Lithium for schizophrenia (Review)

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[Intervention Review]

Lithium for schizophrenia

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ABSTRACT

Background

Many people with schizophrenia do not achieve a satisfactory treatment response with ordinary antipsychotic drug treatment. In these cases, various add-on medications are used, among them lithium.

Objectives

To review the effects of lithium for the treatment of schizophrenia and schizophrenia-like psychoses.

Search strategy

We searched the Cochrane Schizophrenia Group's register (November 2006). This register is compiled by methodical searches of BIOSIS, CINAHL, Dissertation abstracts, EMBASE, LILACS, MEDLINE, PSYINDEX, PsycINFO, RUSSMED, Sociofile, supplemented with hand searching of relevant journals and numerous conference proceedings. We also contacted pharmaceutical companies and authors of relevant studies to identify further trials and to obtain original patient data.

Selection criteria

We included all randomised controlled trials comparing lithium to antipsychotics or to placebo (or no intervention), whether as sole treatment or as an adjunct to antipsychotic medication for the treatment of schizophrenia and/or schizophrenia-like psychoses.

Data collection and analysis

We extracted data independently. For homogenous dichotomous data we calculated random effects, relative risk (RR), 95% confidence intervals (CI) and, where appropriate, numbers needed to treat (NNT) on an intention-to-treat basis. For continuous data, we calculated weighted mean differences (WMD).

Main results

The update search in 2006 did not detect further studies that met our inclusion criteria. The review thus still includes 20 studies with a total of 611 participants. Most studies were small, of short duration and incompletely reported, but a number of authors were willing to share their data with us. Three studies comparing lithium with placebo as the sole treatment showed no difference in any of the outcomes we analysed. In eight studies comparing lithium with antipsychotic drugs as the sole treatment, more participants in the

lithium group left the studies early (n=270, RR 1.8, CI 1.2 to 2.9, NNT 9, CI 5 to 33). Several of the outcomes relating to these studies suggested that lithium is less effective than antipsychotic drugs, but it was difficult to summarise the data because a variety of rating scales were used in the studies. Eleven studies examined whether the augmentation of antipsychotic drugs with lithium salts is more effective than antipsychotic drugs alone. More participants who received lithium augmentation had a clinically significant response (n=244, RR 0.8, CI 0.7 to 0.96, NNT 8, CI 4 to 33). However, statistical significance became borderline when participants with schizoaffective disorders were excluded in a sensitivity analysis (n=120, RR 0.8, CI 0.6 to 1.0, p=0.07). Furthermore, more participants in the lithium augmentation groups left the studies early (n=320, RR 2.0 CI 1.3 to 3.1, NNT 7, CI 4 to 14), suggesting a lower acceptability of lithium augmentation compared to those on antipsychotics alone. No superior efficacy of lithium augmentation in any specific aspect of the mental state was found. While based on very little data, there were no differences between groups for adverse events.

Authors' conclusions

There is no randomised trial-based evidence that lithium on its own is an effective treatment for people with schizophrenia. The evidence available on augmentation of antipsychotics with lithium is inconclusive, but does justify further, large, simple and well-designed trials. These should concentrate on two target groups: 1) people with no affective symptoms, so that trialists can determine whether lithium has an effect on the core symptoms of schizophrenia, 2) people with schizoaffective disorders for whom lithium is widely used in clinical practice, although there is no evidence to support this use.

PLAIN LANGUAGE SUMMARY

Lithium for schizophrenia

Lithium is a mood-stabilising agent which is also used as an adjunctive treatment to antipsychotics for schizophrenia. The findings in this review show that there is no evidence that lithium on its own is effective for people with schizophrenia or schizoaffective disorder. There is some evidence for the effectiveness of lithium as an adjunctive treatment to antipsychotic drugs, but this result was inconclusive.

BACKGROUND

Despite the introduction of antipsychotic (neuroleptic) medication in the 1950s, there is still a sizeable minority of people with schizophrenia and related conditions that do not have complete remission of symptoms (Schooler 1993). Over the last 40 years a variety of adjunctive treatments have been used to treat schizophrenia (Christison 1991). These are often used in addition to antipsychotics in an attempt to alleviate the symptoms of the disease such as hallucinations and delusional beliefs, although they have also been used instead of antipsychotics. Treatments such as lithium (indicated for bipolar affective disorder), carbamazepine (Leucht 2002), benzodiazepines, beta-blockers (Cheine 2001) and electroconvulsive therapy (Tharyan 2005) have all been used for people whose psychoses did not respond to traditional therapy. The situation has improved somewhat in recent years with the re-introduction of clozapine, which has proven efficacy for those that have not responded to traditional medications (Wahlbeck 1999). Whether the other 'atypical' antipsychotics are more effective for the treatment of those with treatment resistant schizophrenia is unclear (Leucht 1999). However, many individuals with psychoses have sub-optimal responses to treatment, and clinicians are faced

with the choice of changing to alternate types of medication, or augmenting existing neuroleptics with other drugs or treatments.

In this review we examine the role of lithium in the treatment of schizophrenia, schizophrenia-like psychoses and schizoaffective psychoses. Lithium is traditionally used for affective psychoses, especially the acute treatment of mania and for relapse prevention in bipolar affective psychoses. Companion reviews examined carbamazepine (Leucht 2007), valproate (Basan 2003) and benzodiazepines (Volz 2007) as sole or adjunctive treatment for schizophrenia.

OBJECTIVES

To examine whether:

1. Lithium alone is an effective treatment for schizophrenia, schizophrenia-like psychoses and schizoaffective psychoses; and
2. Lithium augmentation of antipsychotic medication is an effective treatment for the same illnesses.

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, we included the trial 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 included these in the final analysis. If there was a substantive difference, we only analysed 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

We included people with schizophrenia and other types of schizophrenia-like psychoses (schizophreniform and schizoaffective disorders). There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994).

Types of interventions

1. Lithium alone: any dose.
2. Placebo (or no intervention).
3. Lithium in combination with any antipsychotic treatment: any dose.
4. Placebo (or no intervention) in combination with any antipsychotic treatment.
5. Antipsychotics alone: any dose.

Types of outcome measures

We grouped all outcomes by short term (up to 12 weeks), medium term (13 to 26 weeks) and long term (over 26 weeks).

Primary outcomes

1. Leaving the study early
2. Clinical response
 - 2.1 No clinically significant response - as defined by each of the studies
3. Clinical response
 - 3.1 Relapse - as defined by each of the studies

Secondary outcomes

1. Service utilisation
 - 1.1 Hospital admission
 - 1.2 Days in hospital

- 1.3 Change in hospital status
2. Clinical response
 - 2.1 No clinically significant improvement of global state
 - 2.2 Average score/change in global state
 - 2.3 No clinically significant improvement in mental state - as defined by each of the studies
 - 2.4 Average score/change in mental state
 - 2.5 No clinically significant response on depressive symptoms - as defined by each of the studies
 - 2.6 Average score/change in depressive symptoms
 - 2.7 No clinically significant response on manic symptoms - as defined by each of the studies
 - 2.8 Average score/change in manic symptoms
 - 2.9 No clinically significant response on negative symptoms - as defined by each of the studies
 - 2.10 Average score/change in negative symptoms
 - 2.11 No clinically significant response on positive symptoms - as defined by each of the studies
 - 2.12 Average score/change in positive symptoms
 - 2.13 Additional drug use
 - 2.13.1 Antipsychotics
 - 2.13.2 Benzodiazepines
3. Behaviour:
 - 3.1 General behaviour
 - 3.2 Specific behaviours
 - 3.2.1 Social functioning
 - 3.2.2 Employment status during trial (employed / unemployed)
 - 3.2.3 Occurrence of violent incidents (to self, others, or property)
4. Adverse events
 - 4.1 General adverse events
 - 4.2 Specific adverse events
 - 4.2.1 Allergic reactions
 - 4.2.2 Blood dyscrasia such as agranulocytosis
 - 4.2.3 Central nervous system (ataxia, nystagmus, drowsiness, fits, diplopia, tremor)
 - 4.2.4 Death (suicide and non-suicide deaths)
 - 4.2.5 Gastrointestinal (nausea, vomiting, diarrhoea)
 - 4.2.6 Kidney dysfunction
 - 4.2.7 Movement disorders (extrapyramidal side effects including neuroleptic malignant syndrome)
 - 4.2.8 Thyroid dysfunction (goitre, thyroid hypofunction)
5. Economic (cost of care)

Search methods for identification of studies

Electronic searches

- 1 Update search
We searched the Cochrane Schizophrenia Group Trials Register in November 2006 using the phrase:

[((lithium* or lithicarb* or eskalith* or lithobid* or lithane* or cibalith-s* or quilonum* or hypnorex*) in title, abstract and index fields in REFERENCE) OR (lithium* in interventions field in STUDY)]. This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

2 Previous electronic searches

In March 2002 we also searched the Cochrane Schizophrenia Group's Register with the same phrase.

Searching other resources

1. Reference lists

We searched all references of articles selected for inclusion for further relevant trials.

2. Pharmaceutical companies

We contacted companies performing trials with lithium directly to obtain data on unpublished trials.

3 Personal contact

We contacted the first author of each included study for information regarding unpublished trials.

Data collection and analysis

[For definitions of terms used in this, and other sections, please refer to the Glossary]

1. Selection of trials

Material downloaded from electronic sources included details of author, institution or journal of publication.

The principal reviewer (SL) inspected all reports. These were then re-inspected by JM in order to ensure reliable selection. We resolved any disagreement by discussion, and where there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained, we decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and these trials were added to the list of those awaiting assessment.

2. Quality assessment

We assessed the methodological quality of the trials included in this review using the criteria described in the Cochrane Handbook (Higgins 2005). These criteria are based on the evidence of a strong relationship among the potential for bias in the results and the allocation concealment (Schulz 1995) and is defined as below:

- A. Low risk of bias (adequate allocation concealment)
- B. Moderate risk of bias (some doubt about the results)
- C. High risk of bias (inadequate allocation concealment)

For the purpose of the analysis in this review, we included trials if they meet the criteria A or B at the Handbook.

3. Data extraction

We (SL and JM) independently extracted the data from included studies. We discussed any disagreement, documented the decisions and, if necessary, contacted the authors of the studies for clarification.

We documented justification for excluding references from the review.

4. Data management

4.1 Intention to treat

For studies that did not specify the reasons for people leaving the study early (dropped out), we assumed that these people had no change in the clinical outcome variables. Wahlbeck 2001 highlighted the problem of high drop-out rates in randomised trials of drug treatments for schizophrenia. Since there is no evidence on the degree of attrition which makes a reasonable analysis of the data possible, we included all trials in the main analysis. However we used a sensitivity analysis to test whether the exclusion of trials with drop-out rates higher than 50% significantly changed the results of the primary outcome parameters. When insufficient data were provided to identify the original group size (prior to drop outs), we contacted the authors and allocated the trials to the 'awaiting assessment' list.

4.2 Crossover design

We expected that some trials would use a crossover design. In order to exclude the potential additive effect in the second or more stages on these trials, we only analysed data from the first stage.

4.3 Data types

We assessed outcomes using continuous (for example changes on a behaviour scale), categorical (for example, one of three categories on a behaviour scale, such as 'little change', 'moderate change' or 'much change') or dichotomous measures (for example, either 'no important changes' or 'important changes' in a person's behaviour). Currently RevMan does not support categorical data so they could not be analysed as such.

4.3.1 Dichotomous data: Where possible efforts we converted outcome measures to dichotomous data. This may be done by identifying cut off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. If the authors of a study had used a predefined cut off point for determining clinical effectiveness we used this where appropriate. Otherwise we generally assumed that a 50% reduction of a scale (e.g. the Brief Psychiatric Rating Scale - Overall 1962) or a rating of 'at least much improved' according to the Clinical Global Impression Scale (Guy 1976) could be considered as a clinically significant response.

For dichotomous outcomes, we estimated a relative risk (RR) with the 95% confidence interval (CI) based on a fixed effects model in case of homogeneous outcomes and based on a random effects model in the case of heterogeneous outcomes. When overall results were significant we calculated the Number Needed to Treat (NNT) and/or the Number Needed to Harm (NNH) as the inverse of the risk reduction. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as relative risks by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. However we inspected data to see if an analysis using a Mantel-Haenszel odds ratio and a random effects model made a

substantive difference.

