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Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia (Review)

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[Intervention Review]

Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia

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ABSTRACT

Background

Neuroleptic-induced akathisia is a common, distressing early-onset adverse effect of neuroleptic drugs. It has been associated with poor treatment compliance and an increased risk of relapse.

Objectives

To determine the effects of central action beta-blockers compared with placebo for people with neuroleptic-induced acute akathisia.

Search methods

We updated previous searches of the Cochrane Schizophrenia Group Register (May 1999), Biological Abstracts (January 1982-March 1999), The Cochrane Library (issue 3 1999), EMBASE (January 1980-March 1999), LILACS (January 1982-March 1999), MEDLINE (January 1964-March 1999), PsycLIT (January 1974-March 1999), and SCISEARCH by searching the Cochrane Schizophrenia Group Register (November 2003). We sought further references from published trials and their authors.

Selection criteria

We included all randomised controlled clinical trials of central action beta-blockers versus placebo for people with neuroleptic-induced acute akathisia.

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 identified three randomised controlled trials (total n=51, maximum duration 72 hours). We were not able to draw any firm conclusions from such a small data set. In the two 48 hour studies no-one experienced full remission of akathisia, and only one person in each group experienced a 50% remission (n=11, 1 RCT, RR 1.04 CI 0.59 -1.83). One trial stated that no adverse effects occurred in the two groups (n=20, 1 RCT, RR not estimable). The 72 hour study did not show any statistical difference between the central acting beta-blocker (ICI 118,551) and placebo for the outcome 'no change/worse' (n=10, RR 0.22 CI 0.0 to 1.5).

Authors' conclusions

There are insufficient data to recommend beta-blocking drugs for akathisia. These drugs are experimental for this problem, and this review highlights the need for more evaluative studies.

PLAIN LANGUAGE SUMMARY**Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia**

Akathisia is recognised as one of the most common and distressing of the early-onset adverse effects of neuroleptic drugs. This movement disorder is characterised by a subjective report of inner restlessness, mental unease or dysphoria, which can be intense.

This review highlights the limited evidence available to support the use of central action beta-blockers for neuroleptic-induced acute akathisia.

BACKGROUND

The management of schizophrenia and related disorders was revolutionised in the 1950s by the introduction of neuroleptic (or antipsychotic) medication. These medications are effective in the control of florid symptoms of psychoses such as hallucinations, thought disorder (impaired communication) and delusions. In addition to their therapeutic action in acute psychotic episodes, maintenance therapy with antipsychotic drugs is associated with a reduced risk of relapse (Schooler 1993). However, neuroleptic medications have been associated with a range of adverse effects. These adverse effects can lead to poor compliance with neuroleptic treatment, and thus, ultimately, to an increased risk of relapse (Barnes 1993). Some of the most troublesome adverse effects associated with neuroleptic medications involve the voluntary control of movements.

Shortly after the introduction of neuroleptic drugs, akathisia was recognised as one of the most common and distressing of the early-onset adverse effects. This movement disorder is characterised by a subjective report of inner restlessness, mental unease, or dysphoria, which can be intense (Marder 1991, Halstead 1994). Associated with this experience are patterns of restlessness, including rocking from foot to foot and walking on the spot when standing, shuffling, restless legs, rocking back and forth, swinging one leg on the other when sitting (Braude 1983). In severe cases, patients constantly pace up and down in an attempt to relieve the sense of unrest.

Estimates of the prevalence of akathisia in neuroleptic-treated people range between 20% and 75%, occurring more frequently in the first three months of treatment (Ayd 1961, Grebb 1995). It is usually related not only to acute administration of a neuroleptic, but also to a recent dosage increase. Akathisia may be difficult to distinguish from psychotic agitation or anxiety, especially if the person describes a subjective experience of akathisia in terms of being controlled by an outside force (Grebb 1995). If the akathisia is mistaken for psychosis, a possible increase in the neuroleptic dose may occur that can exacerbate the condition.

Drugs that influence neurotransmitter functions, such as anticholinergics, beta-blockers and benzodiazepines, have been proposed as treatments for neuroleptic-induced acute akathisia. However, there is no clear evidence to support the use of these drugs. In this review we attempt to systematically evaluate the use of central action beta-blockers for neuroleptic-induced acute akathisia.

