nolte - designed the protocol, selected the studies, extracted data and wrote the first draft of the full review.

David Wong - helped write the full review.

Gary Latchford - helped select relevant studies and data extract.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- St James' Teaching Hospital NHS Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Amphetamine-Related Disorders; *Schizophrenia; Amphetamines [*pharmacology]; Diagnosis, Dual (Psychiatry); Randomized Controlled Trials as Topic

MeSH check words

Humans