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Zotepine versus other atypical antipsychotics for schizophrenia

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Abstract

Background—In many parts of the world, particularly in industrialised countries, second generation (atypical) antipsychotic drugs have become first line treatment for people suffering from schizophrenia. The question as to whether the effects of various second generation antipsychotic drugs differ is a matter of debate.

Objectives—To evaluate the effects of zotepine compared with other second generation antipsychotic drugs for people suffering from schizophrenia and schizophrenia-like psychoses.

Search methods—We searched the Cochrane Schizophrenia Group Trials Register (November 2009), inspected references of all identified studies for further trials and contacted authors of trials for additional information.

Selection criteria—We included only randomised clinical controlled trials that compared zotepine with any forms of amisulpride, aripiprazole, clozapine, olanzapine, risperidone,

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Katja Komossa - protocol development, searching, study selection, data extraction, report writing.

Christine Rummel - protocol development, searching, study selection, data extraction.

Stefan Leucht - protocol development, searching, study selection, data extraction, report writing.

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Heike Hunger - helped with data extraction and writing.

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Sandra Schwarz - helped with data extraction and writing.

DECLARATIONS OF INTEREST Selvizhi Subramanian - none.

Katja Komossa - none.

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sertindole or ziprasidone in people suffering from only schizophrenia or schizophrenia-like psychoses.

Data collection and analysis—SS and KK extracted data independently. For dichotomous data we calculated relative risks (RR) and their 95% confidence intervals (CI) on an intention-to-treat basis based on a random-effects model. For continuous data, we calculated weighted mean differences (MD) again based on a random-effects model.

Main results—We included three studies (total n=289; 2 RCTs zotepine vs clozapine; 1 RCT zotepine vs clozapine vs risperidone (at 4 mg, 8 mg doses) vs remoxipride. All studies were of limited methodological quality. When zotepine was compared with clozapine, it was clozapine that was found to be more effective in terms of global state (n=59, 1 RCT, RR No clinically significant response 8.23 CI 1.14 to 59.17). Mental state scores also favoured clozapine (n=59, 1 RCT, MD average score (BPRS total, high = poor) 6.00 CI 2.17 to 9.83) and there was less use of antiparkinson medication in the clozapine group (n=116, 2 RCTs, RR 20.96 CI 2.89 to 151.90). In the comparison of zotepine and risperidone, mental state scoring found no significant difference between the groups (vs 4 mg: n=40, 1 RCT, MD average endpoint score (BPRS total, high=poor) 1.40 CI -9.82 to 12.62; vs 8 mg: n=40, 1 RCT, MD -1.30 CI -12.95 to 10.35) and use of antiparkinson medication was equivocal (vs 4 mg: n=40, 1 RCT, MD 1.80 CI -0.64 to 4.24; vs 8 mg: n=40, 1 RCT, MD 2.50 CI -0.05 to 5.05). Finally, when zotepine was compared with remoxipride, again no effect was found for mental state (n=58, 1 RCT, MD average endpoint score (BPRS total, high=poor) 5.70 CI -4.13 to 15.53) and there was no significant difference between the two groups in terms of use of antiparkinson medication (n=49, 1 RCT, RR 0.97 CI 0.41 to 2.29).

Data on important other outcomes such as other adverse events, service use or satisfaction with care, quality of life were not available.

Authors' conclusions—The evidence base around zotepine is insufficient to provide firm conclusions on its absolute or relative effects. This is despite it being in use in Austria, France, Germany, Japan and the UK.

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Clozapine [adverse effects; therapeutic use]; Dibenzothiepins [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Remoxipride [adverse effects; therapeutic use]; Risperidone [adverse effects; therapeutic use]; Schizophrenia [*drug therapy]

MeSH check words

Humans

BACKGROUND

Description of the condition

Schizophrenia is usually a chronic and disabling psychiatric disorder which affects approximately 1% of the population world-wide. The annual incidence of schizophrenia averages about 15 people per 100000 (point prevalence approximately 4.5/1000, life time

risk 0.7% (Tandon 2008)). The typical manifestations are positive symptoms such as fixed, false beliefs (delusions), perceptions without cause (hallucinations), negative symptoms such as apathy and lack of drive, disorganisation of behaviour and thought, catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994). The degree of disability is considerable with 80-90% of people unable to work (Marvaha 2004) and up to 10% dying from suicide (Tsuang 1978). In the 15-44 years age range, schizophrenia is among the top ten causes of disease-related disability in the world (WHO 2001).

Description of the intervention

Traditionally, the conventional antipsychotic drugs such as chlorpromazine and haloperidol have been used as first line antipsychotic drugs for people suffering from schizophrenia (Kane 1993). Clozapine was introduced in USA in 1990. It was discovered that clozapine appeared to be more effective and associated with fewer movement disorders than chlorpromazine (Kane 1988). This boosted the development of so-called atypical or newer or second generation antipsychotic drugs (SGA). These drugs promised an improvement in the management of schizophrenia in a number of areas such as improving compliance, cognitive functioning, negative symptoms, movement disorders, quality of life and treatment resistance. There is no clear cut definition of what an 'atypical' antipsychotic drug is. However, they are thought to differ from typical antipsychotic drugs in that they do not cause movement disorders (catalepsy) in rats at clinically effective doses (Arnt 1998). The term 'newer drug' is not ideal, as for example, clozapine was formulated in the early 1960s. According to treatment guidelines (APA 2004, Gaebel 2006) the second generation antipsychotic drugs include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine. It is, however, unclear whether some old and inexpensive compounds such as sulpiride or perazine have similar properties (Möller 2000).

How the intervention might work

Zotepine is a second generation antipsychotic drug with a high affinity for human D1-like (D1, D5) and D2-like (D2, D3, D4) dopamine receptors and serotonin subtypes (5HT2a, 5HT2c, 5HT6, 5HT7; Leysen 1993, Roth 1994, Needham 1996). It also inhibits norepinephrine re-uptake and it is claimed to be particularly effective for negative symptoms (DeSilva 2006).

Why it is important to do this review

Despite the debate as to whether second generation antipsychotic drugs are better than conventional neuroleptics (Duggan 2005, El-Sayeh 2006, Lieberman 2005, Jones 2006). In some parts of the world, particularly in industrialised countries, the second generation antipsychotic drugs have become the mainstay of treatment. Therefore, it is important to review the effects of these drugs in head-to-head comparisons.

OBJECTIVES

To evaluate the efficiency and tolerability of zotepine compared with other second generation antipsychotic drugs for people suffering from schizophrenia and schizophrenia-like psychoses.

METHODS

Criteria for considering studies for this review

Types of studies—We searched for only randomised controlled trials, irrespective of the blinding status, published in all languages. We approached relevant translators, to clarify the type of trial and where necessary to collect the data. We excluded case series, diagnostic studies, non-randomised, quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants—We included trials that intervened with people suffering from schizophrenia and schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of the diagnostic criteria used. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or that they require different treatment approaches (Carpenter 1994).

Types of interventions—

1. Zotepine: oral form of application, any dose.
2. Other second generation antipsychotic drugs: amisulpride, aripiprazole, clozapine, olanzapine, risperidone, sertindole, ziprasidone: any form of application, any dose.

Types of outcome measures—We grouped the outcomes into the short term (up to 12 weeks), medium term (13-26 weeks) and long term (over 26 weeks).