Technical background

While the pathophysiology of neuroleptic-induced acute akathisia remains unknown, antagonism of mesocortical and mesolimbic dopaminergic pathways is a plausible if not completely satisfactory hypothesis. The notion that dopaminergic blockade underlies the emergence of akathisia is supported by PET studies (Farde 1992a, Farde 1992b). In one study these investigators examined D2 receptor occupancy from 77%-89%, while the range for those without such symptoms was 74%-80%. These findings link D2 occupancy to extrapyramidal side effects. The efficacy of beta-blockers in akathisia has been explained on the basis of their antagonism of the inhibitory effect of noradrenergic input to the ventral tegmental area (the origin of the mesolimbic and mesocortical dopamine systems), leading to enhanced dopamine neurotransmission (Lipinski 1989).

OBJECTIVES

A primary objective was to determine whether central action beta-blockers are clinically effective for the treatment of neuroleptic-induced acute akathisia.

A secondary objective was to examine a possible differential therapeutic effect of these interventions according to psychiatric diagnosis (schizophrenia and other related disorders, mood disorders and other disorders).

METHODS

Criteria for considering studies for this review

Types of studies

We included all relevant randomised controlled trials. Where a trial was described as 'double-blind', but it was implied that the study was randomised, in cases where the demographic details of participants in each group were similar, we also included these trials. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants

Participants included people with neuroleptic-induced acute akathisia, diagnosed by any criteria, irrespective of sex, age or psychiatric diagnosis.

Types of interventions

1. Adjunctive centrally acting beta-blockers: any dose or means of administration. Centrally acting beta-blockers include propranolol, pindolol, betaxolol and oxprenolol.

2. Placebo.

We did not consider central action beta-blockers compared to other active drugs such as anticholinergics and benzodiazepines in this review.

Types of outcome measures

1. Akathisia symptoms

1.1 Not showing complete remission (100% reduction in symptoms)

1.2 Not showing at least 50% reduction in symptoms*

1.3 Leaving the study due to lack of efficacy

1.4 Mean difference in severity of symptoms at endpoint

1.5 Mean changes in severity of akathisia symptoms between baseline and endpoint (see Methods section)

2. General mental state changes

2.1 Deterioration in general psychiatric symptoms (such as delusions and hallucinations)

2.2 Mean difference in severity of symptoms at endpoint

2.3 Mean changes in severity of symptoms between baseline and endpoint (see Methods section)

3. Acceptability and tolerability of treatment

3.1 Leaving the study early for any reason

3.2 Leaving the study early because of adverse events

4. Adverse effects

4.1 Presenting at least one adverse event

4.2 Severe adverse effects

4.3 Mean difference in severity of adverse effects at endpoint

4.4 Mean changes in severity of adverse effects between baseline and endpoint (see Methods section)

We pre-stated three time periods for reporting of outcomes: short term (less than six weeks), medium term (between six weeks and six months) and long term (over six months).

* Primary outcome

Search methods for identification of studies

See Collaborative Review Group search strategy.

1. Electronic searching for update (November, 2003).

1.1. The Cochrane Schizophrenia Group's Register (2003)

We searched this using the phrase:

```
{
[akathisi* or acathisi* in title or *akathisi* or *acathisi* in abstract,
index terms of REFERENCE] or [Akathisia* in health care condition
of STUDY]}
```

The Schizophrenia Groups trials register is based on regular searches of BIOSIS Inside; CENTRAL; CINAHL; EMBASE; MEDLINE and PsycINFO; the hand searching of relevant journals and conference proceedings, and searches of several key grey literature sources. A full description is given in the Group's module.

2. Details of previous electronic searches.

2.1 The Cochrane Schizophrenia Group's Register (May 1999 and October 2000) was searched using the phrase:

[AKATHISI* or ACATHISI*]

2.2 We searched the Cochrane Library (Issue 3, 1999) using the phrase:

[(akathisia-drug induced in ME) or AKATHISI* or ACATHISI*]

2.3 We searched the BIOLOGICAL ABSTRACTS (January 1982 to March 1999) using the Cochrane Schizophrenia Group's search strategy for randomised controlled trials combined with the phrase:

[and AKATHISI* or ACATHISI*]

2.4 We searched EMBASE (January 1980 to March 1999) using the Cochrane Schizophrenia Group's search strategy for randomised controlled trials combined with the phrase:

[and (akathisia-drug induced in thesaurus -all subheadings) or AKATHISI* or ACATHISI*]

2.5 We searched LILACS (January 1982 to March 1999) using the Cochrane Schizophrenia Group's search strategy for randomised controlled trials combined with the phrase:

[and (akathisia-drug induced in thesaurus -all subheadings) or AKATHISI* or ACATHISI* or (Mh acathisia or Mh acathisia induzida por drogas)].