4.3.2 Continuous data

4.3.2.1 Normal distribution: Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data the following standards were applied to data derived from continuous measures of endpoint ('state' data). The criteria were used before inclusion:

When a scale started from zero, the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean is 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.

When continuous data are presented on a scale which includes a possibility of negative values (such as change on a scale) it is impossible to tell whether data are non-normally distributed (skewed) or not. It is thus preferable to use scale end point data, which typically cannot have negative values. If end point data were not available, we chose to use change data, because the statistics used in MetaView are rather robust towards skewness. If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skewness is present if $2SD > (S - S_{min})$, where S is the mean score and S_{min} is the minimum score.

4.3.2.2 Intention-to-treat versus completer analyses: We assumed that for incomplete continuous data intention-to-treat analyses would be impossible. In these cases we analysed data as they were presented in the original publications.

4.3.2.3 Summary statistic: for continuous outcomes, we estimated a weighted mean difference (WMD) between groups. Again, we used a fixed effects model for homogeneous outcomes and a random effects model for heterogeneous outcomes. Whenever possible we took the opportunity to make direct comparisons between trials that used the same measurement instrument to quantify specific outcomes. Where continuous data was presented from different scales rating the same effect, we presented both sets of data and inspected the general direction of effect.

4.3.2.4 Rating scales: a wide range of instruments is available to measure mental health outcomes. These instruments vary in quality and many are not valid, or even ad hoc. For outcome instruments some minimum standards have to be set. We only included continuous data from rating scales if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000), the instrument was either a self report or completed by an independent rater or relative (not the therapist), and the instrument could be considered a global assessment of an area of functioning. However, as it was expected that therapists would frequently also be the rater, we commented on such data as 'prone to bias'.

4.4 Data display

We entered data into RevMan in such a way that the area to the left of the line of no effect indicated a favourable outcome for lithium

alone or lithium augmentation.

4.5 Cluster trials

Studies increasingly employ '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 unduly narrow and statistical significance overestimated 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 clustering was not accounted for in primary studies, we presented data in a table, with an asterisk (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies, to seek intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, then we presented these 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 were 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 which allowed for clustering.

5. Heterogeneity

After considering the likelihood of clinical heterogeneity based on comparisons of the included studies, we visually inspected graphs to investigate the possibility of statistical heterogeneity. We calculated the value of I-squared to provide an estimate of the percentage of variability due to heterogeneity rather than chance alone. We interpreted an I-squared value of 50% or greater as indicating high levels of heterogeneity (Higgins 2003). When the results were statistically significantly heterogeneous, we sought reasons for the heterogeneity and if these were identified we excluded these studies. If reasons were not found we combined the studies using a random effects model.

6. Publication bias

We entered data from all included trials into a funnel graph (trial effect versus trial size or 'precision') in an attempt to investigate the likelihood of overt publication bias. A formal test of funnel plot asymmetry (suggesting potential publication bias) was undertaken, where appropriate (Egger 1997). We set significance levels of $p < 0.1$ a priori to accept the presence of asymmetry.

7. Sensitivity analysis

We examined whether the exclusion of schizoaffective patients led to a significant change of the primary outcomes by carrying out a sensitivity analysis. We also used a sensitivity analysis to test

whether the exclusion of trials with attrition rates of higher than 50% significantly changed the results of the primary outcome parameters.

8. Post-hoc amendment to the protocol

For a number of studies we were able to examine individual patient data. This enabled us to dichotomise many scale derived data. As explained above (see 4.3.1), a clinical rating of 'at least much improved' or a 50% reduction of a rating scale was used as a cut-off for a clinically significant response whenever the original authors did not present a definition of their own. However, since there is an uncertainty about which cut-off is best, we also analysed the data using a relatively low threshold (at least 20% reduction) and an intermediate threshold (at least 35% reduction) as in the review on carbamazepine (Leucht 2007).

Furthermore, when original patient data were available, we used the Kolmogorov-Smirnov test to assess normal distribution (SPSS 2001). Therefore, continuous data could sometimes be used for meta-analytic calculations, although these data did not meet the criteria stipulated in 4.3.2.1 above.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Please also see tables of included and excluded studies.

1. Excluded studies

The main reasons for exclusion were that studies did not (or did not adequately) randomise (n=34), did not study participants with schizophrenia (n=5), did not include a placebo or no-intervention group (n=5) or did not present any data which could be used for meta-analysis (n=4). We contacted the authors of the latter four studies (Carman 1981, Gerlach 1975, Growe 1979, Jus 1978) but were unable to obtain further data.

2. Studies awaiting assessment

One study is currently awaiting assessment (Kamisada 1988).

3. Included studies

We identified 20 studies for inclusion in this review.

3.1 Study designs

Most studies used a parallel group design, but Garver 1983, Simpson 1976, Small 1975, Small 2001 and Terao 1995 were cross-over studies. Of the latter, only the results of the first phase were used, as described in the methods section.

3.2 Length of trials

Mattes 1984 was the longest study with a duration of one year, Small 1975, Small 2001 and Terao 1995 were medium-term studies with a duration of 16 weeks and 19 weeks, respectively. All the others were in the 'short-term' category, lasting between 3 and

8 weeks within a single treatment phase. Only Mattes 1984 and Schulz 1999 were undertaken in the community; all others were carried out with people who were in hospital at the beginning of the trial.

3.3 Participants

The 20 studies included a total of 611 people. The number of people in each study was low and ranged between 10 and 78. Most participants had schizophrenia but there were also some people with schizoaffective disorder (n=196, of these 155 with schizomania), schizophreniform disorder (n=22), atypical psychoses (n=7), delusional disorder (n=5) and 29 participants where the diagnosis was not clearly indicated. Diagnostic criteria varied to a considerable extent, because the studies were carried out over a long period of time, but most of the studies used some sort of standard diagnostic criteria. Several studies examined specific groups of participants. Biederman 1979 studied participants with "motor hyperactivity" or elevated mood, Hogarty 1995 examined participants with "persistent distress and/or anxiety", Simpson 1976 analysed a chronic group with tardive dyskinesia and Brockington 1978, Collins 1991, Hogarty 1995, Small 1975, Small 2001, Schulz 1999, Simhandl 1996 and Wilson 1993 included only treatment resistant participants according to a variety of criteria.

3.4 Interventions

Three studies compared lithium as a sole agent with placebo as a sole agent (Garver 1983, Johnstone 1988, Simpson 1976); eight studies compared lithium as a sole agent with antipsychotics (Braden 1982, Brockington 1978, Dube 1981, Johnson 1971, Johnstone 1988, Mattes 1984, Prien 1972, Shopsin 1971) and eleven studies compared lithium added to antipsychotic drugs versus placebo added to antipsychotic drugs (Biederman 1979, Collins 1991, Hogarty 1995, Huang 1984, Johnstone 1988, Schulz 1999, Simhandl 1996, Small 1975, Small 2001, Terao 1995, Wilson 1993). Johnstone 1988 provided data for all three comparisons.

The lithium dose was commonly adjusted to be within a therapeutic blood-level range. All but one study which compared lithium as a sole agent with antipsychotics used chlorpromazine as a comparator. The exception was the study by Mattes 1984 which used fluphenazine. The range of chlorpromazine or its equivalent daily doses in the other studies was 300-2000 mg. Of the eleven studies which examined lithium as an adjunct to antipsychotics, three used haloperidol as an antipsychotic (Biederman 1979, Huang 1984, Wilson 1993), two used fluphenazine (Hogarty 1995, Schulz 1999), one used pimozide (Johnstone 1988), one used clozapine (Small 2001). In the other four studies the therapists could choose any antipsychotic drug (Collins 1991, Simhandl 1996, Small 1975, Terao 1995).

3.5 Outcomes

A variety of scales were used to assess clinical response and adverse events. The reporting on efficacy and on side-effects was incomplete in the original publications. However, we were able to substantially improve this situation by contacting the authors, many

of whom agreed to share their data with us.

3.5.1 Outcome scales: details of scales that provided usable data are shown below. We have given reasons for exclusion of data provided by other instruments under 'outcomes' in the 'included studies' table.

3.5.1.1 Global functioning

Clinical Global Impression - CGI ([Guy 1976](#))

A rating instrument commonly used in studies on schizophrenia that enables clinicians to quantify severity of illness and overall clinical improvement during therapy. A seven-point scoring system is usually used with low scores indicating decreased severity and/or greater recovery.

3.5.1.2 Mental state

Brief Psychiatric Rating Scale - BPRS ([Overall 1962](#))

A brief rating scale used to assess the severity of a range of psychiatric symptoms, including psychotic symptoms. The scale has 18 items, and each item can be defined on a seven-point scale varying from 'not present' (1) to 'extremely severe' (7). Scoring goes from 18 -126.

Bech-Rafaelsen Rating Scale for Mania - BRRS ([Bech 1978](#))

This rating scale has 11 items addressing symptoms of mania. The single items can all be defined on a 5 point scale from 0 (normal) to 4 (extreme). A total score is calculated which goes from 0 to 44. New Haven Schizophrenia Index - NH ([Astrachan 1972](#))

A symptom checklist for the evaluation of schizophrenic pathology.

Manchester Scale - MS ([Krawiecka 1977](#))

A brief rating scale used to assess the severity of symptoms associated with schizophrenia and comprising positive, negative and depressive symptoms. Each item can be defined on a five point scale varying from 'not present' (0) to 'severe' (4).

Structured Clinical Interview - SCI ([Burdock 1968](#))

A scale to assess the mental state of those with psychiatric disorders. Higher scores indicate more symptoms.

Hamilton Rating Scale for Depression - HDRS ([Hamilton 1960](#))

The instrument is designed to be used only on patients already diagnosed as suffering from affective disorder of depressive type. It is used for quantifying the results of an interview, and its value depends entirely on the skill of the interviewer in eliciting the necessary information. The scale contains 17 variables measured on either a five-point or a three-point rating scale, the latter being used where quantification of the variable is either difficult or impossible. Among the variables are: depressed mood, suicide, work and loss of interest, retardation, agitation, gastro-intestinal symptoms, general somatic symptoms, hypochondriasis, loss of insight, and loss of weight. It is useful to have two raters independently scoring a patient at the same interview. The scores of the patient are obtained by summing the scores of the two physicians.

Montgomery-Asberg Depression Rating Scale - MADRS ([Montgomery 1979](#))

A 10-item checklist to measure the overall severity of depression symptoms. Items are rated on a scale of 0-6 with anchors at 2-

point intervals. Higher scores indicate more symptoms. Scoring ranges from 0 to 60.

Scale for the Assessment of Negative Symptoms - SANS ([Andreasen 1989](#)).

This six-point scale gives a global rating of the following negative symptoms: alogia, affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. Higher scores indicate more symptoms.

3.5.1.3 Adverse events

Abnormal Involuntary Movement Scale - AIMS ([NIMH 1970](#))

The Abnormal Involuntary Movement Scale has been used to assess tardive dyskinesia, a long-term, drug-induced movement disorder. However, using this scale in short-term trials may also be helpful to assess some rapidly occurring abnormal movement disorders such as tremor.

Simpson Angus Scale - SAS ([Simpson 1970](#))

This 10-item scale, with a scoring system of 0-4 for each item, measures drug-induced parkinsonism; a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

Barnes Akathisia Scale - BAS ([Barnes 1989](#))

Akathisia is a drug-induced movement disorder. The scale comprises items rating the observable, restless movements that characterise akathisia, the subjective awareness of restlessness and any distress associated with the condition. These items are rated from zero (normal) to three (severe). In addition, there is an item for rating the global severity which starts from zero (absent) to five (severe). A low score indicates low levels of akathisia.

3.5.1.4 Missing outcomes

No data are available for many important outcomes such as aggression, length of hospital stay, ability to work or quality of life.