Primary outcomes: No clinically important response: as defined by the individual studies (e.g. global impression less than much improved or less than 50% reduction on a rating scale).

Secondary outcomes:

1. Leaving the studies early (any reason, adverse events, inefficacy of treatment)
2. Global state
 - 2.1 No clinically important change in global state (as defined by individual studies)
 - 2.2 Relapse (as defined by the individual studies)
3. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)
 - 3.1 No clinically important change in general mental state score
 - 3.2 Average endpoint general mental score

- 3.3 Average change in general mental state score
- 3.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
- 3.5 Average endpoint specific symptom score
- 3.6 Average change in specific symptom score
- 4. General functioning
 - 4.1 No clinically important change in general functioning
 - 4.2 Average endpoint general functioning score
 - 4.3 Average change in general functioning score
- 5. Quality of life/satisfaction with treatment
 - 5.1 No clinically important change in general quality of life
 - 5.2 Average endpoint general quality of life score
 - 5.3 Average change in general quality of life score
- 6. Cognitive functioning
 - 6.1 No clinically important change in overall cognitive functioning
 - 6.2 Average endpoint of overall cognitive functioning score
 - 6.3 Average change of overall cognitive functioning score
- 7. Service use
 - 7.1 Number admitted to hospital
- 8. Adverse effects
 - 8.1 Number with at least one adverse effect
 - 8.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders, prolactin increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count)
 - 8.3 Average endpoint in specific adverse effects
 - 8.4 Average change in specific adverse effects

Search methods for identification of studies

Electronic searches—For this, the 2010 update, we searched the Cochrane Schizophrenia Group Trials Register (November 2009). The register was searched using the phrase:

[(*zotepine* or *lodopin* or *nipolett* or *zopite* or *setous* or *majorpin* in STUDY intervention field)]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module). The search undertaken in 2007 is outlined in Appendix 1.

Searching other resources—

1. Reference searching We inspected reference lists of all identified studies for more trials.
2. Personal contact We contacted the first author of each included study for missing information. When there was no response or where information was not available from the first author, we then contacted the other authors enlisted in the study.
3. Drug companies

We contacted manufacturers of the included second generation antipsychotic drugs for additional data.

Data collection and analysis

Selection of studies—SS and KK independently inspected all reports. 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 independently whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and added these trials to the list of those awaiting assessment.

Data extraction and management—

1. Data extraction

SS and KK independently extracted data from the selected trials. When disputes arose we attempted to resolve these by discussion. When this was not possible and further information was necessary to resolve the dilemma, we did not enter the data but added the trial to the list of those awaiting assessment and sought more information.

2. Data management

2.1 Continuous

2.1.1 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aimed to apply the following standards to all data before inclusion: a) standard deviations and means are reported in the paper or obtainable from the authors; b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if $2SD > (SS - \text{min})$, where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a

scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. Skewed data from studies of less than 200 participants were entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

2.1.2 Conversion of continuous to binary

Where possible, efforts were made to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005, Leucht 2005a). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.2 Rating scales

2.2.1 Valid scales

A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are of questionable validity, or even 'ad hoc'. It is accepted generally that measuring instruments should have the properties of reliability and validity (Rust 1989). Unpublished scales are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal. In addition, the following minimum standards for instruments were set: the instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

2.2.2 Endpoint versus change data

We preferred to use scale endpoint data, which typically cannot have negative values and is easier to interpret from a clinical point of view. Change data are often not ordinal and are very problematic to interpret. If endpoint data were unavailable we used change data.

3. Common measure

To facilitate comparison between trials, we intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

4. Direction of graphs

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

5. Summary of findings table

We anticipate including the following long-term main outcomes in a Summary of Findings table:

1. Mental state
 - 1.1 General symptoms - no clinically important improvement
 - 1.2 Specific symptoms
 - 1.2.1 Negative symptoms (poor volition, poor self-care, blunted affect) - no clinically important improvement
2. Global state
 - 2.1 Relapse (as defined in trial)
 - 2.2 Not improved to a clinically meaningful extent (as defined in trial)
3. Behaviour
 - 3.1 General behaviour - no clinically important improvement
4. Adverse effects
 - 4.1 General problems
 - 4.2 Specific problems - important disabling problem

Assessment of risk of bias in included studies—SS and KK independently assessed risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We would have excluded studies where allocation was clearly not concealed.

Trials with high risk of bias (defined as at least three out of six domains categorised as 'No') were removed from the 'included' category. If the raters disagreed, the final rating was made by consensus with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, authors of the studies were contacted in order to obtain further information. Non-concurrence in quality assessment was reported.

Measures of treatment effect—

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

2.1 Summary statistic

For continuous outcomes we estimated a mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, where scales were of such similarity to allow presuming there was a small

difference in measurement, we calculated it and, whenever possible, we transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues—

1. 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 intraclass 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. This can cause type I errors (Bland 1997, Gulliford 1999).

Where clustering is not accounted for in primary studies, we presented data in a table, with a (*) 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 obtain intraclass correlation coefficients for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a ‘design effect’. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) [Design effect = $1 + (m - 1) * ICC$] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies has been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we will only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, the additional treatment arms were presented in comparisons. Where the additional treatment arms were not relevant, these data were not reproduced.

Dealing with missing data—

1. Overall loss of credibility

At some degree of loss of follow-up data must lose credibility (Xia 2007). For any particular outcome should more than 50% of data be unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data were not clearly described, data were presented on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those lost to follow up were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death. A sensitivity analysis was undertaken testing how prone the primary outcomes were to change when 'completed' data only were compared to the intention-to-treat analysis using the above assumption.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50% and completer-only data were reported, we have reproduced these.

3.2 Standard deviations

3.2.1 General

Where there are missing measures of variance for continuous data but an exact standard error and confidence interval are available for group means, either 'p' value or 't' value are available for differences in mean, we will calculate standard deviation value according to methods described in Section 7.7.3 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008; Furukawa 2006). If standard deviations were not reported and could not be calculated from available data, we asked authors to supply the data. In the absence of data from authors, we used the mean standard deviation from other studies.

3.2.2 Standard deviation mean number of days per month in hospital

For the primary outcome, mean number of days per month in hospital, if standard deviations were not reported and could not be calculated from available data, we asked authors for additional information. In the absence of data from authors, we calculated missing standard deviations using a regression analysis of standard deviation against mean, based on data from studies which did report these data.

3.3 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where LOCF data has been used in the trial, if less than 50% of the data had been assumed, we reproduced these data and indicated that they are the product of LOCF assumptions.

Assessment of heterogeneity—

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying situations or people which we had not predicted would arise. Should such situations or participant groups have arisen they were fully discussed.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we had not predicted would arise. Should such methodological outliers have arisen they were fully discussed.

3. Statistical

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

Heterogeneity between studies was investigated by considering the I^2 method alongside the Chi^2 'p' value. The I^2 provides an estimate of the percentage of

inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii.

strength of evidence for heterogeneity (e.g. 'p' value from Chi^2 test, or a confidence interval for I^2).

I^2 estimate greater than or equal to 50% accompanied by a statistically significant Chi^2 statistic, was interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2008) and reasons for heterogeneity were explored. If the inconsistency was high and the clear reasons were found, data were presented separately.