2.6 We searched MEDLINE (January 1966 to March 1999) using the Cochrane Schizophrenia Group's search strategy for randomised controlled trials combined with the phrase:

[and (akathisia-drug induced in thesaurus -all subheadings) or AKATHISI* or ACATHISI*]

2.7 We searched PsycLIT (January 1974 to March 1999) using the Cochrane Schizophrenia Group's search strategy for randomised controlled trials combined with the phrase:

[and (explode akathisia-drug induced in DE) or AKATHISI* or ACATHISI*]

2.8 We searched SCISEARCH - Science Citation Index

We sought each of the included studies as a citation on the SCISEARCH database. We inspected reports of articles that had cited these studies in order to identify further trials.

These electronic searches downloaded sets of reports that were handsearched for possible trials and researched, within the bibliographic package, ProCite (version 4.0 for windows, DataPak software, 1998).

3. Reference searching and personal contact

We inspected references of all identified studies for more studies.

4. Personal contact

We contacted the first author of each included study for further information regarding his or her own study or unpublished trials.

Data collection and analysis

1. Selection of trials

One reviewer, Adriano Resende Lima (ARL) evaluated the abstract of each reference identified by the search to see if the study was likely to be relevant to the review. Potentially relevant abstracts were identified and full papers ordered and reassessed for inclusion and methodological quality. Two reviewers ARL and Karla Soares-Weiser (KSW), each working independently, decided if the acquired studies met the inclusion criteria. An inter-rater reliability study was conducted by means of the weighted Kappa coefficient as a measure of agreement for this inclusion criteria.

2. Quality assessment

We used two methods to assess the quality of the trials included in this review: the Cochrane Handbook quality criteria ([Clarke 2003](#)) and the Jadad Scale ([Jadad 1996](#)). The Cochrane Handbook quality criteria are based on the adequacy of the concealment of treatment allocation. Trials that use well-concealed randomisation techniques for group allocation have reduced potential for bias and confounding ([Khan 1996](#), [Schulz 1995](#)). Methods of randomisation with low potential of bias include central computer generated randomisation, random number tables or coin tossing (criterion A); moderate potential of bias is considered in trials where the allocation procedure is unclear or not reported (criterion B). The use of chart file number or date of birth to decide group allocation are examples of quasi-randomisation and are open to manipulation (criterion C). We included trials meeting criteria A or B in this review.

The Jadad Scale examines a broader range of quality parameters, allocating higher scores to trials that: (i) are stated to be randomised (ii) use a randomisation procedure that is suitably concealed (iii) state that double-blind methodology was used (iv) describe an adequate double-blind procedure; and, (v) use an intention-to-treat-analysis. The range of the Jadad score is 0 to 5, with higher scores indicating higher quality ([Jadad 1996](#)). A cut-off of 2 points was used in the Jadad scale to check the assessment

made by the Cochrane Handbook criteria. However, we did not use these scores as inclusion criteria in this review.

3. Data extraction

We independently extracted data from the included trials. Any disagreement was discussed, the decisions documented and, when necessary, we contacted the authors of trials for clarification.

4. Data analysis

4.1 Binary data: for binary outcomes (remission, clinical improvement and leaving the study early) we calculated a standard estimation of the random effects relative risk (RR) and its 95% confidence interval (CI). DerSimonian-Laird estimate of RR from the individual trials was used to estimate the pooled risk ratio for all strata under the assumption of a random effects model. This model takes into account any difference between studies (even if there is no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no variance between studies (studies are homogeneous). By convention, RRs smaller than one indicate that an event is less likely to occur in the active treatment group than in the placebo group. When overall results were statistically significant ($p < 0.05$) we calculated the number needed to treat or harm statistic (NNT, NNH) on the inverse of the pooled absolute risk difference.

4.2 Continuous data

4.2.1 We included continuous data from rating scales only if the measuring instrument had been described in a peer-reviewed journal, and the instrument was either a self report or completed by an independent rater or relative (not the therapist).

4.2.2 Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data the following standards are applied to all data before inclusion: (i) standard deviations and means were reported in the paper or were obtainable from the authors; (ii) when a scale starts from a finite number (such as 0), 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 is more problematic, and this rule cannot be applied with confidence. We therefore only presented change data if no endpoint data were available.