Risk of bias in included studies

1. Randomisation

All included studies were stated to be randomised. [Brockington 1978](#), [Johnson 1971](#), [Mattes 1984](#), [Small 2001](#), [Terao 1995](#) and [Wilson 1993](#) used lists of random numbers for allocating the participants. [Simpson 1976](#) used a coin-toss method. These studies were classified to the 'A' category for randomisation concealment. All others studies were allocated to the 'B' quality score.

2. Blinding

All but two studies were double-blind. [Collins 1991](#) was randomised but open unblinded, and in [Simpson 1976](#) only the raters were blinded. [Prien 1972](#), [Terao 1995](#) and [Wilson 1993](#) used identical capsules for blinding. In [Shopsin 1971](#) and [Schulz 1999](#) the raters and the participants, but not the therapists, were blind to medication. The other studies did not describe their blinding method.

3. Follow up

Although all studies indicated the numbers of participants who left the study before its completion, the reasons for leaving the

studies early were not consistently indicated. Thus we could only analyse the specific reasons for leaving the studies early in a limited number of studies.

4. Data reporting

Incomplete data were reported. Standard deviations and means were often missing and only p-values were indicated. However many authors sent us original patient data which substantially improved the quality of the review.

Effects of interventions

The search

The initial search in 2002 identified 91 citations of which 65 appeared relevant and the full studies were inspected. The update search in 2006 yielded 56 further citations of which four were potentially relevant. We contacted the authors of these studies; three had to be excluded because they were not appropriately randomised (Chen 2001, Gao 2002, Wang 1995). No information could be obtained on the fourth study (Kamisada 1988). We therefore listed it among those studies awaiting assessment. Therefore, the update of the review still contains twenty seven reports relating to twenty studies.

1. COMPARISON 1. LITHIUM versus PLACEBO AS SOLE TREATMENT

Three studies fell into this category (Garver 1983, Johnstone 1988, Simpson 1976).

1.1 Leaving the study early

In the studies by Simpson 1976 and Garver 1983 no patients left the studies before the end so that only the data from Johnstone 1988 had an impact on the statistical analysis. There was no significant difference between groups (n=65, RR 1.1, CI 0.3 to 4.4).

1.2 No clinically significant response as defined by the authors

The studies by Garver 1983 and Johnstone 1988 both provided data for the calculation of the outcome no clinically significant response defined as a less than 50% reduction of the baseline score on the New Haven Schizophrenia Index or on the Manchester Scale. No significant difference between lithium and placebo as sole treatments was found (n=54, RR 1.2, CI 0.7 to 1.8).

1.3 Mental state

1.3.1 General response/non-response according to two scores

In Garver 1983 no significant differences were found in outcomes in terms of reduction on the New Haven Schizophrenia Index (<20% reduction, n=13, RR 1.2, CI 0.6 to 2.3; <35% reduction, n=13, RR 1.2, CI 0.6 to 2.3; <50% reduction, n=13, RR 1.2, CI 0.6 to 2.3). The same applies to Johnstone 1988 for reductions in the Manchester Scale (<20% reduction, n=39, RR 1.2, CI 0.5 to 3.1; <35% reduction, n=39, RR 1.2, CI 0.6 to 2.3; <50% reduction, n=39, RR 1.1, CI 0.6 to 2.1).

1.3.2 General - average global scores at endpoint

In Johnstone 1988 the mean Manchester Scale scores at endpoint were similar in both groups (n=39, WMD 0.0, CI -2.9 to 2.9).

The mean New Haven Schizophrenia Index scores in Garver 1983 were skewed (see 'other data table').

1.3.3 Specific - depression, mania, negative symptoms, positive symptoms

Only Johnstone 1988 provided usable data on depression, manic symptoms, negative symptoms and positive symptoms. No significant differences in terms of any level of reduction of these symptoms were found.

1.4 Adverse events - movement disorders

Johnstone 1988 presented scale derived data on extrapyramidal side-effects in general and on tardive dyskinesia which were skewed and therefore we only presented these in the 'other data table'. Johnstone 1988 reported no significant differences between groups.

1.5 Missing outcomes

No information about any of the other outcomes which were listed in the method section could be extracted.

1.6 Publication bias

Funnel-plots revealed no obvious publication bias, but this was hampered by the small number of trials which were available for the plot.

2. COMPARISON 2. LITHIUM versus ANTIPSYCHOTICS AS SOLE TREATMENT

Eight studies fell into this category (Braden 1982, Brockington 1978, Dube 1981, Johnson 1971, Johnstone 1988, Mattes 1984, Prien 1972, Shopsin 1971).

2.1 Leaving the study early

Significantly more participants who received lithium as a sole treatment left the studies early (n=270, RR 1.8, CI 1.2 to 2.9, NNT 9, CI 5 to 33). Only four studies, however reported the reasons (Prién 1972, Shopsin 1971, Mattes 1984, Dube 1981). Combining the results of these studies it appears that lack of efficacy (n=178, RR 3.0, CI 1.2 to 7.8, NNT 10, CI 5 to 50) rather than poor tolerability (n=178, RR 1.2, CI 0.1 to 19.2) led to the attrition.

2.2 No clinically important response as defined by the authors

Three studies provided dichotomised data on clinically significant response. Brockington 1978 and Johnson 1971 indicated the numbers of patients who were less than much improved and Johnstone 1988 the number of participants with less than 50% Manchester Scale reduction. Heterogeneous data showed no difference between lithium and antipsychotic drugs (n=80, RR 1.3, CI 0.8 to 2.2).

2.3 Global state

2.3.1 Not improved or worse according to the Clinical Global Impression Scale (CGI)

Brockington 1978 and Johnson 1971 presented data on the number of patients with no improvement of their global state according to the Global Clinical Impression (CGI). There was no significant difference between lithium and antipsychotic drugs (n=36, RR 2.7, CI 0.1 to 135).

2.3.2 Relapse

Only [Mattes 1984](#) reported relapse at one year. More participants who were treated with lithium relapsed (6 out of 7) compared to 1 out of 7 of participants taking an antipsychotic. This result did not reach statistical significance (n=14, RR 6.0, CI 0.95 to 37.8, p=0.06).

2.4 Mental state - General

2.4.1 Less than 20%, 35% or 50% reduction of the Manchester Scale

[Johnstone 1988](#) was the only study which allowed an analysis of dichotomised data derived from the Manchester Scale. More participants in the lithium group than in the pimozide group achieved a less than 20% (n=44, RR 3.8, CI 0.9 to 16.4, p=0.07), 35% (n=44, RR 2.4, CI 1.0 to 5.8, NNT 3, CI 2 to 33) or 50% reduction (n=44, RR 2.2, CI 1.0 to 4.8, p=0.05) of their initial score in this scale.

2.4.2 Mean BPRS at endpoint

Homogeneous results of three trials ([Dube 1981](#), [Johnson 1971](#), [Shopsin 1971](#)) showed a significant superiority of antipsychotic drugs in this regard (n=92, WMD 10.3, CI 6.6 to 14.0). The standard deviations from the study by [Dube 1981](#) and [Johnson 1971](#) were calculated from exact p-values in these publications. Although the data might be skewed according to the criteria stipulated in the methods section, our means of analysing it might justify us deviating from this. Furthermore, both studies used parametric tests in their analyses and [Dube 1981](#) confirmed by e-mail that the data were normally distributed.

2.4.3 Mean MS at endpoint

[Johnstone 1988](#) used the Manchester Scale and also found a significant superiority of antipsychotic drugs (n=44, WMD 3.0, CI 0.4 to 5.6). Original patient data were available for this analysis, and these appeared to be normally distributed.

2.4.4 Mean SCI at endpoint

[Johnson 1971](#) also used the SCI for the evaluation of the mental state and found no significant difference between groups (n=11, WMD -2.0, CI -81.3 to 77.3).

2.5 Mental state - Specific

Only [Johnstone 1988](#) provided data for the analysis of specific aspects of the mental state. They reported on depressive, manic, negative and positive symptoms.

2.5.1 Depressive symptoms

No significant differences were found between lithium and pimozide in terms of a reduction on the Montgomery-Asberg Depression Rating Scale of less than 20% (n=44, RR 1.8, CI 0.7 to 4.5), 35% (n=44, RR 1.6, CI 0.7 to 3.4) and 50% (n=44, RR 1.5, CI 0.8 to 3.0).

2.5.2 Manic symptoms

No significant differences were found between lithium and pimozide in terms of a reduction on the Bech-Rafaelsen-Mania-Scale of less than 20% (n=44, RR 1.3, CI 0.6 to 2.9), 35% (n=44, RR 1.4, CI 0.8 to 2.5) and 50% (n=44, RR 1.6, CI 0.96 to 2.8, p=0.07), although in this last comparison statistical significance

became borderline.

2.5.3 Negative symptoms

Lithium was significantly less effective than pimozide in terms of a reduction in the negative symptoms sub score of the Manchester Scale of less than 20% (n=44, RR 14.2, CI 2.0 to 100, NNT 2, CI 1 to 3), 35% (n=44, RR 7.7, CI 2.0 to 29.8, NNT 2, CI 1 to 3) and 50% (n=44, RR 7.7, CI 2.0 to 29.8, NNT 2, CI 1 to 3).

2.5.4 Positive symptoms

Lithium was significantly less effective than pimozide in terms of a reduction in the positive sub score on the Manchester Scale of less than 20% (n=44, RR 11.0, CI 1.5 to 78.4, NNT 2, CI 1.5 to 5), 35% (n=44, RR 4.4, CI 1.4 to 13.4, NNT 2, CI 1 to 5) and 50% (n=44, RR 4.4, CI 1.4 to 13.4, NNT 2, CI 1 to 5).

2.6 Adverse events

2.6.1 Anticholinergic adverse events

[Prien 1972](#) presented data on blurred vision, dry mouth and constipation. No significant differences between groups were found.

2.6.2 Central nervous system

Only two studies ([Prien 1972](#), [Shopsin 1971](#)) reported data on various adverse events relating to the central nervous system (ataxia, dizziness, hyperactive reflexes, muscle weakness, slurred speech, somnolence and toxic confusion). Somnolence was significantly more frequent in the antipsychotics group (n=83, RR 0.2, CI 0.04 to 0.73, NNH 4, CI 3 to 10) and toxic confusion was more frequent in the lithium group (n=104, RR 9.3, CI 1.2 to 70.6, NNH 7, CI 4 to 17). The other adverse events occurred with similar frequency in both groups.

2.6.3 Dermatologic

In the study by [Prien 1972](#) no significant difference in the occurrence of pruritus was found (n=83, RR 0.4, CI 0.02 to 9.8).

2.6.4 Gastrointestinal adverse events

Again only [Prien 1972](#) presented data. There were no significant differences between groups in terms of dehydration (n=83, RR 3.7, CI 0.2 to 88.5), nausea (n=83, RR 0.6, CI 0.1 to 3.2) and vomiting (n=83, RR 0.8, CI 0.2 to 4.7).

2.6.5 Movement disorder

In the two trials which presented dichotomous data on movement disorder ([Prien 1972](#), [Shopsin 1971](#)) no significant differences were found in terms of parkinsonism (n=83, RR 0.3, CI 0.01 to 5.0), tremor (n=83, RR 2.2, CI 0.7 to 6.9) or use of antiparkinson medication (n=21, RR 0.1, CI 0.01 to 1.7). [Johnstone 1988](#) presented scale derived data about tardive dyskinesia which were skewed (see 'other data table').

2.7 Laboratory abnormalities

Only [Shopsin 1971](#) reported data on laboratory abnormalities. More participants in the antipsychotic group had a decreased white blood cell count which was of borderline statistical significance (n=21, RR 0.1, CI 0.0 to 1.1, p=0.06), whereas more participants in the lithium group had an increased white blood cell count (n=21, RR 17.4, CI 1.1 to 265.4, NNH 1, CI 1 to 2). No significant differences in terms of increased uric acid blood level (n=21, RR 6.4, CI 0.4 to 110.7) or proteinuria (n=21, RR 4.6, CI 0.3 to

85.3) were found.

2.8 Missing outcomes

No data were found for 'service' outcomes such as 'duration of hospital stay'. There were no data on satisfaction with treatment or costs nor was there usable information about specific aspects of mental state such as aggression, positive symptoms, negative symptoms or mood.