Assessment of reporting biases—Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small -study effects. We did not use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis—Where possible we employed a random-effect model for analyses. We understand that there is no closed argument for preference for use of fixed or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This does seem true to us, however,

random-effects does put added weight onto the smaller of the studies, those trials that are most vulnerable to bias.

Subgroup analysis and investigation of heterogeneity—

1. Subgroup analyses

We anticipated no sub-group analyses.

2. Investigation of heterogeneity

2.1 Unanticipated heterogeneity

Should unanticipated clinical or methodological heterogeneity be obvious we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

2.2 Anticipated heterogeneity

We did not anticipate any heterogeneity.

Sensitivity analysis—

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes we included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then all data were employed from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow up (see Dealing with missing data) we compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we reported results and discuss them but continued to employ our assumption.

3. Skewed data

In the sensitivity analyses we excluded outcomes with skewed data.

4. Inappropriate comparator doses

A recent report showed that some of the comparisons of second generation antipsychotic drugs may have been biased by using inappropriate comparator doses (Heres 2006). We, therefore, analysed whether the exclusion of studies with inappropriate comparator doses changed the results of the primary outcome and the general mental state.

RESULTS

Description of studies

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

For substantive description of studies please see Characteristics of included studies and Characteristics of excluded studies.

Results of the search—The search strategy yielded 54 references (from 34 studies). Reports were closely inspected. After excluding ten, we were only able to include three studies. Among the included studies, two compared zotepine with clozapine and one trial compared zotepine with clozapine, risperidone (at 4 mg, 8 mg doses) and remoxipride. Remoxipride is an atypical antipsychotic which was used in Europe in the past, but has been withdrawn due to concerns about toxicity. We included the comparison with remoxipride for completeness and it may assist researchers.

Included studies—Three randomised trials with 289 participants met the inclusion criteria. Klieser 1991 was a parallel, double blind trial (sponsor unclear). Lin 2003 was a parallel, single blind trial (blinded raters) conducted in China (sponsor unclear). Meyer-Lindenberg 1997 was a parallel, double-blind trial (sponsored by zotepine's manufacturer).

1. Length of studies

Klieser 1991 was conducted over a period of four weeks, Lin 2003 over six and Meyer-Lindenberg 1997 over twelve.

2. Setting

Lin 2003 was a hospital-based study, while Klieser 1991 and Meyer-Lindenberg 1997 did not report the setting.

3. Participants

Klieser 1991 included people suffering from acute paranoid hallucinatory schizophrenia (295.3) diagnosed using International Classification of Diseases-9. Lin 2003 included people suffering from schizophrenia, but did not specify the diagnostic criteria used. Meyer-Lindenberg 1997 included people suffering from schizophrenia, diagnosed using Diagnostic and Statistical Manual Version III (DSM-III).

4. Study size

Klieser 1991 included 180 people. Both Lin 2003 and Meyer-Lindenberg 1997 studies were smaller with only 50 participants each.

5. Interventions

British National Formulary (BNF) recommends zotepine for people suffering from schizophrenia. The starting dose is 25 mg, three times daily, increased according to response at intervals of 4 days, to a maximum of 300 mg per day in three divided doses. Different doses are recommended for the elderly and it is not recommended for children and adolescents.

5.1 Zotepine

Klieser 1991 used zotepine at a fixed dose of 225 mg/day. Zotepine was given in flexible doses in the other two studies. The dose range in Meyer-Lindenberg 1997 was 150 to 450

mg/day. Lin 2003 did not report the dose range of zotepine, but the average dose was 387 mg/day.

5.2 Comparison drugs

Klieser 1991 used risperidone 4mg and 8 mg, clozapine 400mg, remoxipride 400mg, haloperidol 15 mg as comparators. We did not compare the effectiveness of zotepine with haloperidol as this is a typical antipsychotic and hence does not address the objective of our review. In Meyer-Lindenberg 1997 the range was 150-450 mg/ day. Lin 2003 and Meyer-Lindenberg 1997 used only clozapine as a comparator. Lin 2003 did not report the range of the dose of clozapine, but the average daily dose was 377 mg/day.

6. Outcomes

6.1 General

Klieser 1991 reported details of total average end point Brief Psychiatry Rating Scale (BPRS) score, average end point extrapyramidal symptom (EPS) score, use of antiparkinson medication, changes in syndrome short test. Lin 2003 used 'at least much improved' as a criterion for response to treatment. Lin 2003 reported values on 'no clinically important response', average BPRS score, average change of prolactin from baseline, use of antiparkinson medication. Meyer-Lindenberg 1997 reported numbers leaving early for any reason, but the specific reasons for leaving the study early (adverse events, lack of efficacy) were not presented. All other outcomes were reported only for a small subgroup of matched participants and therefore could not be used in this review.

6.2 Outcome scales

Details of scales that provided usable data are shown below. Reasons for exclusion of data from other instruments are given under 'Outcomes' in the Included studies section.

6.2.1 Mental state

6.2.1.1 Brief Psychiatric Rating Scale - BPRS (Overall 1962)

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

6.2.2 Adverse effects

6.2.2.1 Simpson Angus scale - SAS (Simpson 1970)

This is used to assess parkinsonian and related extrapyramidal side effects in clinical practice. It is a clinician-rated 10-item rating scale.

6.2.3 Cognitive functioning

6.2.3.1 Syndrome kurz test - SKT Erzigkeit 1989

SKT is a brief neuropsychological test battery to test memory and attention deficit. High scores indicate more severe symptoms.

Excluded studies—

1. Excluded studies

The search strategy identified 54 references. Thirteen studies relevant to this review were closely inspected, of which ten had to be excluded. Among the excluded ten studies, three were found to be case series and two were diagnostic studies. One was open label non-randomised study and another was a naturalistic study. One was a placebo controlled trial. Perro 1999 was a randomised trial with 75 participants, which compared zotepine with risperidone, olanzapine and sertindole. The intended outcomes were a series of scales (PANSS, CGI, GAF, UKU, BDI, SCL-R 90, QLS) but there were no data available in the report. We contacted one of the authors for more details, who confirmed that the full report, along with rest of the data, was not published anywhere. It had to be excluded. Briken 2002 was a randomised controlled trial, which evaluated the effect of zotepine compared with risperidone and olanzapine on hostility in people with schizophrenia. The number of participants in each arm were unclear. Outcomes proposed were PANSS, UKU, PANSS-EC - but no data were available, as confirmed by one of its authors. Hence this study also had to be excluded. All trials found in other languages were either case series or diagnostic studies and were excluded.

2. Awaiting assessment

No studies await assessment.

3. Ongoing studies

Tsai 2007 is an ongoing multi-centre open label, randomised trial, evaluating the anti-aggression effect and safety of zotepine versus risperidone in aggressive people with schizophrenia in an acute ward. The study includes 160 adults of mixed gender. PANSSEC is used as the primary outcome and PANSS, CGI scores are secondary outcomes.

Risk of bias in included studies

Klieser 1991 did not give details of sequence generation or allocation concealment suggesting that it is prone for bias. Meyer-Lindenberg 1997 gave values of a matched subsamples only. Lin 2003 was poorly reported and is prone to considerable risk of bias. For details please refer to Figure 1 and Figure 2.

Allocation

All three included studies were randomised, but details of the randomisation process were not provided.