4.2.3 We analysed data that met the two standards by the estimation of the weight mean difference (WMD) between groups.

4.3. Intention to treat analysis

We excluded data from studies where more than 50% of participants in any group were lost to follow up (this does not include the outcome of 'leaving the study early'). In studies with less than 50% dropout rate, we considered people leaving early to have had no change in their symptoms. We then analysed the impact of including studies with high attrition rates (25%-50%) 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 less attrition, but presented them separately.

4.4. Crossover studies. We used only the first segment of crossover trials in order to exclude the potential additive effect in the subsequent segments of these trials (Armitage 1991).

5. Test for heterogeneity

Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. We then visually inspected the graphs to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 75%, this was interpreted as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency was high, data were not summated, but were presented separately and reasons for heterogeneity investigated.

6. Assessing the presence of publication bias

There is often a tendency to present results which support the investigators hypothesis whilst negative outcomes remain unpublished. To counter this we 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). We used the logarithm of the estimate of effect (Relative Risk) to avoid the naturally asymmetric distribution of this measure.

7. Sensitivity analyses

We analysed the effect of including studies with high attrition rates in a sensitivity analysis. We also hoped to investigate whether there were differences in outcome for people with schizophrenia compared with those with mood disorders and/or other diagnoses.

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 the experimental intervention.

RESULTS

Description of studies

1. Excluded studies

We excluded 17 studies. Eight of these were not randomised. Often they were open studies with outcomes compared before and after the use of central action beta-blockers. Adler 1986, Adler 1993b and Sachdev 1993 did randomise people with neuroleptic-induced akathisia to central action beta-blockers versus placebo, but we could not use any data on outcomes. Adler 1985, Adler 1990, Adler 1991, Aoba 1995, Dumon 1992 and Wells 1991 were randomised, and did include people with neuroleptic-induced akathisia, but they were excluded either because the beta-blockers were not centrally acting, or because no placebo was used as a comparator.

2. Awaiting assessment

There are no studies awaiting assessment.

3. Ongoing studies

We are not aware of any ongoing studies.

4. Included Studies

We included three studies in this review: Adler 1989, Irwin 1988 and Kramer 1988.

4.1 Methods

All three included studies reported they were randomised and stated that they were double-blind. The duration of these studies was no longer than three days.

4.2 Participants

[Adler 1989](#), [Irwin 1988](#) and [Kramer 1988](#) included a total of 51 men, aged between 21 and 75 years. All were diagnosed with both schizophrenia and neuroleptic-induced akathisia.

5. Interventions

[Irwin 1988](#) and [Kramer 1988](#) compared propranolol (oral doses between 60 mg and 80 mg/day), with placebo and used fixed doses of propranolol. [Adler 1989](#) compared the centrally acting beta-blocker ICI 118,551 (100 mg/day) with placebo.

6. Outcomes

6.1 General

[Irwin 1988](#) reported changes in akathisia by presenting data on full remission, or partial remission, as defined by pre-specified changes in the Involuntary Movement and Extrapyramidal Scale ([May 1982](#)). This allowed presentation of data from the continuous scale, as dichotomous (improved/not improved) outcomes. Both [Irwin 1988](#) and [Kramer 1988](#) reported on leaving the study before completion. Only [Kramer 1988](#) reported adverse effects. [Adler 1989](#) reported continuous change data for akathisia with the Simpson and Angus Extrapyramidal Rating Scale (modified version) and also presented the data dichotomised as no change/worse.

6.2 Scales

6.2.1 Involuntary Movement and Extrapyramidal Scale - IMEPS ([May 1982](#))

This consists of a seven point scale to assess the level of symptoms of restlessness. High scores indicate severe restlessness.

6.2.2 Simpson and Angus Scale (Hillside/Long Island Jewish Hospital modification) - SAS ([Simpson 1970](#))

This is a 10-item scale used to evaluate the presence and severity of drug-induced parkinsonian symptomatology. The ten items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 0-4 scale, with a scoring system of 0-4 for each item. A low score indicates low levels of parkinsonism.

7. Missing outcomes

Follow-up in the three studies were no longer than 72 hours. No trial-derived data are reported beyond that period. No study reported hospital/service outcomes, satisfaction with care or outcomes that could have been of use in economic analyses.

Risk of bias in included studies

1. Randomisation

All included studies were not explicit about the process of allocation to the intervention groups.