2.9 Publication bias

Funnel-plots revealed no obvious publication bias, but this was hampered by the small number of trials which were available for the plot.

3. COMPARISON 3. LITHIUM versus PLACEBO AS AN ADJUNCT TO ANTIPSYCHOTIC DRUGS

Ten studies came under this category (Biederman 1979, Collins 1991, Hogarty 1995, Huang 1984, Johnstone 1988, Schulz 1999, Simhandl 1996, Small 1975, Small 2001, Terao 1995).

3.1 Leaving the study early

All ten studies contributed to the outcome of number leaving the study early. Significantly more participants treated with lithium augmentation left the studies early than participants who received antipsychotics alone (n=320, RR 2.0 CI 1.3 to 3.1, NNT 7, CI 4 to 14). Only Biederman 1979 reported on 'leaving early due to adverse events'. There was no significant difference between groups (n=39, RR 4.3, CI 0.2 to 84.5).

3.2 No clinically significant response as defined by the authors

According to the data from eight studies there were more responders in the lithium augmentation group than in the group which received antipsychotic drugs alone (n=244, RR 0.8, CI 0.7 to 0.96, NNT 8, CI 4 to 33).

3.3 Global state

3.3.1 Not improved or worse according to the Clinical Global Impression Scale

Significantly more participants who received lithium augmentation than those who received placebo in addition to antipsychotics had an improvement of their global state according to the Clinical Global Impression Scale in four trials (n=115, RR 0.6, CI 0.4 to 0.9, NNT 5, CI 3 to 20).

3.3.2 Relapse

Only Hogarty 1995 reported relapse rates; no significant differences between groups were found (n=29, RR 0.2, CI 0.01 to 4.8).

3.4 Mental state - general

3.4.1 Less than 20%, 35% or 50% reduction of the BPRS total score

No significant differences in terms of a less than 20% BPRS reduction were found (n=131, RR 0.9, CI 0.7 to 1.2), but more participants who received lithium augmentation had a 35% (n=131, RR 0.8, CI 0.6 to 1.0, p=0.05) and a 50% (n=131, RR 0.8, CI 0.7 to 0.9, NNT 5, CI 3 to 14) reduction of this score.

3.4.2 Less than 20%, 35% or 50% reduction of the MS total score

Johnstone 1988 used the Manchester Scale for the evaluation of the general mental state. No significant differences between groups

were found in terms of a reduction of the baseline MS score of less than 20% (n=45, RR 2.1, CI 0.4 to 10.3), 35% (n=45, RR 1.3, CI 0.5 to 3.5) or 50% (n=45, RR 1.1, CI 0.4 to 2.8).

3.4.3 Mean BPRS total score at endpoint

Four studies presented usable data on the mean BPRS at endpoint. Although all studies showed a trend in favour of lithium augmentation, the pooled mean difference did not reveal a statistically significant superiority (n=102, WMD -3.3, CI -7.1 to 0.6). Individual patient data were available for Terao 1995 which appeared to be normally distributed.

3.4.4 Mean MS total score at endpoint

In Johnstone 1988 the mean MS total score at endpoint was similar in both groups (n=45, WMD 7.0, CI -1.5 to 2.9). Again individual patient data were available which seemed to be normally distributed.

3.5 Mental state - specific

3.5.1 Depressive symptoms

Johnstone 1988 used the Montgomery Asberg Depression Scale to monitor depression and found no differences in terms of participants who had a reduction of less than 20% (n=45, RR 1.1, CI 0.4 to 3.1), 35% (n=45, RR 1.1, CI 0.4 to 2.5) or 50% (n=45, RR 0.9, CI 0.4 to 2.1) of their baseline score. Wilson 1993 used the depression/anxiety sub score of the BPRS and found no differences in terms of participants who had a reduction of less than 20% (n=22, RR 1.0, CI 0.4 to 2.9), 35% (n=22, RR 0.8, CI 0.3 to 2.1) or 50% (n=22, RR 0.8, CI 0.3 to 2.1) of their baseline score. For Johnstone 1988 it was possible to analyse the mean Montgomery Asberg Depression Scale score at endpoint, as well. There was no important difference between groups (n=45, WMD -0.3, CI -1.6 to 1.0). Using the Hamilton Depression Scale, Schulz 1999 found no significant differences in mean endpoint scores between groups (n=16, WMD 3.4, CI -7.7 to 14.5).

3.5.2 Manic symptoms

Only Johnstone 1988 provided usable data and found no significant differences in terms of reduction of the Bech-Rafaelsen-Scale for Mania of less than 20% (n=45, RR 0.9, CI 0.4 to 2.3), 35% (n=45, RR 0.8, CI 0.4 to 1.7) or 50% (n=45, RR 0.8, CI 0.4 to 1.7).

3.5.3 Negative symptoms

Three studies (Simhandl 1996, Terao 1995, Wilson 1993) used the SANS and showed no significant differences in terms of a reduction on this scale of less than 20% (n=70, RR 0.7, CI 0.4 to 1.1), 35% (n=70, RR 0.9, CI 0.6 to 1.3) or 50% (n=70, RR 1.0, CI 0.7 to 1.3). Johnstone 1988 used the negative symptoms score of the Manchester scale. Again no significant differences were found in terms of a reduction on this scale of less than 20% (n=45, RR 2.1, CI 0.2 to 21.5), 35% (n=45, RR 1.1, CI 0.2 to 6.8) or 50% (n=45, RR 1.1, CI 0.2 to 6.8). Finally, Small 2001 used the negative symptoms score of the PANSS and revealed no significant differences in terms of a reduction on this scale of less than 20% (n=20, RR 1.3, CI 0.7 to 2.4), 35% (n=20, RR 1.0, CI 0.8 to 1.3)

or 50% (n=20, RR 0.9, CI 0.7 to 1.1).

For several studies it was possible to analyse mean scores of rating scales for negative symptoms, as well. Two studies (Schulz 1999, Wilson 1993) used the negative symptom sub score of the BPRS and found no significant difference between groups (n=61, WMD 0.6, CI -1.1 to 2.3). Johnstone 1988 provided data about the negative symptom sub score of the MS and found no significant difference (n=45, RR 0.3, CI -0.3 to 0.9). Small 2001 used the negative symptoms sub score of the PANSS and found a similar result (n=20, WMD 1.0, CI -3.4 to 5.4). Finally, Simhandl 1996 and Terao 1995 used the SANS. On combining the results of both trials, a statistically significant superiority of lithium augmentation was found (n=41, WMD -4.5, CI -8.8 to -0.2, p=0.04).

3.5.4 Positive symptoms

Again, a variety of scales was used and no significant differences between groups were found. Simhandl 1996 and Wilson 1993 used the positive symptoms sub score of the BPRS and showed no significant differences in terms of a reduction of this scale of less than 20% (n=49, RR 0.6, CI 0.2 to 0.3), 35% (n=49, RR 0.9, CI 0.5 to 1.5) or 50% (n=49, RR 0.8, CI 0.5 to 1.4).

Johnstone 1988 used the negative symptoms score of the Manchester scale. Again no significant differences were found in terms of a reduction of less than 20% (n=45, RR 0.4, CI 0.0 to 8.1), 35% (n=45, RR 1.4, CI 0.4 to 5.5) or 50% (n=45, RR 2.1, CI 0.6 to 7.4). Finally, Small 2001 used the positive symptoms score of the PANSS and found no significant differences in terms of a reduction of less than 20% (n=20, RR 1.0, CI 0.4 to 2.4), 35% (n=20, RR 1.0, CI 0.5 to 2.1) or 50% (n=20, RR 0.9, CI 0.5 to 1.6).

Concerning mean endpoint scores of scales, Schulz 1999 analysed the BPRS positive sub score at endpoint and found no significant difference between groups (n=41, WMD 0.1, CI -3.5 to 3.7). Johnstone 1988 used the MS positive sub score and found no significant difference between groups (n=45, WMD 0.2, CI -1.3 to 1.8). Small 2001 monitored the participants using the positive sub score of the PANSS but did not find any differences between groups (n=20, WMD -2.8, CI -7.8 to 2.2).

3.6 Medication use

3.6.1 Mean haloperidol dose

The lithium augmentation group received a significantly lower mean haloperidol dose than the group which received haloperidol alone in the study by Wilson 1993 (n=21, WMD -6.9, CI -13.6 to -0.2). The data from other studies were skewed (see 'other data table').

3.6.2 Number of patients using benzodiazepines

In the study by Wilson 1993 a similar number of participants in both groups received benzodiazepines during the study (n=22, RR 0.8, CI 0.5 to 1.4).

3.7 Adverse events

3.7.1 Central nervous system

Two participants in the lithium augmentation groups of Biederman 1979 and Wilson 1993 developed delirium, but this

was not statistically significant (n=61, RR 2.6, CI 0.3 to 23.3).

3.7.2 Movement disorder

3.7.2.1 At least one extrapyramidal adverse event

Wilson 1993 found no significant difference between groups (n=21, RR 6.4, CI 0.4 to 110.7).

3.7.2.2 Use of antiparkinson medication

The pooled data of Simhandl 1996 and Wilson 1993 showed no significant differences between groups (n=49, RR 1.0, CI 0.6 to 1.7).

3.7.2.3 Mean Simpson Angus Scale score at endpoint

The data from Wilson 1993 showed no significant differences between groups (n=21, WMD 2.7, CI -0.5 to 5.9).

3.7.2.4 Movement disorder - unable to use

Some studies indicated other scale derived data about movement disorder, but these were skewed (see 'other data table').

3.7.3 Non specific discomfort

In the study by Wilson 1993 one participant in the lithium group had 'non specific discomfort' but this did not lead to a statistically significant difference between groups (n=21, RR 2.5, CI 0.11 to 56.3).

3.7.4 UKU scale - unable to use

Terao 1995 provided data about the UKU global score at endpoint, but these data were skewed (see 'other data table').

3.8 Missing outcomes

Again, there were no data on aggression or other harmful behaviour. No data were found for 'service' outcomes such as 'duration of hospital stay'. Again, there were no data on satisfaction with treatment or costs.

3.9 Publication bias

Funnel-plots revealed no obvious publication bias, but this was hampered by the small number of trials available for the plot.

4. SENSITIVITY ANALYSIS 1: LITHIUM AUGMENTATION - EXCLUSION OF THOSE WITH SCHIZOAFFECTIVE DISORDER FROM THE ANALYSES

We examined whether the exclusion of those with schizoaffective disorder led to any important change in terms of the primary outcome parameters 'leaving the studies early', 'no clinically significant response' and 'relapse'. This sensitivity analysis was only undertaken for the most important comparison - augmentation of antipsychotic drugs with lithium (comparison 3).

4.1 Leaving the studies early

Again, significantly more participants who received lithium augmentation left the studies early than those who received antipsychotic drugs alone (n= 174, RR 3.5, CI 1.4 to 8.8, NNH 6, CI 4 to 17).

4.2 No clinically significant response

The superiority of lithium augmentation in terms of a clinically significant response was only of borderline statistical significance when participants with schizoaffective disorders were excluded (n=120, RR 0.8, CI 0.6 to 1.0, p=0.07).

4.3 Relapse

No data were available.

5. SENSITIVITY ANALYSIS 2: EXCLUSION OF TRIALS WITH ATTRITION > 50%

No trial included in the comparison of lithium as a sole treatment versus placebo had more than 50% of the participants leave the study early. In comparison 2 (lithium as a sole treatment versus antipsychotic drugs as a sole treatment) this was the case only in [Braden 1982](#). However, this study contributed only to the outcome 'leaving the study early' so that the sensitivity analysis did not change any primary outcome. Finally, in comparison 3 only [Schulz 1999](#) had an attrition rate of higher than 50%. When this trial was excluded from the analysis of the primary outcome 'no clinically significant response', the overall result did not change (n=203, RR 0.8, CI 0.7-0.96, NNT 7, CI 4 to 33).

DISCUSSION

1. General

The use of lithium for schizophrenia and schizoaffective disorders has been of interest to researchers for a long period. Whereas the first randomised controlled trials were published in the early 1970s, six of the studies identified were published in the 1990s and the most recent in 2001. Although we were able to include 20 studies in this review, they had small sample sizes which lacked sufficient power to detect a small to moderate effect, and were incompletely reported in the original publications. However, we are indebted to a number of authors who shared their data with us and made a much better assessment of the available evidence possible (see acknowledgement).

2. COMPARISON 1. Lithium versus placebo as the sole treatment for schizophrenia

We found no difference between lithium and placebo as the sole treatments for schizophrenia in terms of any outcome parameter analysed. Although it should be noted that only three very small trials were relevant for this comparison, if lithium had a strong effect on the symptoms of schizophrenia at least some difference compared to placebo might have been found. As lithium has a number of well-known side-effects its use as a treatment for those with schizophrenia is not justified.

3. COMPARISON 2. Lithium versus antipsychotics as the sole treatment for schizophrenia

3.1 Leaving the study early

More participants who received lithium salts than those who were on antipsychotics left the studies early. According to a subset of trials, this might reflect a lower efficacy of lithium when compared to antipsychotic agents.

3.2 No clinically significant response as defined in the studies

Only three trials reported on this simple measure, and no significant differences were found. Little can be concluded from this analysis including 80 participants. It is disappointing that more trials did not report this simple outcome.

3.3 Global state

3.3.1 Not improved or worse according to the Clinical Global Impression Scale

The data revealed no differences between group, but again only two very small studies provided usable data.

3.3.2 Relapse

It is surprising that there was only one long-term study ([Mattes 1984](#)), because the main indication for lithium salts in affective disorders is the prevention of relapse. A certain superiority of antipsychotics was found (p=0.06), but given the very small number of participants included (n=14) this cannot be considered robust.

3.4 Mental state - general

Pimozide was superior to lithium salts according to several levels of response derived from the MS global score, but only one study ([Johnstone 1988](#)) provided data. However, the mean MS global scores at endpoint in the same study and the mean BPRS at endpoint in three other studies also showed a significant superiority of antipsychotic drugs. Thus there is some evidence that lithium alone is not as effective as antipsychotic drugs alone for the treatment of schizophrenia, as was expected.

3.5 Mental state - specific

Only one study ([Johnstone 1988](#)) provided data for the analysis of specific aspects of the mental state. No significant differences between groups in terms of depressive or manic symptoms were found, but lithium was less effective than pimozide in improving the negative and positive symptoms of schizophrenia. Thus, lithium does not seem to be a viable alternative to antipsychotic drugs for the treatment of the core symptoms of the disorder.

3.6 Adverse events

Again the analysis was clearly hampered by the fact that only one or two trials reported usable data on adverse events. There were no significant differences in terms of anticholinergic, dermatologic, gastrointestinal or extrapyramidal adverse events. Lithium can lead to toxic confusion, especially when its plasma-level is outside the therapeutic range, but it is also possible that it is less sedating than antipsychotic drugs. A significant difference in terms of an increase of the white blood cell count was reported in one trial, but the clinical meaning of this is unclear.

4. COMPARISON 3. Lithium as an adjunct to antipsychotics for schizophrenia

4.1 Leaving the study early

Significantly more people treated with adjunctive lithium than with adjunctive placebo left the studies before completion. Although the reasons for discontinuing the studies were rarely specified, adverse reactions are a likely explanation. Thus it appears that lithium augmentation is not very acceptable for people with schizophrenia and related disorders.

4.2 No clinically significant response

Overall, more participants who received lithium in addition to antipsychotic drugs were classified as having had a clinically significant response. With two exceptions, (Johnstone 1988, Biederman 1979), all studies included treatment resistant participants. Thus, it is possible that lithium augmentation moderately improves the outcome compared to treatment with antipsychotic drugs alone. However, this finding was only of borderline statistical significance when those with schizoaffective disorders were excluded (see results, 4. sensitivity analysis 1). Furthermore, it was not possible to show any effects of specific schizophrenic symptoms, so that lithium may act rather on general symptoms of the disorder.

4.3 Global state

This analysis confirmed the results on 'no clinically significant response' but was based on a lower number of trials. Again, lithium might somewhat improve the global state of those with schizophrenia.

4.4 Mental state - general

It is possible that augmentation with lithium somewhat improves the general mental state of those with schizophrenia. However, this effect was shown only for an at least 50% or 35% reduction of the BPRS, but not for an at least 20% reduction. This effect is thus not consistent. Furthermore, one trial which used the Manchester scale instead of the BPRS as an outcome measure did not find a superiority of lithium augmentation (Johnstone 1988). The reasons for this difference in effects are unclear. Possible explanations are the fact that a different scale was used, that Johnstone 1988 studied acutely ill participants whereas most other studies examined treatment resistant participants, or that pimozide was used as an antipsychotic in the study, whereas most of the other studies used haloperidol. Furthermore, when the mean BPRS at endpoint was used as an outcome measure, no significant effect of lithium augmentation was found.

4.5 Mental state - specific

When studies reported responses to specific symptoms of the mental state (e.g. depressive, manic, negative or positive symptoms) no significant differences were apparent despite the suggestion of an overall improvement outlined above (4.4). The fact that a number of different scales were used in the trials hampered analysis.

4.6 Medication use

Less haloperidol was given in the lithium augmentation group. As only one study (Wilson 1993) provided usable data, the meaning

of this result is unclear. In the same study a similar number of patients in both groups used benzodiazepines at least once. Again, due to the small sample size, no conclusions can be drawn.

4.7 Adverse events

4.7.1 Movement disorder

No significant differences between groups were found. This is not surprising, because lithium is not known to be associated with movement disorders.

4.7.2 Other adverse events

The available data showed no adverse events to be associated with lithium augmentation. However, the studies were so incompletely reported in this regard that no firm conclusions can be drawn.

5. Missing outcomes

It is surprising that although the main indication of lithium for affective disorders is relapse prevention, only one small study (Mattes 1984) provided relevant data. It is hoped that more data on long-term effects and on important 'service' outcomes such as duration of hospital stay, satisfaction with treatment or costs will be available for future updates of this review.

6. Publication bias

Although funnel-plots did not suggest an obvious publication bias, the possibilities of this method were clearly limited by the small number of trials. We cannot therefore exclude the possibility that further unpublished studies exist.

7. Sensitivity analysis

7.1 Exclusion of participants with schizoaffective disorder

Excluding people with schizoaffective disorder from the overall analysis resulted in loss of statistical superiority of lithium augmentation for the outcome of 'no clinically significant improvement'. It is possible that lithium augmentation benefits affective symptoms. As the relative risk did not change after the exclusion of schizoaffective disorders, an alternative explanation could be the loss of statistical power, because the sensitivity analysis reduced the number of participants.

7.2 Exclusion of trials with attrition higher than 50%

Only two studies had an attrition rate of higher than 50%, and their exclusion did not lead to an important change in the primary outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

For clinicians

There is currently no evidence from randomised controlled trials to support the use of lithium alone as treatment for people with schizophrenia. Although there is some evidence to support the use of lithium or as an augmentation of antipsychotics for people with schizophrenia or schizoaffective disorders, the data are not robust. While we lack evidence to predict which patients with schizophrenia might most benefit from lithium augmentation, issues such as past response to lithium, or prominent affective symptoms may warrant consideration by clinicians. For those currently caring for patients who have been receiving lithium as a treatment for schizophrenia, clinicians need to consider whether this treatment should continue to be used. Lithium is associated with a wide range of side effects. If there is no evidence that the treatment has been effective, then it should be gradually tapered off and then stopped.

Those with schizophrenia and schizoaffective disorder

People with schizophrenia should be made aware of the lack of any empirical basis for the use of lithium as a sole agent for their illness. They should know that there is some evidence that lithium is effective as an adjunct to antipsychotics. However, the effect found was not very strong, was not consistent across all outcomes and the underlying evidence-base was small and not robust.

For managers and policy makers

The data are not robust enough to support the use of lithium augmentation as a routine measure. However, since some superiority was shown in some efficacy outcomes, managers and policy makers should support further trials on the question.

Implications for research

General

Any future studies should respect standards of measuring outcomes and of reporting data in order to enhance the comparability of study results (Begg 1996).

Specific

This review revealed some evidence that lithium augmentation for people with schizophrenia may be effective, but the results were not conclusive. Therefore, further studies are warranted. The following populations are of special research interest:

1. People with schizophrenia without prominent affective symptoms. Such a study would allow an analysis of whether lithium really has an effect on the core symptoms of schizophrenia and not just on affective symptoms.
2. People with schizoaffective disorders, because lithium is frequently used in addition to antipsychotic drugs for this disorder in the clinical routine.
3. People with treatment resistant schizophrenia. Here, drugs with additional effects on schizophrenic symptoms are most needed. Even small differences in outcome may be of great importance in this sub-group, and therefore a large simple trial is justified.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Biederman 1979

Methods	Allocation: randomised (no further details). Blinding: double (no further details). Duration: 5 weeks. Design: parallel. Setting: hospital.
Participants	Diagnosis: schizophrenic schizoaffective and affective schizoaffective (RDC). N=36*. Age: mean ~ 30 years.* Sex 25 M, 11 F* History: elevated mood or motor hyperactivity, acute admissions, number of previous admissions and mean duration of illness not indicated.
Interventions	1. Adjunctive lithium: flexible dose of haloperidol which was started at admission + flexible lithium dose started with 1200mg/day and then adjusted according to therapeutic effect and side-effects. N=21. 2. Adjunctive placebo: flexible dose of haloperidol which was started at admission + flexible placebo dose adjusted according to therapeutic effect and side-effects. N=18.
Outcomes	Leaving the study early. Global state (CGI). Adverse events (toxic symptoms). Unable to use - Mental state (mean BPRS, mean mania scale - no SD).
Notes	* The data of three patients who dropped out before the end of week 3 are not considered in the description by the original authors. In total there were 39 participants.

Risk of bias

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

Braden 1982

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 3 weeks. Design: parallel. Setting: hospital.
Participants	Diagnosis: schizophrenia (12)*, schizoaffective disorder, mania and other psychotic disorders (RDC). N=78. Age: not clearly indicated. Sex: not clearly indicated. History: drug-free, at least 2 manic symptoms.
Interventions	1. Lithium: target plasma-level = 1.6mEq/L (mean level of all patients 1.16mEq/L). N=5*. 2. Chlorpromazine up to 2000mg/day (mean all participants 796mg/day). N = 7*.
Outcomes	Leaving the study early. Unable to use - Mental state (BPRS, GAS, structured interview, clinicians overall ratings - no SD, only p-values).
Notes	*Data could be extracted only for those with schizophrenia.

Risk of bias

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

Brockington 1978

Methods	Allocation: randomised (sealed envelopes, allocations within from a table of random numbers). Blindness: double (no further details). Duration: 4 weeks. Design: parallel. Setting: not indicated.
Participants	Diagnosis: schizomania (PSE). N=19. Age: mean ~ 35 years. Sex: 30 M, 12 F. History: "chronic", non-response to > 3 neuroleptics (2 different chemical classes) in last 2 years, duration illness ~ 10 years.
Interventions	1. Lithium: flexible dose (maximum 2500mg/day), to achieve therapeutic level (range not indicated). N = 8. 2. Chlorpromazine: flexible dose (400 - 1000mg/day). N=11.

Brockington 1978 (Continued)

Outcomes	Leaving the study early. Global state (judgement of rater). Unable to use - Mental state (BPRS, PSE - no SD).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Collins 1991

Comments: 1994

Methods	Allocation: randomised (no further description). Blinding: single (rater). Duration: 4 weeks. Design: parallel. Setting: hospital.	
Participants	Diagnosis: schizophrenia (DSM-III-R and PSE). N=44. Age: mean ~ 39 years. Sex: all male. History: all persistent psychotic symptoms for a minimum period of 6 months prior to the study despite adequate neuroleptic treatment, current hospital stay 1-19 years, number of previous hospitalisations and duration of illness not indicated.	
Interventions	1. Adjunctive lithium: starting dose 800mg, then adjusted to keep plasma-levels within 0.4-1.0 mmol/L + flexible dose of antipsychotics (mean chlorpromazine equivalent at week 4=1452mg) N=21. 2. No additional treatment + flexible dose of antipsychotics (mean chlorpromazine equivalent at week 4 = 1257mg). N=23.	
Outcomes	Leaving the study early. Unable to use - Mental state (MS, SANS - no mean, no SD) Medication use (mean antipsychotic dose - no SD).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description

Collins 1991 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Dube 1981

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 7 weeks (1 week placebo, 4 weeks CPZ or lithium, 2 weeks placebo). Design: parallel. Setting: hospital.
Participants	Diagnosis: schizophrenia (ICD-9). N=60. Age: not indicated. Sex: not indicated. History: no details.
Interventions	1. Lithium: flexible dose, adjusted to achieve therapeutic serum-levels (range not indicated), mean dose 827mg/day. N=30. 2. Chlorpromazine: flexible dose, mean 992mg/day. N=30.
Outcomes	Leaving the study early. Unable to use - Global state (CGI - p-value only, no SD). Mental state (BPRS - p-value only, no SD).
Notes	

Risk of bias

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

Garver 1983

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: flexible according to response. Design: cross-over. Setting: hospital.
Participants	Diagnosis: acute schizophrenia, schizophreniform disorder, schizoaffective disorder, major depressive episode (1*) (DSM-III and RDC). N=16.

Garver 1983 (Continued)

	Age: not indicated. Sex: not indicated. History: acute admissions, all had a red blood cell / lithium ratio < 0.31 or > 0.37.	
Interventions	1. Lithium: dose calculated so that level between 0.8-1.4 mEq/L, N=9. 2. Placebo, N=7.	
Outcomes	Leaving early. Mental state (NH). Unable to use - CGI (no individual numbers, no means).	
Notes	*This participant with major depressive episode was excluded from all analyses.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hogarty 1995

Methods	Allocation: randomised - lithium:placebo 2:1 (no further details). Blindness: double (no further details). Duration: 12 weeks (intervention withdrawn at week 6). Design: parallel. Setting: outpatients.	
Participants	Diagnosis: schizophrenia or schizoaffective disorder (RDC). N=29. Age: mean ~ 36 years. Sex: M 15, F 14. History: "persistant distress by anxiety for at least 3 months prior to the study". The participants had not sufficiently responded in two preceeding trials of anticholinergic challenge and fluphenazine dose reduction. Mean duration illness ~ 10 years*, mean number of previous hospitalisations ~ 4*.	
Interventions	1. Adjunctive lithium: dose adjusted to maintain plasma-levels between 0.4-0.8 mmol/L + constant dose of fluphenazine decanoate (median biweekly dose 10mg). N=18. 2. Placebo + constant dose of fluphenazine decanoate (median biweekly dose 10mg). N=11.	
Outcomes	Leaving the study early. No improvement. Relapse. Unable to use -	

Hogarty 1995 (Continued)

	Mental state (BPRS-subscores, BDI, anxiety rating scale, personal comfort scale - no SD). Adverse events (Akathisia scale - no SD).	
Notes	*Data refer to the whole group of distressed patients who had entered the two previous trials.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Huang 1984

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 10 weeks (intervention withdrawn at week 6). Design: parallel. Setting: hospital.	
Participants	Diagnosis: schizophrenia (10*), bipolar depression, mania (DSM-III-R). N=27. Age: mean ~ 34 years*. Sex: 9 M, 1 F*. History of the schizophrenia patients: all chronic paranoid type, duration illness not indicated.	
Interventions	1. Adjunctive lithium: dose adjusted to maintain levels between 0.6-1.2 mEq/L + haloperidol (dose not indicated). N=6*. 2. Adjunctive placebo + haloperidol (dose not indicated). N=4*.	
Outcomes	Leaving the study early. Unable to use - Mental state: (GAS, no mean, no SD).	
Notes	*Only data of those 10 with schizophrenia were used for the review.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Johnson 1971

Methods	Allocation: randomised (table with random numbers). Blindness: double (participant and rater blind, not the treating psychiatrist). Duration: 3 weeks. Design: parallel. Setting: hospital.
Participants	Diagnosis: acute schizophrenia and acute schizoaffective disorder. N=17. Age: mean ~ 39 years. Sex: not indicated. History: duration illness not indicated, but all in “excited” state at time of study.
Interventions	1. Lithium: flexible dose, increased until response or toxic effect, all participants had levels higher than 1mEq/L. N=7. 2. Chlorpromazine: dosage increased until response or toxic effect. N=10.
Outcomes	Leaving the study early. No improvement. Mental state (BPRS, SCI). Unable to use - (Adverse events and laboratory parameters - no clear N's).
Notes	

Risk of bias

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

Johnstone 1988

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 8 weeks (initial study, then open extension of up to 6 years of the responders). Design: parallel. Setting: hospital.
Participants	Diagnosis: “functional psychoses” (schizophrenia, schizophreniform disorder, schizoaffective disorder, atypical psychoses paranoid disorder, mania or depression* (DSM-III and PSE). N=120. Age: mean unclear. Sex: 64 M, 56 F. History: 38 neuroleptic naive and 22 no neuroleptics for at least 1 year, duration of illness unclear.

Johnstone 1988 (Continued)

Interventions	1. Pimozide alone: 16mg/day. N=23*. 2. Lithium alone, levels adjusted to 0.5-1.2 mmol/l. N=21*. 3. Pimozide + lithium (same doses as in the monotherapy group). N=22.* 4. Placebo. N=18*.	
Outcomes	Leaving the study early. Mental state (Krawiecka Scale , Montgomery Asberg Depression Scale, Bech-Rafaelsen scale for mania). Adverse events (AIMS, TAKE). Unable to use: Relapse rates and other long-term data (N's unclear).	
Notes	* The data of only those with schizophrenia or similar psychoses are used in the analyses (schizophrenia, schizophreniform disorder, schizoaffective disorder, atypical psychosis, paranoid disorder).	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mattes 1984

Methods	Allocation: randomised (table with random numbers). Blindness: double (no further details). Duration: 1 year. Design: parallel. Setting: outpatients.	
Participants	Diagnosis: schizophrenic schizoaffective disorder (RDC). N=14. Age: mean ~ 26 years. Sex: not indicated. History: 5 participants chronic, 8 subchronic and 1 subacute according to RDC criteria, on average the patients had not worked 50% of the time they could have worked in the last 5 years; on average 3.7 previous episodes, mean duration illness not indicated.	
Interventions	1. Lithium: flexible dose, plasma-levels >0.6. N=7. 2. Fluphenazine: 5-20mg/day orally or 12.5-50mg biweekly. N=7.	
Outcomes	Leaving the study early. Relapse.	
Notes		

Mattes 1984 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Prien 1972

Methods	Allocation: randomised (no further details). Blindness: double (identical capsules). Duration: 3 weeks. Design: parallel. Setting: hospital, multi-centre.	
Participants	Diagnosis: schizoaffective disorder, excited type (DSM-II). N=83. Age: mean ~ 39 years. Sex: 59 M, 24 F History: duration illness not indicated, median of previous hospitalisation = 3.	
Interventions	1. Lithium carbonate: starting dose 750mg, then adjusted according to patients' clinical condition and side-effects, plasma-levels < 2.0mEq/L. N=37. 2. Chlorpromazine: starting dose 600mg/day, then adjusted according to patients' clinical condition and side-effects. N=46.	
Outcomes	Leaving the study early. Adverse events. Unable to use - Mental state (BPRS, IMPS, PIP - only p-values).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schulz 1999

Methods	Allocation: randomised (stratified for gender and diagnoses). Blindness: double (participant and independent rater blind, not therapist). Duration: 8 weeks. Design: parallel. Setting: outpatients.	
Participants	Diagnosis: schizophrenia, schizophreniform and schizoaffective disorder (DSM-III-R). N=41. Age: mean ~ 29 years. Sex: 34 M, 7 F. History: Severely ill (mean BPRS 47) despite treatment with depot antipsychotics for 6 months before trial. Mean duration illness and mean number of previous episodes not indicated.	
Interventions	1. Adjunctive lithium: plasma-levels maintained between 0.8-1.0 mEq/L + constant dose of fluphenazine. N=21. 2. Placebo + constant dose of fluphenazine. N=20.	
Outcomes	Leaving the study early. Mental state (BPRS, HAMD). Unable to use - Mental state (CGI, SAS - no mean, no SD). Adverse events (monitored but not reported).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shopsin 1971

Methods	Allocation: randomised (no further details). Blindness: double (identical capsules - participant and rater, not the therapist). Duration: 5 weeks (2 weeks placebo run-in, 3 weeks lithium or chlorpromazine, 2 weeks placebo). Design: parallel. Setting: hospital.	
Participants	Diagnosis: acute schizophrenia - (undifferentiated type and, paranoid type), schizoaffective disorder (clinical diagnose by at least 2 psychiatrists). N=21. Age: 21- 62 years. Sex: not indicated.	

Shopsin 1971 (Continued)

	History: included within 3 days of admission, first episode (N=2) or exacerbation of chronic illness (N=19), mean duration illness not indicated.	
Interventions	1. Lithium: starting dose 750-1000mg/day, max. dose 3000mg/day, plasma-levels <1.5mEq/L. N=11. 2. Chlorpromazine: starting dose 300-400mg/day, max. dose 1200mg/day. N = 10.	
Outcomes	Leaving the study early. Use of antiparkinson medication. Adverse events. Laboratory (white blood cell count, blood uric acid, proteinuria). Unable to use - Global state (CGI, only p-value). Mental state (BPRS, IMPS, SCI, SRSS - p-values only). Behaviour (NOSIE - p-value only).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Simhandl 1996

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 8 weeks (intervention withdrawn at week 6). Design: parallel. Setting: not indicated.
Participants	Diagnosis: schizophrenia (DSM-III-R). N=42. Age: mean ~ 35 years. Sex: 30 M, 12 F. History: "chronic", non-response to > 3 neuroleptics of 2 different chemical classes in the last 2 years, mean duration illness ~ 10 years.
Interventions	1. Adjunctive carbamazepine: dose increased during weeks 1-2 until plasma-levels 15-42 micromol/L + constant dose of antipsychotics. N=15. 2. Lithium: dose increased during weeks 1-2 until plasma levels 0.6-1.2 myml/L) + constant dose of antipsychotics. N = 13. 3. Placebo + constant dose of antipsychotics. N=14.

Simhandl 1996 (Continued)

Outcomes	Leaving the study early. Mental state (BPRS, SANS).	
Notes	*The data of this group were not used in the analyses.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Simpson 1976

Methods	Allocation: randomised (coin toss). Blindness: double (raters and participants blind, not the therapists). Duration: 18 weeks (6 weeks baseline for withdrawal of antipsychotics, then two 6-weeks cross-over phases). Design: cross-over. Setting: hospital.	
Participants	Diagnosis: schizophrenia, N=11. Age: mean ~ 72 years. Sex: 3 M, 8 F. History: long-term hospitalised, all with tardive dyskinesia. Mean duration of hospitalisation ~ 30 years, mean duration illness not indicated.	
Interventions	1. Lithium: flexible dose to maintain plasma-levels between 0.6-1.0 MEq/L. N=5. 2. Placebo. N=6.	
Outcomes	Leaving the study early. Unable to use - Global state (CGI - only p-value). Adverse events (Tardive dyskinesia rating scale - only p-value).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Small 1975

Methods	Allocation: randomised (no further details). Blindness: double (no further details). Duration: 16 weeks (4 phases of 4 weeks). Design: cross-over. Setting: hospital.
Participants	Diagnosis: schizophrenia, schizoaffective disorder (Feighner's criteria). N=22. Age: mean ~ 36 years. Sex: 4 M, 18 F. History: "very chronically ill", all had failed to respond to various previous treatment approaches including at least one phenothiazine, haloperidol and thiothixene, mean duration of hospitalisation ~ 9 years, mean duration illness ~ 10 years.
Interventions	1. Adjunctive lithium: flexible dose to maintain plasma-levels between 0.6-1.2 MEq/L + constant dose of antipsychotics. N=12. 2. Placebo + constant dose of antipsychotics. N=10.
Outcomes	Leaving the study early. Unable to use - Global state (CGI - no data of the first cross-over phase). Mental state (BPRS - no data of first cross-over phase). Behaviour (NOSIE - no data of first cross-over phase).
Notes	

Risk of bias

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

Small 2001

Methods	Allocation: randomised (table with random numbers). Blindness: double (lithium and placebo tablets had the same taste). Duration: 16 weeks (4 phases of 4 weeks). Design: cross-over. Setting: hospital.
Participants	Diagnosis: schizophrenia, schizoaffective disorder (DSM-IV). N=20. Age: mean ~ 37 years. Sex: 14 M, 6 F. History: all had failed to respond satisfactorily to adequate treatment with at least 2 different antipsychotics; mean duration of hospitalisation and mean duration illness not indicated.

Small 2001 (Continued)

Interventions	1. Adjunctive lithium: flexible dose to maintain plasma-levels > 0.4 MEq/L + constant dose of clozapine (mean dose ~ 400mg/day). N=10. 2. Placebo + constant dose of clozapine (mean dose ~ 400mg/day). N=10.	
Outcomes	Leaving the study early. Mental state (BPRS). Unable to use - Adverse events (no data of first cross-over phase).	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Terao 1995

Methods	Allocation: randomised (table with random numbers). Blindness: double (identical capsules). Duration: 19 weeks (intervention withdrawn between the two 8 weeks cross-over phases). Design: cross-over. Setting: hospital.
Participants	Diagnosis: schizophrenia (DSM-III-R). N=21. Age: mean ~ 47 years. Sex: all male. History: mean duration illness ~ 21 years, mean number of hospitalisations ~ 2.6, duration of current hospitalisation ~ 6.7 years.
Interventions	1. Adjunctive lithium: dose calculated to reach plasma-level of at least 0.4 mEq/L + constant dose of antipsychotics. N=10. 2. Placebo + constant dose of antipsychotics. N=11. Mean daily antipsychotic dose in haloperidol equivalents 27.1mg (both groups combined).
Outcomes	Leaving the study early. Mental state (BPRS, SANS).
Notes	
Risk of bias	

Terao 1995 (Continued)

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

Wilson 1993

Methods	Allocation: randomised (blocks of 6 participants, sealed envelopes derived from a table of random numbers). Blinding: double (identical placebo capsules prepared by pharmacist). Duration: 6 weeks baseline, followed by 8 weeks experimental phase. Design: parallel. Setting: hospital.
Participants	Diagnosis: schizophrenia without a concurrent major affective disorder (DSM-III-R). N=29* Age: not indicated. Sex: not indicated. History: all with persistent psychosis for at least 8 weeks despite antipsychotic treatment with at least 800mg chlorpromazine equivalent, mean current hospital stay ~ 20 months, mean previous hospitalisations ~ 10 times, mean duration illness ~ 14 years.
Interventions	Baseline phase before randomisation (6 weeks): All patients were put on haloperidol at "best clinical dose". Experimental phase (8weeks): 1. Lithium: flexible dose adjusted to reach plasma level of 1.0mEq/L + haloperidol (dose not indicated). N = 12. 2. Placebo + haloperidol (dose not indicated). N=10.
Outcomes	Leaving the study early. Mental state (BPRS, SANS). Number of patients with delirium. Medication use (mean haloperidol dose, use of benzodiazepines and anticholinergics). Unable to use - EPS (AIMS and Barnes Akathisia Scale - skewed data).
Notes	*7 patients left the study during the baseline phase before randomisation.

Risk of bias

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

General abbreviations:
HPL - haloperidol

EPS - Extrapyramidal side effects.
 M - males
 F - females
 N = number
 mg = milligram
 L=liter
 mEq=milliequivalents
 SD = standard deviation
 Diagnostic tools:
 DSM-II - Diagnostic and Statistical Manual of Mental disorders, second edition.
 DSM-III - Diagnostic and Statistical Manual of Mental disorders, third edition.
 DSM-III-R - Diagnostic and Statistical Manual of Mental disorders, third edition, revised.
 DSM-IV - Diagnostic and Statistical Manual of Mental disorders, fourth edition.
 RDC - Research Diagnostic Criteria
 Global effect scales:
 CGI - Clinical Global Impression
 Mental state scales:
 BPRS - Brief Psychiatric Rating Scale
 IMPS - Inpatient Multidimensional Rating Scale
 SANS - Scale for Assessment of Negative Symptoms
 MS - Manchester Scale
 NH - (Modified) New Haven Schizophrenia Index
 MMSE - Mini Mental State Examination
 PIP - Psychotic Inpatient profile
 NOSIE - Nurses observation scale for inpatient evaluation
 MSRS - Manic state rating scale
 BDI - Beck Depression Inventory
 HAMD - Hamilton Depression Scale
 SCI - Structured Clinical Interview
 SRSS - Self-Rating Symptom Scale
 GAS - Global Assessment of Symptoms Scale
 PSE - Present State Examination
 Side effect scales:
 AIMS - Abnormal Involuntary Movement Scale
 SAS - Simpson and Angus Scale
 SAFTEE - Scale for Assessment of Treatment Emergent Events
 Barnes Akathisia Scale

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

Alexander 1979	Allocation: not randomised, "within patient cross-over".
Baastrup 1967	Allocation: not randomised, observational study, no control group.

(Continued)

Bigelow 1981	Allocation: not randomised, double-blind, cross-over of a single patient.
Bowers 1983	Allocation: not randomised, "within patient cross-over".
Campbell 1972	Allocation: not randomised, matched groups.
Carman 1981	Allocation: randomised, double-blind, cross-over study. Participants: those with schizophrenia or schizoaffective disorder. Interventions: lithium versus placebo added to antipsychotic drugs. Outcomes: no single outcome could be analysed.
Chen 2001	Allocation: alternate allocation by hospital ID number, not randomized.
Dinsmore 1972	Allocation: not randomised, observational study.
Edelstein 1981	Allocation: not randomised, controlled clinical study.
Gao 2002	Allocation: allocated according to odd or even number of date and ID of admission.
Garver 1988	Allocation: not randomised, "within patient cross-over".
Gerlach 1975	Allocation: randomised, double-blind. Participants: diagnostically mixed group, all showing tardive dyskinesia, most had schizophrenia. Interventions: lithium or placebo added to ongoing treatment. Outcomes: focus on tardive dyskinesia, but no data could be extracted.
Gram 1971	Allocation: randomised, double-blind. Participants: unclear diagnosis ("psychotic" children and adolescents).
Greil 1997	Allocation: randomised. Participants: those with schizoaffective disorder. Interventions: lithium versus carbamazepine as sole agents, no placebo/no intervention group.
Growe 1979	Allocation: unclear whether the study was randomised (it was double-blind). Participants: those with schizophrenia or schizoaffective disorder. Interventions: lithium versus placebo added to antipsychotic drugs. Outcomes: no single outcome could be used.
Haastrup 1973	Allocation: controlled clinical trial, it is unclear whether the study was randomised. Participants: those with schizophrenia. Interventions: unclear. Outcomes: not specified.
Harrison 1980	Allocation: not randomised, retrospective chart analysis.

(Continued)

Hofmann 1970	Allocation: not randomised, case series.
Hullin 1975	Allocation: not randomised, case series.
Jus 1978	Allocation: randomised, double-blind. Participants: schizophrenia, all with tardive dyskinesia. Interventions: lithium, deanol or placebo as sole treatments. Outcomes: focus on tardive dyskinesia, but no data could be extracted.
Lenzi 1985	Allocation: randomised, double-blind. Participants: mixed group, 8 out of thirty with schizophrenia-like disorders. Interventions: placebo or carbamazepine added to antipsychotic drugs, no placebo or no intervention control group.
Lerner 1988	Allocation: not adequately randomised (alternate allocation).
Liebowitz 1976	Allocation: not randomised, case report.
Mackay 1980	Allocation: not randomised, matched pairs, then "within patient cross-over".
Martorano JT	Allocation: not randomised, case reports.
Miller 1979	Allocation: not randomised, review, no original data.
Nemes 1986	Allocation: not randomised, "within patient cross-over".
Placidi 1986	Allocation: randomised, double-blind. Participants: mixed group with "major affective, schizoaffective or schizophreniform disorders". Interventions: Lithium versus carbamazepine as sole agents, no placebo or no intervention group.
Prange 1973	Allocation: not randomised, case series.
Prien 1972a	Allocation: randomised, double-blind. Participants: those with mania patients, no participants with schizophrenia or schizoaffective disorder.
Rice 1956	Allocation: not randomised, case series.
Rosenthal 1980	Allocation: not randomised, case series.
Schnexnayder 1995	Allocation: not randomised, no control group, case series.
Schou 1954	Allocation: randomised. Participants: those with mania.

(Continued)

Shaw 1974	Allocation: not randomised, controlled clinical trial. Participants: chronic schizophrenia. Interventions: two different sustained release preparations of lithium carbonate, no placebo or not intervention group.
Shopsin 1975	Allocation: randomised, double-blind. Participants: those with mania.
Smulevitch 1974	Allocation: not randomised, controlled clinical trial.
Taylor 1974	Allocation: not randomised, case series.
Van Kammen 1978	Allocation: not randomised concerning the drug intervention (lithium or pimozide). Only whether patients received an additional amphetamine or placebo infusion was randomised.
Van Kammen 1980	Allocation: not randomised, no control group.
Van Kammen 1985	Allocation: randomised, double-blind. Participants: those with schizophrenia. Interventions: amphetamine + placebo versus amphetamine + lithium.
Van Putten 1975	Allocation: not randomised, "within patient cross-over".
Vieweg 1989	Allocation: not randomised comparison of patients with healthy volunteers.
Volavka 1986	Allocation: randomised. Participants: chronic psychiatric inpatients with tardive dyskinesia Interventions: lithium vs. lecithin, no placebo or no intervention group.
Wang 1995	Allocation: randomised cross-over study, no further details. Participants: people with schizophrenia. Interventions: chlorpromazine + lithium versus chlorpromazine alone, but clozapine could be added to both groups.
White 1966	Allocation: not randomised, case series.
Wilner 1996	Allocation: randomised. Participants: healthy volunteers.
Zemlan 1984	Allocation: not randomised, case series.

DATA AND ANALYSES

Comparison 1. LITHIUM AS SOLE TREATMENT vs PLACEBO AS SOLE TREATMENT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	3	65	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.29, 4.44]
2 No clinically important response as defined by the authors	2	54	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.81]
3 Mental state: 1. General - less than 20% MS or NH reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Less than 20% MS reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.46, 3.13]
3.2 Less than 20% NH reduction	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.60, 2.27]
4 Mental state: 2. General - less than 35% MS or NH reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Less than 35% MS reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.61, 2.28]
4.2 Less than 35% NH reduction	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.60, 2.27]
5 Mental state: 3. General - less than 50% MS or NH reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Less than 50% MS reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.07]
5.2 Less than 50% NH reduction	1	15	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.60, 2.27]
6 Mental state: 4. General - mean MS global score at endpoint (high=poor)	1	39	Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Mental state: 5. General - unable to use (skewed data)			Other data	No numeric data
8 Mental state: 6. Specific - depression - various degrees of MADRS reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 less than 20% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.37, 1.56]
8.2 less than 35% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.50, 1.81]
8.3 less than 50% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.47, 1.32]
9 Mental state: 7. Specific - mania - various degrees of Bech-Rafaelsen scale reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 less than 20% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.44, 2.17]
9.2 less than 35% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.48]
9.3 less than 50% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.67, 1.47]
10 Mental state: 8. Specific - negative symptoms - various degrees of MS-negative subscore reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

10.1 less than 20% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.48]
10.2 less than 35% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.64, 1.56]
10.3 less than 50% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.64, 1.56]
11 Mental state: 9. Specific - positive symptoms - various degrees of MS- positive subscore reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 less than 20% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.81, 5.67]
11.2 less than 35% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.07]
11.3 less than 50% reduction	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.07]
12 Adverse events: 1. Movement disorder - unable to use (skewed data)			Other data	No numeric data

Comparison 2. LITHIUM vs ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Overall	8	270	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.15, 2.93]
1.2 Due to adverse events	4	178	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.08, 19.21]
1.3 Due to inefficacy of treatment	4	178	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [1.16, 7.80]
2 No clinically important response as defined by the authors	3	80	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.74, 2.20]
3 Global state: 1. Not improved or worse	2	36	Risk Ratio (M-H, Random, 95% CI)	2.72 [0.05, 135.10]
4 Global state: 2. Relapse	1	14	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.95, 37.76]
5 Mental state: 1. General - various degrees of MS global score reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 less than 20% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [0.89, 16.44]
5.2 less than 35 % reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.00, 5.79]
5.3 less than 50% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.00, 4.78]
6 Mental state: 2. General - BPRS/MS global score at endpoint (high=poor)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Mean BPRS at endpoint	3	92	Mean Difference (IV, Fixed, 95% CI)	10.34 [6.64, 14.03]
6.2 Mean MS at endpoint	1	44	Mean Difference (IV, Fixed, 95% CI)	3.0 [0.38, 5.62]
6.3 Mean SCI at endpoint	1	11	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-81.29, 77.29]
7 Mental state: 3. Specific - depression, various degrees of MADRS reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 less than 20% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.68, 4.52]
7.2 less than 35 % reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.73, 3.36]
7.3 less than 50% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.75, 3.01]

8 Mental state: 4. Specific - mania various degrees of Bech-Rafaelsen-Mania scale reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 less than 20% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.55, 2.85]
8.2 less than 35 % reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.80, 2.53]
8.3 less than 50% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.96, 2.82]
9 Mental state: 5. Specific - negative symptoms, various degrees of MS negative subscore reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 less than 20% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	14.24 [2.03, 99.68]
9.2 less than 35 % reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	7.67 [1.97, 29.82]
9.3 less than 50% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	7.67 [1.97, 29.82]
10 Mental state: 6. Specific - positive symptoms, various degrees of MS positive subscore reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 less than 20% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	10.95 [1.53, 78.43]
10.2 less than 35 % reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [1.43, 13.40]
10.3 less than 50% reduction	1	44	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [1.43, 13.40]
11 Adverse events: 1. Anticholinergic	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 blurred vision	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.12, 3.21]
11.2 dry mouth	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.28, 1.66]
11.3 constipation	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.07, 1.38]
12 Adverse events: 2. Central nervous system/neurologic	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 ataxia	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.12, 3.21]
12.2 dizziness	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.12, 3.21]
12.3 hyperactive reflexes	1	83	Risk Ratio (M-H, Fixed, 95% CI)	8.66 [0.46, 162.49]
12.4 muscle weakness	1	83	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.18, 8.41]
12.5 slurred speech	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.15, 4.70]
12.6 somnolence	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.04, 0.73]
12.7 toxic confusion	2	104	Risk Ratio (M-H, Fixed, 95% CI)	9.27 [1.22, 70.55]
13 Adverse events: 3. Dermatologic - pruritus	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.02, 9.83]
14 Adverse events: 4. Gastrointestinal	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 dehydration	1	83	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [0.16, 88.51]
14.2 nausea	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.12, 3.21]
14.3 vomiting	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.15, 4.70]
15 Adverse events: 5. Movement disorder	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 parkinsonism	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 5.00]
15.2 tremor	1	83	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.69, 6.87]
15.3 use of antiparkinson medication	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.68]
16 Adverse events: 6. Unable to use (skewed data)			Other data	No numeric data
17 Laboratory abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

17.1 decreased white blood cell count	1	21	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.11]
17.2 increased white blood cell count	1	21	Risk Ratio (M-H, Fixed, 95% CI)	17.42 [1.14, 265.34]
17.3 increased blood uric acid level	1	21	Risk Ratio (M-H, Fixed, 95% CI)	6.42 [0.37, 110.71]
17.4 proteinuria	1	21	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [0.25, 85.33]
18 Mental state: 2. General - BPRS/MS global score at endpoint (high=poor)	4	136	Std. Mean Difference (IV, Fixed, 95% CI)	0.81 [0.46, 1.17]
18.1 Mean BPRS at endpoint	3	92	Std. Mean Difference (IV, Fixed, 95% CI)	0.89 [0.45, 1.33]
18.2 Mean MS at endpoint	1	44	Std. Mean Difference (IV, Fixed, 95% CI)	0.67 [0.06, 1.28]

Comparison 3. ADJUNCTIVE LITHIUM + ANTIPSYCHOTICS vs PLACEBO/NO ADJUNCTIVE TREATMENT + ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Overall	11	320	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.31, 3.08]
1.2 Due to adverse events	1	39	Risk Ratio (M-H, Fixed, 95% CI)	4.32 [0.22, 84.48]
2 No clinically important response as defined by the authors	8	244	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.97]
3 Global state: 1. Not improved or worse	4	115	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.42, 0.94]
4 Global state: 2. Relapse	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Mental state: 1. General - number of patients with less than 20% BPRS/MS reduction	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Less than 20% BPRS reduction	5	131	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.67, 1.19]
5.2 Less than 20% MS reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.42, 10.29]
6 Mental state: 2. General - number of patients with less than 35% BPRS/MS reduction	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Less than 35% BPRS reduction	5	131	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 1.00]
6.2 Less than 35% MS reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.45, 3.52]
7 Mental state: 3. General - number of patients with less than 50% BPRS/MS reduction	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Less than 50% BPRS reduction	5	131	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.94]
7.2 Less than 50% MS reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.40, 2.75]

8 Mental state: 4. General - average BPRS/MS global score at endpoint (high = poor)	5	147	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.48, 0.17]
8.1 BRPS at endpoint	4	102	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.70, 0.09]
8.2 MS at endpoint	1	45	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.41, 0.77]
9 Mental state: 5.1 Specific - depression, less than 20% MADRS/BPRS-depression score reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Montgomery Asberg	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.35, 3.12]
9.2 BPRS depression	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.38, 2.87]
10 Mental state: 5.2 Specific - depression, less than 35 % MADRS/BPRS-depression score reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Montgomery Asberg	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.44, 2.49]
10.2 BPRS depression	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.33, 2.08]
11 Mental state: 5.3 Specific - depression, less than 50% MADRS/BPRS-depression score reduction	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Montgomery Asberg	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.40, 2.10]
11.2 BPRS depression	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.33, 2.08]
12 Mental state: 5.4 Specific - depression, average HS or MAS at endpoint (high=poor)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 Hamilton Depression Scale (HS)	1	16	Mean Difference (IV, Fixed, 95% CI)	3.40 [-7.66, 14.46]
12.2 Montgomery Asberg Scale (MAS)	1	45	Mean Difference (IV, Fixed, 95% CI)	-0.34 [-1.64, 0.96]
13 Mental state: 6.1 Specific - mania, less than 20% Bech-Rafaelsen-Mania Scale reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.36, 2.25]
14 Mental state: 6.2 Specific - mania, less than 35% Bech-Rafaelsen-Mania Scale reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.41, 1.72]
15 Mental state: 6.3 Specific - mania, less than 50% Bech-Rafaelsen-Mania Scale reduction	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.41, 1.72]
16 Mental state: 7.1 Specific - negative symptoms, less than 20% SANS/MS-/PANSS-negative score reduction	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 SANS	3	70	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.33, 1.65]
16.2 MS negative subscore	1	45	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.20, 21.45]
16.3 PANSS negative	1	20	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.74, 2.41]

17	Mental state: 7.2 Specific - negative symptoms, less than 35% SANS/MS-/PANSS-negative score reduction	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1	SANS	3	70	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.64, 1.34]
17.2	MS negative subscore	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.16, 6.79]
17.3	PANSS negative	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.75, 1.34]
18	Mental state: 7.3 Specific - negative symptoms, less than 50% SANS/MS-/PANSS-negative score reduction	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1	SANS	3	70	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.33]
18.2	MS negative subscore	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.16, 6.79]
18.3	PANSS negative	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.18]
19	Mental state: 7.4 Specific - negative symptoms, BPRS, MS, SANS or PANSS negative score at endpoint (high=poor)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
19.1	BPRS negative subscore	2	61	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.13, 2.32]
19.2	MS negative subscore	1	45	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.31, 0.89]
19.3	PANSS negative subscore	1	20	Mean Difference (IV, Fixed, 95% CI)	1.0 [-3.43, 5.43]
19.4	SANS	2	41	Mean Difference (IV, Fixed, 95% CI)	-4.50 [-8.81, -0.19]
20	Mental state: 8.1 Specific - positive symptoms, less than 20% BPRS-/MS-/PANSS positive score reduction	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1	BPRS positive subscore	2	49	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.24, 1.25]
20.2	MS positive subscore	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.11]
20.3	PANSS positive	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.40]
21	Mental state: 8.2 Specific - positive symptoms, less than 35% BPRS-/MS-/PANSS positive score reduction	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1	BPRS positive subscore	2	49	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.50, 1.47]
21.2	MS positive subscore	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.35, 5.53]
21.3	PANSS positive	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.49, 2.05]
22	Mental state: 8.3 Specific - positive symptoms, less than 50% BPRS-/MS-/PANSS positive score reduction	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1	BPRS positive subscore	2	49	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.48, 1.35]
22.2	MS positive subscore	1	45	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.60, 7.35]
22.3	PANSS positive	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.45, 1.64]
23	Mental state: 8.4 Specific - positive symptoms, mean BPRS, MS or PANSS positive subscore (high=poor)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1	BPRS positive subscore	1	41	Mean Difference (IV, Fixed, 95% CI)	0.14 [-3.45, 3.73]
23.2	Manchester Scale positive subscore	1	45	Mean Difference (IV, Fixed, 95% CI)	0.23 [-1.34, 1.80]
23.3	PANSS positive subscore	1	20	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-7.84, 2.24]

24 Medication use: 1. Mean haloperidol dose (high=poor)	1	21	Mean Difference (IV, Fixed, 95% CI)	-6.90 [-13.62, -0.18]
25 Medication use: 2. Mean dose of antipsychotics (unable to use - skewed data)			Other data	No numeric data
26 Medication use: 3. Number of patients taking benzodiazepines	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]
27 Adverse events: 1. Central nervous system - delirium	2	61	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [0.28, 23.28]
28 Adverse events: 2. Movement disorder - dichotomous data	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
28.1 At least one extrapyramidal side-effect	1	21	Risk Ratio (M-H, Fixed, 95% CI)	6.42 [0.37, 110.71]
28.2 Use of antiparkinson medication	2	49	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.57, 1.72]
29 Adverse events: 3. Movement disorder - average SAS score at endpoint (high=poor)	1	21	Mean Difference (IV, Fixed, 95% CI)	2.70 [-0.53, 5.93]
30 Adverse events: 4. Movement disorder - unable to use (skewed data)			Other data	No numeric data
31 Adverse events: 5. Non-specific dyscomfort	1	22	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [0.11, 56.25]
32 Adverse events: 6. UKU at endpoint - unable to use (skewed data)			Other data	No numeric data
33 Leaving the study early	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 Overall	11	320	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.31, 3.08]

Comparison 4. SENSITIVITY ANALYSIS 1: LITHIUM AUGMENTATION - PARTICIPANTS WITH AFFECTIVE SYMPTOMS EXCLUDED

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	7	174	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [1.41, 8.80]
2 No clinically significant improvement	5	120	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.60, 1.03]

Comparison 5. SENSITIVITY ANALYSIS 2: LITHIUM AUGMENTATION - STUDIES WITH ATTRITION > 50% EXCLUDED

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No clinically important response as defined by the authors	7	203	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.97]

WHAT'S NEW

Last assessed as up-to-date: 21 May 2007.

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CONTRIBUTIONS OF AUTHORS

Stefan Leucht - protocol development, searching, data extraction, analysis, data interpretation and writing the final report.

John McGrath - protocol development, data checking, data interpretation.

Werner Kissling - protocol development, data interpretation.

DECLARATIONS OF INTEREST

Stefan Leucht: none known.

John McGrath: none known.

Werner Kissling: none known.

SOURCES OF SUPPORT

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