Blinding

Klieser 1991 and Meyer-Lindenberg 1997 were double-blind and Lin 2003 was single-blind (blinded raters), but further details on the blinding procedure were not provided in any of these studies. None of the studies tested whether blinding was successful. Blinding may be less important for objective outcomes, but the latter two studies reported only subjective outcomes.

Incomplete outcome data

Klieser 1991 appears to have had no loss to follow up, but this has not been explicitly described. Meyer-Lindenberg 1997 reported only leaving the study early because of 'any reason', but specific reasons for leaving the study early were not indicated. Furthermore, the overall attrition was considerable (34%) limiting validity of the findings. Lin 2003 did not provide any data on people leaving the study early.

Selective reporting

Klieser 1991 has reported the data comprehensively. Lin 2003 is only available as an abstract in which only a few outcomes (global state, use of antiparkinson medication, prolactin increase and mental state) have been reported. The only usable outcome of Meyer-Lindenberg 1997 was leaving the study early. All other outcomes have only been reported for a matched (i.e. no longer randomised) sub-sample.

Other potential sources of bias

Klieser 1991 has described EPS values, but it should be noted that biperiden co-medication was permitted. The frequency of the medication administered appears to be dependent on the preparation, but the criteria for using the biperiden has not been made clear.

Meyer-Lindenberg 1997 was sponsored by the manufacturers of zotepine. It has been shown that pharmaceutical companies tend to emphasise the advantages of their drugs and to highlight the problems of comparator compounds (Heres 2006).

Lin 2003 used an "enriched design". All participants had been on stable doses of clozapine before the study and were then randomised to either continuation of clozapine or switch to zotepine. This design could confer advantage for clozapine.

Effects of interventions

See: Summary of findings for the main comparison ZOTEPINE versus CLOZAPINE for schizophrenia (all short term outcomes); Summary of findings 2 ZOTEPINE versus RISPERIDONE for schizophrenia (all short term outcomes); Summary of findings 3 ZOTEPINE versus REMOXIPRIDE for schizophrenia (all short term outcomes)

1. Comparison 1. ZOTEPINE versus CLOZAPINE - all short term outcomes (Summary of findings for the main comparison) This comparison includes data from all three trials with 166 people in groups relevant to this question.

1.1 Global state

1.1.1 No clinically significant response - as defined by the original studies (Analysis 1.1)

There was a significant difference favouring clozapine (n=59, 1 RCT, RR 8.23 CI 1.14 to 59.17).

1.2 Leaving the study early (Analysis 1.2)

There was no clear difference between groups, but about 34% of people in this short study left early (n= 50, 1 RCT, RR 1.43 CI 0.65 to 3.15).

1.3 Mental state

1.3.1. Average score (BPRS total, high = poor) (Analysis 1.3)

There was a significant difference favouring clozapine (n=59, 1 RCT, MD 6.00 CI 2.17 to 9.83).

1.3.2. Average endpoint score (BPRS total, high=poor) (Analysis 1.4)

There was no significant difference between the two groups (n= 57, 1 RCT, MD 2.20 CI -7.77 to 12.17).

1.4 Adverse effects

1.4.1 Extrapyramidal effects - Average end point EPS score (Analysis 1.5)

There was no significant difference in the end point EPS values between the groups (n=57, 1 RCT, MD 2.10 CI -0.25 to 4.45).

1.4.2 Extrapyramidal effects - use of antiparkinson medication (Analysis 1.6)

There was a significant difference in use of antiparkinson medication favouring clozapine in both Klieser 1991 and Lin 2003 studies. This significance was greater when the results of these two studies were combined (n=116, 2 RCT, RR 20.96 CI 2.89 to 151.90).

1.4.3 Prolactin - average change from baseline (ng/ml) (Analysis 1.7)

There was a significant difference favouring clozapine (n=59, 1 RCT, MD 33.40 CI 14.87 to 51.93).

1.5 Cognitive functioning

1.5.1 Cognitive functioning - not improved (SKT) (Analysis 1.8)

There was no significant difference between the groups (n=57, 1 RCT, RR 0.57 CI 0.21 to 1.52).

1.5 Publication bias

Due to small number of included studies we did not perform a funnel plot analysis.

1.6 Investigation for heterogeneity and sensitivity analysis

The reasons for the preplanned sensitivity analyses did not apply and were therefore not performed.

2. Comparison 1. ZOTEPINE versus RISPERIDONE 4 mg, 8 mg - all short term outcomes (Summary of findings 2)

This comparison includes only Klieser 1991 with 60 people in relevant groups.

2.1 Mental state

2.1.1. Average endpoint score (BPRS total, high=poor) (Analysis 2.1)

There was no significant difference between the two groups (vs 4 mg: n=40, 1 RCT, MD 1.40 CI -9.82 to 12.62; vs 8 mg: n=40, 1 RCT, MD -1.30 CI -12.95 to 10.35).

2.2 Adverse effects

2.2.1 Extrapyramidal effects - Average end point EPS score (Analysis 2.2)

There was no significant difference in the end point EPS scores when compared zotepine with risperidone (vs 4 mg: n=40, 1 RCT, MD 1.80 CI -0.64 to 4.24; vs 8 mg: n=40, 1 RCT, MD 2.50 CI -0.05 to 5.05).

2.2.2 Extrapyramidal effects - use of antiparkinson medication (Analysis 2.3)

There was no significant difference in the use of antiparkinson medication, when zotepine was compared with risperidone (vs 4 mg: n=40, 1 RCT, MD 1.80 CI -0.64 to 4.24; vs 8 mg: n=40, 1 RCT, MD 2.50 CI -0.05 to 5.05).

2.3 Cognitive functioning

2.3.1 Cognitive functioning - not improved (SKT) (Analysis 2.4)

There was no significant difference between the zotepine and the risperidone groups (vs 4 mg: n=40, 1 RCT, MD 0.80 CI 0.25 to 2.55; vs 8 mg: n=40, 1 RCT, MD 1.00 CI 0.29 to 3.45).

3. Comparison 1. ZOTEPINE versus REMOXIPRIDE - all short term outcomes (Summary of findings 3)

This comparison includes only Klieser 1991 with 58 people in relevant groups.

3.1 Mental state

3.1.1. Average endpoint score (BPRS total, high=poor) (Analysis 3.1)

There was no significant difference between the two groups (n= 58, 1 RCT, MD 5.70 CI -4.13 to 15.53).

3.2 Adverse effects

3.2.1 Extrapyramidal effects - Average end point EPS score (Analysis 3.2)

There was no significant difference in the end point EPS values between the groups (n=58, 1 RCT, MD 0.00 CI -2.62 to 2.62).

3.2.2 Extrapyramidal effects - use of antiparkinson medication (Analysis 3.3)

There was no significant difference between the two groups (n= 49, 1 RCT, RR 0.97 CI 0.41 to 2.29).

3.3 Cognitive functioning

3.3.1 Cognitive functioning - not improved (SKT) (Analysis 3.4)

There was no significant difference between the groups (n=58, 1 RCT, RR 0.69 CI 0.25 to 1.89).

DISCUSSION

Summary of main results

We identified three studies which compared zotepine with other atypical antipsychotic medications. The total number of participants was 289. Klieser 1991 reported details of total average end point Brief Psychiatry Rating Scale (BPRS) score, average end point extra pyramidal symptom (EPS) score, use of antiparkinson medication, changes in syndrome short test. Lin 2003 used 'at least much improved' as a criterion for response to treatment. Lin 2003 was presented only as an abstract and reported values on "no clinically important response" (as defined by the original studies), average BPRS score, average change of prolactin from baseline, use of antiparkinson medication. Meyer-Lindenberg 1997 reported numbers leaving early for any reason, but the specific reasons for leaving the study early (adverse events, lack of efficacy) were not presented. All other outcomes were reported only for a small subgroup of matched participants. Therefore, for most outcomes of interest no relevant information was available. Though the overall attrition rate of 34% was considerable, it is lower than many other recent antipsychotic drug trials. As these trials were short term, we could not comment on long term effects. The overall data were limited, hence no firm conclusions could be drawn.

1. Clinically important change in global and general mental state

One study (Klieser 1991) suggested that zotepine may be as efficacious as the other three atypical antipsychotics such as clozapine, risperidone 4 mg, 8 mg and remoxipride. Lin 2003 suggested that zotepine may be less efficacious than clozapine. The result presented in Lin 2003 should be interpreted with caution, due to the limited data available in the abstract. This result confirmed the common notion that clozapine is the most effective antipsychotic drug available (Kane 1988), although replication is needed.

2. Leaving the study early

Klieser 1991 appears to have had no loss to follow up, but this is not explicitly described. Only Meyer-Lindenberg 1997 reported the number of participants leaving the study early for any reason but found no significant difference between the groups. Leaving the study early for any reason can be interpreted as a measure of acceptability of treatment. Nevertheless, the study was too small for any interpretation of relative acceptability of both the compounds. It was disappointing that specific reasons for leaving the study early had not been presented.

3. Adverse effects

The movement disorders associated with zotepine are comparable to clozapine, remoxipride and risperidone. The need for antiparkinson medication is similar to risperidone and remoxipride, but may be associated with increased need than necessary with clozapine. The result that more antiparkinson medication may be needed than with clozapine, should be approached with caution, as biperiden co-medication has been permitted in Klieser 1991. The frequency of biperiden administration appears to be dependent on the preparation, and the criteria for using biperiden has not been made clear. Zotepine may be associated with higher prolactin levels than clozapine. Zotepine, clozapine, risperidone, remoxipride are

known to induce many adverse effects, but in the absence of data it is impossible to evaluate their relative tolerability.

4. Missing outcomes

There is no information available on other important outcomes such as service use, adverse events other than movement disorders, prolactin increase, quality of life or satisfaction with care.

5. Summary

To date, zotepine has been compared with only three atypical second generation antipsychotic medications, in three short term trials (n=289). Two studies compared zotepine with clozapine. One study compared zotepine with risperidone, clozapine and remoxipride. Two of these trials were poorly reported. One study has been published only as an abstract, and the other presented usable data on only one outcome. Zotepine may be as effective as risperidone and remoxipride. The evidence base is insufficient to provide firm conclusions as to whether zotepine is as effective or less effective, than clozapine. The movement disorders and the cognitive changes appear to be similar to the other three atypicals clozapine, risperidone and remoxipride. The use of antiparkinson medication is comparable to risperidone and remoxipride, but may be associated with increased need than necessary with clozapine. Zotepine may be associated with higher prolactin levels than clozapine. The cognitive changes on the short syndrome test were comparable to the other three atypicals. There are no other data on other adverse events or other important outcomes. The results should be considered with caution due to high risk of bias.

Overall completeness and applicability of evidence

The three included studies reported only on eight outcomes. Important information on outcomes relevant to clinicians, consumers and policy makers (such as service use, other adverse events, quality of life or satisfaction with care) are not available. The studies were only short term which can be a problem in addressing the management of a typically chronic disorder such as schizophrenia. Furthermore, we could not identify any study which compared zotepine with any other atypical drugs. We feel the evidence to be woefully incomplete and the applicability of results very limited.

Quality of the evidence

The quality of the evidence is low. Klieser 1991 is not a well reported study with limited outcomes and not making explicit numbers leaving early or any data from the laboratory investigations. To date Lin 2003 has been presented only as an abstract. Details of the randomisation process and allocation concealment have not been reported and the study was only single-blind. It provided only limited data on efficacy and movement disorders and simple data such as the number of participants leaving the study early has not been presented. The allocation process of Meyer-Lindenberg 1997 was not described either and the only usable outcome was leaving the study early. Other outcomes could not be analysed because they have only been reported for a matched (i.e. no longer randomised) sub-sample (Figure 2).

Potential biases in the review process

There are always means by which bias could be operating. We could have failed to identify relevant studies. Also, we did change the protocol text in this version of the review. The reason for this was to improve clarity of method for this and future versions of the review. This did not change how we handled any studies or outcomes in this version.

Agreements and disagreements with other studies or reviews

A Cochrane review had previously concluded that there were no clear differences between zotepine and other second generation antipsychotic drugs (DeSilva 2006). This statement is compatible with our finding that zotepine may be as effective [or ineffective] as risperidone and remoxipride.

The evidence-base is insufficient to provide firm conclusions as to whether zotepine is as effective or less effective, than clozapine. The previous version of this review (Komossa 2010) concluded that zotepine may be less effective than clozapine. This was based mainly on one abstract (Lin 2003) with limited data. We have included Lin 2003 study in our current update. We have reached the current conclusions by including another study which compared different atypical antipsychotics and involving larger number of participants.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia

There are three, only short term trials that have compared zotepine with clozapine, risperidone and remoxipride. Zotepine may be as effective as risperidone and remoxipride, and much the same applies to zotepine and clozapine. The movement disorders and cognitive changes appear to be similar to the three atypical antipsychotics clozapine, risperidone and remoxipride. The need for antiparkinson medication is similar to risperidone and remoxipride, but use of clozapine may be associated with increased need than is necessary with clozapine. Zotepine may be associated with higher prolactin levels than clozapine. There are no other data on other adverse events or other important outcomes. The evidence base is small and also prone to bias, making practical recommendations difficult.

2. For clinicians

Other than the comparison presented here, there are hardly any randomised controlled studies available comparing zotepine with other second generation antipsychotic drugs such as amisulpride, aripiprazole, olanzapine, quetiapine, sertindole, ziprasidone. More studies are needed to examine the relative efficacy and effects of zotepine with other second generation antipsychotic drugs and until that happens use of zotepine in comparison to other newer generation drugs is not based on good evidence.

3. For managers/policy makers

Only three small studies on zotepine versus clozapine, risperidone and remoxipride are available. The data relevant for policy makers such as service utilisation or functioning in society do not seem to exist. We are unable to make any particular recommendations for

managers or policy makers except that better data does exist from comparisons of other newer antipsychotics and therefore they may be recommended before zotepine.

Implications for research

1. General

We stress that strict adherence to the CONSORT statement (Moher 2001) would improve the quality of reporting of future studies.

2. Specific

Currently only three short term trials comparing zotepine with clozapine, risperidone and remoxipride are available. There is, therefore, plenty of room for more research. Importantly, future studies should compare zotepine with second generation antipsychotic drugs other than clozapine and should be of longer duration and address real-world effectiveness, in addition to pure efficacy and tolerability (Table 1).

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SOURCES OF SUPPORT

Internal sources

- Cochrane Schizophrenia Group, Nottingham, United Kingdom, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was slightly adapted to new functions available in Review Manager 5 but also refinements of text within the methods section. Although the text has changed and improved, we do not feel that this has made any impact on the results.

CHARACTERISTICS OF STUDIES

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

Klieser 1991

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 4 weeks. Design: parallel.
Participants	Diagnosis: paranoid hallucinatory schizophrenia (ICD 9). N=180. Age:18-65 years. Sex: 44M, 53F. Setting:Unclear.

History: acutely ill, duration ill 2-4months.

Excluded: depot neuroleptic treatment in the preceding 4 weeks, age other than 18-65 years, pregnancy, severe physical disease, allergies, psychoses other than schizophrenia, other history or present impairment of brain functioning, drug addiction or intoxication, anamnestic hyperthermia to anaesthetics or neuroleptics

Interventions	1 Zotepine: fixed dose, 225 mg/day. N=20. 2 Clozapine: fixed dose 400 mg. N=37. 3 Risperidone: fixed dose, 4 mg. N=20. 4 Risperidone: fixed dose, 8 mg. N=20. 5 Remoxipride: fixed dose, 400 mg. N=38. 6 Haloperidol: fixed dose, 15 mg. N=45.
Outcomes	Mental state: BPRS. Cognitive functioning: Short syndrome test (SKT). Adverse effects: CGI, EPS (Simpson & Angus), use of anticholinergic medication Unable to use - Laboratory measures: EEG, ECG, blood pressure, pulse rate (no data)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Double, no further details.
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving early are missing.
Free of selective reporting?	High risk	Data on laboratory measures were not presented.
Free of other bias?	High risk	Biperiden co-medication was permitted.

Lin 2003

Methods	Allocation: random, no further details. Blindness: single, rater-blind. Duration: 12 weeks. Design: parallel.
Participants	Diagnosis: schizophrenia. N=59. Age: 20-65 years. Sex: not described. Setting: inpatient. History: BPRS >30, clozapine treatment for more than 5 months. Excluded: not described.
Interventions	1 Clozapine: flexible dose, mean ~ 387 mg/day. N=24. 2 Zotepine: flexible dose, mean ~ 377 mg/day. N=35.
Outcomes	Mental state: BPRS total score. Adverse effects: use of antiparkinson medication, laboratory (prolactin) Unable to use - Global state: CGI (no data). Adverse effects: BAS, SAS, UKU, weight, laboratory - haematology, biochemistry, urine analysis (no data)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? All outcomes	Unclear risk	Single blind (blind raters). Whether the blinding strategy was successful has not been examined. There were no objective outcomes. Overall, it is unclear whether blinding was a concern
Incomplete outcome data addressed? All outcomes	High risk	The number of participants leaving the study early has not been reported. Therefore, there was no attempt to address incomplete outcome data
Free of selective reporting?	High risk	The study has only been published as an abstract in which only a few outcomes (global state, use of antiparkinson medication and mental state) have been reported
Free of other bias?	High risk	The study used an "enriched design". All participants had been stable on clozapine before the study and were than randomised to either continuation of clozapine or switched to zotepine. This design can mean an advantage for clozapine

Meyer-Lindenberg 1997

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel.
Participants	Diagnosis: schizophrenia catatonic, hebephrenic, paranoid or residual (DSM -III - R). N=50. Age: 18-60 years. Sex: 18M, 8F. Setting: unclear. History: BPRS >40 after washout phase, no previous treatment with either medication. Excluded: former treatment with clozapine or zotepine.
Interventions	1 Clozapine: flexible dose, allowed range 150-450 mg/day. N=25. 2 Zotepine: flexible dose, allowed range 150-450 mg/day. N=25
Outcomes	Leaving the study early: any reason. Unable to use - Global state: CGI (no data). Mental state: BPRS, SANS (reported for a no longer randomised sub -sample, no usable data). General functioning: NOSIE, Cognitive Functioning: maze tests (reported for a no longer randomised sub -sample, no usable data). Adverse events: UKU, ECG, weight gain (reported for a no longer randomised sub - sample, no usable data)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	Not described.

Blinding? All outcomes	Unclear risk	Double, no further details, unclear whether successful.
Incomplete outcome data addressed? All outcomes	High risk	Reasons for leaving early - not reported (overall attrition high - 34%)
Free of selective reporting?	High risk	Apart from 'leaving the study' all other data reported for a no longer randomised subsample
Free of other bias?	Low risk	Sponsored by manufacturer of zotepine.

Diagnostic tool

DSM III-R and DSM-IV - Diagnostic Statistical Manual version 3 Revised and version 4.

ICD 10 - The International Statistical Classification of Diseases and Related Health Problems.

Rating Scales

Global rating scales

CGI - Clinical Global Impressions.

CGI-S - Clinical Global Impression-Severity.

CGI-I - Clinical Global Impression-Improvement.

Mental state

BPRS - Brief Psychiatric Rating Scale.

PANSS - Positive and Negative Syndrome Scale.

SANS - Scale for the Assessment of Negative Symptoms.

Side effects

AIMS - Abnormal Involuntary Movement Scale.

BAS - Barnes Akathisia Scale.

ESRS - Extrapyramidal Syndrome Rating Scale.

SAS - Simpson-Angus Index - for neurological side effects.

UKU - Udvælg for kliniske undersøgelser Side Effect Rating Scale.

Quality of Life

QLS - Quality of Life Scale.

SWN -Subjective Well-being List.

General functioning:

NOSIE - Nurses' observation scale for inpatient evaluation

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

Study	Reason for exclusion
Briken 2002	Allocation: randomised. Participants: people with schizophrenia (number unclear). Interventions: zotepine vs risperidone vs olanzapine. Outcomes: PANSS, UKU, PANSS -EC, but no data available.
Chen 2006	Allocation: not randomised, open label.
Hada 1985	Allocation: not randomised, diagnostic study.
Hen 1987	Allocation: not randomised, diagnostic study.
Komada 1987	Allocation: not randomised, case series.
Lin 2005	Allocation: not randomised, naturalistic study.
Ohhara 1988	Allocation: not randomised, case series.

Study	Reason for exclusion
Perro 1999	Allocation: randomised. Participants: people with schizophrenia (number = 75). Interventions: zotepine vs risperidone vs olanzapine vs sertindole. Outcomes: PANSS, CGI, GAF, UKU, BDI, SCL -R 90, QLS scales but no data available on any of them (PANSS, CGI, GAF, UKU, BDI, SCL -R 90, QLS scales)
Saletu 1987	Allocation: randomised, but placebo controlled.
Takashina 1986	Allocation: not randomised, case series.

Characteristics of ongoing studies [ordered by study ID]

Tsai 2007

Trial name or title	Amulti centre comparative study to evaluate the anti -aggression effect and safety of zotepine versus risperidone in aggressive schizophrenic patients in an acute ward
Methods	Allocation: random, no further details. Blindness: open label. Duration: unknown. Design: parallel.
Participants	Diagnosis: schizophrenia. N=160. Age: adults. Sex: mixed gender. History: aggression.
Interventions	<ul style="list-style-type: none"> • Zotepine. • Risperidone. • Active control.
Outcomes	Mental state: PANSS-EC, PANSS. Global outcome: CGI.
Starting date	17/01/2008
Contact information	Astellas Pharma, Taiwan Inc.
Notes	

DATA AND ANALYSES

Comparison 1

ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1. No clinically important response (as defined by the original studies)	1	59	Risk Ratio (M-H, Random, 95% CI)	8.23 [1.14, 59.17]
2 Leaving the study early - any reason	1	50	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.65, 3.15]
3 Mental state: 1. Average score (BPRS total, high=poor)	1	59	Mean Difference (IV, Random, 95% CI)	6.0 [2.17, 9.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Mental state: 2. Average endpoint score (BPRS total, high=poor)	1	57	Mean Difference (IV, Random, 95% CI)	2.20 [-7.77, 12.17]
5 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)	1	57	Mean Difference (IV, Random, 95% CI)	2.1 [-0.25, 4.45]
6 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication	2	116	Risk Ratio (M-H, Random, 95% CI)	20.96 [2.89, 151.90]
7 Adverse effects: 2. Prolactin - average change from baseline (in ng/ml)	1	59	Mean Difference (IV, Random, 95% CI)	33.4 [14.87, 51.93]
8 Cognitive functioning: Not improved (SKT)	1	57	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.21, 1.52]

Comparison 2

ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: Average endpoint score (BPRS total, high=poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 vs 4 mg Risperidone	1	40	Mean Difference (IV, Random, 95% CI)	1.40 [-9.82, 12.62]
1.2 vs 8 mg Risperidone	1	40	Mean Difference (IV, Random, 95% CI)	-1.30 [-12.95, 10.35]
2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 vs 4 mg risperidone	1	40	Mean Difference (IV, Random, 95% CI)	1.80 [-0.64, 4.24]
2.2 vs 8 mg risperidone	1	40	Mean Difference (IV, Random, 95% CI)	2.5 [-0.05, 5.05]
3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 vs 4 mg risperidone	1	40	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.79, 45.42]
3.2 vs 8 mg risperidone	1	40	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.69, 13.12]
4 Cognitive functioning: Not improved (SKT)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 vs 4 mg risperidone	1	40	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.25, 2.55]
4.2 vs 8 mg risperidone	1	40	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.29, 3.45]

Comparison 3

ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: Average endpoint score (BPRS total, high=poor)	1	58	Mean Difference (IV, Random, 95% CI)	5.70 [-4.13, 15.53]
2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)	1	58	Mean Difference (IV, Random, 95% CI)	0.0 [-2.62, 2.62]
3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication	1	49	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.41, 2.29]
4 Cognitive functioning: Not improved (SKT)	1	58	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.25, 1.89]

Analysis 1.1. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 1 Global state: 1. No clinically important response (as defined by the original studies)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 1 Global state: 1. No clinically important response (as defined by the original studies)

Analysis 1.2. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 2 Leaving the study early - any reason

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 2 Leaving the study early - any reason

Analysis 1.3. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 3 Mental state: 1. Average score (BPRS total, high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 3 Mental state: 1. Average score (BPRS total, high=poor)

Analysis 1.4. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 4 Mental state: 2. Average endpoint score (BPRS total, high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 4 Mental state: 2. Average endpoint score (BPRS total, high=poor)

Analysis 1.5. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 5 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 5 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Analysis 1.6. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 6 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 6 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Analysis 1.7. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 7 Adverse effects: 2. Prolactin - average change from baseline (in ng/ml)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 7 Adverse effects: 2. Prolactin - average change from baseline (in ng/ml)

Analysis 1.8. Comparison 1 ZOTEPINE versus CLOZAPINE - all short term outcomes, Outcome 8 Cognitive functioning: Not improved (SKT)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcome: 8 Cognitive functioning: Not improved (SKT)

Analysis 2.1. Comparison 2 ZOTEPINE versus RISPERIDONE - all short term outcomes, Outcome 1 Mental state: Average endpoint score (BPRS total, high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcome: 1 Mental state: Average endpoint score (BPRS total, high=poor)

Analysis 2.2. Comparison 2 ZOTEPINE versus RISPERIDONE - all short term outcomes, Outcome 2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcome: 2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Analysis 2.3. Comparison 2 ZOTEPINE versus RISPERIDONE - all short term outcomes, Outcome 3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcome: 3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Analysis 2.4. Comparison 2 ZOTEPINE versus RISPERIDONE - all short term outcomes, Outcome 4 Cognitive functioning: Not improved (SKT)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcome: 4 Cognitive functioning: Not improved (SKT)

Analysis 3.1. Comparison 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes, Outcome 1 Mental state: Average endpoint score (BPRS total, high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcome: 1 Mental state: Average endpoint score (BPRS total, high=poor)

Analysis 3.2. Comparison 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes, Outcome 2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcome: 2 Adverse effects: 1a. Extrapyramidal effects - average end point EPS score (high=poor)

Analysis 3.3. Comparison 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes, Outcome 3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcome: 3 Adverse effects: 1b. Extrapyramidal effects - use of antiparkinson medication

Analysis 3.4. Comparison 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes, Outcome 4 Cognitive functioning: Not improved (SKT)

Review: Zotepine versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcome: 4 Cognitive functioning: Not improved (SKT)

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 1, 2010

Date	Event	Description
5 October 2011	Amended	Contact details updated.
10 November 2010	Amended	Contact details updated.
6 October 2010	Amended	Contact details updated.
1 November 2009	New citation required and conclusions have changed	Update on comparing the efficacy of zotepine with other second generation antipsychotics. One additional study has been included in this update (Kleser 1991).

Appendix 1. Search strategy for the version of 2007

We searched the Cochrane Schizophrenia Group Trials Register (April 2007) using the phrase: `(((zotepin* AND(amisulprid* OR aripiprazol*OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR ziprasidon*))) in title, abstract or index terms of REFERENCE) or ((zotepin* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon * OR ziprasidon*)) in interventions of STUDY)]`

The Cochrane Schizophrenia Group Trials Register is maintained on Meerkat 1.5.1. This version of Meerkat stores references as studies. When an individual reference is selected through a search, all references which have been identified as the same study are also selected. This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

ZOTEPINE versus CLOZAPINE for schizophrenia (all short term outcomes)

Patient or population: patients with schizophrenia

Settings: in hospital

Intervention: ZOTEPINE versus CLOZAPINE - all short term outcomes

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk				
	Control				
	ZOTEPINE versus CLOZAPINE - all short term outcomes				
Mental state: Average score (BPRS total, high=poor) Brief Psychiatric Rating Scale. Scale from: 0 to 126. Follow-up: 12 weeks			59 (1 study)	⊕⊕⊕⊕ very low ^{1,2,3}	The mean Mental state: Average score (BPRS total, high=poor) in the intervention groups was *6 higher (2.17 to 9.83 higher)
Global state: No clinically important response (as defined by the original studies) clinical assessment Follow-up: 12 weeks	Low risk population	RR 8.23 (1.14 to 59.17)	59 (1 study)	⊕⊕⊕⊕ very low ^{1,3,4}	
	50 per 1000	411 per 1000 (57 to 1000)			
	Medium risk population				
	100 per 1000	823 per 1000 (114 to 1000)			
	High risk population				
	200 per 1000	1000 per 1000 (228 to 1000)			
Adverse effects: Extrapyramidal effects - use of antiparkinson medication	Low risk population	RR 20.96 (2.89 to 151.9)	116 (2 studies)	⊕⊕⊕⊕ very low ^{1,3,4}	
	10 per 1000	210 per 1000 (29 to 1000)			
	Medium risk population				
	100 per 1000	1000 per 1000 (289 to 1000)			
	High risk population				
	200 per 1000	1000 per 1000 (578 to 1000)			

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ZOTEPINE versus CLOZAPINE - all short term outcomes				
Behaviour: No clinically important response (as defined by the original studies)	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported on this outcome that we had prespecified as being of importance

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Limitations in design - serious: randomisation stated not described, blinding not tested.

² Indirectness: scale derived score, problematic to interpret.

³ Publication bias: likely as small trial with commercial interest.

⁴ Imprecision: considerable because of few events in one arm. Small study/studies.

ADDITIONAL SUMMARY OF FINDINGS

ZOTEPINE versus RISPERIDONE for schizophrenia (all short term outcomes)

Patient or population: patients with schizophrenia

Settings: in hospital

Intervention: ZOTEPINE versus RISPERIDONE - all short term outcomes

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ZOTEPINE versus RISPERIDONE - all short term outcomes				
Mental state: Average endpoint score (BPRS total, high=poor) - vs 4mg Risperidone Scale from: 0 to 129. Follow-up: 12 weeks		The mean Mental state: Average endpoint score (BPRS total, high=poor) - vs 4mg Risperidone in the intervention groups was 1.4 higher (9.82 lower to 12.62 higher)		40 (1 study)	⊕○○○ very low 1,2,3,4	
Mental state: Average endpoint score (BPRS total, high=poor) - vs 8 mg Risperidone Scale from: 0 to 129. Follow-up: 12 weeks		The mean Mental state: Average endpoint score (BPRS total, high=poor) - vs 8 mg Risperidone in the intervention groups was 1.3 lower (12.95 lower to 10.35 higher)		40 (1 study)	⊕○○○ very low 1,2,3,4	
Global state: No clinically important response (as defined by the original studies)	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported on this outcome that we had prespecified as being of importance
Adverse effects: Extrapyramidal effects - use of antiparkinson medication - vs 4mg risperidone Follow-up: 12 weeks	Low risk population	RR 6 (0.79 to 45.42)	RR 6 (0.79 to 45.42)	40 (1 study)	⊕○○○ very low 1,3,4	
	50 per 1000	300 per 1000 (40 to 1000)				
	Medium risk population					
	200 per 1000	1000 per 1000 (158 to 1000)				
	High risk population					
	400 per 1000	1000 per 1000 (316 to 1000)				

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ZOTEPINE versus RISPERIDONE - all short term outcomes				
Adverse effects: Extrapyramidal effects - use of antiparkinson medication - vs 8mg risperidone Follow-up: 12 weeks	Low risk population		RR 3 (0.69 to 13.12)	40 (1 study)	⊕⊕⊕⊕ very low ^{1,3,4}	
	50 per 1000	150 per 1000 (34 to 656)				
	Medium risk population					
	200 per 1000	600 per 1000 (138 to 1000)				
	High risk population					
	400 per 1000	1000 per 1000 (276 to 1000)				
Behaviour: No clinically important response (as defined by the original studies)	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported on this outcome that we had prespecified as being of importance

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Limitations in design - serious: randomisation stated not described, blinding not tested.

² Indirectness: scale derived score, problematic to interpret.

³ Imprecision: considerable because of few events in one arm. Small study/studies.

⁴ Publication bias: likely as small trial with commercial interest.

ZOTEPINE versus REMOXIPRIDE for schizophrenia (all short term outcomes)

Patient or population: patients with schizophrenia

Settings: in hospital

Intervention: ZOTEPINE versus REMOXIPRIDE - all short term outcomes

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk				
	Corresponding risk				
	Control				
Mental state: Average endpoint score (BPRS total, high-poor) Scale from: 0 to 129, Follow-up: 12 weeks	ZOTEPINE versus REMOXIPRIDE - all short term outcomes The mean Mental state: Average endpoint score (BPRS total, high-poor) in the intervention groups was 5.7 higher (4.13 lower to 15.53 higher)		58 (1 study)	⊗⊗⊗⊗ very low 1,2,3,4	
Global state: No clinically important response (as defined by the original studies)	See comment	Not estimable	0 (0)	See comment	No trials reported on this outcome that we had prespecified as being of importance
Adverse effects: Extrapyramidal effects - use of antiparkinson medication Follow-up: 12 weeks	Low risk population	RR 0.97 (0.41 to 2.29)	49 (1 study)	⊗⊗⊗⊗ low 1,4	
	50 per 1000 (20 to 114)				
	Medium risk population				
	200 per 1000 (82 to 458)				
	High risk population				
	400 per 1000 (164 to 916)				
Behaviour: No clinically important response (as defined by the original studies)	See comment	Not estimable	0 (0)	See comment	No trials reported on this outcome that we had prespecified as being of importance

* The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Limitations in design - serious: randomisation stated not described, blinding not tested.

² Indirectness: scale derived score, problematic to interpret.

³ Imprecision: considerable because of few events in one arm. Small study/studies.

⁴ Publication bias: likely as small trial with commercial interest.

WHAT'S NEW

Last assessed as up-to-date: 21 May 2010.

Date	Event	Description
7 December 2011	Amended	Contact details updated.

References to studies included in this review

* Indicates the major publication for the study

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PLAIN LANGUAGE SUMMARY

Zotepine versus other atypical antipsychotic drugs for schizophrenia

This review compares the effects of zotepine to other second generation antipsychotic drugs. Three trials suggest that the efficacy of zotepine may be comparable to risperidone and remoxipride. The evidence base is insufficient to provide firm conclusions as to whether zotepine is as effective or less effective than clozapine. The movement disorders and the cognitive changes appear to be similar to clozapine, risperidone and remoxipride. The need for antiparkinson medication is similar to risperidone and remoxipride, but may be associated with increased need than necessary with clozapine.

Figure 1.

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Klieser 1991	?	?	?	-	-	-
Lin 2003	?	?	?	-	-	-
Meyer-Lindenberg 1997	?	?	?	-	-	+

Figure 2.

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Table 1**Suggested design of future study**

Methods	Allocation: randomised - clearly described generation of sequence and concealment of allocation. Blinding: double - described and tested. Duration: 6 months minimum.
Participants	Diagnosis: schizophrenia (operational criteria). N=2700.* Age: any. Sex: both. History: any.
Interventions	<ol style="list-style-type: none"> 1 Zotepine: dose ~ 100-300 mg/day. N=300. 2 Amisulpride: dose ~ 400-800 mg/day. N=300. 3 Aripiprazole: dose ~ 10-30 mg/day. N=300. 4 Clozapine: dose ~ 300-800 mg/day. N=300. 5 Olanzapine: dose ~ 10-20 mg/day. N=300. 6 Quetiapine: dose ~300-800 mg/day. N=300. 7 Risperidone: dose ~ 4-8 mg/day. N=300. 8 Sertindole: dose ~ 12-24 mg/day. N=300. 9 Ziprasidone: dose ~ 120-160 mg/day. N=300.
Outcomes	Leaving study early (any reason, adverse events, inefficacy). Service outcomes: hospitalised, time in hospital, attending out patient clinics. Global impression: CGI **, relapse. Mental state: Target symptoms - CGI. Adverse events: UKU. Employment, family satisfaction, patient satisfaction.

* power calculation suggested 300/group would allow good chance of showing a 10% difference between groups for primary outcome.

** Primary outcome