2. Blinding at outcome

All included studies stated that blind evaluation of outcome was undertaken, but did not describe any efforts to ensure that the integrity of blinding was maintained.

3. Follow-up

Study duration was no longer than three days and two of the included studies reported that no one was lost to follow up.

4. Outcome - reporting

The studies often reported associations using inexact p-values (" $p < 0.05$ " or " $p > 0.05$ "). The strength of the association was not reported and depends on the sample size of the groups. In order to

pool p-values from different studies, it is necessary to know their exact value. Requests to authors for more data have, so far, been unanswered.

5. Overall

As both randomisation and blinding were poorly described in the trials they were rated in category B as their results would be at moderate risk of inclusion of bias ([Clarke 2003](#)).

Effects of interventions

1. The search

The original search strategy identified 1008 citations. Twenty-five citations were related to beta-blockers but only seventeen referred to controlled clinical trials (all of them published in journals). Sixteen different studies were identified from these citations and two were included in the review. For the update search (November 2003) 289 citations were identified and four were obtained for further inspection, three of which we excluded

2. COMPARISON 1: CENTRAL ACTING BETA-BLOCKERS versus PLACEBO

2.1 Akathisia

[Irwin 1988](#) reported that no one had full remission by 48 hours ($n=11$, 1 RCT, RR not estimable, Risk Difference 0.00 CI -0.29 to 0.29). Only one person in each group had 50% remission ($n=11$, 1 RCT, RR 1.04 CI 0.59 -1.83). [Adler 1989](#) used the Simpson and Angus Scale but as the results were skewed they were not graphically displayed. [Adler 1989](#) also presented dichotomised data (not improved/worse) derived from the SAS scale. The results were equivocal for the central acting beta-blocker ICI 118,551 and placebo ($n=10$, 1 RCT, RR 0.22 CI 0.03-1.45).

[Irwin 1988](#) also used and reported continuous measures on the Involuntary Movement and Extrapyramidal Scale (IMEPS). These endpoint data are slightly skewed and are presented in a table, rather than within a graph. The scores for both groups are slightly and, according to the trialists, not significantly different from each other.

2.2 Acceptability and tolerability of treatment

[Kramer 1988](#) and [Irwin 1988](#) mentioned that central action beta-blockers were well tolerated when compared with placebo, and they allowed good compliance with treatment. No participant left the studies early ($n=31$, 2 RCTs, RR not estimable, Risk Difference 0.00 CI -0.15 to 0.15), although the two studies only lasted 48 hours.

2.3 Adverse effects

[Kramer 1988](#) stated no adverse effects occurred in the two groups ($n=20$, 1 RCT, RR not estimable, Risk Difference 0.00 CI -0.17 to 0.17). [Irwin 1988](#) did not address this item.

DISCUSSION

1. Strengths and weaknesses

In this review we attempted to identify evaluative studies that addressed an important and prevalent problem. We found that several researchers and people with akathisia had considered this problem important enough to invest time and energy in designing and conducting randomised studies. These pioneering studies suggest that such research is possible. The weakness of this review is related to limited data.

2. Applicability of findings.

The studies included in this review involved very small numbers of people from a narrow range of cultural backgrounds. Most people had been given a DSM-III diagnosis so we can assume homogeneity of the participants. However, the restriction to DSM-III diagnoses excludes many people seen in routine practice who develop neuroleptic-induced acute akathisia after receiving anti-psychotic medication.

3. COMPARISON 1: CENTRAL ACTING BETA-BLOCKERS versus PLACEBO

3.1 Akathisia

Despite the use of scales very sensitive to change, no study reported significant differences between interventions. [Kramer 1988](#) did not report usable data from the scale used but [Adler 1989](#) and [Irwin 1988](#) presented data. Even if the scale derived data had not been skewed by the definition above (see Methods) there was no difference at all for people allocated propranolol compared with placebo.

3.2 Acceptability and tolerability of treatment

No-one was reported to have left any of the studies early ([Irwin 1988](#), [Kramer 1988](#)). However, the studies were so small and so short in duration that an effect could have been missed, so little importance should be attached to this outcome.

3.3 Adverse effects

It is odd that [Adler 1989](#) and [Irwin 1988](#) did not rate adverse effects. This is unusual even for short studies and some adverse effects would be expected with use of beta-blockers. [Kramer 1988](#) reported no adverse effects in the two groups.

4. Other outcomes

For future study design it would be beneficial for analysis purposes to record other outcomes. For larger studies: quality of life, satisfaction with care, social functioning and cost effectiveness would all be of interest.

5. Sensitivity analyses

No trial focused on people with diagnoses other than schizophrenia, such as mood disorders or other psychiatric diagnoses. It is therefore impossible to assess whether these people would differ in their treatment response.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with neuroleptic-induced acute akathisia
Currently there is no evidence to support the use of central action beta-blockers for people with neuroleptic-induced acute akathisia.. There is also insufficient data on the adverse effects of this practice.

2. For clinicians

Clinicians are left with solely clinical experience to support their practice. If propranolol or similar drugs are to be offered for neuroleptic-induced akathisia, clinicians do have a responsibility to ensure the creation of better data. Allocating treatments within the context of a real-world pragmatic study could help address the remarkable shortfall of data.

3. Managers, policy makers and funders

Managers and policy makers have no data from which to assess if there are any benefits in prescribing central action beta-blockers to people with neuroleptic-induced acute akathisia. Currently data produced in these few controlled trials do not support its use.

Implications for research

1. General

Clear and strict adherence to the CONSORT statement ([Moher 2001](#)) would have resulted in this review being more informative.

2. Specific

Larger, longer, well planned, conducted and reported randomised controlled trials are needed. This review particularly highlights how pioneering researchers can randomise in this area, how compliance can be good, and outcomes of such research be potentially meaningful.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Adler 1989

Methods	Allocation: "randomised", no further details. Blinding: double, no further details. Design: parallel. Duration: 3 days.
Participants	Diagnosis: schizophrenia (N=9), post traumatic stress disorder (N=1), (DSM-III) plus neuroleptic induced akathisia (SAS) minimum score ≥ 1 . N=10. Age: 35-44 years, mean (37.7). Sex: male. History: chronic.
Interventions	1. ICI 118, 551: dose 50 mg/bid. N=6. 2. Placebo. N=4.
Outcomes	Akathisia: (SAS).
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk B - Unclear

Irwin 1988

Methods	Allocation: "random allocation", no further details. Blinding: double, no further details. Duration: 2 days.
Participants	Diagnosis: schizophrenia (DSM-III-R) plus neuroleptic-induced akathisia (IMEPS score 0-6). N=11. Age: mean ~37 years. Sex: male. History: chronically ill.
Interventions	1. Propranolol: dose 80 mg/day. N=6. 2. Placebo. N=5. Fixed doses at the beginning of the study.
Outcomes	Akathisia: (IMEPS). Leaving the study early. Unable to use -

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Irwin 1988 (Continued)

Mental state: (BPRS - no usable data).

Notes Authors contacted for details (17th March 2000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kramer 1988

Methods Allocation: "random allocation".
Blindness: double, no further details.
Design: cross-over.
Duration: 2 days (first phase).

Participants Diagnosis: schizophrenia (DSM-III-R) plus neuroleptic-induced akathisia (ARS score 0-10).
N=20.
Age: mean ~36 years.
Sex: male.
History: not specified.

Interventions 1. Propranolol: dose 60 mg/day. N=10.
2. Placebo. N=10.
Fixed doses at the beginning of the study.

Outcomes Leaving the study early.
Adverse effects.

Unable to use -
Akathisia: (ARS - no usable data).
Use of antiparkinsonian medication.

Notes Authors contacted for details (17th March 2000).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ARS - Akathisia Rating Scale.

DSM-III-R - Diagnostic Statistical Manual, version 3, revised.

IMEPS - Involuntary Movement and Extrapyrimal Scale.

SAS - Simpson and Angus Scale (Hillside/Long Island Jewish Hospital modification).

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adler 1985	Allocation: randomised. Participants: people with psychotic disorder, suffering from neuroleptic-induced akathisia. Interventions: propranolol versus lorazepam, not versus placebo.

Study	Reason for exclusion
Adler 1986	Allocation: randomised. Participants: people with schizophrenia. Interventions: propranolol versus placebo. Outcomes: no usable data.
Adler 1987	Allocation: not randomised, controlled clinical trial.
Adler 1988a	Allocation: not randomised, controlled clinical trial.
Adler 1988b	Allocation: not randomised, controlled clinical trial.
Adler 1990	Allocation: randomised. Participants: people with psychotic disorder, suffering from neuroleptic-induced akathisia. Interventions: propranolol versus metoprolol, not versus placebo.
Adler 1991	Allocation: randomised. Participants: people with schizophrenia. Interventions: d-propranolol (non-central acting beta-blocker) versus placebo.
Adler 1993a	Allocation: not randomised, controlled clinical trial.
Adler 1993b	Allocation: randomised. Participants: people with schizophrenia. Interventions: propranolol versus placebo versus benzotropine. Outcomes: no usable data.
Aoba 1995	Allocation: randomised. Participants: people with schizophrenia. Interventions: carteolol (non-central acting beta-blocker) versus placebo.
Dumon 1992	Allocation: randomised. Interventions: propranolol versus betaxolol, not versus placebo.
Hermesh 1988	Allocation: not randomised, controlled clinical trial.
Kim 1989	Allocation: not randomised, controlled clinical trial.
Reiter 1987	Allocation: not randomised, controlled clinical trial.
Sachdev 1993	Allocation: randomised. Participants: people with schizophrenia. Interventions: propranolol versus placebo versus benzotropine. Outcomes: no usable data.
Wells 1991	Allocation: randomised. Participants: people with schizophrenia. Interventions: nandanol (non-central acting beta-blocker) versus placebo.
Zubenko 1984	Allocation: not randomised, controlled clinical trial.

DATA AND ANALYSES

Comparison 1. CENTRAL ACTION BETA-BLOCKER versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Akathisia: 1. Not remitted	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 not in full remission (100% reduction in symptoms)	1	11	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 not in partial remission (50% reduction in symptoms)	1	11	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.59, 1.83]
2 Akathisia: 2. No change/worse (SAS scale)	1	10	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.03, 1.45]
3 Akathisia: 3. Average score (skewed data)			Other data	No numeric data
3.1 IMEPS			Other data	No numeric data
3.2 SAS			Other data	No numeric data
4 Leaving the study early - for any reason	2	31	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects: Any adverse event	1	20	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 CENTRAL ACTION BETA-BLOCKER versus PLACEBO, Outcome 1 Akathisia: 1. Not remitted.

Analysis 1.2. Comparison 1 CENTRAL ACTION BETA-BLOCKER versus PLACEBO, Outcome 2 Akathisia: 2. No change/worse (SAS scale).

Analysis 1.3. Comparison 1 CENTRAL ACTION BETA-BLOCKER versus PLACEBO, Outcome 3 Akathisia: 3. Average score (skewed data).

Akathisia: 3. Average score (skewed data)				
Study	Interventions	Mean	SD	N
IMEPS				
Irwin 1988	Propranolol	3.5	1.4	6
Irwin 1988	Placebo	3.2	1.9	5
SAS				
Adler 1989	ICI 118,551	0.8	1.8	6
Adler 1989	Placebo	1.7	2.4	4

Analysis 1.4. Comparison 1 CENTRAL ACTION BETA-BLOCKER versus PLACEBO, Outcome 4 Leaving the study early - for any reason.

Analysis 1.5. Comparison 1 CENTRAL ACTION BETA-BLOCKER versus PLACEBO, Outcome 5 Adverse effects: Any adverse event.

WHAT'S NEW

Date	Event	Description
14 April 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2004

Date	Event	Description
5 August 2009	Amended	Contact details updated.
24 April 2008	Amended	Converted to new review format.
4 August 2004	New citation required and conclusions have changed	Substantive amendment

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Karla Soares-Weiser - protocol production, searching and data extraction.

Josué Bacaltchuk - protocol production.

Thomas Barnes - protocol production.

DECLARATIONS OF INTEREST

Thomas Barnes has acted as a consultant and received fees from pharmaceutical companies, such as Astra-Zeneca, Lilly, Novartis and Pfizer. He is currently conducting an investigator-initiated study of tardive dyskinesia in the elderly, comparing treatment with risperidone and amisulpride. This is funded by Sanofi-Synthelabo. He is a member of the faculty of the Lundbeck International Neuroscience Foundation and of the Guideline Development Group for the NICE Schizophrenia Treatment Guideline, published December 2002.

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External sources

- No sources of support supplied

Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia (Review)

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INDEX TERMS**Medical Subject Headings (MeSH)**

Adrenergic beta-Antagonists [*therapeutic use]; Akathisia, Drug-Induced [*drug therapy]; Antipsychotic Agents [adverse effects]; Placebos; Psychotic Disorders [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans