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Clozapine versus other atypical antipsychotics for schizophrenia

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Abstract

Background—Clozapine is an atypical antipsychotic demonstrated to be superior in the treatment of refractory schizophrenia which causes fewer movement disorders. Clozapine, however, entails a significant risk of serious blood disorders such as agranulocytosis which could be potentially fatal. Currently there are a number of newer antipsychotics which have been developed with the purpose to find both a better tolerability profile and a superior effectiveness.

Objectives—To compare the clinical effects of clozapine with other atypical antipsychotics (such as amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine) in the treatment of schizophrenia and schizophrenia-like psychoses.

Search methods—We searched the Cochrane Schizophrenia Groups Register (June 2007) and reference lists of all included randomised controlled trials. We also manually searched appropriate

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Claudia Asenjo L: protocol development, searching, study selection, data extraction, report writing.
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DECLARATIONS OF INTEREST

Claudia Asenjo L: none known.
Katja Komossa: participated in investigator meetings for clinical trials sponsored by Astra Zeneca, Pfizer, Sanofi Aventis, Servier.
Christine Rummel: received lecture honoraria and travel grants to attend scientific meetings from AstraZeneca, Janssen-Cilag, EliLilly and Pfizer.
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journals and conference proceedings relating to clozapine combination strategies and contacted relevant pharmaceutical companies.

Selection criteria—All relevant randomised, at least single-blind trials, comparing clozapine with other atypical antipsychotics, any dose and oral formulations, for people with schizophrenia or related disorders.

Data collection and analysis—We selected trials and extracted data independently. For dichotomous data we calculated relative risks (RR) and their 95% confidence intervals (CI) based on a random-effects model. We calculated numbers needed to treat/harm (NNT/NNH) where appropriate. For continuous data, we calculated mean differences (MD) again based on a random-effects model.

Main results—The review currently includes 27 blinded randomised controlled trials, which involved 3099 participants. Twelve randomised control trials compared clozapine with olanzapine, five with quetiapine, nine with risperidone, one with ziprasidone and two with zotepine. Attrition from these studies was high (overall 30.1%), leaving the interpretation of results problematic. Clozapine had a higher attrition rate due to adverse effects than olanzapine (9 RCTs, n=1674, RR 1.60 CI 1.07 to 2.40, NNT 25 CI 15 to 73) and risperidone (6 RCTs, n=627, RR 1.88 CI 1.11 to 3.21, NNT 16 CI 9 to 59). Fewer participants in the clozapine groups left the trials early due to inefficacy than risperidone (6 RCTs, n=627, RR 0.40 CI 0.23 to 0.70, NNT 11 CI 7 to 21), suggesting a certain higher efficacy of clozapine.

Clozapine was more efficacious than zotepine in improving the participants general mental state (BPRS total score: 1 RCT, n=59, MD −6.00 CI −9.83 to −2.17), but not consistently more than olanzapine, quetiapine, risperidone and ziprasidone. There was no significant difference between clozapine and olanzapine or risperidone in terms of positive or negative symptoms of schizophrenia. According to two studies from China quetiapine was more efficacious for negative symptoms than clozapine (2 RCTs, n=142, MD 2.23 CI 0.99 to 3.48).

Clozapine produced somewhat fewer extrapyramidal side-effects than risperidone (use of antiparkinson medication: 6 RCTs, n=304, RR 0.39 CI 0.22 to 0.68, NNT 7 CI 5 to 18) and zotepine (n=59, RR 0.05 CI 0.00 to 0.86, NNT 3 CI 2 to 5). More participants in the clozapine group showed decreased white blood cells than those taking olanzapine, more hypersalivation and sedation than those on olanzapine, risperidone and quetiapine and more seizures than people on olanzapine and risperidone. Also clozapine produced an important weight gain not seen with risperidone.

Other differences in adverse effects were less documented and should be replicated, for example, clozapine did not alter prolactin levels whereas olanzapine, risperidone and zotepine did; compared with quetiapine, clozapine produced a higher incidence of electrocardiogram (ECG) alterations; and compared with quetiapine and risperidone clozapine produced a higher increase of triglyceride levels. Other findings that should be replicated were: clozapine improved social functioning less than risperidone and fewer participants in the clozapine group had to be hospitalised to avoid suicide attempts compared to olanzapine.

Other important outcomes such as service use, cognitive functioning, satisfaction with care or quality of life were rarely reported.

Authors' conclusions—Clozapine may be a little more efficacious than zotepine and risperidone but further trials are required to confirm this finding. Clozapine differs more clearly in adverse effects from other second generation antipsychotics and the side-effect profile could be key in the selection of treatment depending on the clinical situation and a patient's preferences. Data on other important outcomes such as cognitive functioning, quality of life, death or service use are currently largely missing, making further large and well-designed trials necessary. It is also important to take into account that the large number of people leaving the studies early limits the validity and interpretation of our findings.

Medical Subject Headings (MeSH)

Antipsychotic Agents [* therapeutic use]; Benzodiazepines [therapeutic use]; Clozapine [* therapeutic use]; Dibenzothiazepines [therapeutic use]; Dibenzothiepins [therapeutic use]; Piperazines [therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [therapeutic use]; Schizophrenia [* drug therapy]; Thiazoles [therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Schizophrenia is a chronic and disabling severe mental disorders, which involves a complex set of disturbances, associated with abnormalities of brain structure and function, disorganised speech and behavior, delusions, and hallucinations (WHO 1998). It is sometimes called a psychotic disorder or a psychosis. Also, people with schizophrenia present dysfunction in one or more major areas of functioning e.g. social and occupational areas (Mueser 2004). The prevalence is between 0.7 - 1% of the adult population (Lehman 2004), however, due to frequent chronicity, this disease leads to high levels of social burden and cost, as well as an incalculable amount of individual pain and suffering (WHO 1998, van Os 2009).

Description of the intervention

The therapeutic arsenal for schizophrenia is wide and varied. Conventional, typical or first generation antipsychotics, such as chlorpromazine and haloperidol have been used as a first choice for treatment for over 50 years (Kane 1990). They are effective in reducing the positive and some of the negative symptoms of schizophrenia, however they could produce unpleasant adverse effects such as sedation, demotivation and movement disorders that often lead to treatment discontinuation which then may result in relapse of symptoms (Gaebel 1997). In 1959 the development of a new generation of neuroleptics, classified as atypical antipsychotics, began with clozapine (ACP 2002). Although clozapine has demonstrated to be superior to the older typical antipsychotics in the treatment of the refractory schizophrenia (Wahlbeck 1999), it can also produce severe adverse effects, particularly hypersalivation and blood disorders which restrict its use.

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After clozapine, a considerable number of newer atypical antipsychotics drugs have been developed in the hope of finding new compounds with a better tolerability profile and higher efficacy (Stroup 2003). These include amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine. The effectiveness of these newer atypical antipsychotics compared to clozapine is not yet established. Some studies suggest that the newer atypical antipsychotics have a similar effectiveness to clozapine, and suggest that they may also be effective in resistant schizophrenia with a better security profile (Kane 2006, Citrome 2002).

How the intervention might work

Clozapine was the first atypical antipsychotic manufactured by Sandoz in 1959 and introduced to the market in the 1960s. Most atypical antipsychotics are antagonists at serotonin and dopamine receptors, but they have different pharmacological profiles according to their level of affinity with the different receptor subtypes (Miyamoto 2005). Clozapine has multiple sites of action such as dopaminergic, serotonergic, cholinergic and histaminergic receptors, with high affinity to D4 and 5HT2A receptors and low affinity to D1, D2 and D3 receptors. The low affinity of striatal D2 receptors and high one of 5HT2A receptors could explain its low extra-pyramidal symptoms liability, its atypical profile (Beaumont 2000, Miyamoto 2005). Clozapine differs from conventional antipsychotics for its greater efficacy in controlling positive symptoms in people with treatment-resistant illness and by inducing few extra-pyramidal effects (Kane 1988, Wahlbeck 1999). In 1975, however, sixteen people in Finland developed severe blood reactions - a substantial decline in the white blood cells (neutropenia) which made the individuals dangerously susceptible to infection (Idänpään-He.1977). From these sixteen, eight died. The drug was then largely withdrawn from the market (in the UK, Australia and USA), although the withdrawal was not worldwide (O'Brien 2004) e.g. Scandinavia, Germany and China kept the drug in the market. The cumulative experience with these patients and the subsequent studies demonstrated its superiority in patients with treatment-resistant schizophrenia and also that clozapine could be administered safely, when patients are carefully monitored (Naheed 2001,O'Brien 2004). Clozapine was reintroduced, over a decade later, for people with schizophrenia who were either resistant to typical neuroleptics or who were intolerant of the adverse effects of them (Wahlbeck 1999).

Why it is important to do this review

So far, reviews have not found any robust evidence that other atypical drugs have a clinical effect and tolerability similar to clozapine (Gilbody 2000, McEvoy 2006). This could in part be due to a lack of primary studies with good methodological quality, which measure important clinical outcomes during a prolonged time with enough statistical power (Tuunainen 2000). By systematically searching for all known randomised controlled trials of clozapine versus other atypical antipsychotics, this review should amass more data and provide robust, useful evidence.

This new review is an update of the previous review "Newer atypical antipsychotic medication vs. clozapine" which compared clozapine with all other atypical antipsychotics pooled into one group (Tuunainen 2000). Since the atypical antipsychotics are a

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heterogenous group with quite different pharmacological profile and the amount of data published on this topic has grown enormously during the last few years, it is now possible to explore atypical comparisons with clozapine separately. For this reason, the title and the review protocol have been modified.

OBJECTIVES

To compare the clinical effects of clozapine with other atypical antipsychotic drugs in the treatment of schizophrenia and schizophrenia-like psychoses.

METHODS

Criteria for considering studies for this review

Types of studies—All relevant randomised controlled trials that compared clozapine with other atypical antipsychotics for treatment of schizophrenia and similar psychotic mental illness. We included only the first treatment phase of randomised cross-over studies. Quasi-randomised trials were excluded. All Included trials needed to be at least single-blind (blind raters).

Types of participants—People with schizophrenia, and other types of schizophrenia-like psychoses (schizophreniform and schizoaffective disorders) diagnosed by any criteria. We included people with schizophreniform and schizoaffective disorders as there is no evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994).

Types of interventions—

1. Clozapine: oral formulation, any dose.
2. New atypical antipsychotics such as amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine: oral formulation, any dose.

We excluded studies where participants were prescribed more than one, or combinations of atypical antipsychotics.

Types of outcome measures—We grouped outcomes by time - short term (up to 12 weeks), medium term (up to 26 weeks) and long term (more than 26 weeks). As schizophrenia is a long term disorder, short treatment studies are not clinically relevant. We decided to exclude studies lasting less than two 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) at long term.

Secondary outcomes

1. Death

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1.1 Suicide

1.2 Natural causes

2. Leaving the studies early

2.1 Any reason

2.2 Specific reason (as described by individual studies)

3. Global state

3.1 No clinically important change in global state (as defined by individual studies) at short and medium term

3.2 Relapse (as defined by the individual studies)

4. Mental state

4.1 No clinically important change in general mental state at short and medium term

4.2 Average endpoint general mental state score

4.3 Average change in general mental state scores

4.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia) at short and medium term

4.5 Average endpoint specific symptom score 4.6 Average change in specific symptom scores

5. General functioning

5.1 No clinically important change in general functioning at short and medium term

5.2 Average endpoint general functioning score

5.3 Average change in general functioning scores

6. Quality of life/satisfaction with treatment

6.1 No clinically important change in quality of life at short and medium term

6.2 Average endpoint quality of life score

6.3 Average change in quality of life scores

7. Cognitive functioning

7.1 No clinically important change in cognitive functioning at short and medium term

7.2 Average endpoint cognitive functioning score

7.3 Average change in cognitive functioning scores

8. Service use

8.1 Number of patients hospitalised

8.2 Number of patients discharged or readmitted (as defined in individual trial)

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9. Adverse effects - general and specific

9.1 Number of participants with at least one adverse effect

9.2 Clinically important specific adverse effects (cardiac effects, movement disorders, prolactin increase and associated adverse events, metabolic side effects (as such weight gain, hyperlipidaemia and hyperglycaemia), effects on white blood cell count)

9.3 Average endpoint specific adverse effects

9.4 Average change in specific adverse effects

Search methods for identification of studies

Electronic searches—We searched the Cochrane Schizophrenia Group's Trials Register (June 2007) using the phrase:

[(*clozapin* OR *clozaril* OR *denzapin* OR *zaponex*) in title, abstract and index terms in REFERENCE and interventions of STUDY]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group module).

Searching other resources

1. Reference lists: We searched references of articles selected for further relevant trials.

2. Conferences: We sought studies from recent conference proceedings if available.

3. Pharmaceutical companies: We contacted companies performing trials with amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine directly to obtain data on unpublished trials.

4. Personal contact: We contacted the first author of each included study for information regarding unpublished trials or for missing information.

Data collection and analysis

Selection of studies—CA 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 independently decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought additional information and these trials were added to the list of those awaiting assessment.

Data extraction and management

1. Data extraction: CA, KK, CR, HH, FS, SS, SL independently extracted the data from 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, the data were not entered and we added the trial to the list of those awaiting assessment.

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2. Management: We extracted the data onto standard simple forms. Where possible, 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 clozapine.

3. Scale-derived data

3.1 Valid scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, or are even ad hoc. It is accepted generally that measuring instruments should have the properties of reliability (the extent to which a test effectively measures anything at all) and validity (the extent to which a test measures that which it is supposed to measure) (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.

Assessment of risk of bias in included studies—We assessed risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009). 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 not have included studies where sequence generation was at high risk of bias or where allocation was clearly not concealed.

Measures of treatment effect

1. Binary data: We calculated the relative risk (RR) and its 95% confidence interval (CI) based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. 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). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number needed to harm (NNH) as the inverse of the risk difference, and its 95% confidence interval (CI).

Where possible, efforts were made to convert outcome measures to dichotomous data. This can 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 2005a, Leucht 2005b). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

We carried out an intention-to-treat analysis. Everyone allocated to the interventions were counted, whether they completed the follow up or not. It was assumed that those who

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dropped out had no change of their outcome. This rule is conservative concerning response to treatment, because it assumes that those discontinuing the studies would not have responded. It is not conservative concerning side-effects, because it assumes that those discontinuing the studies would not have developed the side-effect if they had remained in the study, but we felt that assuming that all drop-outs would have developed side-effects would overestimate the risk.

2. Continuous data

2.1 Rating scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, or are even ad hoc. For outcome instruments some minimum standards have to be set. They were that: (i) the psychometric properties of the instrument should have been described in a peer-reviewed journal (Marshall 2000);and (ii) the instrument should either be: (a) a self report, or (b) completed by an independent rater or relative (not the therapist).

2.2 Summary statistic: For continuous outcomes we estimated a mean difference (MD) between groups. MDs were again based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. When standard errors instead of standard deviations (SD) were presented, we converted the former to standard deviations. If both were missing we estimated SDs from P-values or used the average SD of the other studies (Furukawa 2006).

2.3 Endpoint versus change data: We combined both endpoint data and change data in the analysis, because there is no principal statistical reason why endpoint and change data should measure different effects (Higgins 2009).

2.4 Skewed data: The meta-analytic formulas applied by RevMan Analyses (the statistical programme included in RevMan) require a normal distribution of data. The software is robust towards some skew, but to which degree of skewness meta-analytic calculations can still be reliably carried out is unclear. On the other hand, excluding all studies on the basis of estimates of the normal distribution of the data also leads to a bias, because a considerable amount of data may be lost leading to a selection bias. Therefore, we included all studies in the primary analysis. In a sensitivity analysis we excluded potentially skewed data applying the following rules:

a) When a scale started from the finite number 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).

b) If a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score.

c) In large studies (as a cut-off we used 200 participants) skewed data pose less of a problem. In these cases we entered the data in a synthesis.

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d) The rules explained in a) and b) do not apply to change data. The reason is that when continuous data are presented on a scale which includes a possibility of negative values, it is difficult to tell whether data are non-normally distributed (skewed) or not. This is also the case for change data (endpoint minus baseline). In the absence of individual patient data it is impossible to know if data are skewed, though this is likely. After consulting the ALL-STAT electronic statistics mailing list, we presented change data in RevMan Analyses in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Change data were therefore included and a sensitivity analysis was not applied.

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 1 errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the 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 of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also 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 intraclass 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 had been appropriately analysed taking into account intraclass 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 schizophrenia, we will only use data of the first phase of cross-over studies.

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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—Although high rates of premature discontinuation are a major problem in this field, we felt that it is unclear which degree of attrition leads to a high degree of bias. We, therefore, did not exclude trials on the basis of the percentage of participants completing them. However we addressed the drop-out problem in all parts of the review, including the abstract. For this purpose we calculated, presented and commented on frequency statistics (overall rates of leaving the studies early in all studies and comparators pooled and their ranges).

Assessment of heterogeneity

1. Clinical heterogeneity: We considered all the included studies within any comparison to judge for clinical heterogeneity.

2. Statistical

2.1 Visual inspection: We visually inspected graphs to investigate the possibility of statistical heterogeneity.

2.2 Employing the I-squared statistic: Visual inspection was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 50% we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003). If inconsistency was high and clear reasons explaining the heterogeneity were found, we presented the data separately. If not, we commented on the heterogeneity of the data.

Assessment of reporting biases—Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). We entered data from all identified and selected trials into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias. A formal test for funnel-plot asymmetry was not undertaken. 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.

Data synthesis—We understand that there is a debate around the 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 as we are a priori expecting some clinical heterogeneity between the patients in the different trials. Therefore, we chose the random effects model for all analyses (DerSimonian 1986). This said, we acknowledge that as a disadvantage the random effects model puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect these studies can either inflate or deflate the effect size.

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Subgroup analysis and investigation of heterogeneity

1. Subgroup analysis: We assessed each outcome by trial length. No other subgroup analysis was pre-specified.

2. Investigation of heterogeneity: If data were clearly heterogeneous we checked that data are correctly extracted and entered and that we had not made unit of analysis errors. If high levels of heterogeneity remained we did not undertake a meta-analyse at this point, because if there is considerable variation in results, and particularly if there is inconsistency in the direction of effects, it may be misleading to quote an average value for the intervention effect.

Sensitivity analysis—We excluded studies with potentially skewed data. A recent report showed that some of the comparisons of atypical antipsychotics may have been biased by using inappropriate comparator doses (Heres 2006). We, therefore, also 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 studies awaiting classification.

For substantive descriptions of studies, please see Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

Through the search strategy we found 1341 references, which includes a first search (857) in July 2006 and an update search (484) in June 2007. Two-hundred-and-twenty-six studies compared clozapine versus other atypical antipsychotics, from them only 27 studies fulfilled the review criteria.

Included studies

We selected 27 studies of which all were described as randomised. Only three studies gave details about randomisation methods and their implementation (Kumra 2008, Shaw 2006 and Wahlbeck 2000), the rest did not state methods used to generate the random allocation sequence, the allocation concealment and randomisation implementation. Twenty studies were double-blind and 7 single-blind/rater-blinded. In the studies the blindness was not assessed and no further details about it were given. Twenty-five studies were parallel clinical trials, two were cross-over studies (we included only the first phase) (Conley 2003, Lin 2003).

1. Length of trial—Twenty studies were short term studies (two up to 12 weeks), five studies belong to the medium term category (up to 26 weeks), and only two studies reported long term data (more than 26 weeks).

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2. Participants—The 27 studies involved a total of 3099 participants. The comparison of clozapine versus olanzapine included 1753 participants, clozapine versus quetiapine, 306 participants, clozapine versus risperidone, 843 participants, clozapine versus ziprasidone, 146 participants, and the clozapine versus zotepine comparison, 109 participants.

Almost all studies used operationalised diagnostic criteria. Most studies included participants with diagnoses of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) III - R or IV criteria and only one used *The International Classification of Diseases, 9th Revision* (ICD-9) criteria. Chinese studies used the *Chinese Classification of Mental Disorders* (CCMD) version 2 or 3 criteria. Two studies did not state if any operationalised diagnostic criteria were used. One of them, which compared clozapine versus ziprasidone, enrolled participants with schizophrenia who met criteria for treatment resistance (non-response in three adequate trials in past five years) and/or inability to tolerate antipsychotic treatment. The other one compared clozapine versus zotepine and reported that the participants were people with schizophrenia who have been treated with clozapine for more than five months.

Many participants were diagnosed as treatment resistant to prior antipsychotics. The criteria and definitions used varied.

Moresco 2004 defined treatment resistance as lack of satisfactory clinical response to two previous antipsychotics, with duration of at least six weeks each, given an appropriate dosage (at least 500 mg chlorpromazine equivalent).

Tollefson 2001 included participants who had a history of ‘resistance to previous antipsychotic’, defined as lack of satisfactory clinical response to at least two previous oral neuroleptic treatments, each from a different chemical class, given for a duration of at least six weeks at an appropriate daily dosage equivalent to at least 500 mg/day of chlorpromazine, or to the maximum daily dosage when intolerable side-effects had been documented.

Conley 2003 defined ‘treatment resistant’ when there was evidence of: a persistent positive psychotic symptoms: item score > or = 4 (moderate) on at least two of four positive symptoms items on the Brief Psychiatric Rating Scale (1 - 7) (BPRS); the concurrent presence of at least moderately severe illness as rated by the total BPRS score (score > or = 45 on the 18 item scale) and score of at least moderate on the Clinical Global Impression scale (CGI); two failed historical trials of antipsychotics of at least six weeks duration at doses of at least 600 mg/day chlorpromazine equivalents; and no stable period of good social and/or occupational functioning within the last five years.

McGurk 2005 included subjects who had evidence of ‘treatment resistance’ defined as at least one trial of a conventional antipsychotic at a dose equivalent to 600 mg/day of chlorpromazine, a second trial of a different conventional antipsychotic at a dose equivalent to 250 - 500 mg/day of chlorpromazine and at least a moderate severity score on one of the BPRS psychotics symptoms items or on one of the Scale for the Assessment of Negative Symptoms (SANS) global subscale.

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Wahlbeck 2000 included participants with ‘resistance to previous antipsychotics’, defined as persistent psychotic symptoms for at least six months during which the participants received antipsychotic treatment from at least two different chemical classes at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of at least six weeks each.

Kumra 2008 included participants who had a documented treatment failure of at least two prior adequate antipsychotic trials and a baseline BPRS total score of at least 35 and a score of at least moderate on one or more psychotic items on the BPRS scale.

Breier 1999 included participants who meet the criteria for ‘partial response’ to neuroleptics, i.e. a history of residual positive and/or negative symptoms after at least a six weeks trial of a therapeutic dose of a neuroleptic agent; at least a minimum level of positive and/or negative symptoms at the time of evaluation for the study; and at least a minimum level of positive and/or negative symptoms after a prospective trial of at least two weeks with fluphenazine, 20 mg/day (with dose adjustments between 10 mg/day and 30 mg/day allowed in order to optimise outcome). The minimum positive symptoms level was a total score of at least eight for the four BPRS positive symptoms items (conceptual disorganization, hallucinations, unusual thought content, and suspiciousness). The minimum negative symptoms level was a total score on SANS of at least 20.

Volavka 2002 included participants with a history of ‘sub-optimal treatment response’ defined as

1) persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after at least six contiguous weeks of treatment, presented or documented in the past, with one or more typical antipsychotics at doses 600 mg/day as chlorpromazine equivalents.

2) Poor level of functioning over the past two years, defined by the lack of competitive employment or enrolment in an academic or vocational program and not having age-expected interpersonal relationships with someone outside the biological family of origin with whom ongoing regular contacts were maintained.

Azorin 2001 included participants with ‘poor response to previous treatment’, i.e. the patient’s current episode had been treated continually with neuroleptic for at least the preceding 6 month without significant clinical improvement; the patients had undergone one unsuccessful trial of antipsychotic medication equivalent to 20 mg/day of haloperidol for at least six weeks (less if the patient was experiencing dose-limiting adverse events) since the onset of the concurrent episode. If several drugs have been prescribed simultaneously, the final equivalence dosage could be calculated by adding the individual equivalence and when the participants had not experienced a period of good functioning for at least 24 months despite a sufficient period of use of two antipsychotics from at least two chemical classes, or no period of good functioning for five years despite the use of three antipsychotics.

Lin 2003 included participants with partial response to clozapine, not stating the criteria.

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Another six studies included participants who were treatment resistant and/or intolerant to treatment, again using various definitions:

Naber 2005 included participants who had failed to respond to at least one antipsychotic other than clozapine and olanzapine or had experienced intolerable side-effects during these prior antipsychotics treatment.

Bondolfi 1998 used a similar definition and considered participants who had previously failed to respond to or be intolerant of at least two different antipsychotic drugs given in appropriate dose for at least four weeks each.

Sacchetti 2006 defined treatment resistance as non response to three adequate trials in the past five years and/or inability to tolerate antipsychotic treatment.

Bitter 2004 included participants who had failed to adequately respond to a standard acceptable treatment with a conventional antipsychotic medication (at least one treatment trial of four to six weeks duration 400 -600 mg chlorpromazine equivalents with either insufficient effectiveness or intolerable side-effects caused by the medication).

Lindenberg 1997 included only participants who had been treated before for at least three weeks, each with two conventional neuroleptic using effective doses, without a satisfactory result or with intolerable side-effects.

Shaw 2006 included participants with ‘failure to respond to two antipsychotic medications’ (typical or atypical) used at adequate doses (>100 mg of chlorpromazine equivalents) and for adequate duration (four weeks unless terminated owing to intolerable adverse effects). ‘Failed’ was defined as insufficient response with persistent symptoms significantly impairing the child’s functioning according to child, parental, medical, and school reports or intolerable adverse effects.

Meltzer 2003 included participants who met the DMS-IV criteria for schizophrenia or schizoaffective disorder and had a high risk for suicide.

The following studies did not require treatment resistance as an inclusion criterion (Atmaca 2003, Heinrich 1994, Krakowski 2006, Li 2002, Li 2003, Liu 2004, Li 2005, Ren 2002, Wang 2002 and Zhou 2000).

Some of the studies additionally considered criteria of inclusion based on minimum scores in BPRS, PANSS, CGI or Intelligence Quotient (IQ) (Azorin 2001, Bitter 2004, Bondolfi 1998, Kumra 2008, Naber 2005, Sacchetti 2006 and Tollefson 2001).

The age of the participants ranged from 7 to 70 years old. Most participants were from 18 to 65 years old; except for two studies (Kumra 2008, Shaw 2006) which included younger people (age from 7 to 18 years old). Overall there were more men than women in the included trials.

3. Setting—Trials took place in a mixture of in patient and outpatient settings. Most of the studies were carried out with inpatients (13 studies: Atmaca 2003, Bitter 2004, Conley 2003,

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Heinrich 1994,Krakowski 2006, Li 2003, Li 2005, Lin 2003, Liu 2004, Moresco 2004, Shaw 2006, Volavka 2002 and Zhou 2000), followed by studies performed with in and outpatients (six studies: Azorin 2001, Kumra 2008, Li 2002, McGurk 2005, Meltzer 2003 and Wang 2002). Other studies were carried out initially with inpatients, who were later discharged (four studies: Bondolfi 1998, Naber 2005, Tollefson 2001 and Wahlbeck 2000) and finally one study was performed only with outpatients (Ren 2002). Three studies did not report the setting of the participants. Twelve of the twenty-seven studies were multicenter and the participants were recruited in diverse countries including Turkey, Canada, France, Hungary, Switzerland, USA, China, Croatia, South Africa, Italy, United Kingdom, Czech Republic, Argentina, Chile, Germany, Belgium, Denmark, Finland, Norway, Portugal, Spain, and Ireland, leading to a wide ethnic diversity.

4. Study size—In the studies that compared clozapine and olanzapine, the largest and smallest studies were Meltzer 2003 (n=980) and Conley 2003, respectively. The latter was a cross-over study, of which only the first phase was considered (n=13). The largest study that compared clozapine and risperidone was Azorin 2001 (n=273) and the smallest was Wahlbeck 2000, which is a pilot study (n=20). Li 2003 was the largest study that compared clozapine with quetiapine (n= 76) and the smallest was Atmaca 2003 (n=28). The study that compared clozapine versus ziprasidone randomised 146 participants (Sacchetti 2006), and 109 participants were randomised to the comparison of clozapine versus zotepine studies (Lindenberg 1997, Lin 2003), n=50 and n= 59 respectively).

5. Intervention and comparators—The 27 trials administered clozapine in a wide range of doses, from 207 mg/day to 642 mg/day (mean doses range). The ranges of comparator doses were wide, as well. The range of mean olanzapine doses was 16 mg/day to 30 mg/day. Conley 2003 did not state the mean dose used but mentioned an allowed dose range between 30 - 50 mg/day. For quetiapine the mean dose ranged from 362 mg/day to 536 mg/day, and one study reported a dose range from 400 -700 mg daily after the first 10 days (Liu 2004). Risperidone was used in a range from 3.2 mg/day to 12 mg/day. The mean dose of the single ziprasidone arm was 130 mg/day. Regarding clozapine versus zotepine trials, one study used a mean dose of 377 mg/day (Lin 2003) and the other one used doses from 150 to 450 mg/day (Lindenberg 1997).

6. Outcomes

6.1 Death: Death was reported in some studies that compared clozapine with olanzapine (Conley 2003; Meltzer 2003) and clozapine with risperidone (Azorin 2001; Wahlbeck 2000).

6.2 Leaving the study early: Leaving the study early was frequently reported, but in some studies it was not indicated how many participants of each group left early.

6.3 Global state: Improvement on global state was presented as dichotomous data, the criterion used was of ‘at least much improved’ using Clinical Global Impression (CGI) scales. Olanzapine (Naber 2005,Tollefson 2001) and risperidone (Heinrich 1994) trials reported this outcome. Other studies used the criterion as ‘less than common criteria’ (Li

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2003) and ‘less than successfully treated and no increase on the Clinical Global Impression - Severity scale (CGI-S)’ (Lin 2003).

6.4 Mental state

6.4.1 Mental state - dichotomous: Our predefined criterion was an at least a 50% reduction of the baseline value of the BPRS or Positive and Negative Syndrome Scale (PANSS). When such a criterion was not available, the primary cut-off presented by the original author was used. Some studies also used combined criteria: at least 20% BPRS total score reduction plus CGI-S < 3 or BPRS < 35 (this was described as at least 20% BPRS reduction and ‘mildly ill or better’ in the comparison and data tables). Kumra 2008 used the criterion of at least 30% BPRS total plus ‘very much’ or ‘much improved’ on CGI. One study (McGurk 2005) that compared clozapine with risperidone used the criterion of at least 40% improvement on the BPRS psychotics cluster (cluster: hallucinations, delusions, suspiciousness and conceptual disorganization).

6.4.2 Mental state - continuous: The PANSS total was used in most studies to examine the participants overall mental state. Specific symptoms were mainly measured by the PANSS positive and negative symptoms subscores. Other studies used the Scale for the Assessment of Positive Symptoms (SAPS) or Scale for the Assessment of Negative Symptoms (SANS) scores, respectively. Only a few studies used the BPRS total score and its subscores. The data were presented as average change or average at endpoint on the score.

6.5 General functioning and social functioning: General functioning and social functioning were reported in only one study that compared clozapine with risperidone (Wahlbeck 2000). These outcomes were measured by Global Assessment of Functioning (GAF) and Social Functioning Scale (SFS) respectively. The average scores at endpoint were presented.

6.6 Quality of Life / satisfaction with treatment: Quality of life / satisfaction with treatment was measured in only one study that compared clozapine with olanzapine (Naber 2005) using the Subjective Well Being Under Neuroleptic Treatment (SWN) and Munich Life Dimension List (MLDL) respectively. Average score at endpoint was reported. Wahlbeck 2000 assessed satisfaction with the treatment by the Drug Attitude Inventory (DAI) and reported the average score at endpoint.

6.7 Cognitive functioning: Cognitive functioning was reported in only one study (Volavka 2002) that compared clozapine with risperidone and with olanzapine. The outcome was evaluated through the number of participants who presented a clinically important improvement in the neurocognitive score defined as a reduction of 0.5 SD on neurocognitive score.

In Volavka 2002 continuous data based on the PANSS cognitive subscore (average at endpoint and average change) were reported as a factor score and the neurocognitive global score at endpoint was reported as a Z score. The Z score was based on the mean and SD of each test (16 cognitive tests) at baseline. Only the variables from participants who completed each test at both baseline and follow-up, were used. This Z score result was the

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contribution of each test to each of the four domains chosen by the author. These variables were not useful for the analysis of this review.

6.8 Service use: Service use was missing in all studies, except one that reported the number of participants hospitalised due to risk of suicide (Meltzer 2003).

6.9 Adverse effects: Adverse effects were obtained through routine measures, e.g. blood sample, weight measure, ECG, or recorded from the clinical evaluation and spontaneously reports. Few studies used a checklist to report the adverse effects, i.e. validated questionnaires such as the Association for Methodology and Documentation in Psychiatry (AMDP) somatic scale (Heinrich 1994; Tollefson 2001), and the Udvalg for Kliniske Undersgelser (UKU) (Bondolfi 1998; Lindenberg 1997; Lin 2003), Subjective Treatment Emergent Symptoms Scale (STESS) (Shaw 2006; Kumra 2008) and Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) (Bitter 2004; Tollefson 2001). Additionally some researchers developed their own checklist specially for the study. Data were dichotomous as well as continuous.

There were some adverse effect data that could not be examined because comparator data were not reported (continuous data) or the number of patients assessed were not stated (dichotomous data) (Azorin 2001, Li 2002, Sacchetti 2006, Shaw 2006, Tollefson 2001 and Wang 2002).

Extrapyramidal effects were assessed by specific scales such as Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS), Simpson Angus Scale (SAS), Hillside akathisia scale (HAS), Extrapyramidal Symptom Rating Scale (ESRS) and by means of a checklist or clinical evaluation of adverse effects.

7. Outcome scales—Details of scales that provided usable data are shown below. Reasons for data exclusion from other instruments are given under “Notes” in the “Characteristics of included studies” tables.

7.1 Global state: Clinical Global Impression Scale - CGI Scale (Guy 1972).

This scale is used to assess both severity of illness and clinical improvement, by comparing the conditions of the person standardized against other people with the same diagnosis. A seven-point scoring system is usually used with low scores showing a decrease on severity and/or an overall improvement.

7.2 Mental state

7.2.1 Brief Psychiatric Rating Scale - BPRS (Overall 1962): This scale 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 (0-6 or 1-7) varying from ‘not present’ to ‘extremely severe’. Scores can range from 0 to126, where high scores indicate more severe symptoms.

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7.2.2 Positive and Negative Syndrome Scale - PANSS (Kay 1986): This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from one - absent to seven - extreme. This scale can be divided into three subscales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates less severity.

7.2.3 Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1984): This instrument covers a specific positive symptoms scale (hallucinations, delusions, thought disorder, bizarre/disorganized behavior and inappropriate affect). It is scored from 0 (not present) to 5 (very frequent) points.

7.2.4 Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1984b): 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.

7.3 General Functioning

7.3.1 Global Assessment of Functioning - GAF (APA 1994): The GAF is a clinician-rated assessment of overall functioning, which considers psychological, social, and occupational functioning on a scale 0-100. Lower scores indicate poorer functioning.

7.3.2 Social Functioning Scale - SFS (Birchwood 1990): The SFS assesses function areas that are crucial for the community maintenance of individuals with schizophrenia. The seven areas are social engagement/withdrawal, interpersonal behavior, pro-social activities, recreation, independence-competence, independence-performance and employment/ occupation. The range of total scores is from 418 (poor) to 944.5 (optimum).

7.4 Quality of Life / treatment satisfaction

7.4.1 Subjective well being under neuroleptic treatment - SWN (Naber 1995): This scale assesses the subjective effects of antipsychotics, both benefits and burden, from the perspective of the patients. This scale is a self-rating scale, which has 38 items related to the antipsychotic treatment, each of which can be defined on six point scoring. A high score indicates better subjective well-being.

7.4.2 Munich Life Dimension List - MLDL (Heinisch 1991): The MLDL focuses on the subjective evaluation of the quality of life and comprises 19 areas of life. The scale ranges from zero (very dissatisfied, completely unimportant) to ten (very satisfied, very important).

7.4.3 Drug Attitude Inventory - DAI-10 (Hogan 1983): This scale is a self-report ten-item scale for assessing patient satisfaction with antipsychotic treatment. Each item is rated one (does not favour drug) or two (favour drug). The range of a total score is 10-20. Higher scores indicate a more favourable attitude towards antipsychotic drug treatment.

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7.5 Side-effects

7.5.1 Abnormal Involuntary Movement Scale - AIMS (NIMH 1975): This scale has been used to assess tardive dyskinesia, a long term, drug-induced movement disorder. The AIMS can also be used to assess some short term movement disorders such as tremor.

7.5.2 Barnes Akathisia Scale - BAS (Barnes 1989): The scale comprises items rating the observable, restless movements that characterize akathisia, a 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 global severity (from zero - absent to five - severe). A low score indicates low levels of akathisia.

7.5.3 Extrapyramidal Symptom Rating Scale - ESRS (Chouinard 1980): This scale consists of a questionnaire relating to parkinsonian symptoms (nine items), a physician's examination for parkinsonism and dyskinetic movements (eight items), and a clinical global impression of tardive dyskinesia. High scores indicate severe levels of movement disorder.

7.5.4 Simpson Angus Scale - SAS (Simpson 1970): This ten-item scale, with a scoring system from zero to four for each item, measures drug-induced Parkinsonism, a short term drug-induced movement disorder. A low score indicates low levels of Parkinsonism.

7.5.5 Hillside akathisia scale - HAS (Fleischhaker 1989): Scale comprises two subjective items: inner restlessness and urge to move combined with a division of objective signs in three regional items: axial, upper limbs and lower limbs. Each item is rated from zero to four for each item, with separate evaluations for patient sitting, standing and lying. The global evaluation for each item can also be recorded. The full scale allows the assessment of the effect of activation; global impression items for severity and improvements under treatment are also provided with a scoring system of zero - seven points.

8. Missing outcomes

In general there were the following missing outcomes: global functioning, quality of life, cognitive functioning, service use and mortality. The studies' principal focus was the response to the treatment, leaving the study early and adverse effects, which were not always adequately documented.

Excluded studies

We excluded 189 studies. Thirty-four were not randomised trials, including seven naturalistic, nine open label studies and one naturalistic/open label trial. One-hundred-and-thirty-one were randomised trials but the blindness was unclear. Ten were not clinical trials but rather reviews or observational studies. In another four studies the allocation was unclear. Other studies were excluded because participants or interventions did not fulfil the review criteria (three and five studies respectively). Finally, the CATIE (CATIE) and the CUtLASS (CUTLASS) studies were excluded, the first one because the clozapine trial was an open one concerning the clozapine arm. The second study was excluded because the analysis compared clozapine versus the other newer antipsychotics pooled.

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Awaiting assessment

The ten studies in this category were mostly conference abstracts for which the data reported were not sufficient to decide if they fulfil the criteria to be selected. When it was possible, we contacted the relevant sources and we are waiting for some answers.

Ongoing studies

To the best of our knowledge, there are no ongoing studies during the period of the search.

Risk of bias in included studies

Judgement of risks are illustrated in Figure 1

Allocation

Details regarding randomisation methods as well as sequence generation and allocation concealment, were largely missing. This made it difficult to judge the risk of bias. All studies included were stated to be randomised. From 27 only eight presented some details about the sequence generation, allocation concealment and restriction. Shaw 2006 used a random numbers chart and was conducted in blocks of four, numbered containers were used to implement the allocation sequence. The pharmaceutical development service generated the allocation sequence. Also Kumra 2008 and Wahlbeck 2000 stated that participants were assigned to treatment by computer generated randomisation. The following studies made some statements on restriction: Naber 2005 and Tollefson 2001 stated that they used a 1:1 allocation scheme. Krakowski 2006 used a block randomisation scheme with a block size of three and no baseline stratification. Meltzer 2003 randomised in a 1:1 ratio within blocks of four participants from each medical centre (67 medical centres). Azorin 2001 stated that the allocation was balanced by country, with block size of six. The rest of the studies did not present further details.

Blinding

Twenty studies were double-blind and seven were stated to be single-blind (rater-blinded). Some of the 27 studies gave details about people who were blinded (e.g. psychiatrics, raters, patients, nurses, investigator) (Atmaca 2003, Breier 1999, Krakowski 2006, Meltzer 2003, Moresco 2004, Shaw 2006 and Volavka 2002). Only Meltzer 2003 reported that an external entity regularly monitored the masking of the raters, however the monitoring methods were not explained. No study formally assessed the effectiveness of blinding.

Incomplete outcome data

Most findings were presented in graphs and tables. Some results were described in the text, but often these reports were incomplete (lack of case numbers or standard deviations). Descriptive statistics and statistical test were used to show similarity and equilibrium between the treatment groups and their characteristics at baseline. Often incomplete outcome data were not correctly addressed, because intention-to-treat analysis were not always applied.

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Most studies reported the loss of follow up indicating the specific reason of the dropout. However, not all studies considered these data in their analysis. Intention-to-treat analysis (ITT) was applied by Azorin 2001, Bitter 2004, Bondolfi 1998, Heinrich 1994, Krakowski 2006, Kumra 2008, Meltzer 2003, Naber 2005,Sacchetti 2006, Shaw 2006 and Wahlbeck 2000. The use of this analysis was unclear in Azorin 2001 and Naber 2005 because not all randomised participants were included. Azorin 2001 established as ITT criteria all participants with at least one BPRS evaluation after treatment initiation and Naber 2005 considered as ITT population all participants with a baseline and at least one post baseline value.

Missing values were replaced by the last observed value (LOCF last observation carried forward) in Azorin 2001, Bitter 2004,Bondolfi 1998, Conley 2003, Heinrich 1994, Naber 2005,Sacchetti 2006, Shaw 2006, Tollefson 2001 and Wahlbeck 2000.

Selective reporting

Many authors reported only adverse events that occurred in at least 5% of the participants. This procedure could miss rare but important adverse events.

There is some evidence that pharmaceutical companies sometimes highlight the benefits of their compounds and tend to suppress their disadvantages (Heres 2006). Data on sponsoring of six studies were not available.

Other potential sources of bias

Eight studies were sponsored by pharmaceutical companies (Azorin 2001, Bitter 2004, Bondolfi 1998, Krakowski 2006,Lindenberg 1997, Meltzer 2003, Moresco 2004 and Naber 2005) and in Breier 1999 and Tollefson 2001 authors work for a pharmaceutical company. From eight studies, six studies did not declare if the study methods and data analysis were performed independently of the sponsor. Two of the eight studies were supported by pharmaceutical companies marketing clozapine (Azorin 2001 and Meltzer 2003), five trials were supported by pharmaceutical companies marketing the comparator substances and only one was supported by pharmaceutical companies of both clozapine and its comparator (Bondolfi 1998). Pharmaceutical companies have an inevitable conflict of interest which may well lead to bias (Heres 2006 and Leucht 2008).

Effects of interventions

1. Comparison 1. CLOZAPINE versus OLANZAPINE

Twelve studies fulfilled the review criteria. Seven were short term studies (Atmaca 2003; Krakowski 2006; Kumra 2008; Moresco 2004; Shaw 2006; Wang 2002) four medium term studies (Bitter 2004; Naber 2005; Tollefson 2001; Volavka 2002) and one was a long term study (Volavka 2002). Most of these studies were performed in America and Europe. Two studies were multinational including participants from Latin American and Africa and another one was performed in China.

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1.1 Death—Only two studies reported the mortality during the trials (Conley 2003; Meltzer 2003). Deaths from any reason (1 RCT, n=980, RR 1.50 CI 0.62 to 3.64), natural causes (2 RCTs, n=993, RR 1.40 CI 0.45 to 4.38) and suicide (2 RCTs, n=993, RR 1.67 CI 0.40 to 6.94) were all similarly likely whether allocated to clozapine or olanzapine.

1.2.Leaving the study early: 1. Any reason—Overall a high percentage of attrition for any reason were observed in both groups. The percentage of participants that discontinued the trials was 40% and 38% for clozapine and olanzapine groups, respectively. There was no significant difference between groups (11 RCTs, n=1702, RR 1.04 CI 0.93 to 1.17).

1.3. Leaving the study early: 2. Adverse effects—Leaving the study early due to adverse effects was more common in the clozapine group (10%) than in the olanzapine group (6%). This difference was statistically significant (9 RCTs, n=1674, RR 1.60 CI 1.07 to 2.40, NNT 25 CI 15 to 73).

1.4. Leaving the study early: 3. Inefficacy—Both groups showed similar attrition rates due to inefficacy (5% clozapine and 6% olanzapine) there was no significant difference between groups (10 RCTs, n=1674, RR 0.72 CI 0.40 to 1.30).

Meltzer 2003 found that in the long term clozapine was associated with less attrition due to lack of efficacy than olanzapine (1 RCT, n=980, RR 0.33 CI 0.12 to 0.91, NNT 49 CI 26 to 364).

1.5 Global state

1.5.1 No clinically important change: less than much improved: No clinically important change in global state was defined as the number of people who were not ‘at least much improved’ according to the CGI improvement rating. The frequencies in both groups were similar (clozapine: 61%; olanzapine: 54%) and not statistically significantly different (2 RCTs, n=294, RR 1.13 CI 0.93 to 1.38).

1.5.2 Relapse: Naber 2005 reported that one participant of each group suffered a relapse (2%) during the trial. Hence no significant difference between groups was found (1 RCT, n=114, RR 1.00 CI 0.06 to 15.60).

1.6 Mental state: 1. No clinically important change - various criteria

1.6.1. Less than 20% reduction on BPRS-24 (1-7) total score: The short term study Shaw 2006 found that fewer people taking clozapine (67%) than those taking olanzapine (85%) did not have an improvement on their mental state, however this difference was not statistically significant (1 RCT, n=25, RR 0.79 CI 0.50 to 1.25).

1.6.2 Less than 50% reduction on BPRS-18 (1-7) total score: The short term study Wang 2002 found that 45% of the participants of the clozapine group and 40% of the olanzapine group did not improve as this criterion. There was no significant difference between groups (1 RCT, n=61, RR 1.13 CI 0.63 to 2.03).

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1.6.3 Less than 20% reduction on BPRS-24 (1-7) total score and mildly ill or better (short term): Shaw 2006 reported that 100% of the participants from clozapine group and 92% from olanzapine group did not improve. This difference was not significant (1 RCT, n=25, RR 1.08 CI 0.87 to 1.33).

1.6.4 Less than 20% reduction on BPRS-18 (1-7) total score and mildly ill or better (medium term): Fifty-four per cent of those participants allocated to clozapine and fifty-three per cent of those allocated to olanzapine did not improve as this criterion. There was no significant difference between groups (2 RCTs, n=327, MD 1.03 CI 0.85 to 1.25).

1.6.5 Less than 30% reduction on BPRS total score and much improved or very much improved: Even though more participants in the olanzapine group (67%) than in the clozapine group (33%) were not improved. There is some suggestion that this difference reached a borderline level of significance (1 RCT, n=39, RR 0.50 CI 0.24 to 1.03).

1.6.6 Less than 50% reduction on PANSS total: Through this criterion, Bitter 2004 and Tollefson 2001 medium term studies indicated that 82% of the people taking clozapine and 81% on olanzapine did not improve. No statistically significant difference between the groups was demonstrated (2 RCTs, n=327, RR 1.00 CI 0.92 to 1.10).

1.7 Mental state: 2a. PANSS total score—A trend in favour of olanzapine was observed at the short to medium terms, however this difference was not statistically significant (7 RCTs, n=618, MD 1.97 CI −0.71 to 4.66).

1.8 Mental state: 2b. BPRS-18 (1-7) total score—The pooled analysis showed a trend in favour of olanzapine at the short to medium terms, but this difference did not reach the conventional levels of significance (5 RCTs, n=304, MD 1.31 CI −0.30 to 2.92).

1.9 Mental state: 2c. BPRS total score (various version)—Since different versions of the BPRS score were used we present the results of the single studies separately.

1.9.1 BPRS-24 l: One short term study (Shaw 2006) assessed the mental state using the BPRS-24 (1-7) total score. The clozapine group presented a greater reduction from baseline to endpoint than the olanzapine group, but this difference was not significant (1 RCT, n=25, MD −7.00 CI −28.47 to 14.47).

1.9.2 BPRS-18 (0-6): In one medium term study (Naber 2005) olanzapine produced a greater reduction on average change on BPRS-18 (0-6) total score compared to clozapine, however this difference was not significant (1 RCT, n=108, MD 2.80 CI −4.05 to 9.65).

1.10 Mental state: 3a. Positive symptoms: PANSS positive subscore—Two short term study and four medium term studies assessed the positive symptoms by the PANSS positive subscore. The results did not indicate that one drug was clearly more efficacious than the other one (6 RCTs, n=592, MD 0.08 CI −0.96 to 1.11).

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1.11 Mental state: 3b. Positive symptoms: SAPS—One short term study Shaw 2006 found a greater SAPS decrease in the clozapine group. However this difference was not statistically significant (1 RCT, n=25, MD −9.00 CI −22.06 to 4.06).

1.12 Mental state: 3c. Positive symptoms: BPRS-18 positive subscore

1.12.1 BPRS-18 (1-7): Positive symptoms, measured by the BPRS18 (1-7) positive subscore, were not significantly different between groups (2 RCTs, n= 189, MD −0.01 CI −1.39 to 1.37).

1.12.2 BPRS-18 (0-6): There was no significant difference (1 RCT, n=108, MD 0.40 CI −1.57 to 2.37).

1.13 Mental state: 4a. Negative symptoms: PANSS negative subscore—There was no indication of any significant superiority of clozapine or olanzapine in this outcome (6 RCTs, n=592, MD 0.78 CI −0.21 to 1.77).

1.14 Mental state: 4b. Negative symptoms: SANS—Two short term studies assessed the negative symptoms using the SANS and the results were heterogeneous. Kumra 2008 found a trend in favour of clozapine, but this difference was not statistically significant (2 RCTs, n=39, MD −1.00 CI −3.6 to 1.6). Furthermore, in Shaw 2006 clozapine reduced the mean SANS score more than the olanzapine group (1 RCT, n=25, MD −11.00 CI −20.90 to −1.10).

1.15 Mental state: 4c. Negative symptoms: BPRS-18 negative subscore

1.15.1 BPRS-18 (1-7) negative sub-score: There was no significant difference between groups (2 RCTs, n= 189, MD −0.29 CI −1.17 to 0.60).

1.15.2 BPRS-18 (0-6) negative sub-score: One medium term study (Naber 2005) analysed this outcome but did not find a significant difference between groups (1 RCT, n= 108, MD 0.20 CI −1.29 to 1.69).

1.16 Cognitive functioning: 1. No clinically important change less than 0.5 SD reduction—Most studies did not report data about cognitive function of participants. One medium term study (Volavka 2002) defined no clinically important response as ‘less than 0.5 SD reduction on global neurocognitive score’. More people taking clozapine (80%) than people taking olanzapine (49%) met this criterion, a statistically significant difference was found (1 RCT, n=79, RR 1.64 CI 1.15 to 2.35, NNT 3 CI 2 to 9).

1.17 Quality of life: 1. SWN-38 score—In one medium term study there was no significant difference between clozapine and olanzapine in the SWN-38 score (1 RCT, n=99, MD −8.20 CI −21.67 to 5.27).

1.18 Quality of life: 2. MLDL score—There was no significant difference in the average change of the MLDL satisfaction scale (1 RCT, n=97, MD 0.00 CI −0.72 to 0.72).

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1.19 Service use: Hospital re-admission—Most of studies did not provide data on service use. Only one long term study (Meltzer 2003) reported the hospitalisation for imminent risk of suicide as a rescue intervention. Significantly fewer people taking clozapine (20%) were hospitalised compared to those taking olanzapine (26%)(1 RCT, n=980, RR 0.78 CI 0.62 to 0.98, NNT 18 CI 9 to 230).

1.20 Adverse effects: 1. At least one adverse effect—Due to the high heterogeneity (I-square=81%) we did not perform the meta-analytic combination of data. Five short term studies presented the number of participants that suffered at least one adverse effect. Only one of them, Wang 2002 study, showed a statistically significant difference between treatment groups in favour of olanzapine (1 RCT, n=61, RR 3.39 CI 1.85 to 6.20, NNH 2 CI 1 to 2). All the rest reported the same trend in favour olanzapine, but the differences were not significant.

Two homogeneous medium term studies (Bitter 2004 and Naber 2005) reported that people allocated to clozapine (49%) were significantly more susceptible to experience at least one adverse effect than those in the olanzapine group (39%), (2 RCTs, n=261, RR 1.19 CI 1.02 to 1.40, NNH 10 CI 4 to infinity).

1.21 Adverse effects: 2. Cardiac problems—A lack of data about the appearance of cardiac problems was a common factor for almost all studies. Overall, a low incidence of ECG anomalies was observed in both groups.

Four per cent of the clozapine group (3 of 74 participants) showed ECG alterations, in two participants the anomalies were not specified and in the other one the alteration was a QT time prolongation. One per cent in the olanzapine group (1 of 78 participants) presented any ECG alterations. This difference was not significant (3 RCTs, n=152, RR 2.42 CI 0.38 to 15.33).

1.22 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use—A similar proportion of participants from each group (7% clozapine versus 8% olanzapine) required antiparkinson medication during the trials. The combined analysis of the studies did not show any difference between the treatment groups (6 RCTs, n=561, RR 0.87 CI 0.46 to 1.67).

1.23 Adverse effects: 3b. Extrapyramidal: various symptoms

1.23.1 At least one EPS: In a short term study (Wang 2002, n=61) none of the participants experienced ‘at least one EPS’.

1.23.2 Akathisia: Four studies reported the akathisia incidence during the trials. Overall there was no significant difference (4 RCTs, n=1320, RR 0.73 CI 0.38 to 1.41). Only the long term study by Meltzer 2003 found that more people in the olanzapine group (8%) experienced akathisia than those in the clozapine group (4%), (1 RCT, n=980, RR 0.54 CI 0.32 to 0.90, NNH 27 CI 15 to 147).

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1.23.3 Dyskinesia: A trend in favour of clozapine was observed which did not reach the conventional level of significance (2 RCTs, n=327, RR 0.53 CI 0.20 to 1.43).

1.23.4 Extrapyramidal symptoms: No extrapyramidal events were reported in Moresco 2004 and Wang 2002 studies.

1.23.5 Parkinsonism: No parkinsonism events were reported in Bitter 2004 study.

1.23.6 Pseudoparkinsonism: There was no significant difference in pseudoparkinsonism symptoms between clozapine and olanzapine (1 RCT, n=180, RR 1.29 CI 0.50 to 3.30).

1.23.7 Rigor: There was no significant difference between groups (1 RCT, n= 980, RR 0.17 CI 0.02 to 1.38).

1.24 Adverse effects: 3c. Extrapyramidal: ESRS total score at end-point—A medium term study (Volavka 2002) found no significant difference in the ESRS score at endpoint (1 RCT, n=79, MD 1.30, CI −0.23 to 2.83).

1.25 Adverse effects: 3d. Extrapyramidal: SAS change or endpoint—Three short term studies and three medium term studies reported on this outcome. Overall, there was not significant difference between groups (6 RCTs, n=481, MD 0.43 CI −0.45 to 1.30).

1.26 Adverse effects: 3e. Extrapyramidal: akathisia - BARS change—A medium term study (Tollefson 2001) assessed akathisia by the BARS change from baseline to endpoint. There was no significant difference between groups (1 RCT, n=175, MD −0.10 CI −0.38 to 0.18).

1.27 Adverse effects: 3f. Extrapyramidal: Hillside Akathisia Scale—There was no significant difference between groups (1 RCT, n= 137, MD −0.40 CI −3.10 to 2.3).

1.28 Adverse effects: 3g. Extrapyramidal: tardive dyskinesia - AIMS change or endpoint—There was no significant difference between groups in one short term and two medium term studies (3 RCTs, n=352, MD 0.13, CI −0.25 to 0.51).

1.29 Adverse effects: 4a. Glucose: number of participants with significant increase—One long term study (Meltzer 2003) indicated the number of participants with significant increase of glucose levels during the study. Three per cent and four per cent of participants had an elevation of glucose levels taking clozapine and olanzapine, respectively. Hence no significant difference between clozapine and olanzapine groups was found (1 RCT, n=980, RR 0.76 CI 0.40 to 1.44).

1.30 Adverse effects: 4b. Glucose: average change or endpoint—Two short term studies showed an advantage of olanzapine (2 RCTs, n= 50, MD 9.70 CI 1.73 to 17.68). The medium term study reported an opposite result but the difference was not statistically significant (1 RCT, n=39, MD −9.9 CI −23.30 to 3.50).

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1.31 Adverse effects: 5. Hypersalivation—Five studies reported that hypersalivation was more frequent in participants taking clozapine than those taking olanzapine in the short term (2 RCTs, n=64, RR 1.64 CI 1.14 to 2.38, NNH 3 CI 2 to 9), in the medium term (2 RCTs, n=289, RR 5.33 CI 1.76 to 16.68, NNH 3 CI 2 to 4), as well as in the long term (1 RCT, n=980, RR 8.18 CI 5.64 to 11.86, NNH 2, CI 2 to 3).

1.32 Adverse effects: 6a. Lipids: number of participants with significant increase

1.32.1 Increase on cholesterol total: A short term study (Shaw 2006) reported that one of twelve in clozapine group and none in the olanzapine group presented moderate hypercholesterolaemia during the trial. No significant difference between the groups was found (1 RCT, n=25, RR 3.23 CI 0.14 to 72.46).

1.32.2 Increase on triglycerides: Two short term studies provided the number of participants that presented an increase on triglycerides during the study. 17% in clozapine group and 15% in olanzapine group showed an increase on triglyceride levels, but this difference was not significant (2 RCTs, n=64, RR 1.08 CI 0.37 to 3.20).

1.33 Adverse effects:6b. Lipids: average cholesterol change or end-point—Two short term and one medium term study assessed cholesterol total levels. The two short term studies were heterogeneous showing an opposite tendency. The combined analysis of all three studies did not demonstrate any clear difference between groups (3 RCTs, n=89, MD −1.16 CI −19.85 to 17.52).

1.34 Adverse effects: 6c. Lipids: average triglycerides change—Two short term studies provided data regarding triglyceride levels. No significant difference between clozapine and olanzapine was found (2 RCTs, n=38, MD 36.07 CI −83.57 to 155.71).

1.35 Adverse effects: 7. Prolactin: average change or endpoint

1.35.1 Average change from baseline: A medium term study (Tollefson 2001) assessed prolactin levels (ng /mL). A statistically significant difference was observed between clozapine and olanzapine groups, where clozapine group showed a slightly decrease while olanzapine group had a mild increase on prolactin levels (1 RCT, n=120, MD −0.57 CI −1.05 to −0.09).

1.35.2 Average endpoint ng/ml - men only: Two heterogeneous studies (Kumra 2008 and Volavka 2002) assessed on prolactin levels in men, only one of them (Kumra 2008) showed a significant superiority of clozapine (1 RCT, n=21, MD −14.20 CI −23.8 to −5.32).

1.35.3 Average endpoint ng/ml - women only: The same study reported on prolactin levels in women. Again, the results were in favour of clozapine (1 RCT, n=18, MD −54.4, CI −86.74 to −22.06).

1.36 Adverse effects: 8. Sedation—Seven studies reported the number of participants that experienced sedation. All studies observed a tendency in favour of olanzapine. Due to

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high degrees of heterogeneity we did not perform a meta-analysis (I-square= 88%). Four heterogeneous short term studies reported a trend in favour of olanzapine. In Wang 2002 this difference was significant (1 RCT, n=61, RR 3.06 CI 1.42 to 6.61, NNH 3 CI 2 to 7). The studies by Shaw 2006 and Kumra 2008 did not find any significant difference (1 RCT, n=25, RR 1.08 CI 0.18 to 6.53 and 1 RCT, n=39, RR 1.10 CI 0.93 to 1.30, respectively), while in Conley 2003 study all participants experienced sedation. Two medium term studies showed the same trend in favour of olanzapine, but only Bitter 2004 reported a significant difference between groups (1 RCT, n=147, RR 5.73 CI 1.32 to 24.96, NNH 8 CI 5 to 28). The single long term study (Meltzer 2003) found a significant superiority of olanzapine in this regard (1 RCT, n=490, RR 1.86 CI 1.55 to 2.24, NNH 5 CI 4 to 7).

1.37 Adverse effects: 9. Seizures—Four studies (two short, one medium and one long term) assessed this outcome. Clozapine group participants were more likely to experience seizures than olanzapine participants (3% versus 0.4%; 4 RCTs, n=1097, RR 6.50 CI 1.73 to 24.47, NNH 39 CI 25 to 94).

1.38 Adverse effects: 10a. Weight: number of participant with weight gain— More than 50% of the studies reported the number of participants that presented a weight increase. These studies were highly heterogeneous and a meta-analysis was not undertaken.

1.38.1 Short term: 20% of the participants in each group reported a weight increase according to various criteria (Wang 2002 study did not specify the criterion, Kumra 2008 used the criterion more than 7% increase of the baseline body weight), therefore there was no difference between groups (2 RCTs, n=100, RR 0.99 CI 0.45 to 2.16).

1.38.2 Medium term: Four medium term studies reported this outcome. There was no clear difference between groups (4 RCTs, n=520, RR1.03 CI 0.60 to 1.78).

1.38.3 Long term: The only long term study (Meltzer 2003) showed a significant superiority in favour of olanzapine (30% clozapine versus 52% olanzapine; 1 RCT, n=980, RR 0.57 CI 0.48 to 0.66, NNH 4 CI 3 to 6).

1.39 Adverse effects: 10b. Weight: average weight change—Three short term and four medium term studies reported on average weight change in kg. There was no significant difference between groups (7 RCTs, n=581, MD −0.04 CI −1.06 to 0.97).

1.40 Adverse effects: 11. White blood cell count: number of participants with a decrease—Four studies (one short term, two medium term and one long term) reported a higher number of participants with a decrease of the WBC in the clozapine group (6%) than in the olanzapine group (1%). This difference was statistically significant (4 RCTs, n=1264, RR 5.68 CI 2.48 to 13.00, NNH 20, CI 14 to 33).

1.41. Publication bias—Due to the small number of included studies a funnel plot analysis was not performed.

1.42. Missing outcomes—No data were reported for general and social functioning.

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2. CLOZAPINE versus OLANZAPINE Sensitivity analysis

When studies with possibly skewed data were excluded the following changes were noted: Excluding Kumra 2008 from the analysis of the SANS total score clozapine was significantly more efficacious than olanzapine (1 RCT, n=25, MD −11.00 CI −20.90 to −1.10). The results of other sensitivity analyses on the PANSS total score (excluded study: Moresco 2004), the BPRS-18 (1-7) total score (excluded studies: Kumra 2008,Wang 2002), the PANSS positive subscore (excluded study: Moresco 2004) and the BPRS positive subscore (Excluded studies:Tollefson 2001) did not change to an important degree.

3. Comparison 2. CLOZAPINE versus QUETIAPINE

From five studies selected, four were carried out in China (Li 2002; Li 2003; Li 2005; Liu 2004) and one in Turkey (Atmaca 2003).

All of them were short term studies.

3.1 Leaving the studies early—Only three studies reported this outcome.

3.1.1 any reason: More people allocated to clozapine (11%) left the study early for any reason in comparison with those allocated of quetiapine (6%), however this difference was not statistically significant (2 RCTs, n=94, RR 1.51 CI 0.42 to 5.50).

3.1.2 adverse effects: Eight per cent of the participants taking clozapine and none of those taking quetiapine left the study early due to adverse effects, but this difference was not significant (1 RCT, n=72, RR 7.0 CI 0.37 to 130.82).

3.1.3 inefficacy: No participant left a study early for this reason.

3.2 Global state: no clinically important change - less than “common criteria” —One study reported the number of participants showing no clinically important change in global state according to ‘common criteria’. The author did not give further details about this criterion. There was no significant difference between groups (1 RCT, n= 76, RR 1.07 CI 0.85 to 1.35).

3.3 Mental state: 1. No clinically important change - less than 50% reduction PANSS total—Only one study (Li 2002) reported this outcome. 32% of the participants in the clozapine group and 34% in the quetiapine group did not improve. There was no significant difference between both antipsychotics (1 RCT, n=63, RR 0.94 CI 0.47 to 1.89).

3.4 Mental state: 2a. PANSS total score—Four studies reported the average PANSS total score at endpoint. There was no significant difference between clozapine and quetiapine in this regard (4 RCTs, n=232, MD 0.50 CI −1.86 to 2.85).

3.5 Mental state: 2b. BPRS-18 (1-7) total score—There was no statistical significant difference in this outcome (1 RCT, n=72, MD 0.89 CI −1.33 to 3.11).

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3.6 Mental state: 3. Positive symptoms: PANSS positive subscore—There was no evidence of a significant difference between clozapine and quetiapine in this aspect (2 RCTs, n=142, MD 0.70 CI −0.68 to 2.07).

3.7 Mental state: 4. No clinically important change - less than 50% reduction SANS—One study defined no important clinical response on negative symptoms as the number of people of each treatment group who did not present 'at least a 50% reduction on SANS'. 89% of those taking clozapine and 83% of those allocated to quetiapine did not improve as this criterion. This difference was not significant (1 RCT, n=72, RR 1.07 CI 0.89 to 1.29).

3.8 Mental state: 5a. Negative symptoms: PANSS negative subscore—People taking clozapine had a higher score on the PANSS negative subscore than those allocated to quetiapine. A statistically significant superiority of quetiapine over clozapine was found (2 RCTs, n=142, MD 2.23 CI 0.99 to 3.48).

3.9 Mental state: 5b. Negative symptoms:SANS—The study that used SANS score to assess the negative symptoms, showed a trend in favour quetiapine, however this difference did not reach the conventional levels of significance (1 RCT, n=72, MD 1.64 CI −4.66 to 7.94).

3.10 Adverse effects: 1. At least one adverse effect—In Li 2002 significantly more participants allocated to clozapine (90%) than to quetiapine (38%) experienced at least one adverse effect (1 RCT, n= 63, RR 2.41 CI 1.52 to 3.82, NNH 2 CI 2 to 5).

3.11 Adverse effects: 2. Cardiac problems—The incidence of cardiac effects was missing in almost all studies. Overall, in the two studies that reported this outcome the incidence was low.

3.11.1 ECG abnormalities: Liu 2004 showed that those taking clozapine were significantly more likely to experience ECG abnormalities than those allocated to quetiapine (1 RCT, n=72, RR 8.00 CI 1.05 to 60.72, NNH 5 CI 3 to 21), but this outcome must be interpreted with caution due to the large confidence interval.

3.11.2 Palpitation: Li 2002, reported the incidence of palpitation (45% clozapine versus 38% quetiapine). There was no significant difference in this regard (1 RCT, n=63, RR 1.20 CI 0.67 to 2.18).

3.12 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use—In Atmaca 2003 no participants (of 27) used antiparkinson medication.

3.13 Adverse effects: 3b. Extrapyramidal: various symptoms

3.13.1 akathisia: There was no significant difference (2 RCTs, n=135, RR 2.52 CI 0.50 to 12.61).

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3.13.2 tremor: There was no significant difference (2 RCTs, n=135, RR 1.01 CI 0.30 to 3.43).

3.13.3 rigor: There was no significant difference (1 RCT, n=63, RR 0.52 CI 0.05 to 5.41).

3.14 Adverse effects: 4. Hypersalivation—In two studies significantly more people taking clozapine (76%) experienced hypersalivation than those taking quetiapine (1%), (2 RCTs, n=135, RR 33.91 CI 6.96 to 165.24, NNH 1 CI 1 to 2). However, this outcome must be interpreted with caution due to the large confidence interval.

3.15 Adverse effects: 5. Lipids: average triglyceride change—Clozapine group presented a significantly more pronounced increase in triglycerides levels than quetiapine (n=27, MD 24.64 CI 20.76 to 28.52).

3.16 Adverse effects: 6. Sedation—People allocated to clozapine (48%) were significantly more likely to suffer sedation than those allocated to quetiapine group (10%), (2 RCTs, n= 135, RR 4.47 CI 2.11 to 9.49, NNH 3 CI 2 to 4).

3.17 Adverse effects: 7a. Weight: number of participant with weight gain—The combined analysis of two studies suggested that weight increase was more common with clozapine than quetiapine (25% clozapine versus 13% quetiapine), however this difference was not significant (2 RCTs, n=135, RR 1.89 CI 0.90 to 3.96).

3.18 Adverse effects: 7b. Weight: average weight change—One study showed a trend in favour quetiapine regarding weight increase, but this difference did not reach conventional levels of statistical significance (1 RCT, n=27, MD 2.11 CI −0.08 to 4.30).

3.19 Adverse effects: 8. White blood cell count: number of participants with a decrease—Decrease of white blood cells (WBC) was evaluated in the Li 2002 study, where those taking clozapine (6%) were more likely to experience decrease in WBC (criterion not stated) than those allocated to quetiapine (0%). However, no statistically significant difference was found between groups (1 RCT, n=63, RR 5.16 CI 0.26 to 103.27).

3.20 Publication bias—Due to the small number of included studies a funnel plot analysis was not performed.

3.21 Missing outcomes—No data were reported for death, service use, general and social functioning, cognitive functioning, quality of life/satisfaction with treatment and some adverse effects such as increase glucose levels, increase triglycerides, increase prolactin levels and seizures.

4. CLOZAPINE versus QUETIAPINE sensitivity analysis

The results of the comparison of clozapine with quetiapine regarding the average on PANSS total score at endpoint did not change when studies with possible skewed data were excluded (Li 2002,Li 2003 and Li 2005).

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5. Comparison 3. CLOZAPINE versus RISPERIDONE

Ten studies were selected according to the criterion of this review. Eight were short term studies (Atmaca 2003; Azorin 2001; Bondolfi 1998; Breier 1999; Heinrich 1994; Ren 2002; Wahlbeck 2000; Zhou 2000), one medium term (Volavka 2002) and one long term (McGurk 2005). Most studies were carried out in Europe and America and two were performed in China.

5.1 Death—Only two short term studies reported on death. There were no reports of suicides (Wahlbeck 2000). Regarding death due to natural causes, no difference was found between clozapine and risperidone (2 RCTs, n=293, RR 0.98 CI 0.06 to 15.48).

5.2. Leaving the study early: 1. Any reason—There was a similar number of participants leaving the studies early due to any reason (32% clozapine versus 35% risperidone, 7 RCTs, n=655, RR 0.92 CI 0.73 to 1.16).

5.3 Leaving the study early: 2. Adverse effects—Twelve per cent of the participants in treatment with clozapine and six per cent of those in treatment with risperidone left the study early due to adverse effects. A statistically significant difference between groups was observed (6 RCTs, n=627, RR 1.88 CI 1.11 to 3.21, NNT 16 CI 9 to 59).

5.4 Leaving the study early: 3. Inefficacy—In contrast, fewer people allocated to clozapine left the studies early due to inefficacy (5% versus 13% respectively). This difference was again statistically significant (6 RCTs, n=627, RR 0.40 CI 0.23 to 0.70, NNT 11 CI 7 to 21).

5.5 Global state: No clinically important change - less than much improved on CGI—The number of participants with no clinical improvement were all those categorized as ‘less than much improved’ on the CGI. A single, small, short term study (Heinrich 1994) found no significant difference in this regard (1 RCT, n=60, RR 0.80 CI 0.43 to 1.49).

5.6 Mental state: 1. No clinically important change - various criteria—Various criteria were used to assess an improvement of the mental state.

5.6.1 less than 20% reduction on BPRS-18 (1-7) total score: One short term study, Breier 1999, reported that 64% of the participants taking clozapine and 80% of those taking risperidone did not improve at this criterion. No statistically significant difference was observed between groups (1 RCT, n=29, RR 0.80 CI 0.50 to 1.28).

5.6.2 less than 20% reduction on BPRS-18 (1-7) total score and mildly ill or better: No significant difference was found between clozapine and risperidone in Azorin 2001 study (1 RCT, n=273, RR 0.95 CI 0.78 to 1.17).

5.6.3 less than 20% reduction on the 4-item on BPRS psychosis and no psychotic symptoms rated less than mild: This criterion was used to define ‘remission’ during the McGurk 2005 study. No significant difference between groups was observed (1 RCT, n=107, RR 0.97 CI 0.78 to 1.21).

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5.6.4 less than 40% improvement on the 4-item on BPRS psychosis cluster: There was no significant difference between groups (1 RCT, n= 107, RR 0.96 CI 0.69 to 1.32).

5.6.5 less than 20% reduction on PANSS total score: There was no significant difference between clozapine (39% not improved) and risperidone (33% not improved) (2 RCTs, n=106, RR 1.18 CI 0.70 to 1.99).

5.7 Mental state: 2a. PANSS total score—Four short term studies and one medium term study provided data, but we did not combine the data due to significant heterogeneity (I-square=52%).

The short term Azorin 2001 study was the only study that showed a statistically significant difference in favour of clozapine (n=273, MD −7.60, CI −13.28 to −1.92).

Atmaca 2003 and Volavka 2002 suggested a better improvement on mental state using clozapine than risperidone, but these differences did not reach the conventional significance level (n=26, MD −1.20 CI −5.01 to 2.61 and n=81, MD −3.60 CI −13.32 to 6.12 respectively).

Contrarily, the short term Bondolfi 1998 study and Wahlbeck 2000 showed a trend in favour of risperidone, but both differences were not significant (n=86, MD 4.20 CI −5.34 to 13.74 and n= 19, MD13.00 CI −4.59 to 30.59 respectively).

5.8 Mental state: 2b. BPRS-18 (1-7) total score—Three heterogeneous studies (I-square=80%) provided data on the BPRS-18 (1-7) total score. Two homogeneous short term studies (Azorin 2001 and Breier 1999) showed a statistically significant difference in favour of clozapine (2 RCTs, n=285, MD −5.11 CI −7.99 to −2.23). The long term study, McGurk 2005, did not show any clear difference between drugs (1 RCT, n=52, MD 0.40 CI −3.52 to 4.32).

5.9 Mental state: 3a. Positive symptoms: PANSS positive subscore—There was no clear difference between clozapine and risperidone (5 RCTs, n=562, MD −0.99 CI −2.29 to 0.32).

5.10 Mental state: 3b. Positive symptoms: BPRS-18 (1-7) positive subscore—The short term Breier 1999 study showed a trend in favour of clozapine on BPRS positive subscore at endpoint, but this difference was not significant (1 RCT, n=29, MD −2.10 CI −4.76 to 0.56).

5.11 Mental state: 4a. Negative symptoms: PANSS negative subscore—Five studies reported heterogeneous results (I-square= 61%), only one of them (Wahlbeck 2000) showed a significant difference between groups in favour of risperidone (1 RCT, n=19, MD 4.00 CI 0.40 to 7.60).

5.12 Mental scale: 4b. Negative symptoms: SANS—The meta-analysis of two short term studies found no significant difference between clozapine or risperidone (2 RCTs, n=69, MD 0.62 CI −2.51 to 3.74).

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5.13 General functioning: 1. GAF score—Only the short term study by Wahlbeck 2000 reported on this outcome and found no significant difference between groups (1 RCT, n=19, MD −9.00 CI −18.44 to 0.44).

5.14 Social functioning: SFS score—Again, only Wahlbeck 2000 examined social functioning and found a higher (= better) average SFS score at endpoint in the risperidone group. This result should be considered with caution due to the great variability of the scores.

5.15 Treatment satisfaction: DAI score—In the short term Wahlbeck 2000 study there was no significant difference between clozapine and risperidone regarding treatment satisfaction (1 RCT, n=19, MD 0.10 CI −2.57 to 2.77).

5.16 Cognitive Functioning: no clinically important change - less than 0.5 SD improved—The medium term study by Volavka 2002 defined ‘important clinical response in cognition’ as those who presented an ‘at least 0.5 SD reduction in neurocognitive score’. A trend in favour of risperidone was observed but this difference did not reach the conventional levels of significance (1 RCT, n=81, RR 1.26 CI 0.95 to 1.67).

5.17 Adverse effects: 1. At least one adverse effect—The proportion of participants experiencing ‘at least one adverse effect’ was reported by two short term studies. The combined analysis was impossible to perform due to the heterogeneity amongst them (I-square= 83%).

Azorin 2001 showed similar proportion of participants that experience at least one adverse effect (78% clozapine and 82% risperidone). No significant difference was observed between groups (1 RCT, n=273, RR 0.94 CI 0.84 to 1.06).

Heinrich 1994 compared one clozapine group with two risperidone groups (two different doses). To analyse this study the data of the two groups of risperidone were pooled. Significantly more people allocated to clozapine reported at least one adverse effect (75%) than those taking risperidone (48%) (1 RCT, n=60, RR 1.58 CI 1.05 to 2.39, NNH 4 CI 2 to 33).

5.18 Adverse effects: 2. Cardiac problems—Data cardiac effects were missing in most studies. The short term Heinrich 1994 study mentioned that only one participant of the risperidone group presented ECG abnormalities. There was no significant difference between groups (1 RCT, n=60, RR 0.65 CI 0.03 to 15.30). The long term McGurk 2005 study assessed the presence of myocarditis, but found that no participants experienced this cardiac alteration during the study. The combined analysis showed no significant difference between groups (2 RCTs, n= 167, RR 0.65 CI 0.03 to 15.30).

5.19 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use—Most studies reported on the use of antiparkinson medication. The meta-analysis of four short term studies and one medium term study revealed that the participants taking clozapine (13 from 142 participant) were less likely to use antiparkinson medication than those taking

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risperidone (37 of 162 participants). There was a statistically significant difference between groups (6 RCTs, n= 304, RR 0.39 CI 0.22 to 0.68, NNH 7 CI 5 to 18).

This tendency persisted over time and it was statistically significant in the combined analysis of the short term subcategory (5 RCTs, n=223, RR 0.39 CI 0.19 to 0.77, NNH 8 CI 5 to 32).

5.20 Adverse effects: 3b. Extrapyramidal: various symptoms

5.20.1 at least one EPS: Two short term studies reported the participants who experienced at least one EPS, but due to heterogeneity (I-square=81%) we analysed them separately. The smaller study Heinrich 1994 did not reveal any significant difference between groups, while Azorin 2001 reported a significant difference in favour of clozapine (1 RCT, n=273, RR 0.46 CI 0.28 to 0.77, NNT 7 CI 4 to 18).

5.20.2 akathisia: The short term Zhou 2000 study reported the incidence of akathisia. Only four out of twenty people in the clozapine group and none of the twenty participants in the risperidone group experienced akathisia. However, this difference was not significant (1 RCT, n=40, RR 9.00 CI 0.52 to 156.91).

5.20.3 dyskinesia: The short term Bondolfi 1998 study reported on the incidence of dyskinesia defined as a score of one or more on ESRS. There was no significant difference between the groups (1 RCT, n=86, RR 1.00 CI 0.38 to 2.61).

5.20.4 dystonia: According to the same criterion, there was no significant difference in the frequency of dystonia (1 RCT, n=86, RR 0.50 CI 0.05 to 5.31).

5.20.5 parkinsonism: Again in Bondolfi 1998 there was a higher risk to have a score of at least one in the parkinsonism item of the ESRS in people taking clozapine than those taking risperidone (63% clozapine versus 40% risperidone, 1 RCT, n=86, RR 1.59 CI 1.03 to 2.45, NNH 4 CI 2 to 37).

5.20.6 tremor: More participants in the clozapine group (40%) experienced tremor during the study than in the risperidone group (20%). There was no indication of superiority of either drug (1 RCT, n= 40, RR 2.00 CI 0.72 to 5.59).

5.21 Adverse effects: 3c. Extrapyramidal: symptom scales

5.21.1 ESRS score: Skewed data of the ESRS score did not show any difference between clozapine and risperidone (1 RCT, n=81, MD 0.30 CI −1.31 to 1.91).

5.21.2 SAS score: Pooled data from two studies (Breier 1999 and Heinrich 1994) did not reveal any significant difference between groups (2 RCTs, n=69, MD −0.81 CI −1.73 to 0.10).

5.21.3 BARS score: The long term McGurk 2005 study assessed akathisia by the BARS scale. No statistically significant difference was found (1 RCT, n= 107, MD −0.20 CI −0.50 to 0.10).

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5.22 Adverse effects: 4. Glucose: average change—Both treatments produced an average increase of glucose level at medium term (14 weeks) (clozapine +4 mg/dl versus risperidone +3 mg/dl), but there was no significant difference between groups (1 RCT, n=31, MD 1.70 CI −8.64 to 12.04).

5.23 Adverse effects: 5. Hypersalivation—In the short term those receiving clozapine were significantly more likely to experience hypersalivation than those receiving risperidone (37% clozapine, 10% risperidone; 3 RCTs, n=373, RR 4.38 CI 1.86 to 10.30, NNH 4 CI 3 to 5).

5.24 Adverse effects: 6. Lipids: average change

5.24.1 average cholesterol change: The Volavka 2002 study reported a higher increase of cholesterol levels in the clozapine group than in the risperidone group, but this difference was not significant (1 RCT, n=31, MD 7.10 CI −19.81 to 34.01).

5.24.2 average triglyceride change: The short term Atmaca 2003 study measured the average change of triglyceride levels which was more pronounced in the clozapine group (1 RCT, n=26, MD 32.41 CI 29.26 to 35.46).

5.25. Adverse effects: 7a. Prolactin: associated side effects—Only one short term study (Bondolfi 1998) reported on diminished sexual drive and found no significant difference between clozapine (5%) and risperidone (10%) (1 RCT, n=86, RR 0.50 CI 0.10 to 2.59).

5.26 Adverse effects: 7b. Prolactin: average at endpoint—Two studies found a statistically significant difference in favour of clozapine, but we did not combine the results due to significant heterogeneity (I-square=72%): Breier 1999 (short term, women and men combined: 1 RCT, n= 27, MD −38.50 CI −53.70 to −23.30) and Volavka 2002 (medium term, only men: 1 RCT, n= 28, MD −20, CI −31.81 to −8.19).

5.27 Adverse effects: 8. Sedation—The combined analysis of five short term studies showed that sedation is more common in participants taking clozapine (30%) than those taking risperidone (17%). A significant difference between groups was demonstrated. (5 RCTs, n=479, RR 1.73 CI 1.24 to 2.42, NNH 8 CI 5 to 18).

5.28 Adverse effects: 9. Seizures—In two studies (one short term and one medium term) people taking clozapine were more likely to experience seizures than those in the risperidone group (9% versus 2% respectively: 2 RCTs, n= 354, RR 4.47 CI 1.43 to 14.01, NNH 14, CI 8 to 38).

5.29 Adverse effects: 10a. Weight: number of participants with weight gain—Two short term studies and one medium term study assessed the frequency of participants who reported weight gain. The pooled results were slightly heterogeneous (I-square= 53%) but the trend was the same in all studies.

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The short term Bondolfi 1998 study showed that more people in the clozapine group (37%) reported weight gain than those in the risperidone group (23%), but this difference was not significant (1 RCT, n=86, RR 1.60 CI 0.82 to 3.12).

The short term Zhou 2000 study showed that 55% of the participants of the clozapine group and none of the risperidone group participants reported weight gain. This difference was significant (1 RCT, n=40, RR 23 CI 1.45 to 365.61, NNH 2 CI 1 to 3) but should be considered with caution due to the great data variability. In the medium term Volavka 2002 study 18% of participants taking clozapine and 10% of those taking risperidone reported weight increase. This difference was not significant (1 RCT, n= 81, RR 1.79 CI 0.57 to 5.66).

5.30 Adverse effects: 10b. Weight: average weight change—Three short term studies and one medium term study assessed the weight change. Again there was a consistent superiority of risperidone, although the degree of difference varied, leading to significant heterogeneity (I-square=80%).

In the short term studies by Atmaca 2003 (1 RCT, n=26, MD 5.98 CI 4.09 to 7.87) and Azorin 2001 (1 RCT, n=270, MD 2.20, CI 1.28 to 3.12) the superiority of risperidone was statistically significant, while Bondolfi 1998 found no significant difference between groups (1 RCT, n=86, MD 1.60 CI −0.03 to 3.23).

In the medium term study of Volavka 2002 clozapine again produced more weight gain than risperidone (1 RCT, n=77, MD 1.90 CI 0.17 to 3.63).

5.31 Adverse effects: 11. White blood cell count: number of participants with a decrease—Overall it was observed a low incidence on WBC decrease in the treatment groups.

Three percent (4/147) of those treated with clozapine (one person suffered from leucopenia/ neutropenia, two reported only neutropenia and one agranulocytosis), and two per cent (3/147) of those treated with risperidone (three people suffered from neutropenia) experienced a decrease in WBC. This difference was not statistically significant (4 RCTs, n=294, RR 1.27 CI 0.33 to 4.99).

5.32 Publication bias—Due to the small number of included studies a funnel plot analysis was not performed.

5.33 Missing outcomes—Data on service use were not reported.

6. CLOZAPINE versus RISPERIDONE - Sensitivity analysis

When the study with potentially skewed data on the BPRS-18 (1-7) total score was excluded, there was still no significant difference between groups according to the remaining two studies (Breier 1999 and McGurk 2005). The remaining sensitivity analysis excluding possibly skewed data (PANSS positive subscore - excluded studies: Ren 2002 and

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Wahlbeck 2000) and PANSS negative subscore (Excluded study: Ren 2002) did not lead to an important change either.

7. Comparison 4. CLOZAPINE versus ZIPRASIDONE

Only one study (Sacchetti 2006, n=146) fulfilled the criteria of our review, it was a medium term study (18 weeks), published as a poster, which provided data on only a few outcomes.

7.1 Leaving the study early: any reason—Sacchetti 2006 reported on 'leaving the study early' due to any reason. 38% of the participants in each group left the study before its end (1 RCT, n=146, RR 1.00 CI 0.66 to 1.51).

7.2 Mental state: PANSS total score—There was no significant difference between clozapine and ziprasidone in the mean change from baseline (1 RCT, n=146, MD 0.50 CI −6.72 to 7.72).

7.3 Adverse effects: Cardiac problems—No participants experienced QT interval prolongation on the ECG during the trial.

7.4 Publication bias—Due to small number of included studies a funnel plot analysis was not performed.

7.5 Investigation of heterogeneity and sensitivity analysis—The reasons for the preplanned sensitivity analysis did not apply.

7.6 Missing outcomes—Data on death, leaving the study early (adverse effects and inefficacy), cognitive functioning, quality of life, service use and relevant adverse effects, other than cardiac effects, were missing.

8. Comparison 5. CLOZAPINE versus ZOTEPINE

Two studies fulfilled the criteria for this review (Lin 2003 and Lindenberg 1997). Lin 2003 was a short term study from Taiwan which has to date only been published as a poster. The Lindenberg 1997 study was from Germany. Only results on leaving the study early could be analysed, because all other outcomes were not analysed on the basis of the randomised participants.

8.1 Leaving the study early: any reason—The Lindenberg 1997 study showed a trend in favour of clozapine in this aspect, but this was not statistically significant (1 RCT, n= 50, RR 0.70 CI 0.32 to 1.54).

8.2 Global state: no clinically important change - less than successfully and no increase on CGI-S—Significantly fewer people allocated to clozapine (1/24) were considered to be not improved than those allocated to zotepine (12/35), (1 RCT, n=59, RR 0.12 CI 0.02 to 0.87, NNT 3 CI 2 to 8).

8.3 Mental state: BPRS-18 total score—The people taking clozapine had a small reduction of the mean BPRS score total, while the mean BPRS in the zotepine group

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increased. This difference was significant in favour of clozapine (1 RCT, n=59, MD −6.00 CI −9.83 to −2.17).

8.4. Adverse effects: 1. Extrapyramidal: antiparkinson medication use—No people allocated to clozapine used antiparkinson medication, but 13 of 35 participants on the zotepine group used it. A statistical significant difference was found (1 RCT, n=59, RR 0.05 CI 0.00 to 0.86, NNH 3 CI 2 to 5).

8.5 Adverse effects: 2. Prolactin: average change—Risperidone increased the mean prolactin level significantly more than clozapine (1 RCT, n=59, MD −33.40, CI −48.67 to −18.13).

8.6 Publication bias—Due to the small number of included studies a funnel plot analysis was not performed.

8.7 Investigation of heterogeneity and sensitivity analysis—The reasons for the preplanned sensitivity analysis did not apply.

8.8 Missing outcomes—There were no data on death, leaving the study early (adverse effects and inefficacy), cognitive functioning, quality of life, service use, and adverse effects, other than EPS and prolactin levels.

DISCUSSION

Clozapine is an atypical antipsychotic which is thought to be superior to conventional antipsychotic drugs in the treatment of refractory schizophrenia, and it causes fewer movement disorders. Clozapine, however, entails a significant risk of serious blood disorders such as agranulocytosis, which could be potentially fatal. Currently there are a number of newer antipsychotics which have been developed with the purpose to find both a better tolerability profile, and a superior effectiveness.

In the last years the number of randomised clozapine trials has dramatically increased. A previous Cochrane review comparing clozapine with newer atypical antipsychotics medication included 8 studies (Tuunainen 2000). The current review includes 27 randomised controlled trials. Nevertheless, many problems that were identified by the previous review have not been solved.

The number of participants leaving schizophrenia trials prematurely remains high. The overall attrition rate of 30% in the included studies is a threat to the validity of the findings.

Often adverse events were only reported if they had occurred in 5% of the participants or greater. This procedure results in under-reporting of rare but important adverse effects. We suggest it would be better to abandon the rules for reporting of adverse effects and that all adverse events should be reported instead, for example as online supplements that are nowadays made available by most journals.

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Most trials provide data on leaving the studies early and overall efficacy. Outcomes that are possibly more important to improve the quality of life such as general functioning or satisfaction with treatment are rarely presented. Authors keep using different criteria for 'response to treatment' making comparison difficult, although validated suggestions for the presentation of response to treatment are available (Van Os 2006, Leucht 2005a, and Leucht 2005b).

Twenty of the included trials were categorised as 'short term' studies and only two were 'long term' studies with a length of more than 26 weeks. Schizophrenia is a chronic, often life-long disorder making more long term studies necessary.

Eight studies were sponsored by pharmaceutical companies producing either clozapine or its comparator drugs. Seven studies did not declare if data and/or implementation of the study were carried out without input from the industry. Due to the inevitable conflict of interest, industry sponsorship is a concern (Heres 2006).

Finally, most studies compared clozapine with olanzapine, risperidone and quetiapine. Fewer randomised controlled trials comparing clozapine with zotepine and ziprasidone are available, and comparisons with amisulpride, aripiprazole and sertindole are missing.

Summary of main results

The review currently includes 27 blinded randomised controlled trials, which involve 3099 participants that compare clozapine versus olanzapine, quetiapine, risperidone, ziprasidone and olanzapine. There were no studies that met the criteria for this review comparing clozapine with amisulpride, aripiprazole or sertindole. Attrition from these studies was high (30.1%), making the interpretation of the results problematic. Clozapine had a higher attrition rate due to adverse effects than olanzapine and risperidone. Contrarily, fewer participants in the clozapine groups left the trials early due to inefficacy than risperidone.

Clozapine was more efficacious than zotepine (and risperidone in one of two rating scales) in improving the participants' general mental state. However it is necessary to replicate these findings in order to confirm these assertions with more robust evidence. Regarding olanzapine, quetiapine and ziprasidone, no differences were observed on this issue.

There was no significant difference between clozapine, olanzapine and risperidone in terms of positive or negative symptoms of schizophrenia. According to two studies from China, quetiapine was more efficacious for improving negative symptoms than clozapine. One of the most important adverse effects of clozapine is the white blood cell decrease, where it was found that only olanzapine is safer than clozapine in this regard. No differences were observed when it was compared with quetiapine and risperidone. This important side effect was not documented in the comparisons with zotepine and ziprasidone.

More participants of the clozapine group showed hypersalivation and sedation than those on olanzapine, risperidone and quetiapine, and there were more seizures than in people on olanzapine and risperidone. Also clozapine produced an important weight gain not observed with risperidone. Clozapine produced somewhat fewer extrapyramidal side-effects (use of antiparkinson medication) than risperidone and zotepine.

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Other differences in adverse effects were less documented and should be replicated, clozapine did not alter prolactin levels in contrast to olanzapine, risperidone and zotepine; compared with quetiapine, clozapine produced a higher incidence of ECG alterations and compared with quetiapine and risperidone, clozapine produce a higher increase of triglyceride levels.

Other findings that should be replicated were that clozapine improved social functioning less than risperidone and fewer participants in the clozapine group had to be hospitalised to avoid suicide attempts in comparison with those from olanzapine group.

It was observed that pharmaceutical companies generally compare newer atypical antipsychotic against a very low dose of clozapine. These doses are lower than those used in the pivotal study of Kane 1988. For this reason, it is not fully clear if this can be included in a sensitivity analysis/meta-regression, because there are only a limited number of studies that use adequate doses. Future research comparing adequate doses are needed.

1. Comparison 1: CLOZAPINE versus OLANZAPINE

1.1 Death: Only two studies assessed this outcome. Data on deaths for any reason as well as for natural causes and suicide were available. A tendency in favour of olanzapine was observed, but these differences were not statistically significant. Hence, it can be concluded that the incidence of death was generally low and similar between treatment groups.

1.2 Leaving the study early: 1. Any reason: Both groups presented a high rate of leaving the studies early for any reason. An overall attrition rate of 39% limits the interpretation of most other findings. The meta-analysis did not show any significant difference between clozapine and olanzapine which may be equally acceptable for individuals with schizophrenia.

1.3 Leaving the study early: 2. Adverse effects: In regard to leaving the study early due to adverse effects, significantly more people taking clozapine left the studies early in comparison with those taking olanzapine, suggesting that olanzapine is tolerated better than clozapine, although the lower limit of the confidence interval is located near the line ‘no difference’. The results of the Bitter 2004, Naber 2005 and Meltzer 2003 studies may have affected our result in this regard due to the low clozapine dose (less 300 mg/day) used in their studies.

1.4 Leaving the study early: 3. Inefficacy: Despite the certain heterogeneity observed on leaving the study due to inefficacy there was a trend in favour of clozapine which did not reach a conventional level of statistical significance. The heterogeneity could be due to Naber 2005, which, unlike other studies, reported a higher attrition rate in the clozapine group than in the olanzapine group.

1.5 Global state: This analysis was based on two medium term studies not finding a significant difference between clozapine and olanzapine on the CGI improvement scale. During these studies more than 50% of the participants in each group did not improve. Only

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Naber 2005 reported relapses and no significant difference between groups was found. The numbers of relapses was very low in both groups.

1.6 to 1.15 Mental state: Various criteria were used to evaluate a clinically significant improvement of the participants mental state, using the PANSS or the BPRS. Neither in the short term nor in the medium term was there a statistically significant superiority displayed by either group. Nevertheless it is interesting to note a slight trend in favour of clozapine in the two small studies with children (Kumra 2008; Shaw 2006).

The mean values on PANSS and BPRS total scores showed a trend in favour of olanzapine, but this difference did not reach conventional levels of statistical significance even when we excluded studies with skewed data. These results were probably affected due to the low doses of clozapine used (< 400 mg/day) and it may be the sample power was not enough to find a statistical difference between groups. New studies are necessary to assess the effect and impact of this difference, if any exists.

Observing the primary studies, both drugs produced a score decrease from baseline. However, the degree of reduction in short term studies by Krakowski 2006 and Volavka 2002 (less than 10 PANSS points) may not be clinically important. Studies with duration of more than 18 weeks showed a more pronounced reduction of symptoms (more than 10 points, Naber 2005, Bitter 2004 and Tollefson 2001).

The studies in children again showed a trend in favour of clozapine which was not statistically significant (Kumra 2008 and Shaw 2006). It could be interesting to clarify by further studies whether children respond differently to therapy than adults.

There was no significant difference between clozapine and olanzapine in the reduction of positive and negative symptoms of schizophrenia. Again, the small studies with children showed a non-significant trend in favour of clozapine in terms of the average SAPS and SANS change, which could stimulate further studies. On SANS, which excluded the study with possibly skewed data, clozapine showed a superiority over olanzapine, but this finding has a limited utility due to the low power of the sample (one study), and because the participants were children.

1.16 Cognitive functioning: This outcome was evaluated by only one study, which reported that significantly more participants in the olanzapine group than those assigned to the clozapine group presented a clinically relevant improvement, defined as a decrease of at least 0.5 standard deviation units on the neurocognitive score. More evidence on this important outcome is needed.

1.17 to 1.18 Quality of life: Subjective well being and quality of life were assessed in one study at medium term using SWN-38 score and MLDL satisfaction with treatment score, respectively. The SWN-38 showed a marked tendency in favour of olanzapine, but due to a great variability of the data the difference was not statistically significant. Furthermore, when the MLDL instead of the SWN-38 was considered, the satisfaction with clozapine and olanzapine was similar.

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1.19 Service use: A long term study, Meltzer 2003, showed a significant difference, where more participants in the olanzapine group had to be hospitalised to avoid suicide attempts. The relevance of this finding is limited due to the small effect size and the CI observed, which showed that it is possible that the true RR value is likely to be very close to 1.

1.20 Adverse effects: 1. At least one adverse effects: The results on the number of participants with at least one adverse effect were statistically significantly heterogeneous and were therefore not combined. In general, all studies showed a trend indicating more people in the clozapine group had at least one adverse effect, but only one showed a significant difference between groups. Although this study presented an important effect size its generality is limited because only Chinese participants were included who might have a different idiosyncratic response to the treatment. It is possible that the biological and cultural variability between studies was the cause of the heterogeneity among them.

1.21 Adverse effects: 2. Cardiac effects: Regarding cardiac effects, a low incidence of ECG alteration was observed in both groups, even when the alteration incidence was lower in the olanzapine group, there was no statistical significant difference.

1.22 to 1.28 Adverse effects: Extrapyramidal effects: Concerning extrapyramidal side-effects there was no significant difference between clozapine and olanzapine in terms of the use of antiparkinson medication. There was also no significant difference in terms of specific extrapyramidal symptoms such as akathisia, dyskinesia, pseudoparkinsonism and rigor. All of them, except pseudoparkinsonism, showed a trend in favour of clozapine. Both antipsychotic drugs may cause some extrapyramidal effects because a number of participants needed antiparkinson medication during the trials and movement disorders occurred in both groups. Rating scales for general and specific extrapyramidal side-effects (ESRS, BARS, AIMS, SAS and HAS) did not reveal statistically significant differences.

1.29 to 1.30 Adverse effects: Glucose: There was no conclusive difference between clozapine and olanzapine in terms of glucose levels. Dichotomous data from Meltzer 2003 showed no difference regarding the incidence of diabetes mellitus (criterion not specified). Continuous glucose data were heterogeneous. Only short term studies significantly favoured olanzapine, but there was a high variability of the results and the sample sizes were small. In contrast, a medium term study showed a non-significant trend in favour of clozapine.

1.31 Adverse effects: Hypersalivation: Five studies reported on hypersalivation but as the results were heterogeneous we did not combine them in a meta-analysis. Nevertheless four studies reported a significant difference in favour of olanzapine. The results of the single studies suggest that longer study durations were associated with larger effect sizes and indeed when only studies of each duration category were pooled the results were homogeneous. It can be clearly concluded that people using clozapine are more prone to present hypersalivation than those using olanzapine.

1.32 to 1.34 Adverse effects: Lipids: Data on lipid levels were equivocal and heterogeneous. Currently there is no evidence for any superiority of one drug over the other. In order to obtain a valid conclusion further studies would be necessary.

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1.35 Adverse effects: Prolactin: According to a small study, the average change in prolactin levels at medium term showed a statistically significant difference in favour of clozapine, which slightly decreased the level, while the prolactin level in the olanzapine group increased. Whether this difference is clinically important or not is questionable, but at least in specific situations (e.g. women with a history of breast cancer) it may be relevant. Others studies indicated prolactin levels by gender. The results in men were heterogeneous, possibly due to different participant ages. The study in children and adolescents found a significant difference in favour of clozapine (Kumra 2008: male only). The same study also found a significant superiority of clozapine in female participants. The effect sizes were relatively large and probably clinically meaningful, at least in female participants in whom the mean prolactin level in the olanzapine group was above normal. These results should be replicated in larger samples to corroborate the evidence base. The clinical importance of prolactin increase should also be addressed by recording associated side-effects (galactorrhoea, impotence etc).

1.36 Adverse effects: Sedation: In seven studies sedation was more frequent in participants using clozapine than in participants using olanzapine. Although all studies showed at least a trend in favour of olanzapine (irrespective of their duration), the results were heterogeneous. The heterogeneity could be caused by differences in participants age because the two studies in children and adolescents found only minimal differences between groups (Shaw 2006 and Kumra 2008). This observation suggests that children may differ in their sensitivity to sedative effects from adults but this needs to be confirmed in further trials.

1.37 Adverse effects: Seizures: Participants using clozapine presented a 6.5 times higher risk for seizures than those using olanzapine. Therefore olanzapine is more secure on this regard.

1.38 to 1.39 Adverse effects: Weight gain: Results on weight gain were inconclusive. The results in terms of ‘number of patients with weight gain’ were heterogeneous and only one study (Meltzer 2003) showed a significant difference between groups in favour of clozapine. The heterogeneity could be due to different criteria applied to define ‘weight gain’. There was also no significant difference in the mean weight gain between clozapine and olanzapine. We highlight that both drugs produced a considerable increase of weight, clozapine from 1.5 to 6.5 kg and olanzapine from 1.6 to 8.9 kg.

1.40 Adverse effects: White blood cell count: Significantly more participants in the clozapine group experienced an important reduction of the white blood cell count during the studies. The risk in the clozapine group was six times higher than in the olanzapine group. Therefore, olanzapine is a safe drug regarding this important outcome.

2. CLOZAPINE versus OLANZAPINE - Sensitivity analysis—The sensitivity analysis carried -out did not show any significant change in the results, except for the comparison average change on SANS excluding the studies with potentially skewed data. This result was difficult to interpret due to the small size sample from one study.

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3. Comparison 2: CLOZAPINE versus QUETIAPINE—These studies have a limited external validity mainly for two reasons: time (only short term results) and participants' ethnicity (80% of the studies were of oriental origin).

3.1 Leaving the study early: A trend was observed indicating that more people receiving clozapine than quetiapine left the study early due to any reason and/or adverse effects. However these differences did not reach the conventional statistical significance level. Probably due to the small size of the trial, the possibility to detect any difference between the groups, if any existed, was low. The outcome 'leaving the study early due inefficacy' could not be estimated since the trial that reported this result did not have any attrition due to this cause.

3.2 Global state: In practice several criteria have been used to measure the participants' global state during the treatment. The only study that reported the number of participants with no clinical important change on the global state did not give any details regarding the criterion and only stated that a 'common criterion' was used. There was no evidence of any difference amongst the groups on this regard. Since the study was done in China, where criteria and medical praxis could differ from the ones used in other countries, its applicability could be limited.

3.3 to 3.9 Mental state: A similar percentage of participants in both groups (32% in clozapine versus 34% in quetiapine) did not improve their mental state using the criterion of at least 50% of reduction on PANSS at short term. The participants also had similar scores on PANSS or BPRS total at endpoint. No statistically significant evidence of superiority of either drug regarding the efficacy of them on mental state was found.

Regarding positive symptoms, both treatment groups at short term presented similar PANSS positive subscore at endpoint. Concerning the clinical improvement of negative symptoms (at least 50% diminution on SANS score), no evidence of any difference was found amongst groups. Skewed data pooled of average PANSS negative subscore at endpoint showed a quetiapine superiority over clozapine, but due to the asymmetry this result had a limited confidence level (<95%). One study that used SANS total score showed the same trend, but without reaching the conventional significance levels. Summarising both treatments were not different in efficacy on general mental state or positive and negative symptoms.

3.10 Adverse effects: At lease one adverse effects: Participants receiving clozapine presented two times more risk of at least one adverse effect than those with quetiapine treatment (NNH 2, CI 2 to 5). This NNH suggests that adverse effects were common in participants receiving clozapine.

3.11 Adverse effects: Cardiac effects: Participants on clozapine had a higher risk of presenting ECG abnormalities, but this result should be taken with precaution due to its low statistical power, which limits its interpretation (NNH 5, CI 3 to 21). The incidence of specific cardiac effects was similar in both groups.

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3.12 to 3.13 Adverse effects: Extrapyramidal effects: Regarding extrapyramidal symptoms, the effect of both treatments on the use during the study of antiparkinson medication could not be estimated since only one study reported this outcome without any event amongst groups.

Evaluating the specific extrapyramidal symptoms, a trend in favour of quetiapine and clozapine was found with respect to the incidences of akathisia and rigor respectively. Regarding tremor, the trend was the same for both groups. By general rule there were no statistically significant differences between treatment groups, therefore is not possible to establish which drug was safest with regard to specific extrapyramidal adverse effects.

3.14 Adverse effects: Hypersalivation: Hypersalivation was significantly more frequent in people allocated to clozapine (NNH 1, CI 1 to 2), the NNH value indicates that this adverse effect was very common with clozapine. Although a great variability in the relative risk values, the minimum value, which is likely to include RR, was clinically important and the maximum one was overrated.

3.15 Adverse effects: Lipids: There was statistically significant evidence that participants receiving clozapine had a greater increase in triglyceride levels. This result was based only on a small study (n=25). It would be necessary to replicate this finding.

3.16 Adverse effects: Sedation: People on treatment with clozapine had 4.47 times more risk of suffering sedation (NNH 3, CI 2 to 4) than people allocated to quetiapine. This adverse effect was common in this group of participants.

3.17 to 3.18 Adverse effects: Weight: People taking clozapine were more prone to weight gain than those receiving quetiapine, the magnitude of this increase was higher in the clozapine group (+ 6.5 kg) than quetiapine group (+ 4.4 kg), however both differences were not statistically significant.

3.19 Adverse effects: White blood cell count: Concerning white blood cell decrease, there was no statistically significant difference between the treatment groups. Due to the small power of the trial it was not possible to detect any difference between the groups, if any existed. Furthermore it is necessary to have more details e.g. if the decrease was transient or conserved, the decrease severity, etc. in order to evaluate the clinical importance, as well as data from longer trials.

Overall, evaluating the results of the adverse effect analysis, it is possible to mention the existence of a trend in favour of quetiapine, but it is not statistically significant.

4. Comparison CLOZAPINE versus QUETIAPINE Sensitivity analysis—The sensitivity analysis for the comparison average PANSS total score at endpoint excluding the studies with potentially skewed data, showed no change in the results, supporting that there was no evidence to indicate a difference between clozapine and quetiapine in these aspects.

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5. Comparison 3: CLOZAPINE versus RISPERIDONE

5.1 Death: Death is an outcome not usually evaluated in studies. There was no evidence of any difference between short term treatment groups with respect of the incidence of death due to natural causes. In the case of death by suicide, a small study reported that it did not occur, therefore the treatment effect was not estimable.

5.2 to 5.4 Leaving the study early: Overall, a high percentage of participants withdrew from the study in both treatments. No statistically significant difference between comparison groups was found on leaving the study early due to any reason.

More people treated with clozapine left the treatment because of adverse effects than those allocated to risperidone. Clozapine is more prone to produce important adverse effects such as sedation, seizures, hypersalivation, agranulocytosis, etc. which could explain this result. More participants allocated to risperidone left early due to the ineffectiveness compared to the people who received clozapine, suggesting a certain superior efficacy of clozapine.

5.5 Global state: This outcome is based on a single study and showed that there was no clear difference between clozapine and risperidone for CGI clinical response.

5.6 to 5.12 Mental state: A wide variety of criteria to measure the clinical improvement on mental state were used in different studies. Regardless of the criterion used either using PANSS or BPRS, studies at short and long term did not find robust evidence to demonstrate the superiority of one drug over the other.

Heterogeneous data could not be combined to estimate the treatment effects on mental state using PANSS or BPRS scale. Therefore it was difficult to obtain any conclusions on this regard. Only the short term Azorin 2001 study showed a statistically significant difference in favour of clozapine on PANSS, which was replicated in the same study by using BPRS scale.

Overall, the studies reported that mental state scale data showed a wide variability in their measurements, which could be caused by differences in sample sizes, length of the studies, clozapine doses used and methodology used in the analysis (LOCF and/or ITT). The results of combined analysis of the short term studies were strongly influenced by Azorin's study (Azorin 2001) showing a statistically significant difference in favour of clozapine on BPRS, but the PANSS analysis did not support these results, which makes it difficult to define if there is any superiority in efficacy of either drug over the other. It would be desirable to have further studies using appropriate doses with a high quality methodological procedure, in order to include them in future versions of this review to obtain the best evidence in this regard.

There was a slight trend in favour of clozapine on the PANSS positive subscore, which was not significant. It was observed that the results of individual studies are contradictory and equivocal; this could be the cause of certain level of heterogeneity among them. Skewed data in subscores suggests the same trend on the BPRS positive, but neither was significant.

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For negative symptoms, again data from PANSS were heterogeneous and equivocal, hampering the analysis. Two studies used SANS score (only short term) and did not find any statistically significant differences between groups.

5.13 General functioning: A trend in favour of risperidone is noted on GAF measures, where risperidone presented a score greater than clozapine at endpoint. The small sample size of the single available study makes any conclusions impossible.

5.14 Social functioning: Risperidone was superior to clozapine on measures of social functioning (short term). It is important to take into account the low power of the sample, which implies a high degree of variability in the measurements, therefore the clinical significance of this finding is difficult to interpret.

5.15 Treatment satisfaction: Skewed data showed no difference between clozapine and risperidone in treatment satisfaction.

5.16 Cognitive Functioning: There were no statistically significant differences between groups in terms of participants who showed a neurocognitive improvement. This study used a score composed by four neurocognitive domains performed especially for this study, therefore its application to clinical practice would require a validation procedure.

5.17 Adverse effects: At least one adverse effect: Two heterogeneous studies compared clozapine and risperidone regarding the number of people who experienced ‘at least one side effect’ during the study. One of them showed a significant difference, where more people taking clozapine suffered at least one adverse effect than those receiving risperidone. This result should be interpreted with caution due to the low sample power. The other, larger, study did not show a difference between treatment groups.

5.18 Adverse effects: Cardiac effects: There was no evidence that the treatment groups were different in terms of the incidence of cardiac alterations (ECG abnormalities - myocarditis).

5.19 to 5.21 Adverse effects: Extrapyramidal: With regard to extrapyramidal symptoms, fewer people in the clozapine group received an antiparkinson medication compared with those assigned to risperidone (NNH 6, CI 4 to 12). Two heterogeneous studies assessed the number of people who experienced at least one extrapyramidal symptom, only one of them showed a significant statistical difference in favour of clozapine. It was difficult to contrast these results with the other outcomes appraised regarding extrapyramidal symptoms since no comparison showed any statistically significant difference between clozapine and risperidone. The evaluation of the relative risk of presenting some specific extrapyramidal symptoms did not show any difference between groups with respect to akathisia, dyskinesia, tremor and dystonia. Surprisingly parkinsonism was significantly more frequent in participants with clozapine than risperidone, but the clinical significance is unclear because the criterion used was an ESRS score considering only ‘participants with score of 1 or more in ESRS’, because the mean score was not reported and because the confidence interval was very large and the lower limit very close to one (equal effects).

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When extrapyramidal symptoms were evaluated by means of ESRS and BARS scores, skewed data were equivocal. Using SAS, a small study showed no difference between the treatment groups.

In general studies did not report or at least not clearly, the occurrence of extrapyramidal symptoms. In further studies a clear description of the criteria for reporting adverse effects and along with it, the way of reporting the use of antiparkinson medication during the trial, is necessary. Thus the process could systematically eliminate confusion factors. As a result it might be possible to demonstrate whether there is any difference between clozapine and risperidone in this aspect.

5.22 Adverse effects: Glycaemia: There was no evidence that the drugs were different with respect to glycaemia. Clearly, both drugs produced an average increase of glucose of 3 - 4 mg/dL on glucose level at 14 weeks (medium term). It would be interesting to know their long term effects, as well as with a bigger sample size to evaluate their clinical importance in particular situations.

5.23 Adverse effects: Hypersalivation: Hypersalivation was 4.34 times more common in participants taking clozapine than those with risperidone (NNH 4, CI 3 to 5).

5.24 Adverse effects: Lipids: With regard to lipid levels, both drugs increased the cholesterol and triglycerides levels. Although no significant differences between groups in the average change of total cholesterol at medium term was observed, a marked trend in favour of risperidone was noted, which might reflect a type II error. By contrast, there was a statistical significant difference between clozapine and risperidone in the average change on the triglycerides level, where the clozapine group showed a pronounced increase. Despite the small sample size, the precision of the measurements contributed to increase the magnitude of treatment effect, clinically and statistically significant but limited because these results were based on only one small study, and should be replicated.

5.25 to 5.26 Adverse effects: Prolactin: A single short term study reported the outcome of the diminution of sexual drive, which is a side-effect associated with an increase of prolactin levels. This side-effect presented a higher incidence in the risperidone group but without reaching the conventional levels of statistical significance. People treated with risperidone showed a high level of prolactin at endpoint (short and medium term) over the adults' reference levels unlike those treated with clozapine who presented values inside the reference levels. Two studies reported these findings showing significant differences between groups in favour of clozapine, but these results could not be combined due to the heterogeneity amongst them. The difference between these two studies could be due to the variability of the measurements caused by the small power of the samples. Also the results in the Volavka 2002 study were biased, since the measures reported were obtained from a subgroup of male patients and not from the entire group. It would be desirable to replicate these results, in order to support with more confidence these findings. Nevertheless, it is very likely that risperidone is associated with much more prolactin increase than clozapine.

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5.27 Adverse effects: Sedation: Sedation was statistically more frequent in participants using clozapine than those using risperidone (NNH 7 CI 4 to 17).

5.28 Adverse effects: Seizures: People taking clozapine were more prone to suffer seizures than those on risperidone (NNH 14 CI 8 to 38).

5.29 to 5.30 Adverse effects: Weight: The studies that reported the outcome of 'number of participants with weight gain' were heterogeneous. These studies showed that more participants using clozapine suffered weight gain than those using risperidone. Only a small short term study conducted in China reached levels of statistical significance in favour of risperidone, however the ample confidence interval made it difficult to conclude its clinical significance. The heterogeneity could be due to the different criteria used to define weight gain and the idiosyncratic sample variability. This trend was supported by the results of individual heterogeneous studies at short and medium term that measured average weight change, where three of four studies showed statistical significant differences between the treatment groups. Clozapine treatment produced an increase between 2 - 6 kg more than risperidone.

5.31 Adverse effects: White blood cell count: There was no evidence of difference in the incidence of white blood cell decrease between clozapine and risperidone. In general, the incidence was very low and non-fatal in both groups, neutropenia being the most frequent alteration.

6. Comparison 4: CLOZAPINE versus ZIPRASIDONE—These results are based on only one unpublished short term study including people with refractory schizophrenia.

6.1 Leaving the study early: Overall, in both groups a high number of participants left the study early due to any reason. Clozapine and ziprasidone were similar in this aspect showing a 38% rate of attrition to medium term (18 weeks). This high attrition value could affect the validity of the results.

6.2 Mental state: Both drugs produced a similar diminution, near to 24.5 points on PANSS total score after 18 weeks of treatment. Both antipsychotics drugs showed to be efficacious in decreasing schizophrenia symptoms. There was no evidence of superiority by either drug.

6.3 Adverse effects: Cardiac problems: None of participants suffered any cardiac alteration during the length of the trial, therefore both treatments were shown to be safe in this aspect at 18 weeks. Again, this result was based on a single study which has only been published as a poster.

7. Comparison 5: CLOZAPINE versus ZOTEPINE—Only two studies provided data to compare clozapine with zotepine. The Lindenberg 1997 study was based on six weeks of the following of only Caucasian participants which limited its external validity. This study provided only data for leaving the study early for any reason. The other data are based only in one short term study from Taiwan (Lin 2003). The objective of this study was to evaluate switching from clozapine to zotepine in patients with partial response to clozapine.

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Therefore the results presented two limitations: they are only applicable to the drug-switching situation and the external validity is limited since the study only included oriental participants.

7.1 Leaving the study early: No statistically significant difference was found between clozapine and zotepine in the rate of participants who left the study early for any reason. The specific reasons for leaving the study early were not reported.

7.2 Global state: The limited data showed a clear difference between groups, where more people on zotepine did not improve ('less than successfully and no increase on CGI-S') during the twelve weeks of the study in comparison with those from the clozapine group (NNT 3, CI 2 to 8). It is difficult to support this finding as results are based on one small single study.

7.3 Mental state: A statistically significant difference in favour of clozapine in the average change on BPRS total was found. The effect size was influenced by an unexpected increase of 4.7 points in the score of participants taking zotepine, while in the clozapine group only a slight decrease of 1.3 points was noted. This finding suggests that those on clozapine treatment conserved their score almost without changes and those using zotepine worsened in the twelve weeks, therefore despite clozapine being superior in comparative terms, its effect on the participants' improvement was not clinically important.

7.4 Adverse effects: Extrapyramidal effects: The relative risk of use of antiparkinson medication was higher in the zotepine group than in the clozapine group (NNH 3, CI 2 to 5). This study reported that only participants who switched to zotepine needed medication at some point within the 12 weeks, whereas participants treated with clozapine did not require it. Due to the study features it is important to consider that participants treated with clozapine probably experienced some transient extrapyramidal symptoms before the study, therefore the conclusion obtained from this study could, in some way, be biased.

7.5 Adverse effects: Prolactin: Another adverse effect assessed in this study was increase of the prolactin level. Participants treated with zotepine presented a significant increase of the prolactin levels. Although the wide confidence interval indicates low precision of estimated effect, the increase in values over the normal levels suggest that zotepine could have some negative implications for patient health. Again, the limited data make any conclusive statement difficult and a replication is needed.

Limited data made it impossible to compare these antipsychotics regarding other important adverse effects.

Overall completeness and applicability of evidence

Data on five out of eight possible comparisons were found, hence the evidence is incomplete. Limited information on general functioning, satisfaction with the treatment or care, cognition and service use was available. Most studies were short term, which limits the applicability considering that schizophrenia is a chronic, often life-long disorder. The high attrition in the studies also limits the applicability of the evidence to practice.

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Quality of the evidence

Twenty of twenty-seven studies were double-blind and seven were single-blind, and the reporting of details were limited. Without an adequate description of the methodology of the studies, it was difficult to assess their quality. Moreover, many outcomes were assessed in sample sizes that were not large enough to detect significant differences if they exist.

Potential biases in the review process

We are not aware of any obvious flaws in our review process.

Agreements and disagreements with other studies or reviews

The former Cochrane review that compared clozapine with other second generation antipsychotic drugs (Tuunainen 2000) included only eight studies, while the current report comprises 27 studies. This large increase in the evidence base makes the two reviews hardly comparable. Nevertheless, some differences in adverse events found in Tuunainen 2000 persisted in the current review making these results more robust.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—People with schizophrenia need to know that clozapine differs most clearly in adverse effects from other second generation antipsychotic drugs. It seems to produce somewhat fewer movement disorders than risperidone and zotepine, and is likely to increase prolactin levels less than olanzapine, risperidone and zotepine. On the other hand, clozapine is associated with more frequent decrease of white blood cells than olanzapine, more hypersalivation and sedation than olanzapine, quetiapine and risperidone, and more seizures than olanzapine and risperidone. Compared to risperidone, clozapine may also lead to more weight gain. Differences in efficacy are less clear, but clozapine may be slightly more efficacious than risperidone and zotepine.

2. For clinicians—The overall attrition in the included studies of this review was considerable (30%) making the interpretation of the results difficult. Furthermore, a reasonable amount of evidence is only available compared to olanzapine (12 trials) and risperidone (9 trials). Five small trials on quetiapine were conducted outside the US and Europe, limiting generalisability. Only two small studies compared clozapine with zotepine and one with ziprasidone. Randomised clinical trials comparing clozapine with other second generation antipsychotic drugs (e.g. amisulpride, aripiprazole and sertindole) are not available.

Although clozapine is usually considered to be the most efficacious antipsychotic drug available, this review could not document convincing differences in efficacy.

Adverse effects profiles are very similar, some specific differences could be crucial to selecting the more adequate treatment according to the characteristics of each patient and their expectations. Here, clozapine seems to produce more hypersalivation and sedation than olanzapine, quetiapine and risperidone; more seizures than olanzapine and risperidone; more

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weight gain than risperidone and more frequent leukopenia than olanzapine. On the other hand, clozapine was associated with fewer movement disorders than risperidone and zotepine, and less prolactin increase than olanzapine, risperidone and zotepine.

3. For managers/policy makers—There is insufficient information to guide the decisions of managers and policy makers. The abandonment of treatment often leads to worsening of patients' health and therefore a greater demand for medical care. Clozapine, risperidone, olanzapine and ziprasidone show similar rates of abandonment of treatment, nearly 31%, which makes it necessary to apply efforts to improve the patient compliance. Service use was reported by only one large study which showed fewer hospitalisations to avoid suicide attempts. This evidence base is too limited for making recommendations. This review did not attempt to measure the economic impact of clozapine compared to other second generation antipsychotic drugs.

Implications for research

1. General—There is room for improvement in the conduct and reporting of randomised controlled schizophrenia trials. Rating scale derived efficacy outcomes dominate the trials and even in this regard authors keep using different definitions for response to treatment making a comparison of the results difficult. Potentially important outcomes such as satisfaction with care, functioning in the community or service use are rarely examined. Simple descriptions of the randomisation or blinding methods are usually not presented. Strict adherence to the CONSORT statement (Moher 2001) would improve the reporting and conduct of future trials.

2. Specific—Studies comparing clozapine with the second generation antipsychotic drugs amisulpride, aripiprazole and sertindole are currently completely missing and are therefore mandatory. But even the available evidence on the other comparisons was incomplete, most importantly concerning global outcomes such as satisfaction with care, death, quality of life or service use. Furthermore, only 8% of the included studies fell in the long term category. As schizophrenia is usually a chronic disorder, there is a need for further long term trials. Table 1 makes a suggestion as to how such a study could look. Limited available evidence addressed the effects of clozapine in children and adolescents with schizophrenia. As children may have a different response treatment, this evidence should be extended.

Pharmaceutical companies generally compare new drugs against a very low dose of clozapine. These doses are lower than used in the pivotal study of Kane 1988 and his collaborators. It is not fully clear if this can be included in sensitivity analysis/meta-regression, because there are only a limited number of studies that use adequate doses. This certainly indicates the need for future research using adequate doses

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CHARACTERISTICS OF STUDIES

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

Atmaca 2003

Methods	Allocation: randomised. Blindness: single, rater-blinded. Duration: 6 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia. N=56. Age: 19-46 years (mean clozapine=31.3 years, mean olanzapine=29.6 years, mean quetiapine=30.1 years, mean risperidone=27.9 years, mean control group=32.1 years). Gender: 24 M, 29 F. Setting: inpatient. History: duration ill mean clozapine=6.6 years, mean olanzapine=6.3 years, mean quetiapine=5.9 years, mean risperidone=5.6, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: not reported. Mean dose: 207.1 mg/day. N=14. **2** Olanzapine: flexible dose. Allowed dose range: not reported. Mean dose: 15.7 mg/day. N=14. **3** Quetiapine: flexible dose. Allowed dose range: not reported. Mean dose: 535.7 mg/day. N=14. **4** Risperidone: flexible dose. Allowed dose range: not reported. Mean dose: 6.7 mg/day. N=14
Outcomes	Leaving the study early: any reason. Mental state: PANSS total score. Adverse effects: use of antiparkinson medication, extrapyramidal side effects, lipid change, weight change
Notes	There was a control group (N=11) (not randomised) receiving no pharmacologic treatment

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The patients were randomly divided into 4 treatment group.." Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "raters were blind to drug assignment." "The prescribing physician was not blind to assignment" Comment: Single/rater blind study. Subjective measures may lead a source of bias. Also review authors believe that the fact the prescribing physician was not blind will introduce bias. The success of blinding was not evaluated
Incomplete outcome data addressed?	Unclear	6/62 patients were excluded (four due to requirement of additional drug and two due to intolerance). The author

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All outcomes		did not state from which group they were excluded. Another three patients did not complete the study (one clozapine / one olanzapine / one risperidone) Intention-to-treat analysis was not undertaken.
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	Yes	Review authors have not found other sources of bias.

Azorin 2001

Methods	Allocation: randomised. Blindness: double. Duration: 12 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia disorganised, catatonic, paranoid, residual or un-differentiated. N=273. Age: 18-65 years (mean clozapine=37.8, mean risperidone=39.5) (of intent-to-treat population). Gender: 182 M, 74 F (of intent-to-treat population, N=256). Setting: in- and outpatient. History: duration ill mean clozapine=13.0 years, mean risperidone=15.5 years (of intent-to-treat population), age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-900 mg/day. Mean dose: 642 mg/day. N=138. **2** Risperidone: flexible dose. Allowed dose range: 2-15 mg/day. Mean dose: 9 mg/day. N=135
Outcomes	Death. Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: PANSS total score, BPRS total score, PANSS positive and negative sub-score. Adverse effects: at least one adverse effect, extrapyramidal side-effects, sedation, seizures, weight gain, white blood cell count. Unable to use: Change of weight (no SD).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " patients who satisfied the eligibility criteria were then randomly assigned.. (balanced by country, with a block size of six)" Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "..assigned to double-blind treatment". Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	Unclear	38/138 missing from clozapine group. 34/135 missing from risperidone group. Analysis by intention to treat and LOCF Comment: ITT "considered patients randomly assigned with at least one post-dose BPRS evaluation"
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	Unclear	Study supported by a grant from Novartis Pharma S.A.

Bitter 2004

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Methods	Allocation: randomised. Blindness: double. Duration: 18 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of, standard an-tipsychotic therapy. N=147. Age: 18-65 years (mean=37.6). Gender: 88 M, 59 F. Setting: inpatient. History: duration ill not reported, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 100-500 mg/day. Mean dose: 216.2 mg/day. N=72. **2** Olanzapine: flexible dose. Allowed dose range: 5-25 mg/day. Mean dose: 17.2 mg/day. N=75
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: PANSS total score, PANSS positive and negative subscore. Adverse effects: at least one adverse effect, extrapyramidal side effects (akathisia, dyskinesia, parkinsonism, use of antiparkinson medication, AIMS, Hillside Akathisia Scale, SAS), sedation, weight change Unable to use: Leukopenia (no data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote:"This was a Phase III, 18-week, randomised.. (1:1 ratio)" Comment: Incomplete information.
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote: "This was a Phase III, 18-week, randomised, double blind, parallel study" Comment: The success of blinding was not evaluated.
Incomplete outcome data addressed? All outcomes	No	33/74 missing from clozapine and 30/76 missing from olanzapine. Analysis by intention to treat and LOCF Comment: patients analysed were all those had at least one post-baseline measurement
Free of selective reporting?	No	Quote: "Spontaneously reported adverse events with an incidence of 5% in either treatment group or with a statistically significant difference (P < . 05) between groups"
Free of other bias?	Unclear	The study was sponsored by Eli Lilly and company.

Bondolfi 1998

Methods	Allocation: randomised. Blindness: double. Duration: 8 weeks.
Participants	Diagnosis: (DSM-III-R) chronic schizophrenia, non-responders or intolerance. N=86. Age: 18-65 years (mean=37.3). Gender: 61 M, 25 F. Setting: inpatient.

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	History: age at first hospitalisation mean clozapine=25.0, mean risperidone=26.0, age at onset mean clozapine=23.5, mean risperidone=22.4
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 150-400 mg/day. Mean dose: 291.2 mg/day. N=43. **2** Risperidone: flexible dose. Allowed dose range: 3-10 mg/day. Mean dose: 6.4 mg/day. N=43
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, PANSS positive and negative subscore. Adverse effects: cardiac effects (any significant cardiac effect), extrapyramidal side-effects (akinesia, dystonia, parkinsonism, use of antiparkinson medication), prolactin associated side-effects (sexual dysfunction), sedation, weight (as "weight gain" reported adverse event), white blood cell count Unable to use: Change of weight in kg (no usable data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " Patients randomly assigned to receive risperidone or clozapine.." Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "Double blind, double dummy protocol" Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	Yes	9/43 missing from clozapine group. 9/43 missing from risperidone group Analysis by intention to treat and LOCF.
Free of selective reporting?	No	Quote: "Adverse events reported by 5% or more of either treatment group during the trial"
Free of other bias?	Yes	Study supported by a grant from industry of both study drugs. The study used low clozapine doses

Breier 1999

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis: (DSM-IV) chronic schizophrenia. N=29. Age: 18-55 years (mean clozapine=37.7, mean risperidone=32.4). Gender: 19 M, 10 F. Setting: not reported. History: duration ill mean clozapine=13.9 years, mean risperidone=11.1 years, age at onset mean clozapine=23.7, mean risperidone=21.3
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 403.6 mg/day. N=14. **2** Risperidone: flexible dose. Allowed dose range: 2-9 mg/day. Mean dose: 5.9 mg/day. N=15

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Outcomes	Mental state: BPRS total score, PANSS positive and negative subscore. Adverse effects: extrapyramidal side-effects (use of antiparkinson medication, SAS), prolactin (change of prolactin in ng/ml)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "All patients were then randomly assigned to treatment with clozapine or risperidone.." Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "..double blind comparison trial." Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	Exclusion of 5 patients after randomisation who were not considered in the total sample. Incomplete information. ITT was not performed
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	No	Quote: "Nineteen of the 29 patients underwent a drug-free period before random assignment". Comment: Probably performance bias. Author from Industry

Conley 2003

Methods	Allocation: randomised. Blindness: double. Duration: 16 weeks (first 8 weeks observed).
Participants	Diagnosis: (DSM-IV) schizophrenia, resistance to previous treatment. N=13. Age: mean=37.58 years. Gender: 8 M, 5 F. Setting: not reported. History: duration ill not reported, age at onset not reported
Interventions	**1** Clozapine: fixed dose: 450 mg/day. N=5. **2** Olanzapine: fixed dose: 50 mg/day. N=8.
Outcomes	Death: natural causes, suicide. Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: BPRS total score, PANSS positive and negative subscore. Adverse effects: at least one adverse effect; cardiac effects (QTc prolongation), lipids (change on cholesterol from baseline in mg/dl), extrapyramidal side effects (akathisia, use of antiparkinson medication, SAS), glucose (change from baseline in mg/dl), sedation, seizures, weight change
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "In a randomised crossover design.." Comment: Probably not done.
Allocation concealment?	No	No information. Probably not done.

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Blinding? All outcomes	Yes	Quote: “randomised double-blind 16 week..” Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	0/5 missing from clozapine and 3/8 missing from olanzapine. LOCF for patients completing at least two weeks. ITT was not performed
Free of selective reporting?	No	Adverse events that occurred only in one person were not reported
Free of other bias?	Yes	Review authors have not found other sources of bias.

Heinrich 1994

Methods	Allocation: randomised. Blindness: double. Duration: four weeks.
Participants	Diagnosis:(ICD-9) acute schizophrenia, disorganised, catatonic, paranoid, unspecified type. Schizoaffective psychosis, schizodominant type. N=59. Age: 19-65 years. Gender: 31 M, 28 F. Setting: not reported. History: duration ill not reported, age at onset not reported
Interventions	**1** Clozapine: fixed dose: 400 mg/day. N=20. **2** Risperidone: fixed dose: 4 mg/day. N=20. **3** Risperidone: fixed dose: 8 mg/day. N=19.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: BPRS total score, BPRS subscore. Adverse effects: at least one adverse effect, cardiac effects (pre terminal negative T-wave), extrapyramidal side-effects (extrapyramidal symptoms, use ofantiparkinson medication, Simpson-Angus Scale), sedation. Unable to use: White blood cell count: agranulocytosis (no data).
Notes	

Risk of bias

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: “This is a randomised, double blind study..” Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: “This is a randomised, double blind study..” Tablets were identical appearance. Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	Yes	6/20 missing from clozapine, 13/19 from risperidone 8 mg and 9/20 from risperi-done 4 mg. Intention to treat analyses and LOCF
Free of selective reporting?	No	There was incomplete information about some adverse events as body weight, blood pressure, ECG

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		Adverse events considered only the most frequent spontaneously reported adverse experience
Free of other bias?	Yes	Review authors have not found other sources of bias.

Krakowski 2006

Methods	Allocation: randomised - block randomisation (block size of three). Blindness: double. Duration: 12 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia (N=71) or schizoaffective disorder (N=39), persistent aggression. N=110. Age: 18-60 years (mean clozapine=35.1 years, mean haloperidol=32.7 years, mean olan-zapine=35.6 years). Gender: 90 M, 20 F. Setting: inpatient. History: duration ill mean clozapine=15.7 years, mean haloperidol=13.9 years, mean olanzapine=16.8 years, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.5 mg/day (at the end of the last six weeks). N=37. **2** Haloperidol: flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 23.3 mg/day (at the end of the last six weeks). N=36. **3** Olanzapine: flexible dose. Allowed dose range: 10-35 mg/day. Mean dose: 24.7 mg/day (at the end ofthe last six weeks). N=37
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, PANSS positive and negative subscore. Unable to use: Extrapyramidal Symptom Rating Scale (ESRS / EPS) (no data) ECG (no data) White cell count (no data) Adverse events (no data)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " patients were randomly assigned to 1 of 3 treatment arm.." "The study used block randomisation scheme with a block size of 3.." Comment: Incomplete information.
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote: "The medication was administered in a double-blind fashion.." The success of blinding was not evaluated Comment: Probably done.
Incomplete outcome data addressed? All outcomes	Yes	13/37 missing from clozapine and 11/37 missing from olanzapine. Analysis by intention-to-treat was used
Free of selective reporting?	No	Adverse events assessed but it was not reported in the article
Free of other bias?	No	Quote: "The setting limits the generalis-ability of the findings"

Kumra 2008

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Methods	Allocation: randomised - computer-generated randomisation. Blindness: double. Duration: 12 weeks.
Participants	Diagnosis: children and adolescents with (DSM-IV) schizophrenia (N=25) or schizoaffective disorder (N=14) (of intent-to-treat population), resistant to, or intolerant of, at least two antipsychotic treatments. N=40. Age: 10-18 years (mean=15.6 years). Gender: 21 M, 18 F (of intent-to-treat population). Setting: in- and outpatient. History: duration ill not reported, age at onset mean clozapine=12.7 years, mean olan-zapine=11.7 years (of intent-to-treat population)
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 50-700 mg/day. Mean dose: 403.1 mg/day. N=18 (of intent-to-treat population). **2** Olanzapine: flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 26.2 mg/day. N=21 (of intent-to-treat population)
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: BPRS total score, SANS total score. Adverse effects:at least one adverse effect, extrapyramidal side effects (AIMS, SAS), glucose (change from baseline in mg/dl), lipids (change on cholesterol from baseline in mg/dl), prolactin associated side effects (change from baseline in ng/ml - ofmen only, change from baseline in ng/ ml - of women only), sedation, weight change Unable to use: Extrapyramidal symptoms (no data) Diabetes mellitus (no data). Hyperglycemia (no data). Neutropenia (no data).
Notes	One person was excluded owing to withdrawal of parental consent after randomisation

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "…medication were assigned to their groups by research pharmacist with a computer-generated randomisation schedule."
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote: "medication was administered under double-blind condition". The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	4/19 missing from clozapine and 7/21 missing from olanzapine Quote:"…analyses were performed on the intent-to-treat population" Comment: ITT considered all patients who received at least one dose of study medication
Free of selective reporting?	No	Side-effects: Study reported only the participants who gained >7% of their baseline body weight
Free of other bias?	Yes	Review authors have not found other sources of bias.

Li 2002

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Methods	Allocation: randomised. Blindness: double. Duration: 8 weeks.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=63. Age: mean clozapine=30 years, mean quetiapine=28 years. Gender: not reported. Setting: in- and outpatient. History: duration ill mean clozapine=0.63 years, mean quetiapine=0.65 years, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 270.5 mg/day. N=31. **2** Quetiapine: flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 478.5 mg/day. N=32
Outcomes	Global state: CGI. Mental State: PANSS total score. Adverse effects: at least one adverse effect, cardiac effects (palpitation), extrapyramidal side effects (akathisia, rigor, tremor), sedation, weight gain, white blood cell count Unable to use: Leaving the study early due to adverse events (no data). Cardiac effects (no data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Double, probably identical capsules. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	Unclear	The authors only mention two participants leaving the study early due to adverse events in the clozapine group. There is some doubt whether all data on leaving the study early have been presented
Free of selective reporting?	Yes	We did not find evidence for selective reporting.
Free of other bias?	Unclear	There were no data on pre study medication, therefore baseline imbalance can not be excluded

Li 2003

Methods	Allocation: randomised. Blindness: single, rater-blinded. Duration: 8 weeks.
Participants	Diagnosis: (CCMD-2) schizophrenia. N=76. Age: mean clozapine=36.2 years, mean quetiapine=34.7 years. Gender: not reported. Setting: inpatient. History: duration ill mean clozapine= 6.12 years, mean quetiapine=5.71 years, age at onset not reported

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Interventions	**1** Clozapine: fixed/flexible dose: not reported. Allowed dose range: start with 25 mg, in two weeks supposed dose, no further details. Mean dose: 325 mg/day. N=38. **2** Quetiapine: fixed/flexible dose: not reported. Allowed dose range: start with 25 mg, in two weeks supposed dose, no further details. Mean dose: 375 mg/day. N=38
Outcomes	Global state: CGI. Mental state: PANSS total score, PANSS positive and negative subscore Unable to use: Leaving the study early due to inefficacy (no data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	Unclear	The authors describe only one participant in the quetiapine group who left the study early due to inefficacy. This participant was not included in the analysis. There is some doubt whether all data on leaving the study early have been presented
Free of selective reporting?	No	The study duration was eight weeks, but outcomes only at four weeks were available
Free of other bias?	Unclear	The allowed dose range was not indicated.

Li 2005

Methods	Allocation: randomised. Blindness: double. Duration: 12 weeks.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=67. Age: mean=26.18 years. Gender: not reported. Setting: inpatient. History: duration ill mean clozapine=0.49 years, mean quetiapine=0.5 years, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 100-550 mg/day. Mean dose: 255.96 mg/day. N=34. **2** Quetiapine: flexible dose. Allowed dose range: 150-650 mg/day. Mean dose: 362.09 mg/day. N=33
Outcomes	Leaving the study early: any reason. Mental state: PANSS total score, PANSS positive and negative subscore. Unable to use: Extrapyramidal symptoms (no data). Sedation (no data).
Notes	

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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	No	The overall attrition was 9.1%. Those leaving early were only reported due to any reason. Only completer data were assessed
Free of selective reporting?	No	There was no reporting on adverse effects
Free of other bias?	Unclear	Baseline characteristics have not been presented for both groups separately. Therefore, baseline imbalance can not be excluded. Furthermore, there was no washout period

Lin 2003

Methods	Allocation: randomised. Blindness: single, rater-blind. Duration: 12 weeks.
Participants	Diagnosis: schizophrenia. N=59. Age: 20-65 years. Gender: not reported. Setting: inpatient. History: BPRS >30, clozapine treatment for more than 5 months
Interventions	**1** Clozapine: flexible dose, mean ~ 387 mg/day. N=24. **2** Zotepine: flexible dose, mean ~ 377 mg/day. N=35.
Outcomes	Global state: CGI. Mental state: BPRS total score. Adverse effects:use of antiparkinson medication. Unable to use: BAS, SAS, UKU (no data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "59 patients were allocated on a random.." Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: ".. patients were allocated on a random, rater blind basis.." Probably done. The success ofblinding was not evaluated.
Incomplete outcome data addressed? All outcomes	Unclear	No information on abstract.
Free of selective reporting?	Unclear	No information on abstract.

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Free of other bias?	No	Quote: “Patients taking clozapine for more 5 month were allocated on a random to two groups: one maintained on clozapine and another switched to zotepine”

Lindenberg 1997

Methods	Allocation: randomised. Blindness: double. Duration: 6 weeks.
Participants	Diagnosis:(DSM-III-R) schizophrenia catatonic, hebephrenic, paranoid or residual. N=50. Age: 18-60 years. Gender: not reported. History: BPRS >40 after washout phase, no previous treatment with either medication
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: CGI, BPRS, SANS, adverse events: ECG, weight gain (matched samples)
Notes	

Risk of bias

Item	Authors’ judgement	Description
Adequate sequence generation?	Unclear	Quote: “They were randomly assigned..” Comment: Incomplete information.
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote: “They were randomly assigned in a double design to clozapine or zotepine” Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	7/25 missing from clozapine and 10/25 missing from zotepine. ITT was not performed
Free of selective reporting?	No	Quote: “Analysis refers to a sub-sample of 26 patients, (matched for age).” Comment: Data from sub sample was not used in our review.
Free of other bias?	Unclear	Quote: “This study was sponsored and monitored by Klinge Pharma (manufacturer of zotepine)”

Liu 2004

Methods	Allocation: randomised Blindness: single, rater-blinded. Duration: 12 weeks.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=72. Age: mean clozapine=37.44 years, mean quetiapine=36.86 years. Gender: not reported. Setting: inpatient.

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	History: duration ill mean clozapine=9.36 years, mean quetiapine=8.64 years, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: initial dose: 50 mg/day, after 10 days: 400-600 mg/day. Mean dose: not reported. N=36. **2** Quetiapine: flexible dose. Allowed dose range: initial dose: 100 mg/day, after 10 days: 400-700 mg/day. Mean dose: not reported. N=36
Outcomes	Leaving the study early: adverse events, inefficacy. Global state: CGI. Mental state: BPRS total score, SANS total score. Adverse effects: cardiac effects (ECG abnormalities), extrapyramidal side effects (akathisia, tremor), sedation, weight gain Unable to use: Leaving the study early due to any reason (no data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	Unclear	The authors mention five participants leaving the study early, three due to adverse events in the clozapine group and two due to unclear reasons in the quetiapine group. These five subjects were not included in the analysis. There is some doubt whether all data on leaving the study early have been presented
Free of selective reporting?	No	The mean doses of the medications used were not indicated.
Free of other bias?	No	Clozapine was titrated to 400 mg/day within 10 days. Such a fast dose increase can be accompanied by a higher rate of adverse effects

McGurk 2005

Methods	Allocation: randomised. Blindness: double, double-dummy protocol. Duration: 29 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia (n=93) or schizoaffective disorder (n=14), treatment resistance. N=107. Age: 18-60 years (mean=42 years). Gender: 84 M, 23 F. Setting: in- and outpatient. History: duration ill not reported, age at onset mean clozapine=23 years, mean risperi-done=22 years
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 500-800 mg/day. Mean dose: 456.7 mg/day. N=53. **2** Risperidone: flexible dose. Allowed dose range: 6-16 mg/day. Mean dose: 6.8 mg/day. N=54

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Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: BPRS total score. Adverse effects: white blood cell count. Unable to use: SANS (modified version).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: " random assignment trial.." Comment: Incomplete information.
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote: " double-blind, 29 week trial.." Comment: Probably done.
Incomplete outcome data addressed? All outcomes	Yes	30/47 missing from clozapine and 32/50 risperidone. ITT was not performed
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	Yes	Review authors have not found other sources of bias.

Meltzer 2003

Methods	Allocation: randomised. Blindness: single, rater-blinded. Duration: 104 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia (N=609) or schizoaffective disorder (N=371), high suicidal risk. N=980. Age: 18-65 years (mean=37.1 years). Gender: 602 M, 378 F. Setting: in- and outpatient. History: duration ill not reported, age at onset mean=24.7 years
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-900 mg/day. Mean dose: 274.2 mg/day. N=490. **2** Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 16.6 mg/day. N=490
Outcomes	Death: any reason, suicide attempt, suicide. Leaving the study early: any reason, adverse events, inefficacy. Service use: number of participants re-hospitalised. Adverse effects: extrapyramidal side effects (akathisia, rigor), glucose (diabetes mellitus) , sedation, seizures, weight gain, white blood cell count Unable to use: ESRS (no data)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "For randomisation, patients were blocked by country and medical centre" ".. The 2 treatment groups were allocated randomly in a 1:1 ratio within blocks of 4 patients in each medical centre" Comment: Probably not done.
Allocation concealment?	No	No Information. Probably not done.

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Blinding? All outcomes	Yes	Single-open label/blind raters. Comment: Probably done. The rater's masking was monitored by external service
Incomplete outcome data addressed? All outcomes	Yes	192/490 missing from clozapine and 187/ 490 missing from olanzapine Quote: "All data obtained was used in intent-to-treat analysis"
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	Yes	The study sponsor was Novartis Pharmaceuticals Corp.

Moresco 2004

Methods	Allocation: randomised. Blindness: double. Duration: 8 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia, treatment resistance to two previous antipsychotic medications, BPRS score of 27 or more. N=23. Age: 18 years or more (mean clozapine=38.3 years, mean olanzapine=34.1 years) (of completer population). Gender: 16 M, 7 F. Setting: inpatient. History: duration ill not reported, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 300-400 mg/day. Mean dose: 325.4 mg/day. N=12. **2** Olanzapine: flexible dose. Allowed dose range: 15-20 mg/day. Mean dose: 18.3 mg/day. N=11
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, BPRS total score, PANSS positive and negative sub-score. Adverse effects: at least one adverse effect, extrapyramidal side effects (SAS) Unable to use: AIMS (no useable data)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Before randomisation.." Comment: Information incomplete.
Allocation concealment?	No	Probably not done.
Blinding? All outcomes	Yes	Quote:" A double blind, parallel study." Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	6/12 missing from clozapine and 2/11 missing from olanzapine ITT not performed.
Free of selective reporting?	Unclear	No information about form to assess the adverse events.
Free of other bias?	Unclear	Quote: "Study was partially supported by Eli-Lilly"

Naber 2005

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Methods	Allocation: randomised - computer-generated randomisation. Blindness: double. Duration: 26 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of, standard an-tipsychotic therapy. N=114. Age: 18-65 years (mean=34.0 years). Gender: 69 M, 45 F. Setting: in- and outpatient, initially inpatient. History: duration ill not reported, age at onset 26.9 years.
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 100-400 mg/day. Mean dose: 209 mg/day. N=57 **2** Olanzapine: flexible dose. Allowed dose range: 5-25 mg/day. Mean dose: 16.2 mg/day. N=57
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: PANSS total score, BPRS total score, PANSS positive and negative subscore, BPRS positive and negative subscore. Quality of life: SWN. Adverse effects: at least one adverse effect, cardiac effects (QTc prolongation), extrapyra-midal side effects (use of antiparkinson medication, SAS), weight change. Unable to use: Glucose elevation (non fasting)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "This randomised double blind controlled trial.." Patients were allocated 1: 1 ratio Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "This randomised double blind controlled trial.." Comment: Probably done. Identical capsules were used.The success ofblinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	35/57 missing from clozapine and 36/57 from olanzapine.Intention to treat analyses and LOCF was used Comment: ITT considered the patients with at least one post-baseline value
Free of selective reporting?	No	Adverse event were recorded from spontaneously report. Probably reporting bias
Free of other bias?	Unclear	Study funded by Lilly Deutschland GmbH.

Ren 2002

Methods	Allocation: randomised - ball drawing out of box. Blindness: double. Duration: 12 weeks.
Participants	Diagnosis:(CCMD-3) schizophrenia. N=120

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	Age: mean clozapine=33.5 years, mean risperidone=35.4 years. Gender: not reported. Setting: outpatient. History duration ill: clozapine: 6.2 years risperidone 6.4 years
Interventions	**1** Clozapine: mean dose: 350 mg/day.N=60 **2** Risperidone:mean dose: 3.2 mg/day.N=60
Outcomes	Mental state: PANSS positive and negative subscore.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Allocation: random, ball drawing out of a covered box. Probably yes
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	No	Data on leaving the study early were not provided.
Free of selective reporting?	No	Secondary outcomes were poorly reported.
Free of other bias?	Unclear	The allowed dose ranges were not indicated.

Sacchetti 2006

Methods	Allocation: randomised. Blindness: double. Duration: 18 weeks.
Participants	Diagnosis: schizophrenia - treatment resistance (non-response in 3 adequate trials in past 5 years) and/or inability to tolerate antipsychotic treatment. N=146. Age: mean clozapine= 38.3 years, mean ziprasidone= 41.6 years. Gender: 101 M, 45 F. Setting: not reported. History: duration ill not reported, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 250-600 mg/day. Mean dose: 345.7 mg/day. N=73. **2** Ziprasidone: flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 130.4 mg/day. N=73
Outcomes	Leaving the study early: any reason. Mental state: PANSS total score. Adverse effects: cardiac effects (QTc prolongation). Unable to use: Global state:CGI (no data). Mental state: PANSS positive and negative subscore (no data). Laboratory parameters (no usable data).
Notes	

Risk of bias

Item	Authors' judgement	Description

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Adequate sequence generation?	Unclear	Quote: “Patients completed a 3-7 day screening period before being randomised” Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: “Patients completed a 3-7 day screening period before being randomised, double-blind..” Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	Yes	Analysis by intention to treat and LOCF.
Free of selective reporting?	Unclear	No information on abstract.
Free of other bias?	Unclear	No information on abstract.

Shaw 2006

Methods	Allocation: randomised. Blindness: double. Duration: 18 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia catatonic (N=3), disorganised (N=34), paranoid (N=101), residual (N=8) or undifferentiated (N=34), previous treatment resistance. N=180. Age: 18-70 years (mean=38.6 years). Gender: 115 M, 65 F. Setting: in- and outpatient. History: duration ill not reported, age at onset mean=22.8 years
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 303.6 mg/ day. N=90. **2** Olanzapine: flexible dose. Allowed dose range: 15-25 mg/day. Mean dose: 20.5 mg/ day. N=90
Outcomes	Death: natural causes. Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, BPRS total score, PANSS positive and negative subscore, BPRS positive and negative subscore. Adverse effects: extrapyramidal side effects (akathisia, akinesia, parkinsonism, use of antiparkinson medication, AIMS, BAS, SAS), prolactin (change from baseline in ng/ml) , sedation, weight gain, white blood cell count (leukopenia)
Notes	

Risk of bias

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Yes	Quote: “Random allocation used a random-numbers chart and was conducted in blocks of 4”
Allocation concealment?	Yes	Quote: “Numbered containers were used to implement the random allocation sequence..”
Blinding? All outcomes	Yes	Double blind. Identic tablet form. Quote: “Participants and those administering and assessing the intervention and assessing outcomes were blind..” “The success of the blinding was not formally assessed”

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Incomplete outcome data addressed? All outcomes	Yes	No participant was loss during trial on clozapine group. 1/13 was missing from olanzapine group. Analysis by intention to treat and LOCF
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	Yes	Review authors have not found other sources of bias.

Tollefson 2001

Methods	Allocation: randomised. Blindness: double. Duration: 18 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia catatonic (N=3), disorganised (N=34), paranoid (N=101), residual (N=8) or undifferentiated (N=34), previous treatment resistance. N=180 Age: 18-70 years (mean=38.6 years). Gender: 115 M, 65 F. Setting: in- and outpatient. History: duration ill not reported, age at onset mean=22.8 years
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-600 mg/day.Mean dose: 303.6 mg/day. N=90. **2** Olanzapine: flexible dose. Allowed dose range: 15-25 mg/day. Mean dose: 20.5 mg/day. N=90
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: clinical improvement (at least 20%BPRS reduction+CGI-S<3 or BPRS<35) (> or = 50% reduction on PANSS total), PANSS total, positive and negative subscore, BPRS total score. Adverse effects:extrapyramidal effects (SAS, AIMS, BAS), prolactin levels, weight change
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "patients were randomly allocated in a 1:1 ratio to treatment with olanzapine 15-25 mg/day or clozapine 200-600 mg/day" Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "An 18-week double-blind therapy" Comment: Probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	No	37/90 missing from clozapine and 36/90 missing from olanzapine Quote: "All end point analyses used a last observation carried forward (LOCF) algorithm" Comment: OC technique for weekly measures of patients with at least one post-baseline measurement. ITT analysis was not performed
Free of selective reporting?	No	Spontaneously Reported Treatment-Emergent Adverse Events with an Incidence of ≥5% in either Treatment Group, or with a statistically significant difference (P< . 05) between treatment Groups. Solicited treatment-emergent adverse events with statistically significant difference

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Free of other bias?	Yes	Review authors have not found other sources of bias.

Volavka 2002

Methods	Allocation: randomised Blindness: double, identical capsules. Duration: 14 weeks.
Participants	Diagnosis: (DSM-IV) chronic schizophrenia (N=135) or schizoaffective disorder (N=22), sub optimal response to previous treatment, PANSS of 60 or more. N=167. Age: 18-60 years (mean=40.8 years) (of intent-to-treat population). Gender: 133 M, 24 F (of intent-to-treat population). Setting: inpatient. History: duration ill mean=19.5 years (of intent-to-treat population), age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 526.6 mg/day (at the end of the last six weeks). N=40. **2** Haloperidol: flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 25.7 mg/day (at the end of the last six weeks). N=37. **3** Olanzapine: flexible dose. Allowed dose range: 10-40 mg/day. Mean dose: 30.4 mg/day (at the end of the last six weeks). N=39. **4** Risperidone: flexible dose. Allowed dose range: 4-16 mg/day. Mean dose: 11.6 mg/day (at the end of the last six weeks). N=41
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, PANSS positive and negative subscore. Cognitive functioning: Global Neurocognitive Score. Adverse effects: extrapyramidal effects (use of antiparkinson medication, ESRS), glucose (change from baseline in mg/dl), lipids levels (change on cholesterol from baseline in mg/dl), prolactin associated side effects (change from baseline in ng/ml), seizures, weight gain, white blood cell count (agranulocytosis, neutropenia) Unable to use: Quality of life scale (no data). Cognitive functioning (PANSS cognitive subscore, at endpoint and change, was reported as factor score and the neurocognitive global score at endpoint was reported as Z score, which didn't allow its use as comparator)
Notes	The two participants with neutropenia (clozapine) are additional participants to the one with agranulocytosis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: ".. patients were randomly assigned to one of the four treatment arm.." Comment: Incomplete information.
Allocation concealment?	No	No information. Probably not done.
Blinding? All outcomes	Yes	Quote: "In a double blind trial.." ".. all tablets looked alike" Comment: Probably done.
Incomplete outcome data addressed? All outcomes	No	18/40 missing from clozapine, 13/39 from olanzapine and 19/41 from risperidone. ITT was not performed
Free of selective reporting?	No	Some outcomes were reported on subgroup from the entire sample (Czobor 2002, Volavka 2004, Bilder 2001, Lindenmayer 2003).The author reported the use of the Quality ofLife Scale, but the results are not on article, (Bilder 2001)

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Free of other bias?	No	"The olanzapine arm was added in November 1997 and required a modified randomisation procedure"… " it entails the potential for a bias that could be manifested as a cohort effect."

Wahlbeck 2000

Methods	Allocation: randomised - computer-generated randomisation. Blindness: single, rater-blinded. Duration: 10 weeks.
Participants	Diagnosis: (DSM-IV) schizophrenia, resistance to previous treatment. N=20. Age: 24-55 years (mean clozapine=35.7 years, mean risperidone=36.8 years) (of intent-to-treat population). Gender: 10 M, 9 F (of intent-to-treat population). Setting: in- and outpatient (initially inpatient). History: duration ill mean clozapine=12.6 years, mean risperidone=13.1 years (of intent-to-treat population), age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 25-600 mg/day. Mean dose: 385 mg/day. N=11. **2** Risperidone: flexible dose. Allowed dose range: 2-10 mg/day. Mean dose: 7.8 mg/day. N=9
Outcomes	Death: natural causes, suicide. Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS total score, PANSS positive and negative subscore. General functioning: GAF, SFS. Treatment satisfaction: DAI. Adverse effects: extrapyramidal side effects (use of antiparkinson medication), sedation, white blood cell count
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Patients were individuallyassigned to open label treatment by computer-generated randomisation"
Allocation concealment?	Yes	Quote: "..the treating physician contacted the senior investigator, who provided the allocation information.." Comment: Probably done.
Blinding? All outcomes	Yes	Open label/assessor blinded study. Comment: probably done. The success of blinding was not evaluated
Incomplete outcome data addressed? All outcomes	Yes	6/11 missing from clozapine and 1/9 missing from risperidone. Analysis by intention to treat and LOCF
Free of selective reporting?	Yes	Review authors do not believe this will introduce bias.
Free of other bias?	No	Quote: "Readers have to bear in mind that the low statistical power of this study may hides some clinically relevant differences in drug efficacy"

Wang 2002

Methods	Allocation: randomised. Blindness: double.

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	Duration: 8 weeks.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=61. Age: mean clozapine=30 years, mean olanzapine=25.8 years. Gender: 29 M, 32 F. Setting: in- and outpatient. History: duration ill mean= 4.2 years, age at onset not reported
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 25-400 mg/day. Mean dose: not reported. N=31. **2** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: not reported. N=30
Outcomes	Mental state: BPRS total score. Adverse effects: at least one adverse effect, extrapyramidal side effects (extrapyramidal symptoms), sedation, weight gain Unable to use: White blood cell countleukopenia (no usable data). Leaving the study early -adverse events (no usable data). Hypersalivation (no usable data).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	No	Data on leaving the study early were not provided.
Free of selective reporting?	No	Data were not available for all of the predefined adverse effect outcomes
Free of other bias?	No	The sponsor was unclear. The upper dose range limit of clozapine was 400 mg/day which was reached rather quickly (10 days), which could mean a disadvantage for cloza-pine in terms of side-effects

Zhou 2000

Methods	Allocation: randomised Blindness: single, rater-blinded. Duration: 8 weeks.
Participants	Diagnosis: (CCMD-2) schizophrenia. N=40. Age: mean clozapine=27.6 years, mean risperidone=29 years. Gender: 23 M, 17 F. Setting: inpatient History: duration ill mean clozapine=2.7 years, mean risperidone=3.2 years, age at onset not reported
Interventions	**1** Clozapine: fixed and flexible dose (first two weeks). Allowed dose range: 25-300 mg/day (first two weeks), then 300 mg/day fixed. Mean dose: not reported. N=20.

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	2 Risperidone: Fixed and flexible dose (first two weeks). Allowed dose range: 1-6 mg/day (first two weeks), then 6 mg/day fixed. Mean dose: not reported. N=20
Outcomes	Mental state: SANS. Adverse effects: extrapyramidal side-effects (akathisia, tremor), sedation, weight gain
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? All outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding. This latter, probably leads a low risk of bias
Incomplete outcome data addressed? All outcomes	Yes	No participant left the study early.
Free of selective reporting?	Yes	No clear evidence for selective reporting.
Free of other bias?	Unclear	The description of blinding differed between the abstract (double-blind) and the method section (single-blind)

Scales:

AIMS: Abnormal Involuntary Movement Score

BAS: Barnes Akathisia Scale

BPRS: Brief Psychiatric Rating Scale.

CGI: Clinical Global impression.

ESRS: Extrapyramidal Symptoms Rating Scale

GAF: Global Assessment of Functioning

HAS: Hillside Akathisia Scale

MLDL: Munich Life Dimension List

PANSS: Positive and Negative Syndrome Scale for Schizophrenia

SANS: Scale for the Assessment of Negative Symptoms

SAPS: Scale for the Assessment of Positive Symptoms

SAS: Simpson Angus scale

SFS: Social Functioning scale.

SWN: Subjective Well Being under Neuroleptic Treatment - 38 Items

Diagnostic Tools:

DSM -III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revised.

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

ICD-9: International Classification of Disease.

CCMD-2: Chinese Classification of Mental Disorders, Second Edition.

CCMD-3: Chinese Classification of Mental Disorders, Third Edition.

Others:

ECG: electrocardiogram

ITT: intent- to- treat.

mg: milligram.

SD: standard deviation.

N: number

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

Study	Reason for exclusion
Agelink 2001	Allocation: not randomised.
Allison 2001	Allocation: unclear
Altamura 1999	Allocation: not randomised (naturalistic).
Anonymous 1994	Allocation: unclear.
Ascher-Svanum 2006	Allocation: not randomised (naturalistic).
Baumann 1993	Allocation: unclear.
Beasley 2001	Allocation: unclear.
Bondolfi 1996	Allocation: not applicable (review) .
Cai 2000	Allocation: randomised, no blinding.
CATIE	Allocation: randomised, open label trial for clozapine, double-blind for other atypicals. Raters were blinded only to the newer, not for clozapine
Cavazzoni 2002	Allocation: unclear (analysis of extracted data from olanzapine clinical trial database)
Cha 2002	Allocation: randomised, no blinding.
Chen 2002	Allocation: randomised, no blinding.
Chen 2003	Allocation: randomised, no blinding.
Chen 2003b	Allocation: randomised, no blinding.
Chen 2004	Allocation: randomised, no blinding.
Chen 2005	Allocation: randomised, no blinding.
Chen 2005b	Allocation: randomised, no blinding.
Cheng 2004	Allocation: randomised, no blinding.
Chou 1999	Allocation: randomised, no blinding.
Chouinard 1994	Allocation: not randomised (case reports).
Conley 1999a	Allocation:unclear, open label.
Cui 2002	Allocation: randomised, no blinding.
CUTLASS	Allocation: randomised. Participants: people with schizophrenia, treatment-resistant. Intervention: clozapine vs. other pooled newer antipsychotics
Dai 2004	Allocation: randomised, no blinding.
David 1999	Allocation: not randomised (review).
Deng 2000	Allocation: randomised, no blinding.
Ding 2005	Allocation: randomised, no blinding.
Du 2003	Allocation: randomised, no blinding.
Du 2003b	Allocation: randomised, no blinding.
Du 2004	Allocation: randomised, no blinding.
Du 2005	Allocation: randomised, no blinding.

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Earnst 1999	Allocation: not randomised (naturalistic).
Ellis 2000	Allocation: randomised. Participants: people with Parkinson's disease and psychosis, not schizophrenia
Fan 2003	Allocation: randomised, no blinding.
Fang 2005	Allocation: randomised, no blinding.
Feng 2004	Allocation: randomised, no blinding.
Fleming 1999	Allocation: not randomised.
Flynn 1997	Allocation: not randomised.
Fu 2005	Allocation: randomised, no blinding.
Gaertner 1999	Allocation: not randomised (retrospective study).
Gallhofer 1995	Allocation: not randomised.
Gallhofer 1996	Allocation: not randomised.
Ganguli 2005	Allocation: randomised. Participants: people with schizophrenia, schizoaffective disorder. Intervention: behaviour therapy vs. standard care.
Gao 2003	Allocation: randomised, no blinding.
Goldberg 2000	Allocation: not randomised.
Green 2001	Allocation: randomised. Participants: people with schizophrenia and cannabis use disorder
Guan 2005	Allocation: randomised, no blinding.
Guo 2001	Allocation: randomised, no blinding.
Guo 2003	Allocation: randomised, no blinding.
Han 2005	Allocation: randomised, no blinding.
Hang 2000	Allocation: randomised, no blinding.
He 2005	Allocation: randomised, no blinding.
Hu 2000	Allocation: randomised, no blinding.
Hu 2005	Allocation: randomised, no blinding.
Huang 2001	Allocation: randomised, no blinding.
Huang 2003	Allocation: randomised, no blinding.
Kelemen 2006	Allocation: randomised, no blinding.
Kong 2001	Allocation: randomised, no blinding.
Konrad 1996	Allocation: not randomised (naturalistic).
Kufferle 1997	Allocation: not randomised.
Lee 1995	Allocation: unclear, open trial.
Lei 2002	Allocation: randomised, no blinding.
Lei G 2004	Allocation: randomised, no blinding.
Li 2003b	Allocation: randomised, no blinding.
Li 2001	Allocation: randomised, no blinding.
Li 2003	Allocation: randomised, no blinding.
Li 2004	Allocation: randomised, no blinding.
Liang 2002	Allocation: randomised, no blinding.
Liang 2005	Allocation: randomised, no blinding.

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Lindenmayer 1996	Allocation: unclear.
Liu 1999	Allocation: randomised, no blinding.
Liu 2001	Allocation: randomised, no blinding.
Liu 2003	Allocation: randomised, no blinding.
Liu 2003b	Allocation: randomised, no blinding.
Liu 2004	Allocation: randomised, no blinding.
Liu 2004b	Allocation: randomised, no blinding.
Liu 2004c	Allocation: randomised, no blinding.
Liu 2005	Allocation: randomised, no blinding.
Liu 2005b	Allocation: randomised, no blinding.
Liu 2005c	Allocation: randomised, no blinding.
Louwerens 1996	Allocation: not randomised.
Lu 2002	Allocation: randomised, no blinding.
Lu 2005	Allocation: randomised, no blinding.
Luo 2005	Allocation: randomised, no blinding.
Ma 1999	Allocation: randomised, no blinding.
McKenna 2004	Allocation: randomised. Participants: people with schizophrenia or psychotic disorders. Intervention: risperidone augmentation therapy of clozapine.
Meehan 2000	Allocation: not randomised (data report from 8 different trials)
Mei 2001	Allocation: randomised, no blinding.
Mulqueen 2000	Allocation:not randomised.
Nan 2001	Allocation: randomised, no blinding.
Ni 2001	Allocation: randomised, no blinding.
Opjordsmoen 2000	Allocation: not randomised (naturalistic).
Pajonk 1998	Allocation: not randomised.
Pan 2006	Allocation: randomised, no blinding.
Pao 2004	Allocation: randomised, no blinding.
Peng 2001	Allocation: randomised, no blinding.
Qian 2004	Allocation: randomised, no blinding.
Qin 2005	Allocation: randomised, no blinding.
Rapoport 1997	Allocation: not randomised.
Ren 2000	Allocation: randomised, no blinding.
Ren 2004	Allocation: randomised, no blinding.
Rettenbacher 2004	Allocation: not randomised.
Saletu 1987	Allocation: randomised. Participants: healthy people.
Scherer 2004	Allocation: not randomised.
Schlogelhofer 2006	Allocation: not randomised.
Schuld 2000	Allocation: not randomised.
Shao 1999	Allocation: randomised, no blinding.
Sharma 2002	Allocation: not randomised (naturalistic).

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Sheng 2003	Allocation: randomised, no blinding.
Sheng 2005	Allocation: randomised, no blinding.
Shi 2000	Allocation: randomised, no blinding.
Shi 2001	Allocation: randomised, no blinding.
Smith 2004	Allocation: randomised. Participants: people with schizophrenia. Intervention: addition of pioglitazone or placebo to clozapine and olanzapine
Speer 1997	Allocation: not randomised.
Su 1996	Allocation: not randomised.
Sun 2001	Allocation: randomised, no blinding.
Swanson 2006	Allocation: non applicable (observational study)
Tandon 2004	Allocation: randomised, open label study.
Tang 2003	Allocation: randomised, no blinding.
Tang 2005	Allocation: randomised, no blinding.
Tang 2005b	Allocation: randomised, no blinding.
Tian 2005	Allocation: randomised, no blinding.
Tong 2005	Allocation: randomised, no blinding.
Trichard 1998	Allocation: not randomised.
Turrone 2002	Allocation: not randomised.
Vaughan 2000	Allocation: not randomised.
Wang 2002b	Allocation: randomised, no blinding.
Wang 2003	Allocation: randomised, no blinding.
Wang 2003b	Allocation: randomised, no blinding.
Wang 2003c	Allocation: randomised, no blinding.
Wang 2004	Allocation: randomised, no blinding.
Wang 2004b	Allocation: randomised, no blinding.
Wang 2005	Allocation: randomised, no blinding.
Wang 2005b	Allocation: randomised, no blinding.
Wang 2005c	Allocation: randomised, no blinding.
Wang 2005d	Allocation: randomised, no blinding.
Wang 2005e	Allocation: randomised, no blinding.
Wang 2005f	Allocation: randomised, no blinding.
Weickert 2003	Allocation: not randomised.
Weng 1998	Allocation: randomised, no blinding.
Wirshing 1999	Allocation: not randomised (cross-sectional study).
Wu 2002	Allocation: randomised, no blinding.
Wu 2004	Allocation: randomised, no blinding.
Wudarsky 1999	Allocation: not randomised (data report from different studies)
Xiang 2005	Allocation: randomised, no blinding.
Xiao 2000	Allocation: randomised, no blinding.
Xie 2005	Allocation: randomised, no blinding.

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Xin 2001	Allocation: randomised, no blinding.
Xu 2001	Allocation: randomised, no blinding.
Xu 2002	Allocation: randomised, no blinding.
Yagdiran 2000	Allocation: non applicable (observational study).
Yang 1998	Allocation: randomised, no blinding.
Yang 2002	Allocation: randomised, no blinding.
Yang 2004	Allocation: randomised, no blinding.
Yang L 2004	Allocation: randomised, no blinding.
Yang X 2004	Allocation: randomised, no blinding.
Ye 2005	Allocation: randomised, no blinding.
Yin 2004	Allocation: randomised, no blinding.
Yu 2002	Allocation: randomised, no blinding.
Yuan 2002	Allocation: randomised, no blinding.
Yuan 2005	Allocation: randomised, no blinding.
Yuo 1999	Allocation: randomised, no blinding.
Zelaschi 2000	Allocation: not randomised.
Zelaschi 2006	Allocation: not randomised (naturalistic).
Zhan 2002	Allocation: randomised, no blinding.
Zhang 2002	Allocation: randomised, no blinding.
Zhang 2002b	Allocation: randomised, no blinding.
Zhang 2004	Allocation: randomised, no blinding.
Zhang 2005	Allocation: randomised. Participants: people with schizophrenia + obsessive compulsive symptoms
Zhang 2005b	Allocation: randomised, no blinding.
Zhang 2005c	Allocation: randomised, no blinding.
Zhang 2005d	Allocation: randomised, no blinding.
Zhang 2005e	Allocation: randomised, no blinding.
Zhang 2005f	Allocation: randomised, no blinding.
Zhang 2005g	Allocation: randomised, no blinding.
Zhao 2005	Allocation: randomised, no blinding.
Zheng 2001	Allocation: randomised, no blinding.
Zheng 2003	Allocation: randomised, no blinding.
Zheng X 2001	Allocation: randomised, no blinding.
Zhong 2003	Allocation: randomised, no blinding.
Zhou 2003	Allocation: randomised, no blinding.
Zhou 2003b	Allocation: randomised, no blinding.
Zhou 2005	Allocation: randomised, no blinding.
Zhu 1999	Allocation: randomised, no blinding.
Zhu 2002	Allocation: randomised, no blinding.
Zhu 2003	Allocation: randomised, no blinding.
Zhu Q 2003	Allocation: randomised, no blinding.

Zoccali 2003	Allocation: not randomised.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Anand 1999

Methods		
Participants	Diagnosis:chronic, severe schizophrenia.	
Interventions	**1**	Clozapine.
	2	Risperidone.
Outcomes		
Notes	No abstract.	

Byerly 1999

Methods		
Participants	Diagnosis:schizophrenia who have not responded to olanzapine or risperidone. N= 60	
Interventions	**1**	Clozapine.
	2	Quetiapine.
Outcomes		
Notes	Abstract incomplete.	

Chengappa 2001

Methods	Allocation:randomised. Binding: double. Duration:29 week.	
Participants	Diagnosis:Moderately treatment refractory. N=180. Setting: inpatients.	
Interventions	**1**	Clozapine.
	2	Risperidone.
Outcomes	Cognition. Psychosocial functioning. Adverse effects. Psychopathology	
Notes	Protocol abstract available.	

Chowdhury 1999

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Methods	Allocation: randomised. Blinding: not stated. Duration:17 weeks.
Participants	Diagnosis: (ICD-10) resistant schizophrenia. N=60. Age:15 - 60 years. Gender: 45 M - 15 F. History:duration of illness clozapine:6.92±5.07 and risperidone:18±4.38 years
Interventions	**1** Clozapine:dose 342.86±84.21 mg/day. N=30. **2** Risperidone: dose 5.8±1.33 mg/day. N=30.
Outcomes	Leaving the study early: any reason, adverse effects, inefficacy. Clinically important change: at least 20% improvement on PANSS. Mental state: PANSS total, BPRS modified score, PANSS positive and negative subscore. Adverse effects: cardiac (tachycardia), extrapyramidal (akatisia), hypersalivation, sedation, weight change
Notes	Full text available.

Daniel 1996

Methods	Allocation:randomised-dose (cross-over trial). Blinding: single-blind. Duration:12 weeks.
Participants	Diagnosis:(DSM-III-R) chronic schizophrenia or schizoaffective disorder. N=20. Age: mean: 33.8 years (range=22-51). Gender: 7M-13F. Setting:19 outpatients and 1 inpatient. History:mean age at onset of psychosis was 22.7 years (range=15-32)
Interventions	**1** Clozapine:dose 375 mg/day (range=75-800).N=10. **2** Risperidone:dose 6.1 mg/day (range=1-10). N=10.
Outcomes	Leaving the study early: adverse effects. Global state: severity of illness sub scale of the CGI. Mental state: PANSS total score and positive and negative subscore. dverse effects: extrapyramidal (antiparkinson medication use), sedation, weight gain
Notes	No report of first arm outcomes (6 weeks).

Estrella 1996

Methods	Allocation:randomised. Blinding: open label.
Participants	Diagnosis: resistant schizophrenia. N=22
Interventions	**1** Clozapine **2** Risperidone.
Outcomes	Mental state: PANSS. Adverse effects: Dimascio and UKU Side Effect Scale.
Notes	Abstract available. No outcome information.

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Lieberman 2001

Methods	Allocation: randomised. Blinding: double. Duration:12 weeks.	
Participants	Diagnosis: treatment resistant schizophrenia. N=224.	
Interventions	**1**	Clozapine.
	2	Risperidone doses: 6 mg/day and 16 mg/day.
	3	Haloperidol.
Outcomes	Global functioning: CGI. Mental state: PANSS total score. Social functioning: NOSIE. Quality of life: Quality of Life Interview. Adverse effects: extrapyramidal: ESRS.	
Notes	Only abstract available.	

Loza 2002

Methods	Allocation: randomised. Blinding: not stated.	
Participants	Diagnosis:paranoid schizophrenia (first-episode). N:39. Age:18 - 29 years.	
Interventions	**1**	Clozapine
	2	Olanzapine
	3	Risperidone.
Outcomes	Mental state: PANSS total score.	
Notes	Abstract available.	

Magnuson 2001

Methods	Allocation: unclear Blinding: double	
Participants	Diagnosis: (DSM-III-R) several psychotic conditions (schizophrenia, schizoaffective disorder, and psychotic disorders not otherwise specified).who have not responded to at least two prior typical neuroleptics. Age:6 to 18 years History: onset of psychosis by age 12.	
Interventions	**1**	Clozapine.
	2	Olanzapine.
Outcomes		
Notes	Abstract available.	

Oliemeulen 2000

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Methods	Allocation: randomised. Blinding: not stated. Duration:8 weeks.	
Participants	Diagnosis:(DSM-IV) resistant schizophrenia or other psychotic disorder. N:40	
Interventions	**1**	Olanzapine.
	2	Clozapine.
Outcomes	Mental state: PANSS total score, positive and negative subscore	
Notes	Abstract available.	

DATA AND ANALYSES

Comparison 1
CLOZAPINE versus OLANZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Any reason	1	980	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.62, 3.64]
1.2 Natural causes	2	993	Risk Ratio (M-H, Random, 95% CI)	1.4 [0.45, 4.38]
1.3 Suicide	2	993	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.40, 6.94]
2 Leaving the study early: 1. Any reason	11	1702	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.17]
2.1 short term	6	202	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.65, 1.74]
2.2 medium term	4	520	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.26]
2.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.88, 1.20]
3 Leaving the study early: 2. Adverse effects	10	1674	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.07, 2.40]
3.1 short term	5	174	Risk Ratio (M-H, Random, 95% CI)	3.30 [0.95, 11.47]
3.2 medium term	4	520	Risk Ratio (M-H, Random, 95% CI)	1.83 [0.80, 4.17]
3.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.84, 2.02]
4 Leaving the study early: 3. Inefficacy	10	1674	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.40, 1.30]
4.1 short term	5	174	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.16, 1.64]
4.2 medium term	4	520	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.53, 2.00]
4.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.12, 0.91]
5 Global state	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 no clinically important change: less than much improved - medium term	2	294	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]
5.2 relapse - medium term	1	114	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.60]
6 Mental state: 1. No clinically important change - various criteria	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 less than 20% BPRS reduction (short term)	1	25	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.25]
6.2 less than 50% BPRS reduction (short term)	1	61	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.63, 2.03]
6.3 less than 20% BPRS reduction and mildly ill or better (short term)	1	25	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.87, 1.33]
6.4 less than 20% BPRS reduction and mildly ill or better (medium term)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
6.5 less than 30% BPRS reduction and much improved or very much improved (short term)	1	39	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.24, 1.03]
6.6 less than 50% PANSS reduction (medium term)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.92, 1.10]
7 Mental state: 2a. PANSS total score (high = poor)	7	618	Mean Difference (IV, Random, 95% CI)	1.97 [−0.71, 4.66]
7.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	1.97 [−1.48, 5.42]
7.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	1.99 [−2.29, 6.27]
8 Mental state: 2b. BPRS-18 (1-7) total score (high = poor)	5	304	Mean Difference (IV, Random, 95% CI)	1.31 [−0.30, 2.92]
8.1 short term	4	128	Mean Difference (IV, Random, 95% CI)	0.89 [−2.02, 3.79]
8.2 medium term	1	176	Mean Difference (IV, Random, 95% CI)	1.20 [−3.03, 5.43]
9 Mental state: 2c. BPRS total score, various versions (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 BPRS - 24 - only short term	1	25	Mean Difference (IV, Random, 95% CI)	−7.0 [−28.47, 14.47]
9.2 BPRS - 18 (0-6) - only medium term	1	108	Mean Difference (IV, Random, 95% CI)	2.80 [−4.05, 9.65]
10 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)	6	592	Mean Difference (IV, Random, 95% CI)	0.08 [−0.96, 1.11]
10.1 short term	2	89	Mean Difference (IV, Random, 95% CI)	−0.63 [−2.27, 1.00]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	0.54 [−0.78, 1.87]
11 Mental state: 3b. Positive symptoms: SAPS - short term (high = poor)	1	25	Mean Difference (IV, Random, 95% CI)	−9.0 [−22.06, 4.06]
12 Mental state: 3c. Positive symptoms: BPRS positive subscore (high = poor)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 BPRS-18 (1-7)	2	189	Mean Difference (IV, Random, 95% CI)	−0.01 [−1.39, 1.37]
12.2 BPRS-18 (0-6) - only medium term	1	108	Mean Difference (IV, Random, 95% CI)	0.40 [−1.57, 2.37]
13 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)	6	592	Mean Difference (IV, Random, 95% CI)	0.78 [−0.21, 1.77]
13.1 short term	2	89	Mean Difference (IV, Random, 95% CI)	1.32 [−0.42, 3.05]
13.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	0.52 [−0.68, 1.72]
14 Mental state: 4b. Negative symptoms: SANS - short term (high = poor)	2	64	Mean Difference (IV, Random, 95% CI)	−4.81 [−14.33, 4.71]
15 Mental state: 4c. Negative symptoms: BPRS negative subscore -(high = poor)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
15.1 BPRS – 18 (1-7)	2	189	Mean Difference (IV, Random, 95% CI)	−0.29 [−1.17, 0.60]
15.2 BPRS-18 (0-6)	1	108	Mean Difference (IV, Random, 95% CI)	0.20 [−1.29, 1.69]
16 Cognitive functioning: 1. No clinically important change - less than 0.5 SD improved - medium term	1	79	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.15, 2.35]
17 Quality of Life: 1. SWN-38 total score - medium term (high= good)	1	99	Mean Difference (IV, Random, 95% CI)	−8.2 [−21.67, 5.27]
18 Quality of Life: 2. MLDL total score - medium term (high = good)	1	97	Mean Difference (IV, Random, 95% CI)	Not estimable
19 Service use: Hospital readmission - long term	1	980	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.98]
20 Adverse effects: 1. At least one adverse effect	7	422	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.03, 1.89]
20.1 short term	5	161	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.85, 2.85]
20.2 medium term	2	261	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.02, 1.40]
21 Adverse effects: 2. Cardiac problems	1	152	Risk Ratio (M-H, Random, 95% CI)	2.42 [0.38, 15.33]
21.1 short term	6	38	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.22, 20.94]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 medium term	1	114	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.13]
22 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use	6	561	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.46, 1.67]
22.1 short term	2	41	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.02, 10.34]
22.2 medium term	4	520	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.42, 1.86]
23 Adverse effects: 3d. Extrapyramidal: SAS change or endpoint (high = poor)	6	481	Mean Difference (IV, Random, 95% CI)	0.43 [−0.45, 1.30]
23.1 short term	3	66	Mean Difference (IV, Random, 95% CI)	−0.47 [−1.69, 0.76]
23.2 medium term	3	415	Mean Difference (IV, Random, 95% CI)	0.92 [−0.17, 2.01]
24 Adverse effects: 3c. Extrapyramidal: ESRS score at endpoint - medium term (high = poor)	1	79	Mean Difference (IV, Random, 95% CI)	1.30 [−0.23, 2.83]
25 Adverse effects: 3b. Extrapyramidal: various symptoms	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 at least one EPS - only short term	6	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable
25.2 akathisia	4	1320	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.38, 1.41]
25.3 dyskinesia	2	327	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.20, 1.43]
25.4 extrapyramidal symptoms	2	84	Risk Ratio (M-H, Random, 95% CI)	Not estimable
25.5 parkinsonism	1	147	Risk Ratio (M-H, Random, 95% CI)	Not estimable
25.6 pseudoparkinsonism - only medium term	1	180	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.50, 3.30]
25.7 rigor - only long term	1	980	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.38]
26 Adverse effects: 3e. Extrapyramidal: akathisia - BARS change - medium term (high = poor)	1	175	Mean Difference (IV, Random, 95% CI)	−0.10 [−0.38, 0.18]
27 Adverse effects: 3f. Extrapyramidal: Hillside Akathisia Scale - medium term (high=poor)	1	137	Mean Difference (IV, Random, 95% CI)	−0.40 [−3.10, 2.30]
28 Adverse effects: 3g. Extrapyramidal: tardive dyskinesia - AIMS change or endpoint - (high = poor)	3	352	Mean Difference (IV, Random, 95% CI)	0.13 [−0.25, 0.51]
28.1 short term	1	38	Mean Difference (IV, Random, 95% CI)	0.30 [−0.23, 0.83]
28.2 medium term	2	314	Mean Difference (IV, Random, 95% CI)	−0.05 [−0.60, 0.49]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 Adverse effects: 4a. Glucose: number of participants with significant increase - long term	1	980	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.40, 1.44]
30 Adverse effects: 4b. Glucose: average change or endpoint (high = poor)	3	89	Mean Difference (IV, Random, 95% CI)	2.62 [−11.09, 16.34]
30.1 short term	2	50	Mean Difference (IV, Random, 95% CI)	9.70 [1.73, 17.68]
30.2 medium term	1	39	Mean Difference (IV, Random, 95% CI)	−9.9 [−23.30, 3.50]
31 Adverse effects: 5. Hypersalivation	5	1333	Risk Ratio (M-H, Random, 95% CI)	3.87 [1.49, 10.05]
31.1 short term	2	64	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.14, 2.38]
31.2 medium term	2	289	Risk Ratio (M-H, Random, 95% CI)	5.33 [1.76, 16.08]
31.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	8.18 [5.64, 11.86]
32 Adverse effects: 6a. Lipids: number of participants with significant increase	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
32.1 increase cholesterol	1	25	Risk Ratio (M-H, Random, 95% CI)	3.23 [0.14, 72.46]
32.2 increase triglycerides	2	64	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.37, 3.20]
33 Adverse effects: 6b. Lipids:average cholesterol change or endpoint (high = poor)	3	89	Mean Difference (IV, Random, 95% CI)	−1.16 [−19.85, 17. 52]
33.1 short term	2	50	Mean Difference (IV, Random, 95% CI)	6.83 [−35.03, 48.69]
33.2 medium term	1	39	Mean Difference (IV, Random, 95% CI)	−3.80 [−25.70, 18.10]
34 Adverse effects: 6c. Lipids: average triglyceride change - short term (high = poor)	2	38	Mean Difference (IV, Random, 95% CI)	36.07 [−83.57, 155.71]
35 Adverse effects: 7. Prolactin: average change or endpoint (high=poor)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
35.1 average change from baseline ng/ml	1	120	Mean Difference (IV, Random, 95% CI)	−0.57 [−1.05,−0.09]
35.2 average endpoint ng/ml - men only	2	47	Mean Difference (IV, Random, 95% CI)	−8.65 [−20.55, 3.26]
35.3 average endpoint ng/ml - women only	1	18	Mean Difference (IV, Random, 95% CI)	−54.4 [−86.74, −22. 06]
36 Adverse effects: 8. Sedation	7	1445	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.05, 2.58]
36.1 short term	4	138	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.76, 2.31]
36.2 medium term	2	327	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.92, 7.78]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.55, 2.24]
37 Adverse effects: 9. Seizures	4	1097	Risk Ratio (M-H, Random, 95% CI)	6.50 [1.73, 24.47]
37.1 short term	2	38	Risk Ratio (M-H, Random, 95% CI)	Not estimable
37.2 medium term	1	79	Risk Ratio (M-H, Random, 95% CI)	8.78 [0.49, 157.85]
37.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	6.0 [1.35, 26.67]
38 Adverse effects: 10a. Weight: number of participants with weight gain	7	1600	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.42]
38.1 short term	2	100	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.45, 2.16]
38.2 medium term	4	520	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.60, 1.78]
38.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.48, 0.66]
39 Adverse effects: 10b. Weight: average weight change (high = poor)	7	581	Mean Difference (IV, Random, 95% CI)	−0.04 [−1.06, 0.97]
39.1 short term	3	64	Mean Difference (IV, Random, 95% CI)	−1.70 [−3.69, 0.28]
39.2 medium term	4	517	Mean Difference (IV, Random, 95% CI)	0.41 [−0.56, 1.37]
40 Adverse effects: 11. White blood cell count: number of participants with a decrease	4	1264	Risk Ratio (M-H, Random, 95% CI)	5.68 [2.48, 13.00]
40.1 short term	1	25	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.22, 20.94]
40.2 medium term	2	259	Risk Ratio (M-H, Random, 95% CI)	5.57 [1.00, 31.14]
40.3 long term	1	980	Risk Ratio (M-H, Random, 95% CI)	7.0 [2.47, 19.81]

Comparison 2
CLOZAPINE versus OLANZAPINE - Sensitivity Analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1a. PANSS total score, excluding possibly skewed data (high = poor)	5	577	Mean Difference (IV, Random, 95% CI)	2.16 [−1.23, 5.54]
1.1 short term	1	74	Mean Difference (IV, Random, 95% CI)	2.44 [−3.10, 7.98]
1.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	1.99 [−2.29, 6.27]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Mental state: 1b. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)	3	204	Mean Difference (IV, Random, 95% CI)	1.12 [−3.03, 5.27]
2.1 short term	2	28	Mean Difference (IV, Random, 95% CI)	0.32 [−8.74, 9.38]
2.2 medium term	1	176	Mean Difference (IV, Random, 95% CI)	1.20 [−3.03, 5.43]
3 Mental state: 2a. PANSS positive subscore, excluding possibly skewed data (high = poor)	5	577	Mean Difference (IV, Random, 95% CI)	0.34 [−0.77, 1.44]
3.1 short term	1	74	Mean Difference (IV, Random, 95% CI)	−0.13 [−2.12, 1.86]
3.2 medium term		503	Mean Difference (IV, Random, 95% CI)	0.54 [−0.78, 1.87]
4 Mental state: 2b. BPRS positive subscore, excluding possibly skewed data (high = poor)	1	13	Mean Difference (IV, Random, 95% CI)	−1.11 [−4.32, 2.10]
5 Mental state: 3. SANS, excluding possibly skewed data (high=poor)	1	25	Mean Difference (IV, Random, 95% CI)	−11.0 [−20.90, −1.10]

Comparison 3
CLOZAPINE versus QUETIAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early - short term	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 any reason	2	94	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.42, 5.50]
1.2 adverse effects	1	72	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.37, 130.82]
1.3 inefficacy	1	72	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Global state: No clinically important change - less than “common criteria” - short term	1	76	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.85, 1.35]
3 Mental state: 1. No clinically important change - less than 50% reduction PANSS total -short term	1	63	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.47, 1.89]
4 Mental state: 2a. PANSS total score - short term (high = poor)	4	232	Mean Difference (IV, Random, 95% CI)	0.50 [−1.86, 2.85]
5 Mental state: 2b. BPRS-18 (1-7) total score - short term (high = poor)	1	72	Mean Difference (IV, Random, 95% CI)	0.89 [−1.33, 3.11]
6 Mental state: 3. Positive symptoms: PANSS positive	2	142	Mean Difference (IV, Random, 95% CI)	0.70 [−0.68, 2.07]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
subscore - short term (high = poor)				
7 Mental state: 4 No clinically important change - less than 50% reduction SANS - short term	1	72	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.89, 1.29]
8 Mental state: 5a. Negative symptoms: PANSS negative subscore - short term (high = poor)	2	142	Mean Difference (IV, Random, 95% CI)	2.23 [0.99, 3.48]
9 Mental state: 5b. Negative symptoms: SANS - short term (high = poor)	1	72	Mean Difference (IV, Random, 95% CI)	1.64 [−4.66, 7.94]
10 Adverse effects: 1. At least one adverse effect - short term	1	63	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.52, 3.82]
11 Adverse effects: 2. Cardiac problems - short term	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 ECG abnormalities	1	72	Risk Ratio (M-H, Random, 95% CI)	8.00 [1.05, 60.72]
11.2 palpitation	1	63	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.67, 2.18]
12 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use - short term	1	27	Risk Ratio (M-H, Random, 95% CI)	Not estimable
13 Adverse effects: 3b. Extrapyramidal: various symptoms - short term	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 akathisia	2	135	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.50, 12.61]
13.2 tremor	2	135	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.30, 3.43]
13.3 rigor	1	63	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.05, 5.41]
14 Adverse effects: 4. Hypersalivation - short term	2	135	Risk Ratio (M-H, Random, 95% CI)	33.91 [6.96, 165.24]
15 Adverse effects: 5. Lipids: average triglyceride change - short term (high = poor)	1	27	Mean Difference (IV, Random, 95% CI)	24.64 [20.76, 28.52]
16 Adverse effects: 6. Sedation -short term	2	135	Risk Ratio (M-H, Random, 95% CI)	4.47 [2.11, 9.49]
17 Adverse effects: 7a. Weight: number of participant with weight gain - short term	2	135	Risk Ratio (M-H, Random, 95% CI)	1.89 [0.90, 3.96]
18 Adverse effects: 7b. Weight: average weight change - short term (high = poor)	1	27	Mean Difference (IV, Random, 95% CI)	2.11 [−0.08, 4.30]
19 Adverse effects: 8. White blood cell count: number of participant with a decrease - short term	1	63	Risk Ratio (M-H, Random, 95% CI)	5.16 [0.26, 103.27]

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Comparison 4
CLOZAPINE versus QUETIAPINE - Sensitivity Analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. PANSS total score - excluding possibly skewed data - short term (high = poor)	1	27	Mean Difference (IV, Random, 95% CI)	−0.18 [−4.47, 4.11]

Comparison 5
CLOZAPINE versus RISPERIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death - short term	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Natural causes	2	293	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.48]
1.2 Suicide	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Leaving the study early: 1. Any reason	7	655	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.16]
2.1 short term	5	467	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.60, 1.54]
2.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.60, 1.56]
2.3 long term	1	107	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.57, 1.18]
3 Leaving the study early: 2. Adverse effects	6	627	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.11, 3.21]
3.1 short term	4	439	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.82, 2.70]
3.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	4.1 [0.93, 18.14]
3.3 long term	1	107	Risk Ratio (M-H, Random, 95% CI)	7.13 [0.91, 56.00]
4 Leaving the study early: 3. Inefficacy	6	627	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.23, 0.70]
4.1 short term	4	439	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.96]
4.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.15, 6.93]
4.3 long term	1	107	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.80]
5 Global state: No clinically important change - less than much improved on CGI - short term	1	60	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.43, 1.49]
6 Mental state: 1. No clinically important change - various criteria	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 less than 20% reduction on BPRS-18 (1-7) total score -short term	1	29	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.50, 1.28]
6.2 less than 20% reduction on BPRS and mildly ill or better - short term	1	273	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.17]
6.3 less than 20% reduction on 4-item BPRS psychosis and no psychotic symptoms rated less than mild - long term	1	107	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.21]
6.4 less than 40% improvement on the 4-item BPRS psychosis cluster - long term	1	107	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.32]
6.5 less than 20% reduction on PANSS total - short term	2	106	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.70, 1.99]
7 Mental state: 2a. PANSS total score (high = poor)	5	468	Mean Difference (IV, Random, 95% CI)	−1.49 [−6.42, 3.44]
7.1 short term	4	387	Mean Difference (IV, Random, 95% CI)	−0.75 [−6.85, 5.35]
7.2 medium term	1	81	Mean Difference (IV, Random, 95% CI)	−3.60 [−13.32, 6.12]
8 Mental state: 2b. BPRS-18 (1-7) total score - short term (high = poor)	3	337	Mean Difference (IV, Random, 95% CI)	−2.98 [−6.93, 0.97]
8.1 short term	2	285	Mean Difference (IV, Random, 95% CI)	−5.11 [−7.99, −2.23]
8.2 long term	1	52	Mean Difference (IV, Random, 95% CI)	0.40 [−3.52, 4.32]
9 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)	5	562	Mean Difference (IV, Random, 95% CI)	−0.99 [−2.29, 0.32]
9.1 short term	4	481	Mean Difference (IV, Random, 95% CI)	−0.89 [−2.59, 0.81]
9.2 medium term	1	81	Mean Difference (IV, Random, 95% CI)	−0.40 [−3.58, 2.78]
10 Mental state: 3b. Positive symptoms: BPRS-18 (1-7) positive subscore - short term (high = poor)	1	29	Mean Difference (IV, Random, 95% CI)	−2.10 [−4.76, 0.56]
11 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)	5	562	Mean Difference (IV, Random, 95% CI)	0.13 [−1.71, 1.96]
11.1 short term	4	481	Mean Difference (IV, Random, 95% CI)	0.55 [−1.71, 2.80]
11.2 medium term	1	81	Mean Difference (IV, Random, 95% CI)	−1.40 [−4.22, 1.42]
12 Mental state: 4b. Negative symptoms:	2	69	Mean Difference (IV, Random, 95% CI)	0.62 [−2.51, 3.74]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
SANS - short term (high = poor)				
13 General functioning: GAF score - short term (high = good)	1	19	Mean Difference (IV, Random, 95% CI)	−9.0 [−18.44, 0.44]
14 Social functioning: SFS score - short term (high = good)	1	19	Mean Difference (IV, Random, 95% CI)	−47.0 [−93.55, −0.45]
15 Treatment satisfaction: DAI score - short term (high = good)	1	19	Mean Difference (IV, Random, 95% CI)	0.10 [−2.57, 2.77]
16 Cognitive functioning: No clinically important change -less than 0.5 SD improved -medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.95, 1.67]
17 Adverse effects: 1. At least one adverse effect - short term	2	333	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.71, 1.95]
18 Adverse effects: 2. Cardiac problems	2	167	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.03, 15.30]
18.1 short term	1	60	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.03, 15.30]
18.2 long term	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable
19 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use	6	304	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.22, 0.68]
19.1 short term	5	223	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.77]
19.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.15, 1.00]
20 Adverse effects: 3b. Extrapyramidal: various symptoms - short term	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 at least one EPS	2	333	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.26, 2.28]
20.2 akathisia	1	40	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]
20.3 dyskinesia	1	86	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.38, 2.61]
20.4 dystonia	1	86	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 5.31]
20.5 parkinsonism	1	86	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.03, 2.45]
20.6 tremor	1	40	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.72, 5.59]
21 Adverse effects: 3c. Extrapyramidal: symptom scales (high = poor)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 ESRS score	1	81	Mean Difference (IV, Random, 95% CI)	0.30 [−1.31, 1.91]
21.2 SAS score	2	69	Mean Difference (IV, Random, 95% CI)	−0.81 [−1.73, 0.10]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.3 BARS score	1	106	Mean Difference (IV, Random, 95% CI)	−0.20 [−0.42, 0.02]
22 Adverse effects: 4. Glucose: average change - medium term (high = poor)	1	31	Mean Difference (IV, Random, 95% CI)	1.70 [−8.64, 12.04]
23 Adverse effects: 5. Hypersalivation -short term	3	373	Risk Ratio (M-H, Random, 95% CI)	4.38 [1.86, 10.30]
24 Adverse effects: 6. Lipids: average change (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
24.1 average cholesterol change	1	31	Mean Difference (IV, Random, 95% CI)	7.10 [−19.81, 34.01]
24.2 average triglyceride change	1	26	Mean Difference (IV, Random, 95% CI)	32.41 [29.26, 35.56]
25 Adverse effects: 7a. Prolactin: associated side effects - short term	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 disminished sexual drive	1	86	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.10, 2.59]
26 Adverse effects: 7b. Prolactin: average at endpoint (high = poor)	2	55	Mean Difference (IV, Random, 95% CI)	−28.61 [−46.69, −10. 52]
26.1 short term	1	27	Mean Difference (IV, Random, 95% CI)	−38.5 [−53.70, −23.
26.2 medium term	1	28	Mean Difference (IV, Random, 95% CI)	30] −20.0 [−31.81, −8.19]
27 Adverse effects: 8. Sedation -short term	5	479	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.24, 2.42]
28 Adverse effects: 9. Seizures	2	354	Risk Ratio (M-H, Random, 95% CI)	4.47 [1.43, 14.01]
28.1 short term	1	273	Risk Ratio (M-H, Random, 95% CI)	3.91 [1.13, 13.56]
28.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	9.22 [0.51, 165.87]
29 Adverse effects: 10a. Weight: number of participants with weight gain	3	207	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.80, 6.46]
29.1 short term	2	126	Risk Ratio (M-H, Random, 95% CI)	4.65 [0.24, 88.47]
29.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.57, 5.66]
30 Adverse effects: 10b. Weight: average weight change (high=poor)	4	459	Mean Difference (IV, Random, 95% CI)	2.84 [1.17, 4.50]
30.1 short term	3	382	Mean Difference (IV, Random, 95% CI)	3.16 [0.92, 5.41]
30.2 medium term	1	77	Mean Difference (IV, Random, 95% CI)	1.90 [0.17, 3.63]
31 Adverse effects: 11. White blood cell count: number of participants with a decrease	4	294	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.33, 4.99]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 short term	2	106	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.10, 8.58]
31.2 medium term	1	81	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.27, 8.72]
31.3 long term	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 6
CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)	1	256	Mean Difference (IV, Random, 95% CI)	−5.5 [−8.78, −2.22]
2 Mental state: 2. PANSS positive subscore, excluding possibly skewed data (high = poor)	3	423	Mean Difference (IV, Random, 95% CI)	−0.85 [−2.91, 1.21]
2.1 short term	2	342	Mean Difference (IV, Random, 95% CI)	−0.66 [−4.20, 2.87]
2.2 medium term	1	81	Mean Difference (IV, Random, 95% CI)	−0.40 [−3.58, 2.78]
3 Mental state: 3. PANSS negative subscore, excluding possibly skewed data (high = poor)	4	442	Mean Difference (IV, Random, 95% CI)	−0.14 [−2.31, 2.02]
3.1 short term	3	361	Mean Difference (IV, Random, 95% CI)	0.39 [−2.59, 3.37]
3.2 medium term	1	81	Mean Difference (IV, Random, 95% CI)	−1.40 [−4.22, 1.42]

Comparison 7
CLOZAPINE versus ZIPRASIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early: any reason - medium term	1	146	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.66, 1.51]
2 Mental state: PANSS total score - medium term (high = poor)	1	146	Mean Difference (IV, Random, 95% CI)	0.5 [−6.72, 7.72]
3 Adverse effects: 1. Cardiac problems	1	146	Risk Ratio (M-H, Random, 95% CI)	Not estimable

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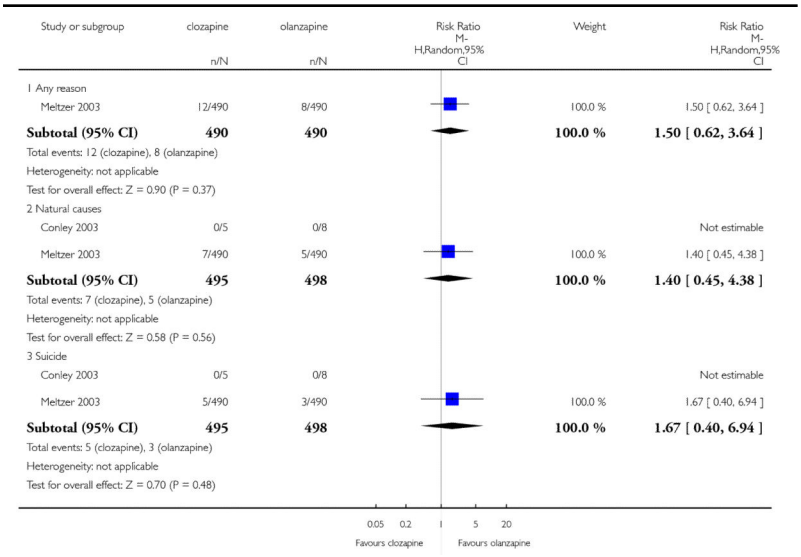
Comparison 8
CLOZAPINE versus ZOTEPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early: any reason	1	50	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.32, 1.54]
2 Global state: no clinically important change - less than successfully and no increase on CGI-S - short term	1	59	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.87]
3 Mental state: BPRS-18 total score - short term (high=poor)	1	59	Mean Difference (IV, Random, 95% CI)	−6.0 [−9.83, −2.17]
4 Adverse effects: 1. Extrapyramidal: antiparkinson medication use - short term	1	59	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.86]
5 Adverse effects: 2. Prolactin: average change - short term (high=poor)	1	59	Mean Difference (IV, Random, 95% CI)	−33.4 [−48.67, −18.13]

Analysis 1.1
Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 1 Death

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 1 Death



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Analysis 1.2

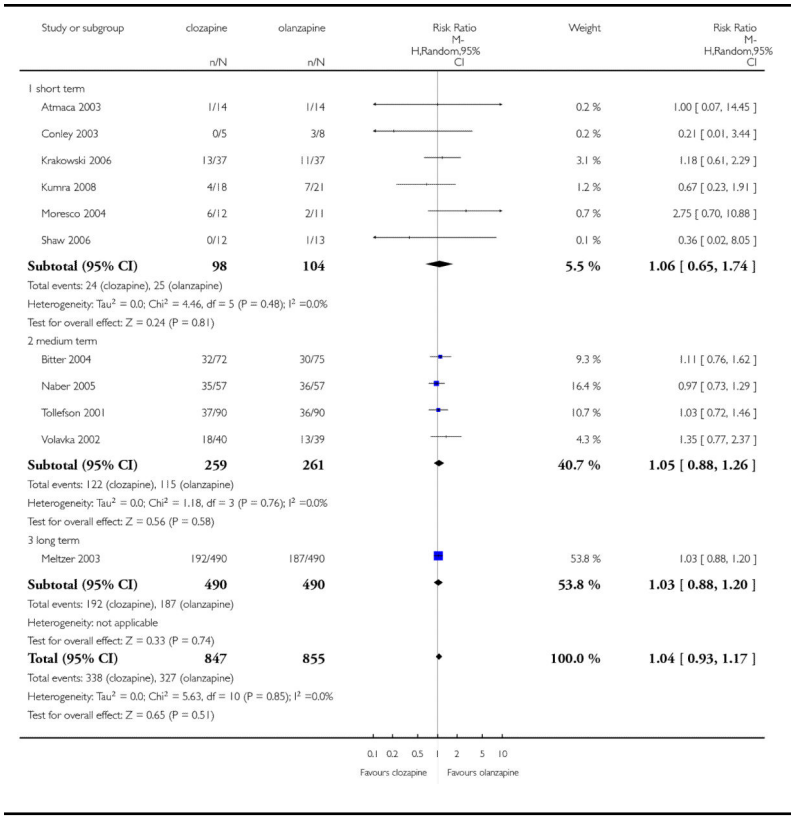
Comparison 1 CLOZAPINE versus OLANZAPINE,

Outcome 2 Leaving the study early: 1. Any reason

Review: Clozapine versus other atypical antipsychotics for schizophrenia

Comparison: 1 CLOZAPINE versus OLANZAPINE

Outcome: 2 Leaving the study early: 1. Any reason



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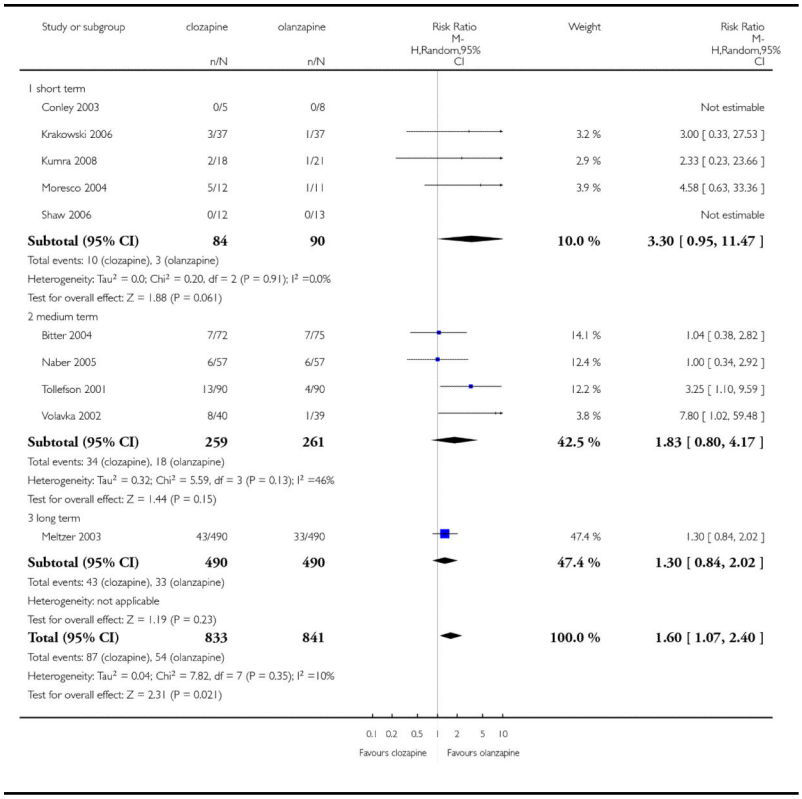
Analysis 1.3
Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 3 Leaving the study early: 2. Adverse effects

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 3 Leaving the study early: 2. Adverse effects



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Analysis 1.4

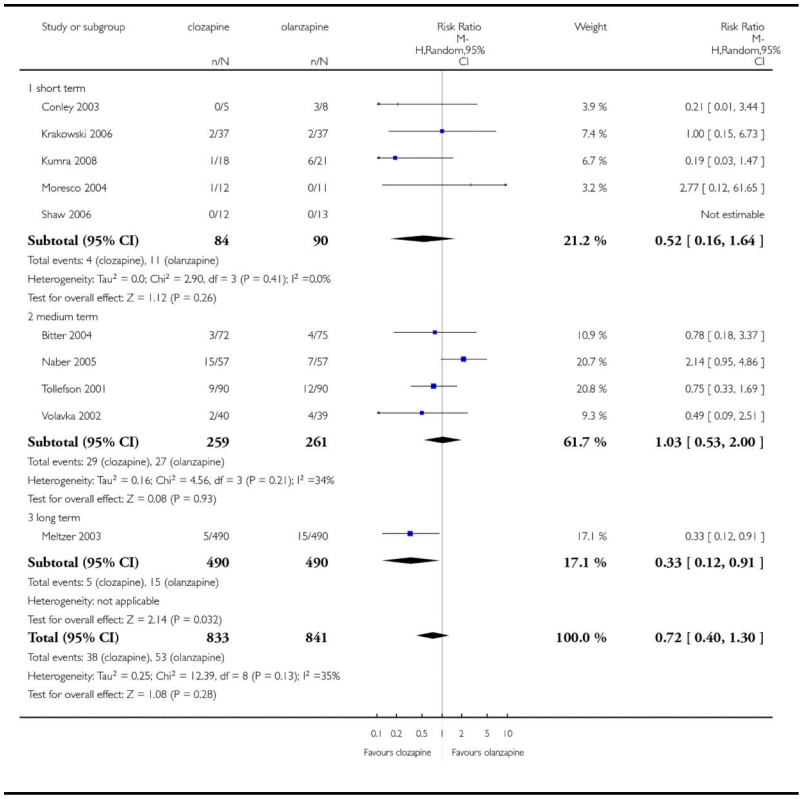
Comparison 1 CLOZAPINE versus OLANZAPINE,

Outcome 4 Leaving the study early: 3. Inefficacy

Review: Clozapine versus other atypical antipsychotics for schizophrenia

Comparison: 1 CLOZAPINE versus OLANZAPINE

Outcome: 4 Leaving the study early: 3. Inefficacy



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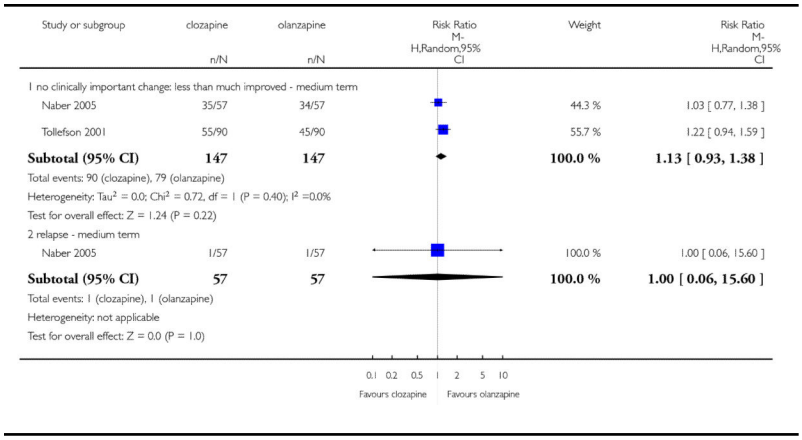
Analysis 1.5
Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 5 Global state

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 5 Global state



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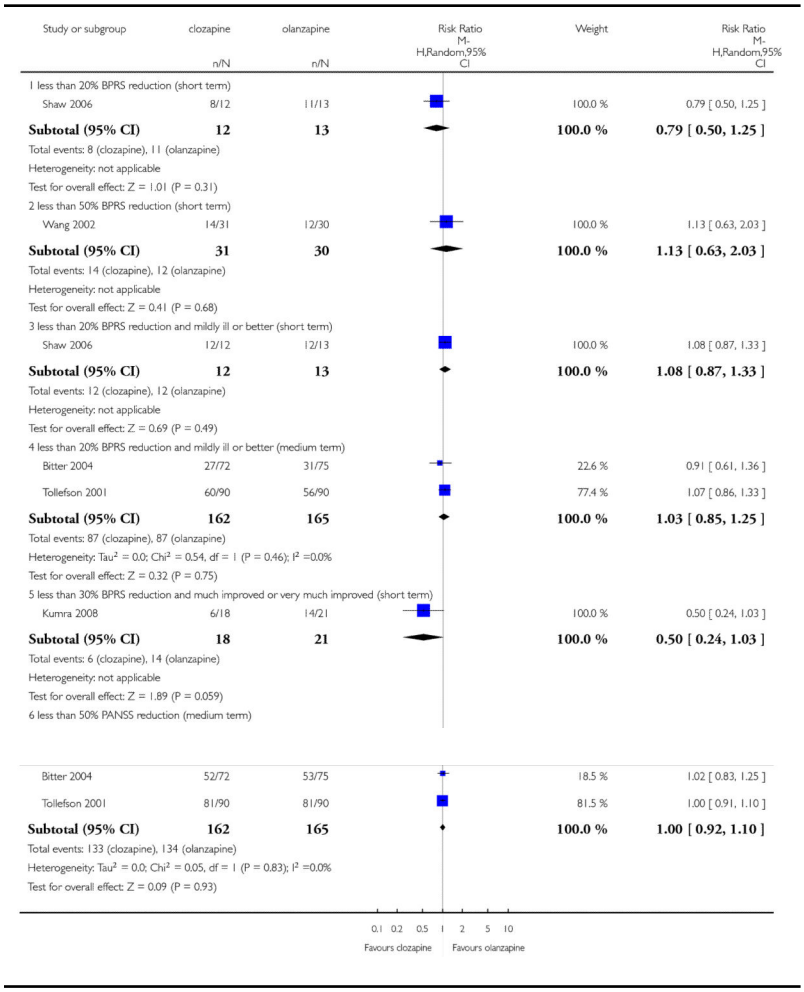
Analysis 1.6

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 6 Mental state: 1. No clinically important change - various criteria

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 6 Mental state: 1. No clinically important change - various criteria



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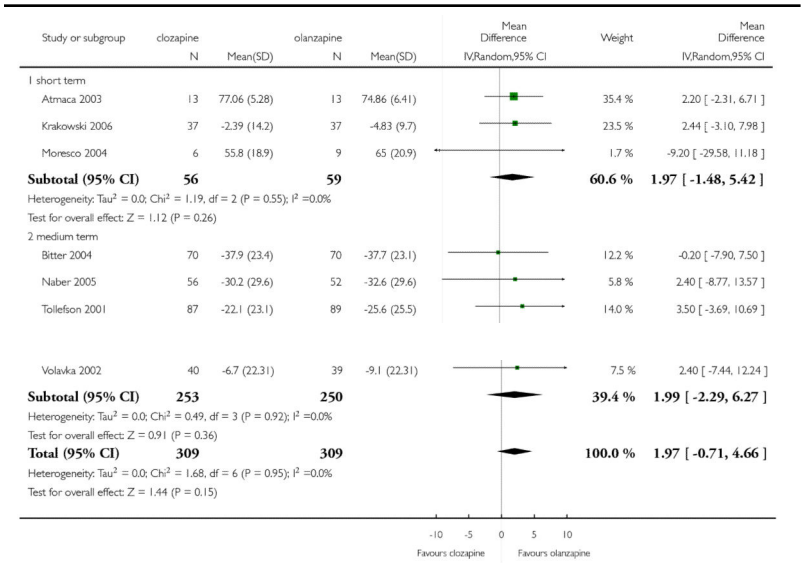
Analysis 1.7

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 7 Mental state: 2a. PANSS total score (high = poor)

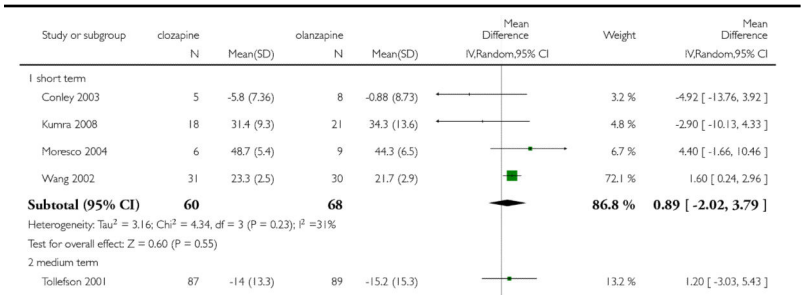
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 7 Mental state: 2a. PANSS total score (high = poor)

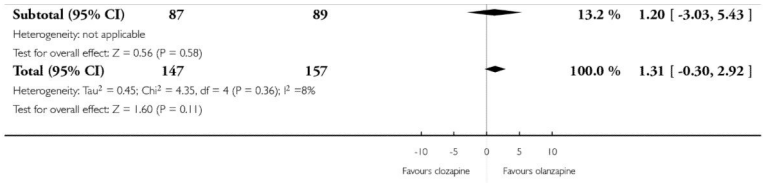


Analysis 1.8

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 8 Mental state: 2b. BPRS-18 (1- 7) total score (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 8 Mental state: 2b. BPRS-18 (1-7) total score (high = poor)





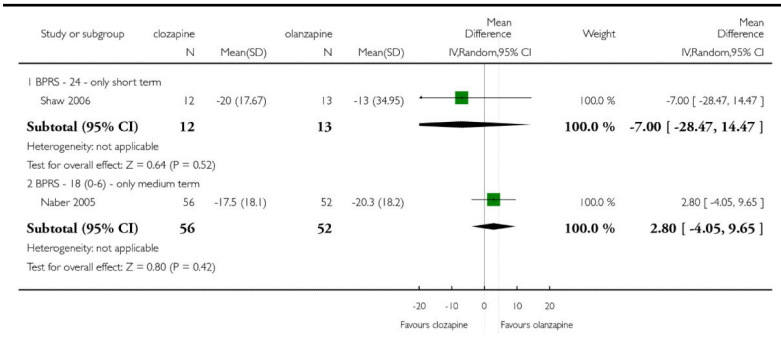
Analysis 1.9

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 9 Mental state: 2c. BPRS total score, various versions (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia

Comparison: 1 CLOZAPINE versus OLANZAPINE

Outcome: 9 Mental state: 2c. BPRS total score, various versions (high = poor)



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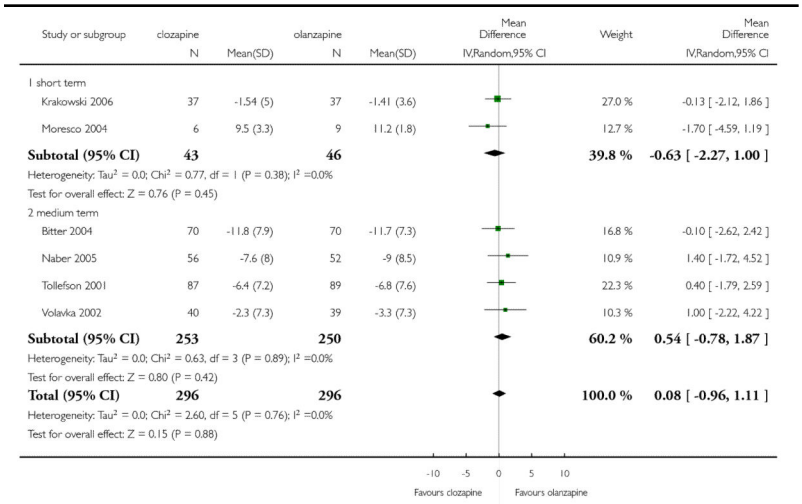
Analysis 1.10

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 10 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)

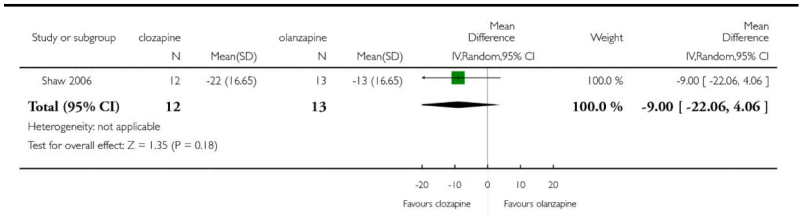
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 10 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)



Analysis 1.11

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 11 Mental state: 3b. Positive symptoms: SAPS - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 11 Mental state: 3b. Positive symptoms: SAPS - short term (high = poor)



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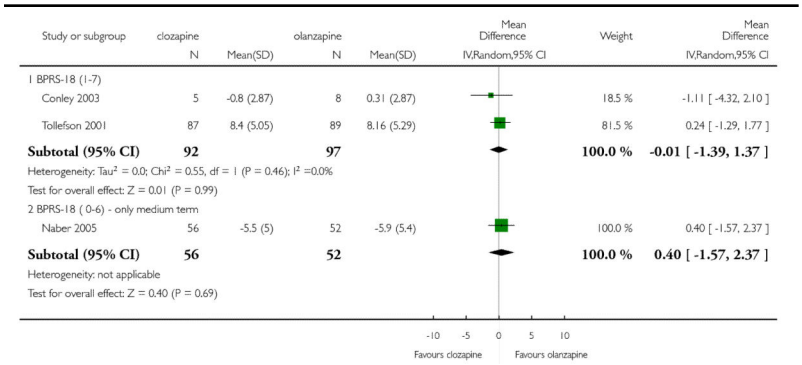
Analysis 1.12

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 12 Mental state: 3c. Positive symptoms: BPRS positive subscore (high = poor)

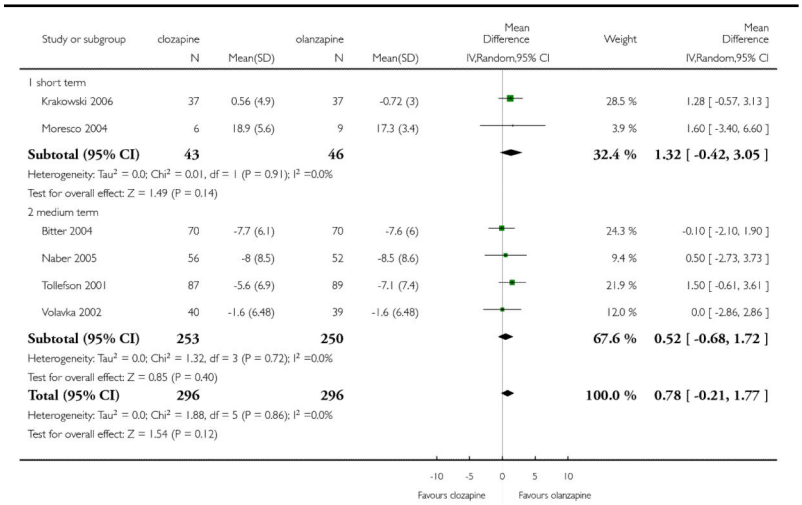
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 12 Mental state: 3c. Positive symptoms: BPRS positive subscore (high = poor)



Analysis 1.13

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 13 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 13 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)



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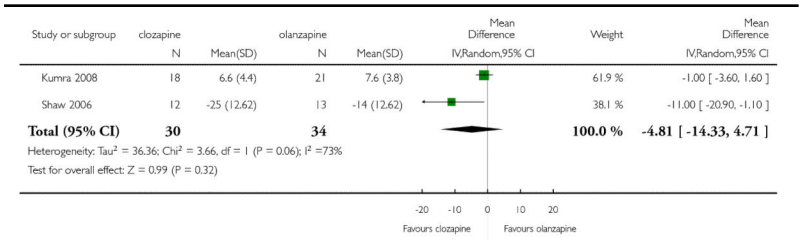
Analysis 1.14

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 14 Mental state: 4b. Negative symptoms: SANS - short term (high = poor)

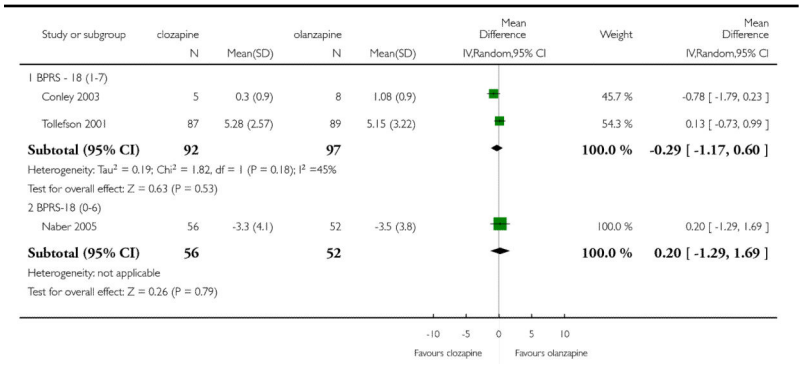
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 14 Mental state: 4b. Negative symptoms: SANS - short term (high = poor)



Analysis 1.15

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 15 Mental state: 4c. Negative symptoms: BPRS negative subscore -(high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 15 Mental state: 4c. Negative symptoms: BPRS negative subscore -(high = poor)



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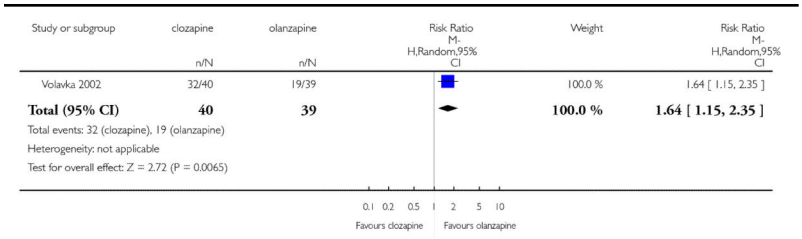
Analysis 1.16

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 16 Cognitive functioning: 1. No clinically important change - less than 0.5 SD improved - medium term

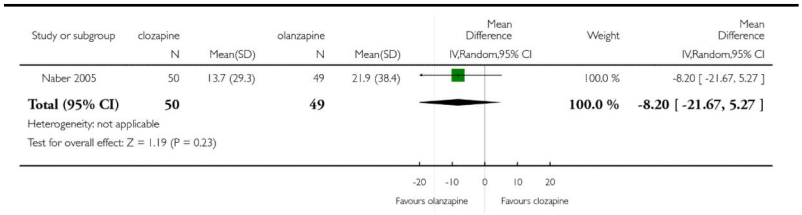
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 16 Cognitive functioning: 1. No clinically important change - less than 0.5 SD improved - medium term



Analysis 1.17

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 17 Quality of Life: 1. SWN-38 total score - medium term (high= good)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 17 Quality of Life: 1. SWN-38 total score - medium term (high= good)



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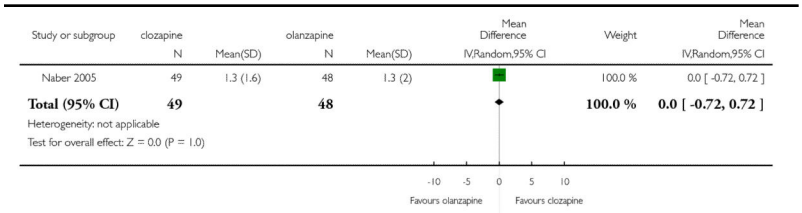
Analysis 1.18

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 18 Quality of Life: 2. MLDL total score - medium term (high = good)

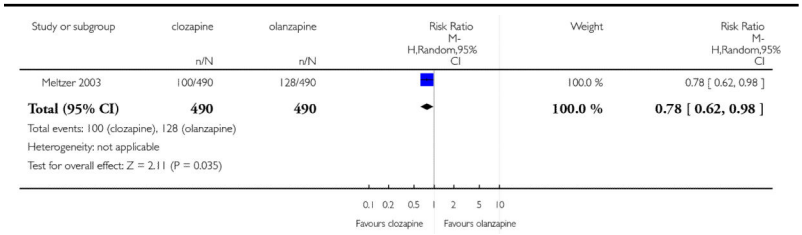
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 18 Quality of Life: 2. MLDL total score - medium term (high = good)



Analysis 1.19

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 19 Service use: Hospital readmission - long term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 19 Service use: Hospital readmission - long term



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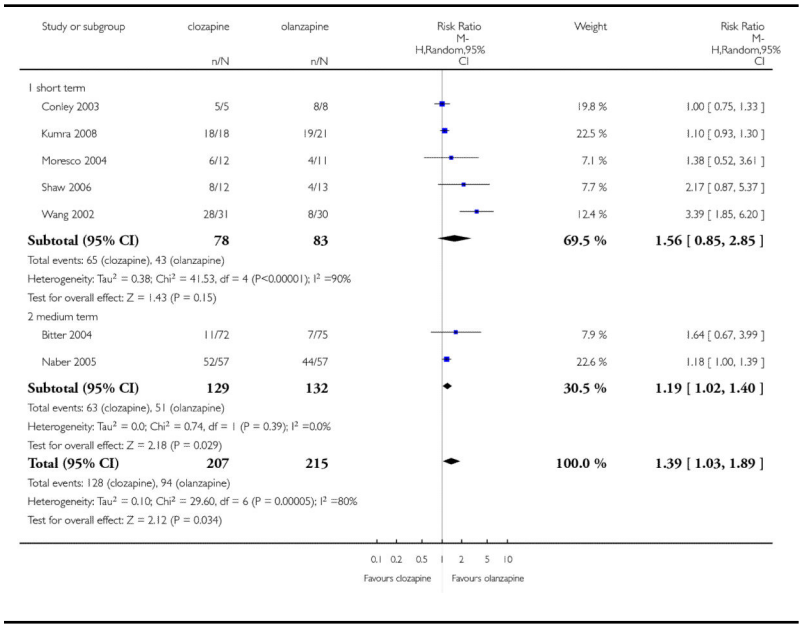
Analysis 1.20

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 20 Adverse effects: 1. At least one adverse effect

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 20 Adverse effects: 1. At least one adverse effect



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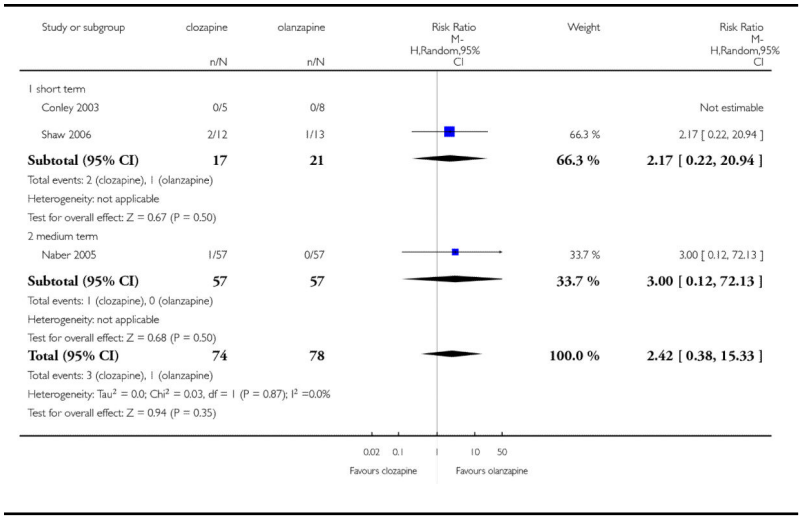
Analysis 1.21

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 21 Adverse effects: 2. Cardiac problems

Review: Clozapine versus other atypical antipsychotics for schizophrenia

Comparison: 1 CLOZAPINE versus OLANZAPINE

Outcome: 21 Adverse effects: 2. Cardiac problems



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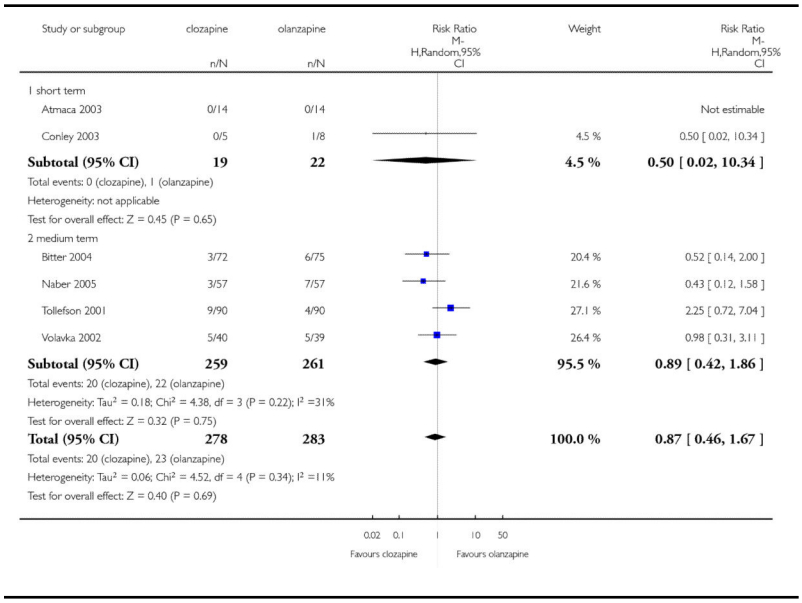
Analysis 1.22

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 22 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 22 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use



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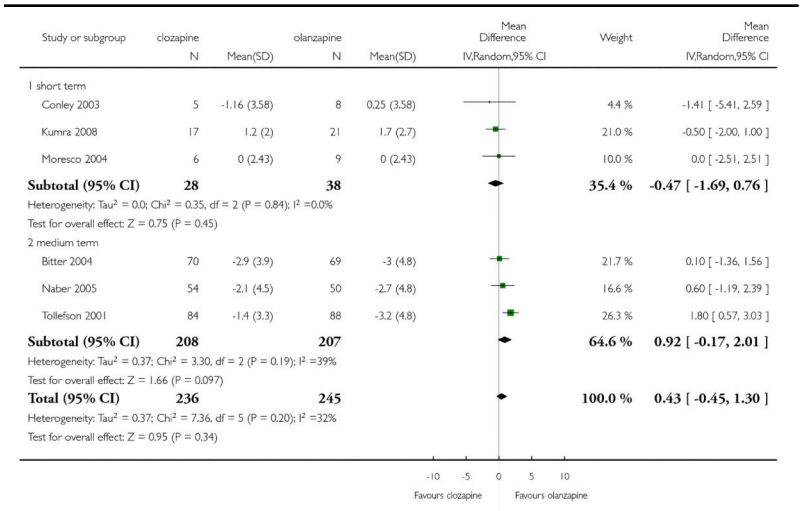
Analysis 1.23

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 23 Adverse effects: 3d. Extrapyramidal: SAS change or endpoint (high = poor)

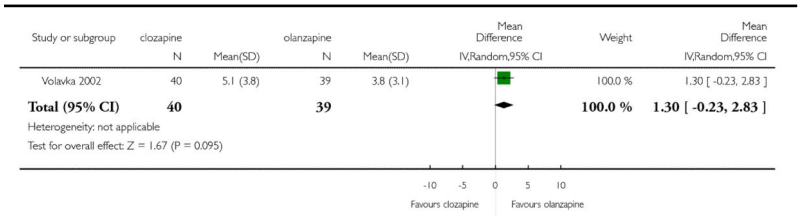
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 23 Adverse effects: 3d. Extrapyramidal: SAS change or endpoint (high = poor)



Analysis 1.24

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 24 Adverse effects: 3c. Extrapyramidal: ESRS score at endpoint - medium term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 24 Adverse effects: 3c. Extrapyramidal: ESRS score at endpoint - medium term (high = poor)



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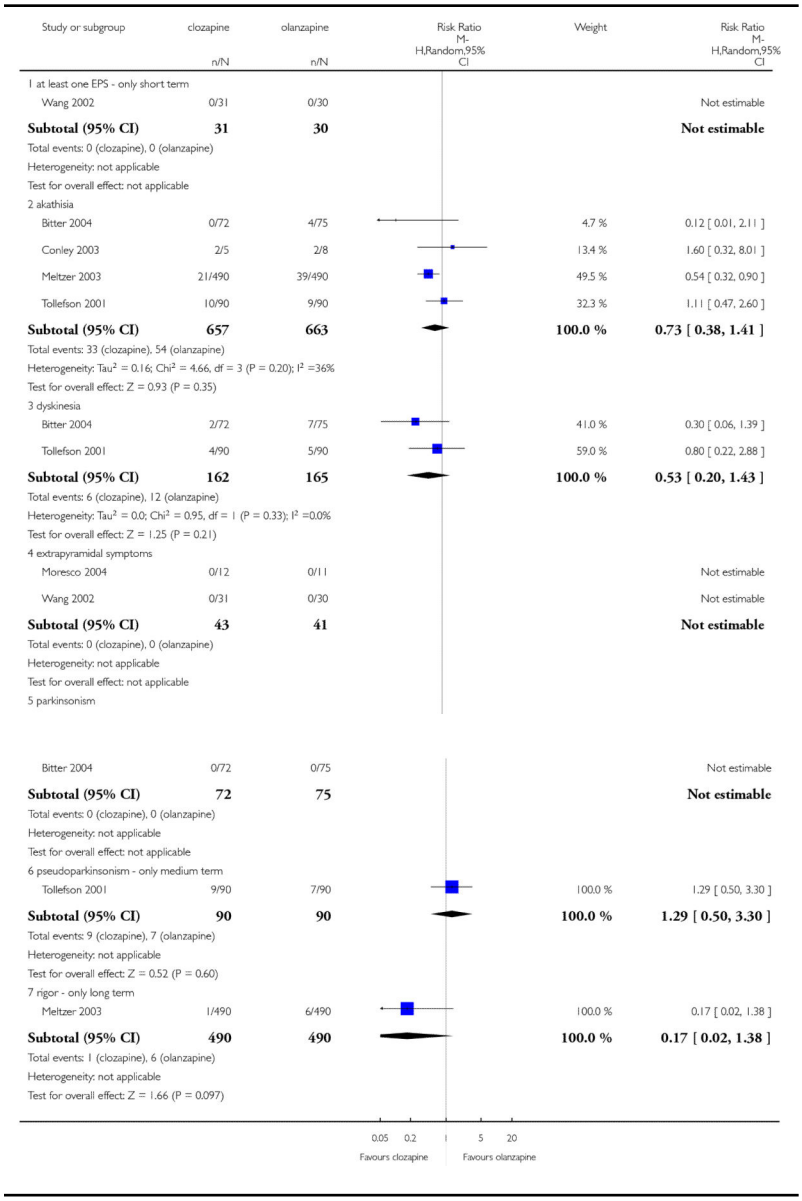
Analysis 1.25

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 25 Adverse effects: 3b. Extrapyramidal: various symptoms

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 25 Adverse effects: 3b. Extrapyramidal: various symptoms



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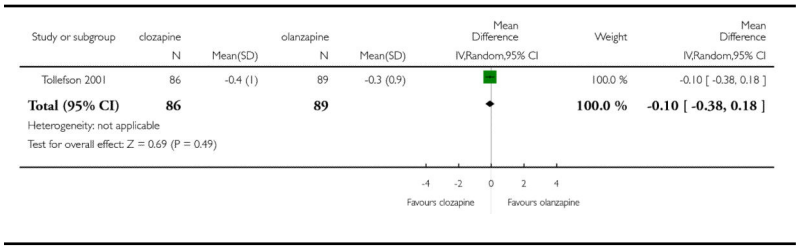
Analysis 1.26

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 26 Adverse effects: 3e. Extrapyramidal: akathisia - BARS change - medium term (high = poor)

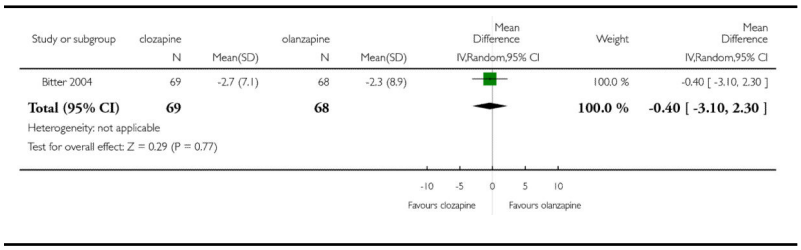
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 26 Adverse effects: 3e. Extrapyramidal: akathisia - BARS change - medium term (high = poor)



Analysis 1.27

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 27 Adverse effects: 3f. Extrapyramidal: Hillside Akathisia Scale - medium term (high=poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 27 Adverse effects: 3f. Extrapyramidal: Hillside Akathisia Scale - medium term (high=poor)



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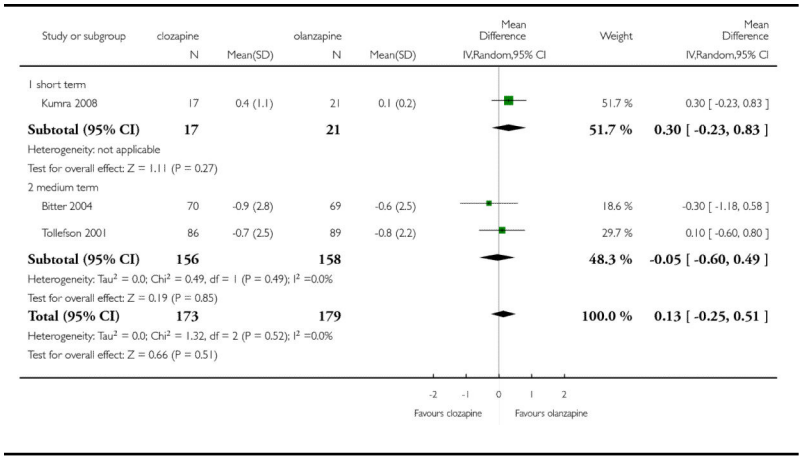
Analysis 1.28

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 28 Adverse effects: 3g. Extrapyramidal: tardive dyskinesia - AIMS change or endpoint - (high = poor)

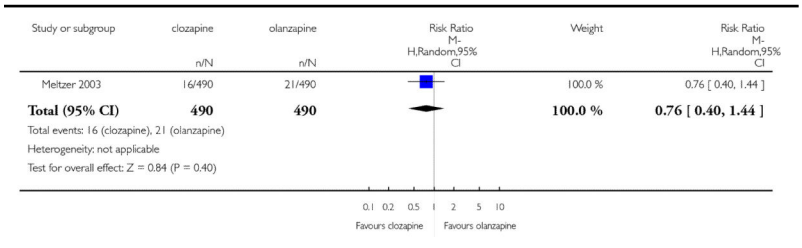
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 28 Adverse effects: 3g. Extrapyramidal: tardive dyskinesia - AIMS change or endpoint - (high = poor)



Analysis 1.29

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 29 Adverse effects: 4a. Glucose: number of participants with significant increase - long term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 29 Adverse effects: 4a. Glucose: number of participants with significant increase - long term



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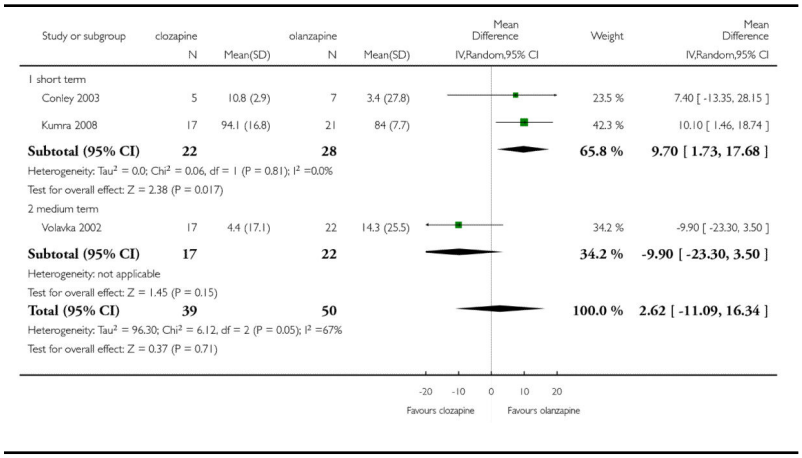
Analysis 1.30

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 30 Adverse effects: 4b. Glucose: average change or endpoint (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 30 Adverse effects: 4b. Glucose: average change or endpoint (high = poor)



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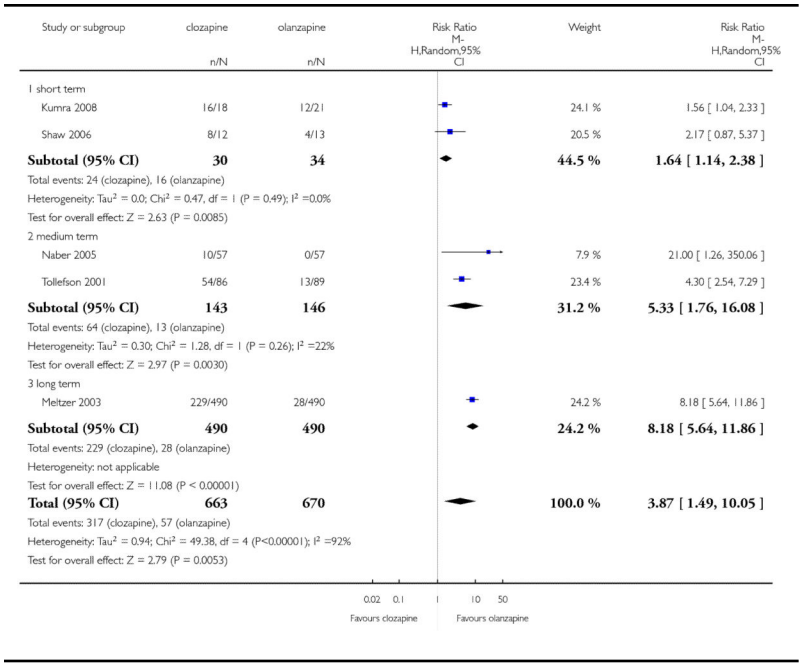
Analysis 1.31
Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 31 Adverse effects: 5. Hypersalivation

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 31 Adverse effects: 5. Hypersalivation



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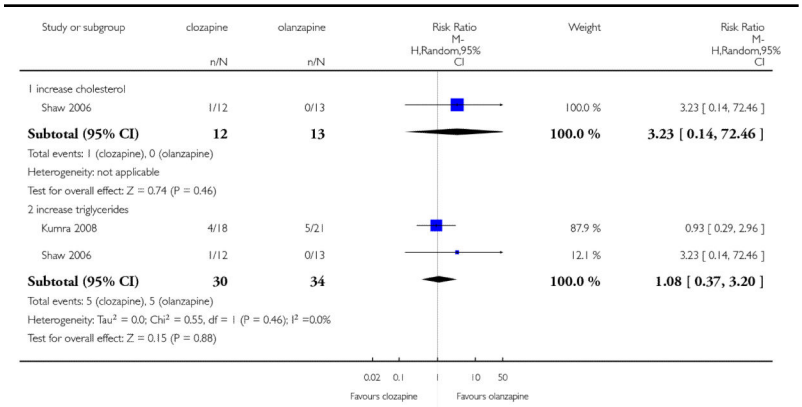
Analysis 1.32

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 32 Adverse effects: 6a. Lipids: number of participants with significant increase

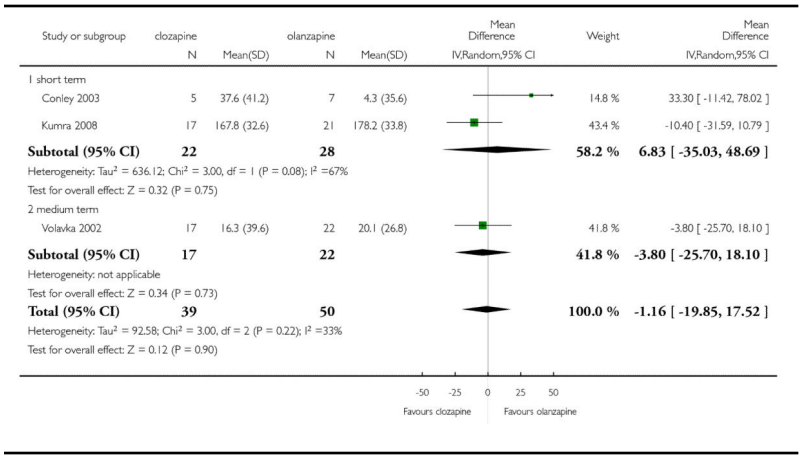
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 32 Adverse effects: 6a. Lipids: number of participants with significant increase



Analysis 1.33

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 33 Adverse effects: 6b. Lipids:average cholesterol change or endpoint (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 33 Adverse effects: 6b. Lipids:average cholesterol change or endpoint (high = poor)



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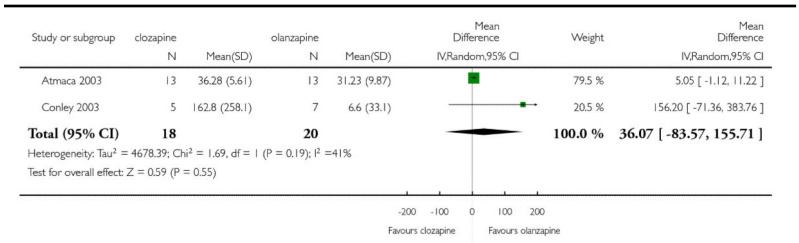
Analysis 1.34

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 34 Adverse effects: 6c. Lipids: average triglyceride change -short term (high = poor)

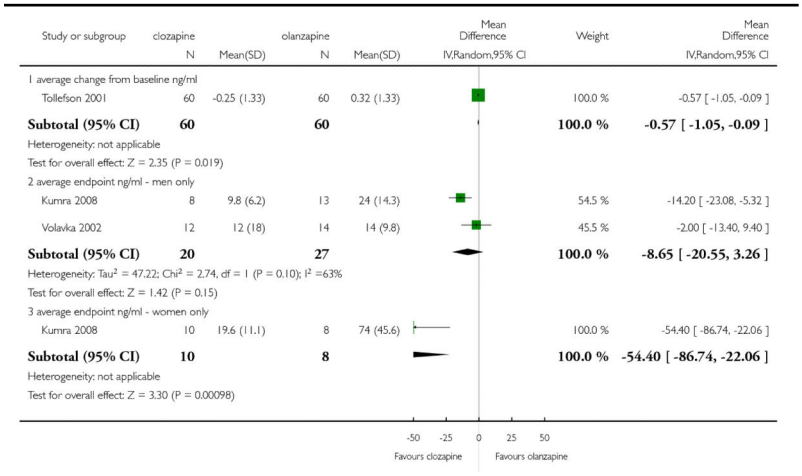
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 34 Adverse effects: 6c. Lipids: average triglyceride change -short term (high = poor)



Analysis 1.35

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 35 Adverse effects: 7. Prolactin: average change or endpoint (high=poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 35 Adverse effects: 7. Prolactin: average change or endpoint (high=poor)



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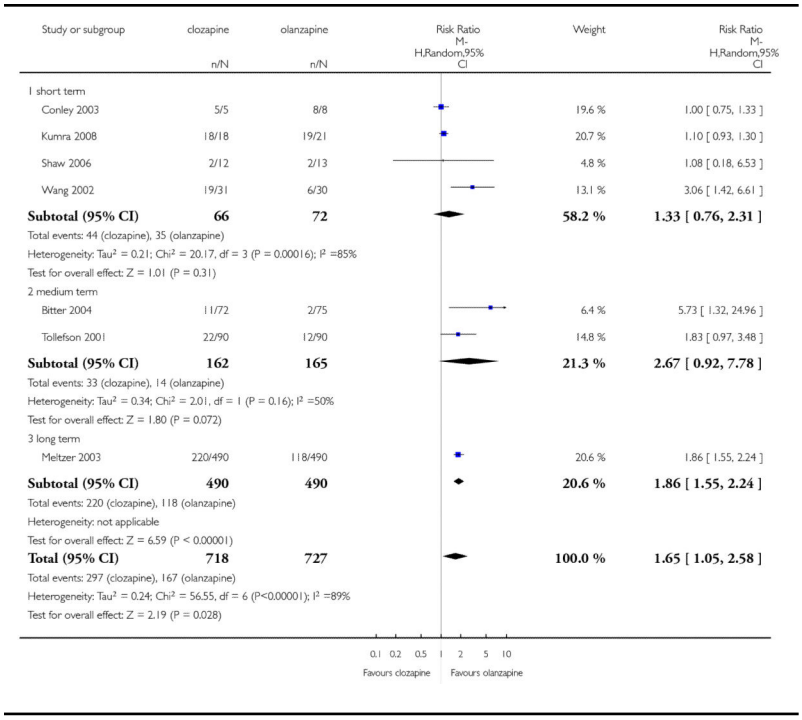
Analysis 1.36
Comparison 1 CLOZAPINE versus OLANZAPINE,
Outcome 36 Adverse effects: 8. Sedation

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 36 Adverse effects: 8. Sedation



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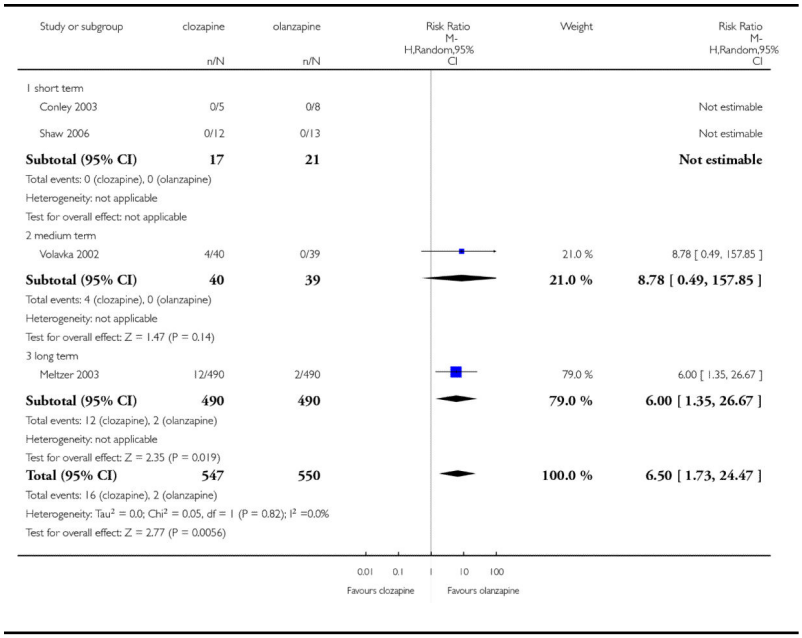
Analysis 1.37
Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 37 Adverse effects: 9. Seizures

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 37 Adverse effects: 9. Seizures



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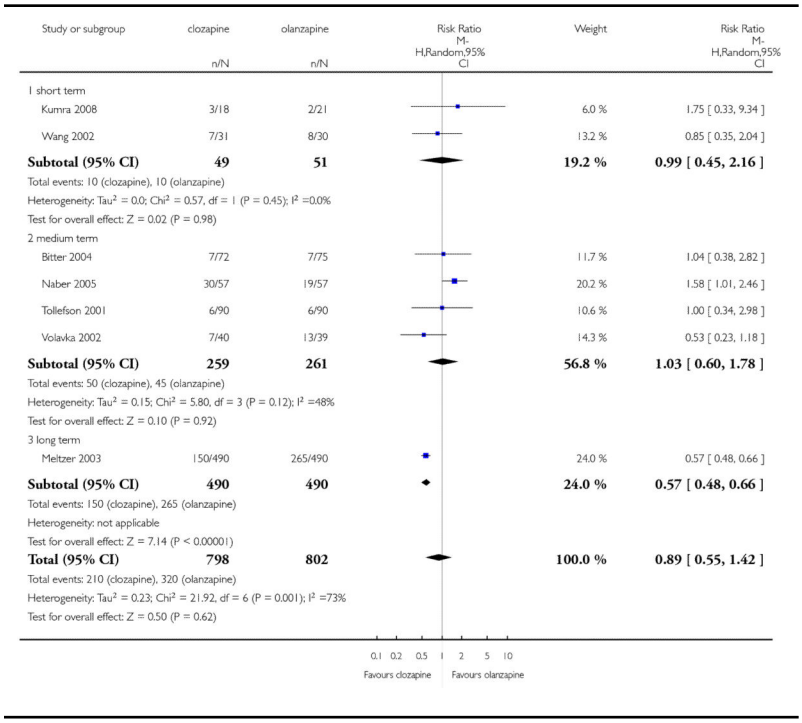
Analysis 1.38

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 38 Adverse effects: 10a. Weight: number of participants with weight gain

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 38 Adverse effects: 10a. Weight: number of participants with weight gain



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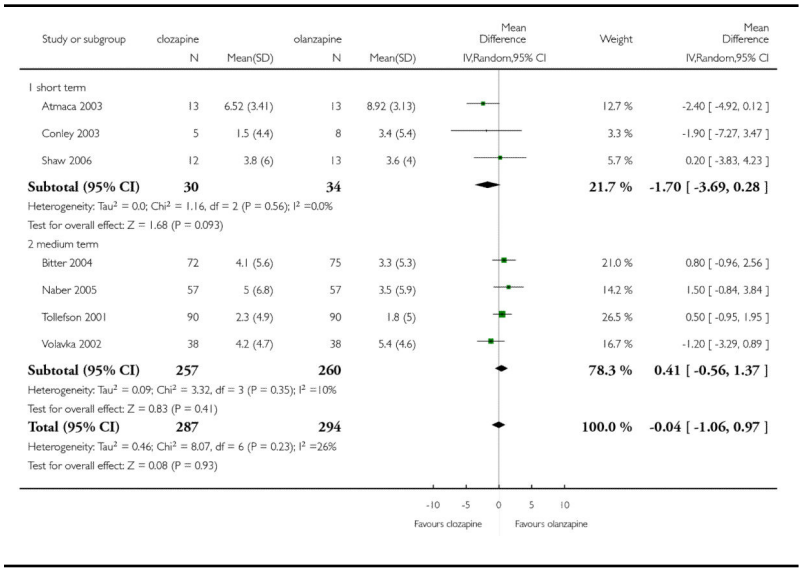
Analysis 1.39

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 39 Adverse effects: 10b. Weight: average weight change (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 39 Adverse effects: 10b. Weight: average weight change (high = poor)



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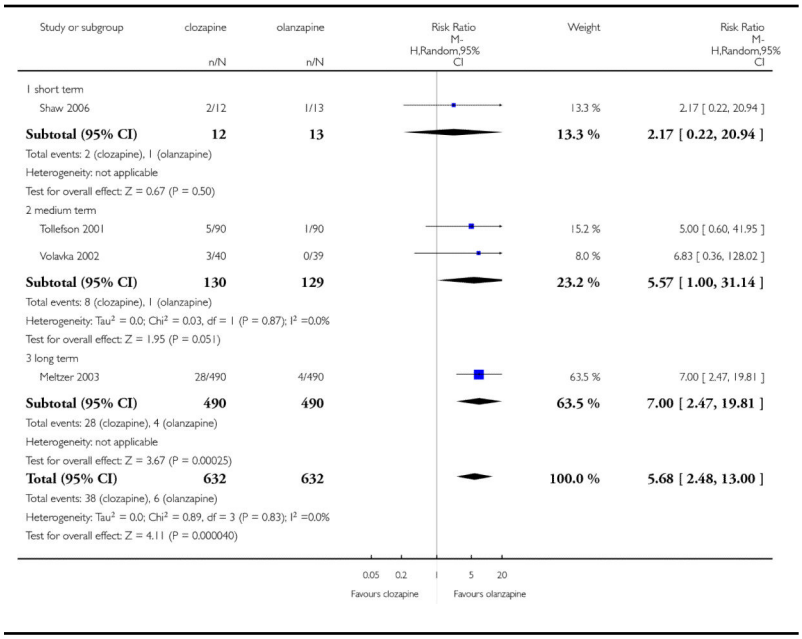
Analysis 1.40

Comparison 1 CLOZAPINE versus OLANZAPINE, Outcome 40 Adverse effects: 11.White blood cell count: number of participants with a decrease

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 CLOZAPINE versus OLANZAPINE
Outcome: 40 Adverse effects: 11. White blood cell count: number of participants with a decrease



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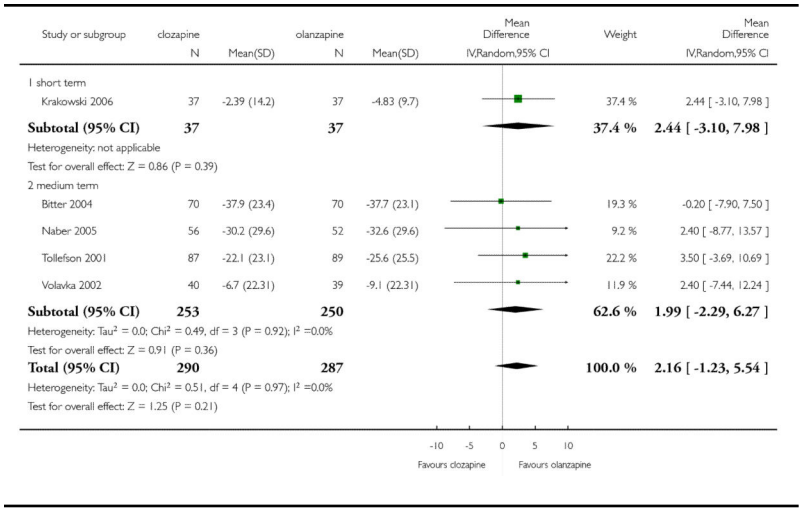
Analysis 2.1

Comparison 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis, Outcome 1 Mental state: 1a. PANSS total score, excluding possibly skewed data (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis
Outcome: 1 Mental state: 1a. PANSS total score, excluding possibly skewed data (high = poor)



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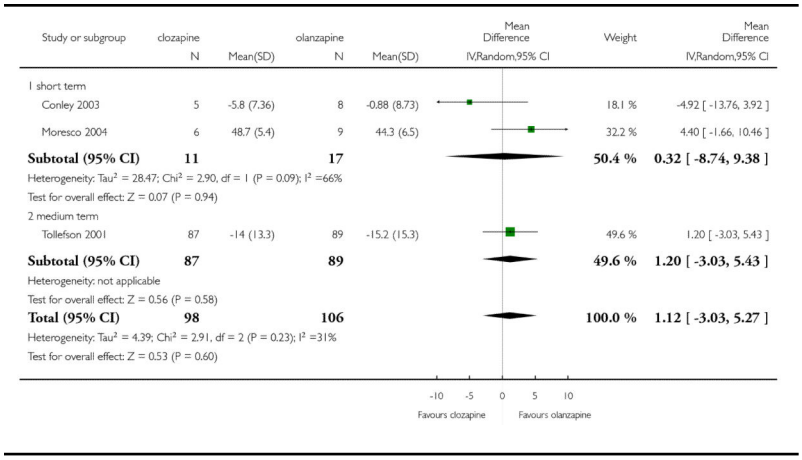
Analysis 2.2

Comparison 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis, Outcome 2 Mental state: 1b. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis
Outcome: 2 Mental state: 1b. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)



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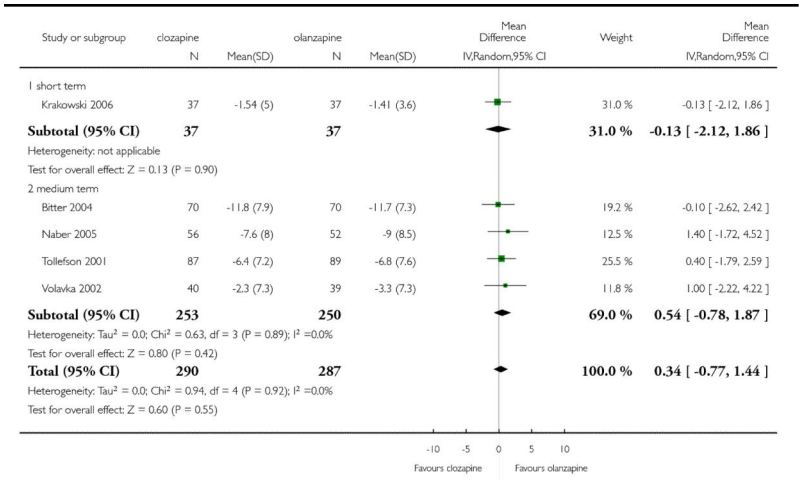
Analysis 2.3

Comparison 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis, Outcome 3 Mental state: 2a. PANSS positive subscore, excluding possibly skewed data (high = poor)

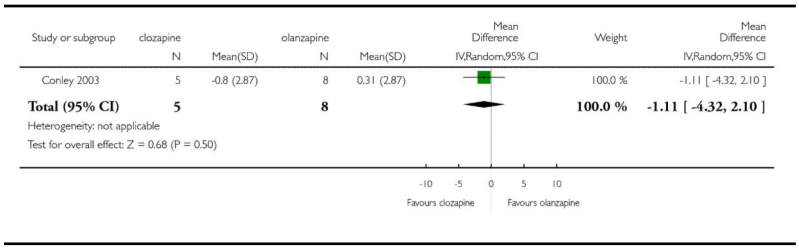
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis
Outcome: 3 Mental state: 2a. PANSS positive subscore, excluding possibly skewed data (high = poor)



Analysis 2.4

Comparison 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis, Outcome 4 Mental state: 2b. BPRS positive subscore, excluding possibly skewed data (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis
Outcome: 4 Mental state: 2b. BPRS positive subscore, excluding possibly skewed data (high = poor)



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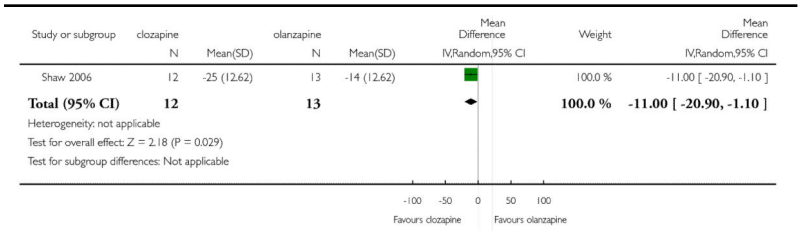
Analysis 2.5

Comparison 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis, Outcome 5 Mental state: 3. SANS, excluding possibly skewed data (high=poor)

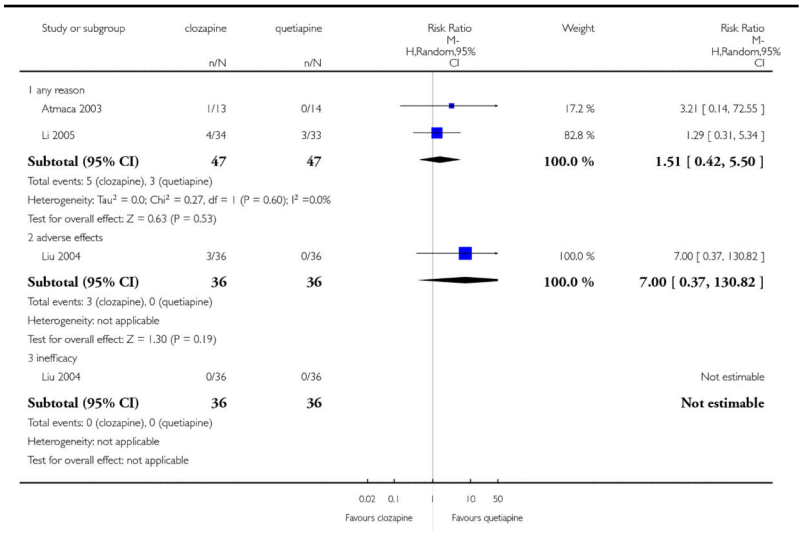
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 CLOZAPINE versus OLANZAPINE - Sensitivity Analysis
Outcome: 5 Mental state: 3. SANS, excluding possibly skewed data (high=poor)



Analysis 3.1

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 1 Leaving the study early - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 1 Leaving the study early - short term



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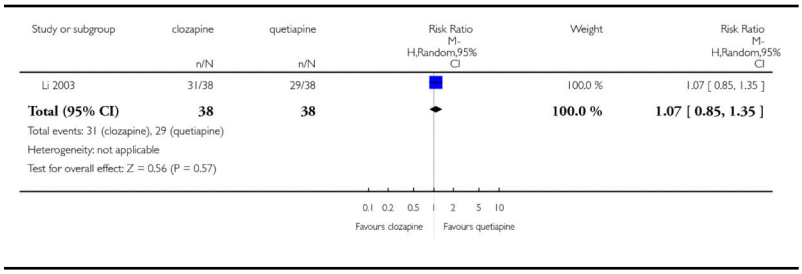
Analysis 3.2

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 2 Global state: No clinically important change - less than “common criteria” - short term

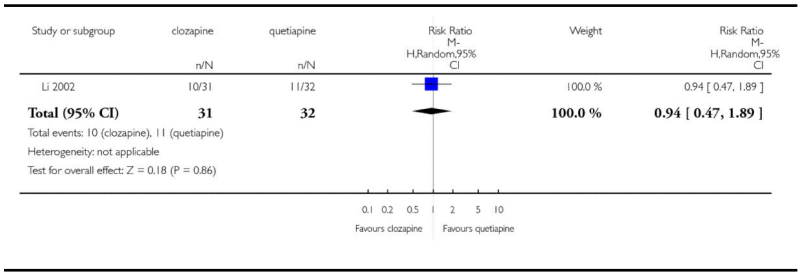
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 2 Global state: No clinically important change - less than “common criteria” - short term



Analysis 3.3

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 3 Mental state: 1. No clinically important change - less than 50% reduction PANSS total - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 3 Mental state: 1. No clinically important change - less than 50% reduction PANSS total - short term



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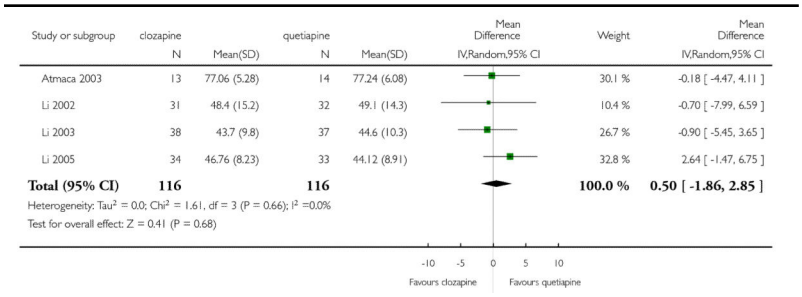
Analysis 3.4

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 4 Mental state: 2a. PANSS total score - short term (high = poor)

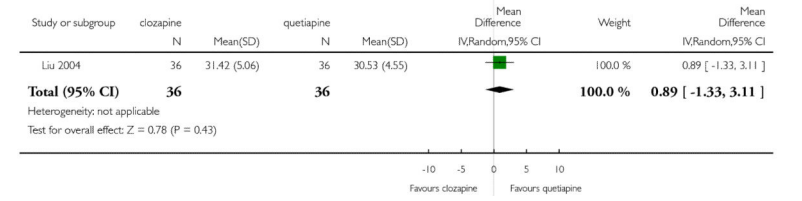
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 4 Mental state: 2a. PANSS total score - short term (high = poor)



Analysis 3.5

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 5 Mental state: 2b. BPRS-18 (1-7) total score - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 5 Mental state: 2b. BPRS-18 (1-7) total score - short term (high = poor)



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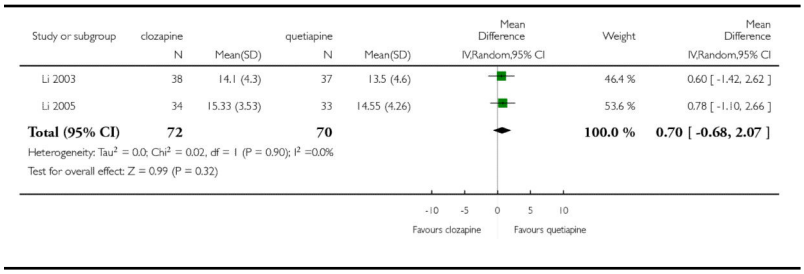
Analysis 3.6

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 6 Mental state: 3. Positive symptoms: PANSS positive subscore - short term (high = poor)

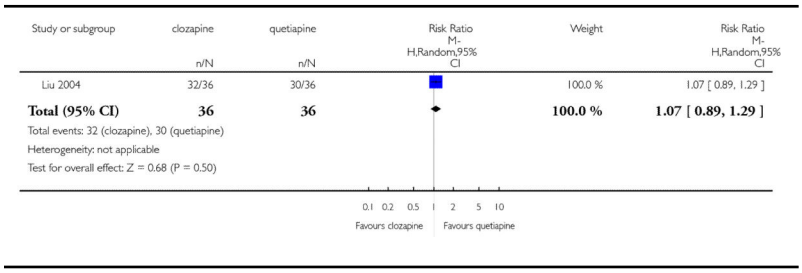
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 6 Mental state: 3. Positive symptoms: PANSS positive subscore - short term (high = poor)



Analysis 3.7

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 7 Mental state: 4 No clinically important change - less than 50% reduction SANS - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 7 Mental state: 4 No clinically important change - less than 50% reduction SANS - short term



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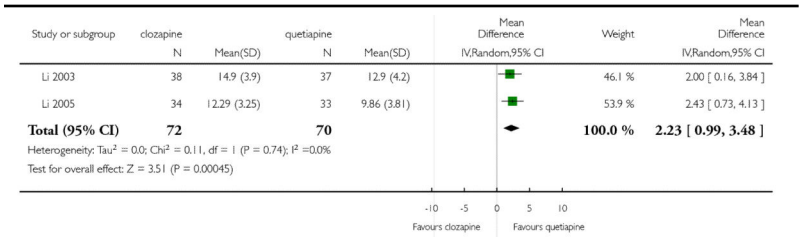
Analysis 3.8

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 8 Mental state: 5a. Negative symptoms: PANSS negative subscore - short term (high = poor)

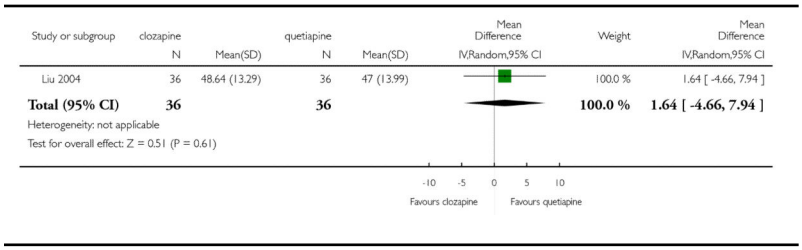
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 8 Mental state: 5a. Negative symptoms: PANSS negative subscore - short term (high = poor)



Analysis 3.9

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 9 Mental state: 5b. Negative symptoms: SANS - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 9 Mental state: 5b. Negative symptoms: SANS - short term (high = poor)



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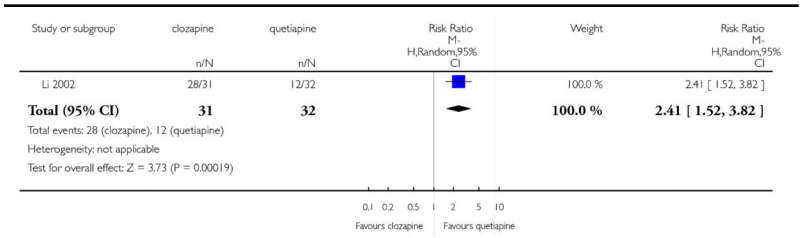
Analysis 3.10

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 10 Adverse effects: 1. At least one adverse effect - short term

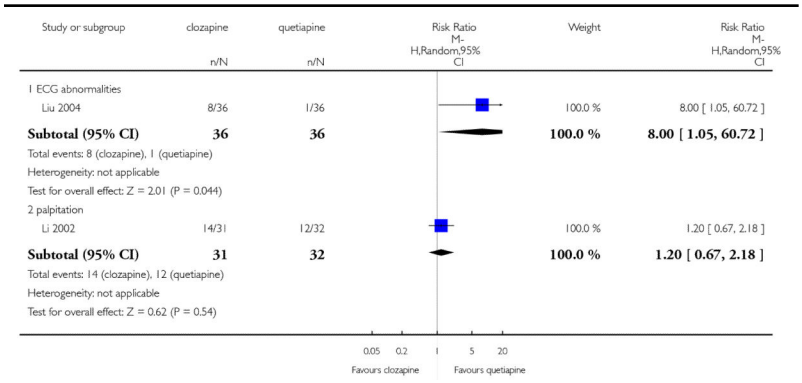
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 10 Adverse effects: 1. At least one adverse effect - short term



Analysis 3.11

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 11 Adverse effects: 2. Cardiac problems - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 11 Adverse effects: 2. Cardiac problems - short term



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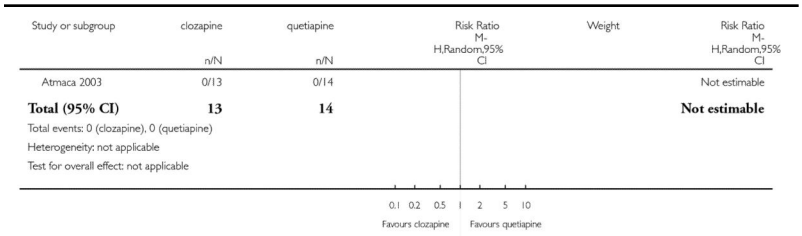
Analysis 3.12

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 12 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use - short term

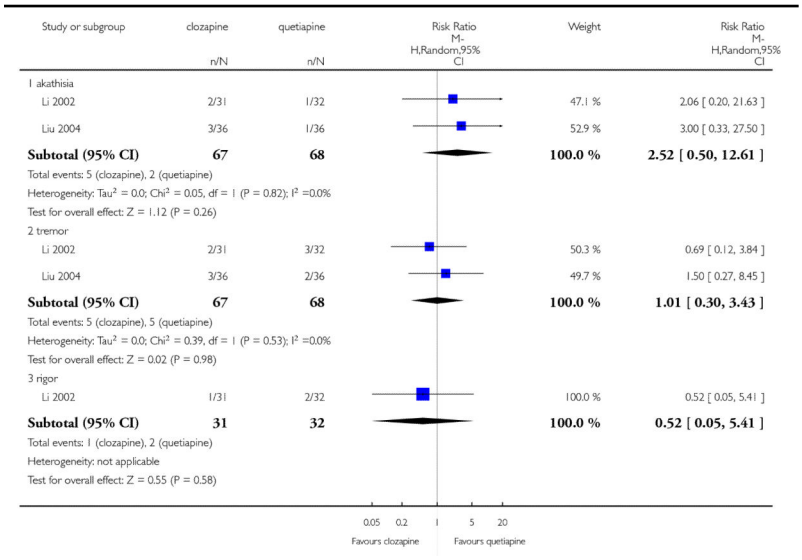
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 12 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use - short term



Analysis 3.13

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 13 Adverse effects: 3b. Extrapyramidal: various symptoms - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 13 Adverse effects: 3b. Extrapyramidal: various symptoms - short term



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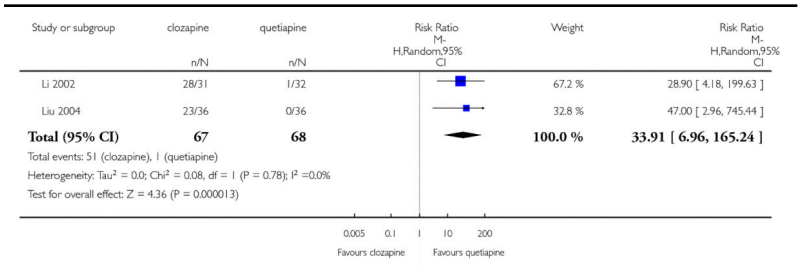
Analysis 3.14

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 14 Adverse effects: 4. Hypersalivation - short term

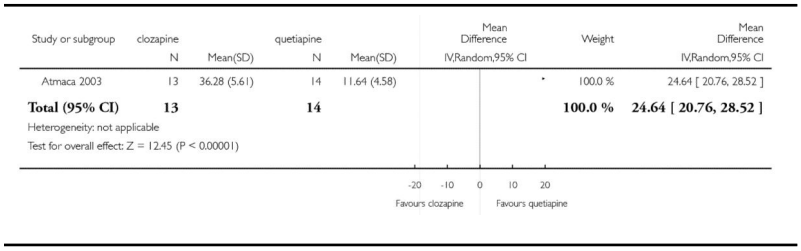
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 14 Adverse effects: 4. Hypersalivation - short term



Analysis 3.15

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 15 Adverse effects: 5. Lipids: average triglyceride change - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 15 Adverse effects: 5. Lipids: average triglyceride change - short term (high = poor)



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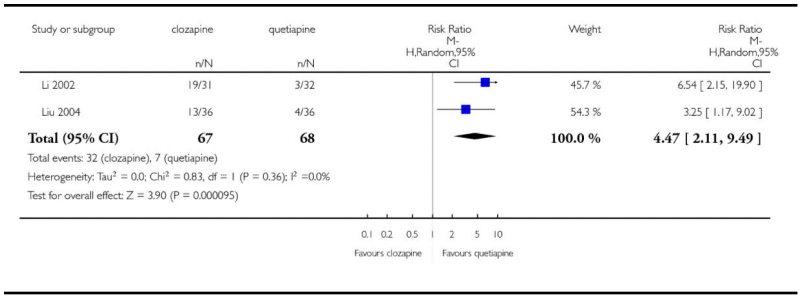
Analysis 3.16

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 16 Adverse effects: 6. Sedation - short term

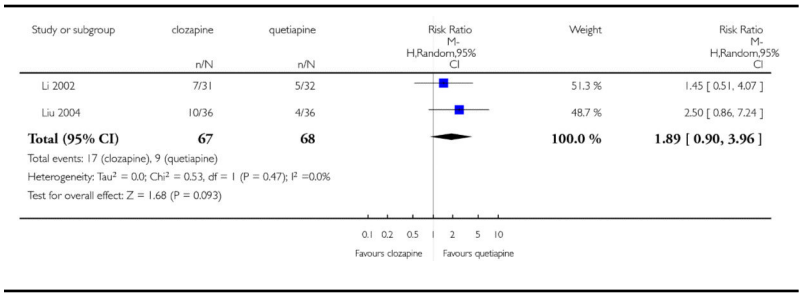
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 16 Adverse effects: 6. Sedation - short term



Analysis 3.17

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 17 Adverse effects: 7a.Weight: number of participant with weight gain - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 17 Adverse effects: 7a. Weight: number of participant with weight gain - short term



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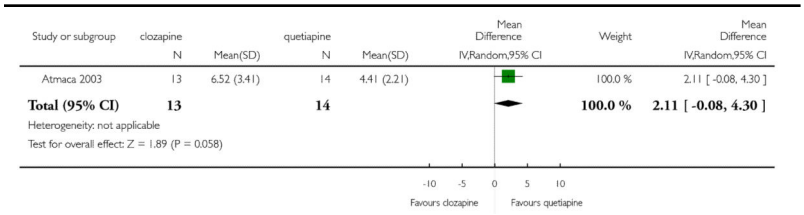
Analysis 3.18

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 18 Adverse effects: 7b.Weight: average weight change - short term (high = poor)

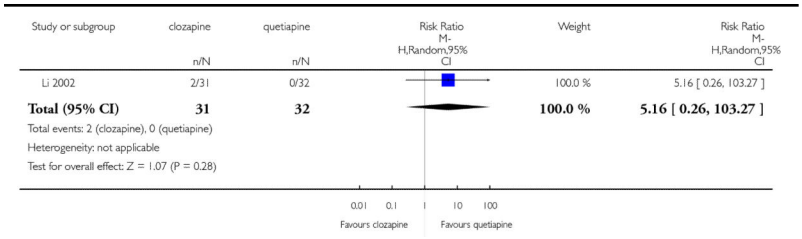
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 18 Adverse effects: 7b. Weight: average weight change - short term (high = poor)



Analysis 3.19

Comparison 3 CLOZAPINE versus QUETIAPINE, Outcome 19 Adverse effects: 8.White blood cell count: number of participant with a decrease - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 CLOZAPINE versus QUETIAPINE
Outcome: 19 Adverse effects: 8. White blood cell count: number of participant with a decrease - short term



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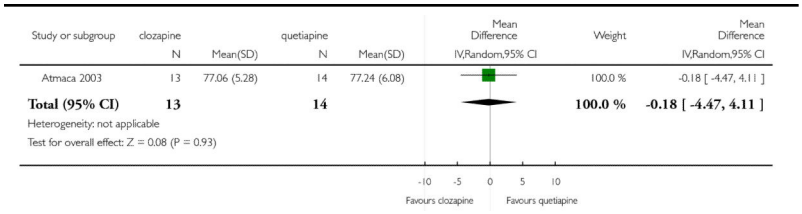
Analysis 4.1

Comparison 4 CLOZAPINE versus QUETIAPINE - Sensitivity Analysis, Outcome 1 Mental state: 1. PANSS total score - excluding possibly skewed data - short term (high = poor)

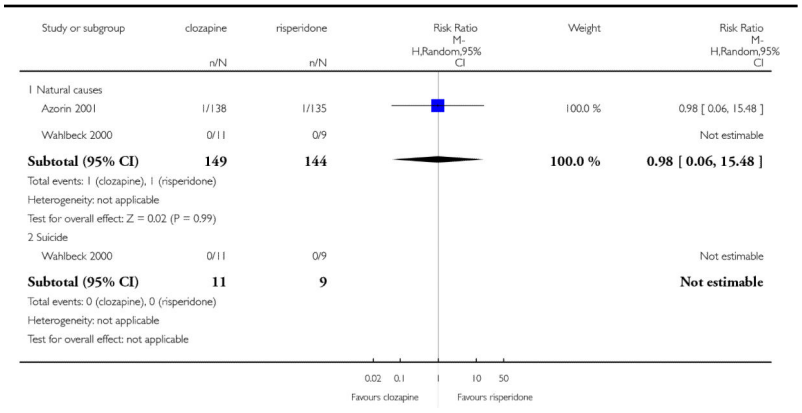
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 CLOZAPINE versus QUETIAPINE - Sensitivity Analysis
Outcome: 1 Mental state: 1. PANSS total score - excluding possibly skewed data - short term (high = poor)



Analysis 5.1

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 1 Death - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 1 Death - short term



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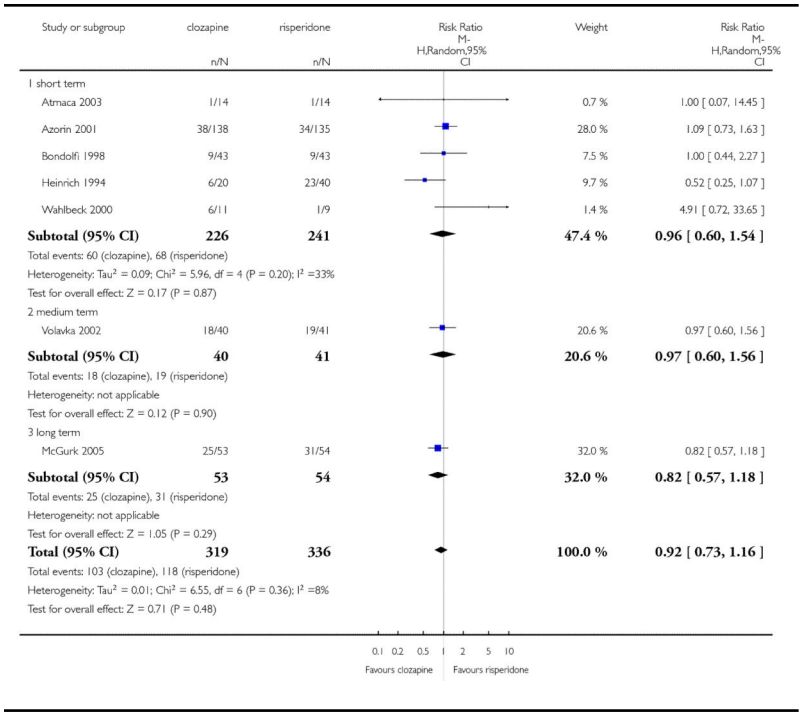
Analysis 5.2
Comparison 5 CLOZAPINE versus RISPERIDONE,
Outcome 2 Leaving the study early: 1. Any reason

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 2 Leaving the study early: 1. Any reason



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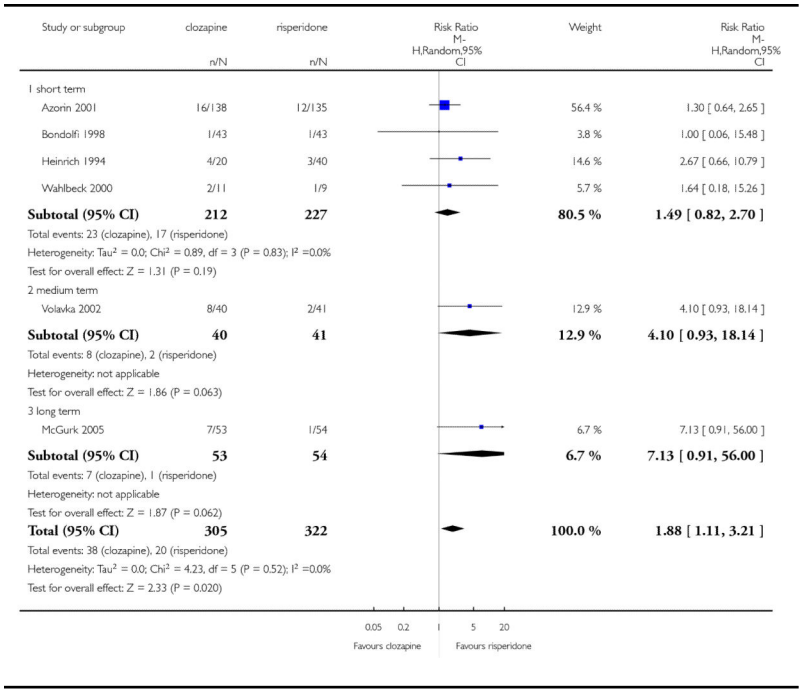
Analysis 5.3
Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 3 Leaving the study early: 2. Adverse effects

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 3 Leaving the study early: 2. Adverse effects



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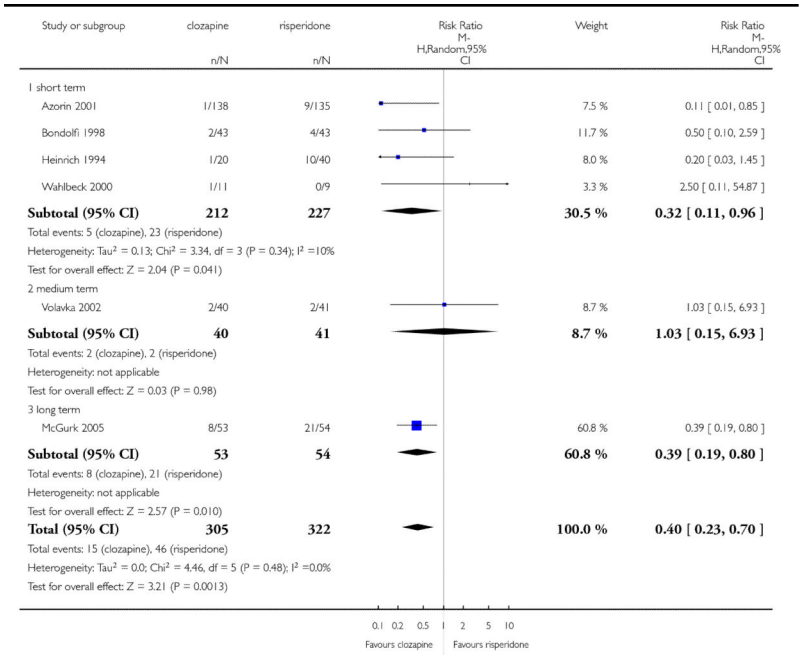
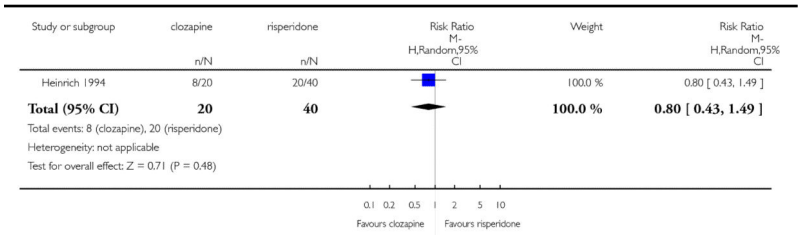
Analysis 5.4
Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 4 Leaving the study early: 3. Inefficacy

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 4 Leaving the study early: 3. Inefficacy



Analysis 5.5
Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 5 Global state: No clinically important change - less than much improved on CGI - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 5 Global state: No clinically important change - less than much improved on CGI - short term



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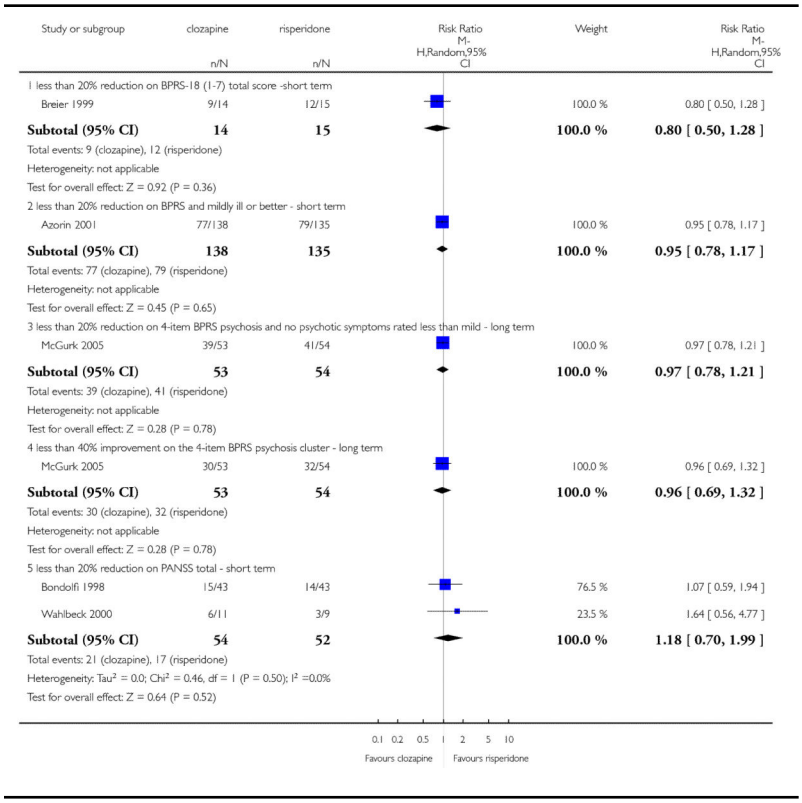
Analysis 5.6

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 6 Mental state: 1. No clinically important change - various criteria

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 6 Mental state: 1. No clinically important change - various criteria



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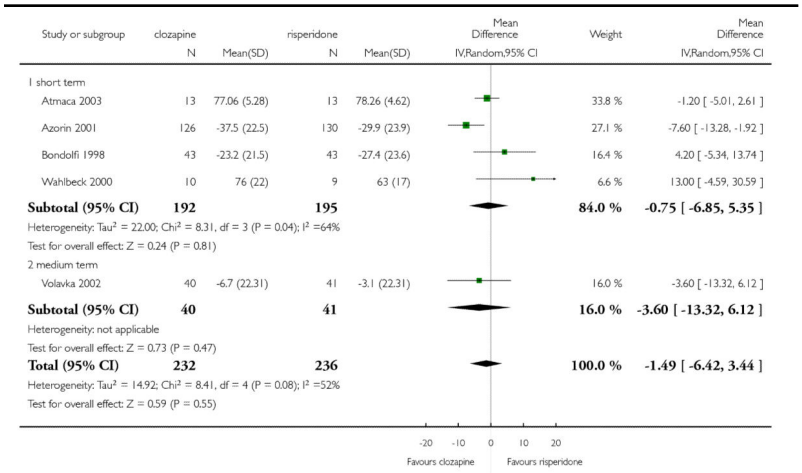
Analysis 5.7

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 7 Mental state: 2a. PANSS total score (high = poor)

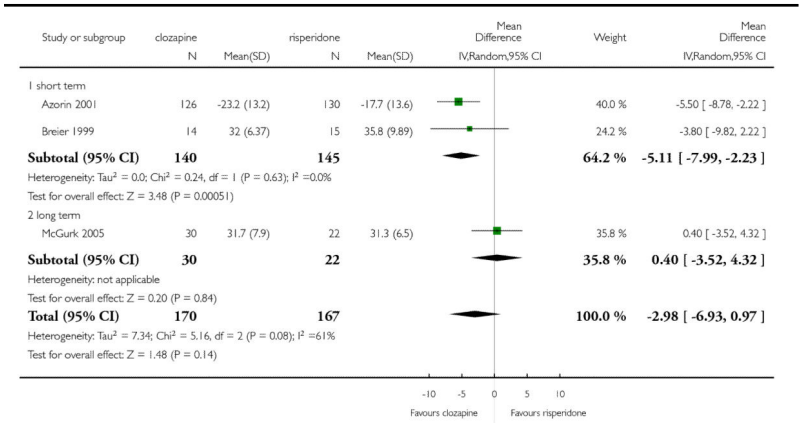
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 7 Mental state: 2a. PANSS total score (high = poor)



Analysis 5.8

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 8 Mental state: 2b. BPRS-18 (1- 7) total score - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 8 Mental state: 2b. BPRS-18 (1-7) total score - short term (high = poor)



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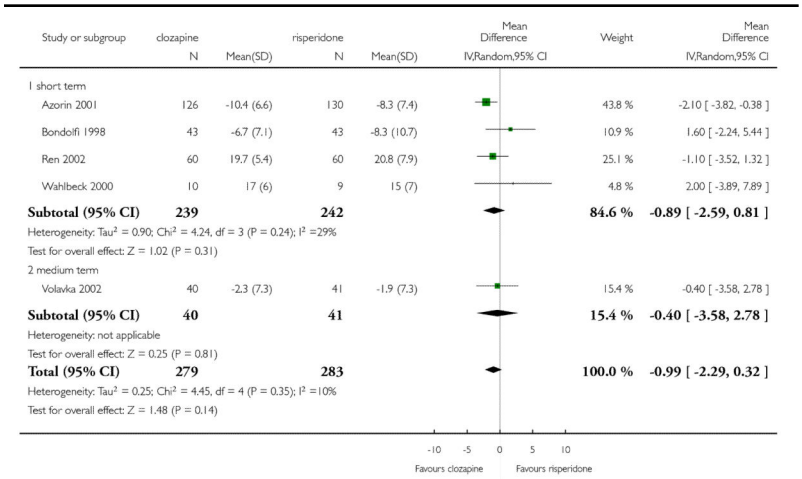
Analysis 5.9

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 9 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)

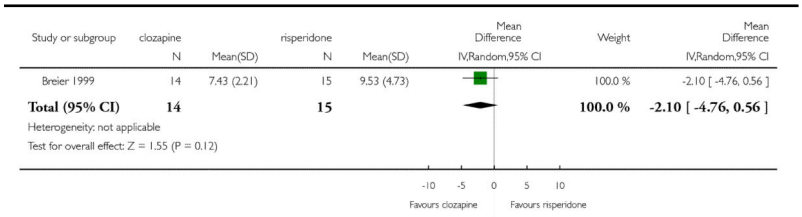
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 9 Mental state: 3a. Positive symptoms: PANSS positive subscore (high = poor)



Analysis 5.10

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 10 Mental state: 3b. Positive symptoms: BPRS-18 (1-7) positive subscore - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 10 Mental state: 3b. Positive symptoms: BPRS-18 (1-7) positive subscore - short term (high = poor)



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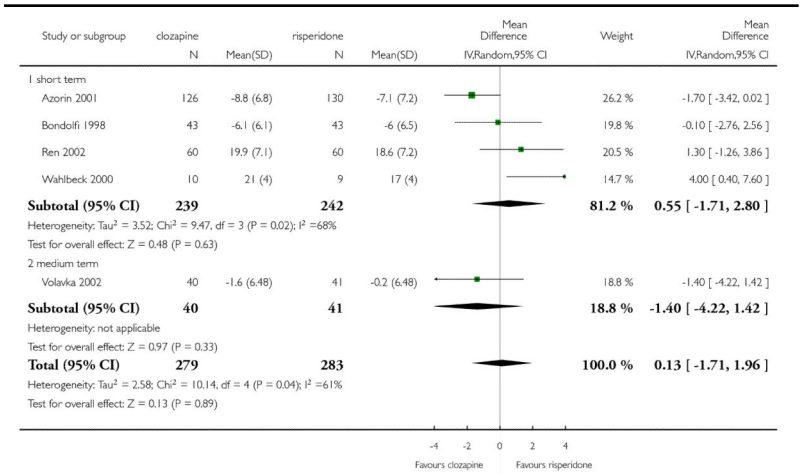
Analysis 5.11

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 11 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)

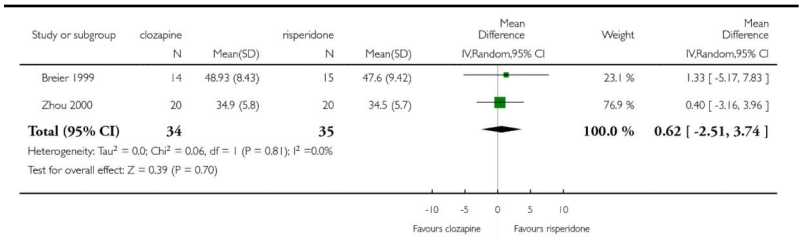
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 11 Mental state: 4a. Negative symptoms: PANSS negative subscore (high = poor)



Analysis 5.12

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 12 Mental state: 4b. Negative symptoms: SANS - short term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 12 Mental state: 4b. Negative symptoms: SANS - short term (high = poor)



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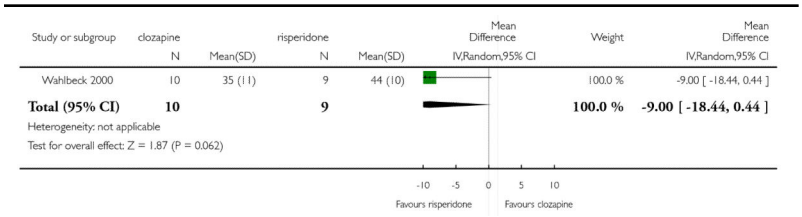
Analysis 5.13

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 13 General functioning: GAF score - short term (high = good)

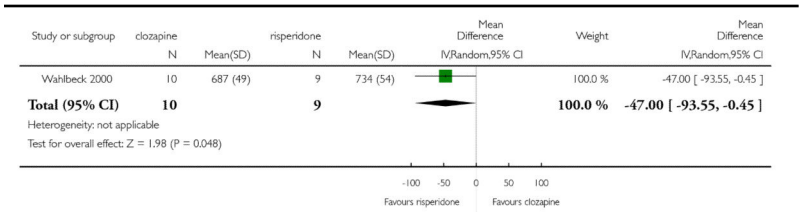
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 13 General functioning: GAF score - short term (high = good)



Analysis 5.14

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 14 Social functioning: SFS score - short term (high = good)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 14 Social functioning: SFS score - short term (high = good)



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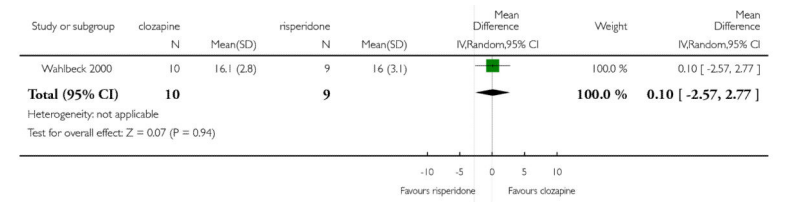
Analysis 5.15

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 15 Treatment satisfaction: DAI score - short term (high = good)

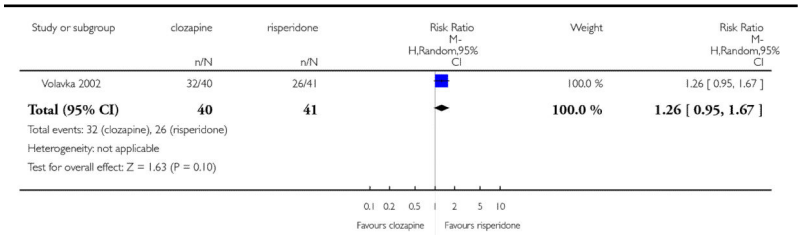
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 15 Treatment satisfaction: DAI score - short term (high = good)



Analysis 5.16

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 16 Cognitive functioning: No clinically important change - less than 0.5 SD improved - medium term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 16 Cognitive functioning: No clinically important change - less than 0.5 SD improved - medium term



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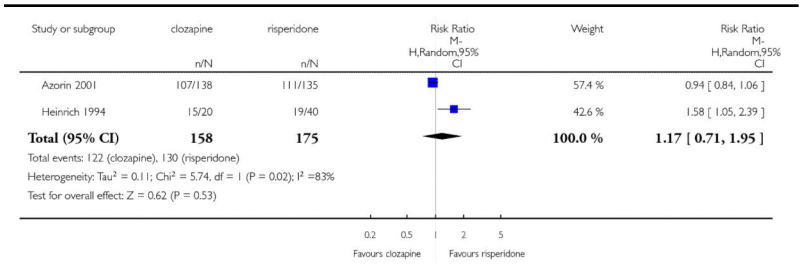
Analysis 5.17

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 17 Adverse effects: 1. At least one adverse effect - short term

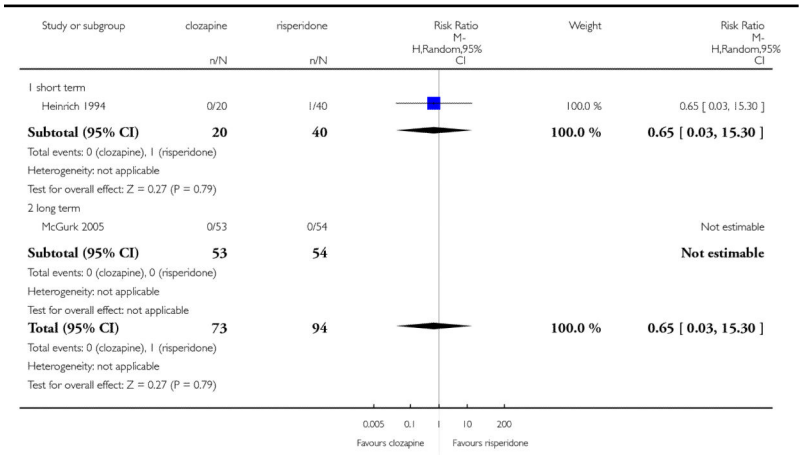
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 17 Adverse effects: 1. At least one adverse effect - short term



Analysis 5.18

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 18 Adverse effects: 2. Cardiac problems

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 18 Adverse effects: 2. Cardiac problems



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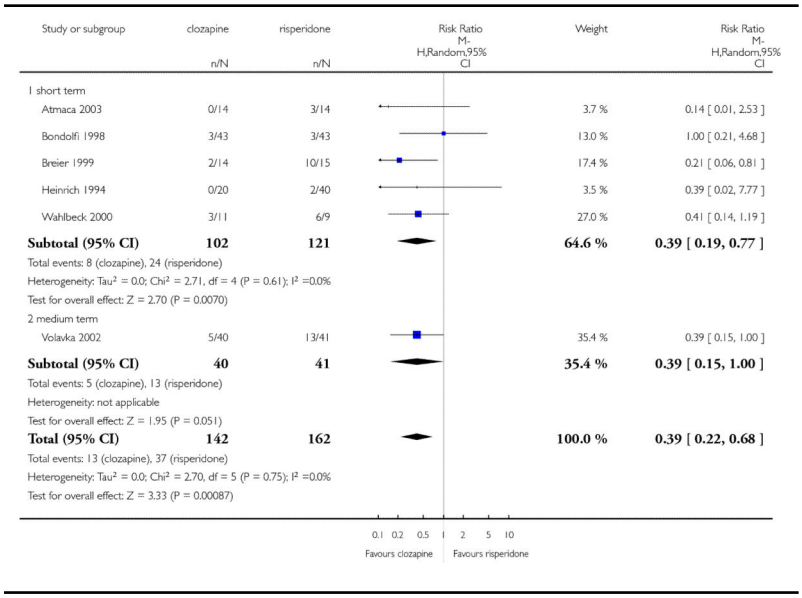
Analysis 5.19

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 19 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 19 Adverse effects: 3a. Extrapyramidal: antiparkinson medication use



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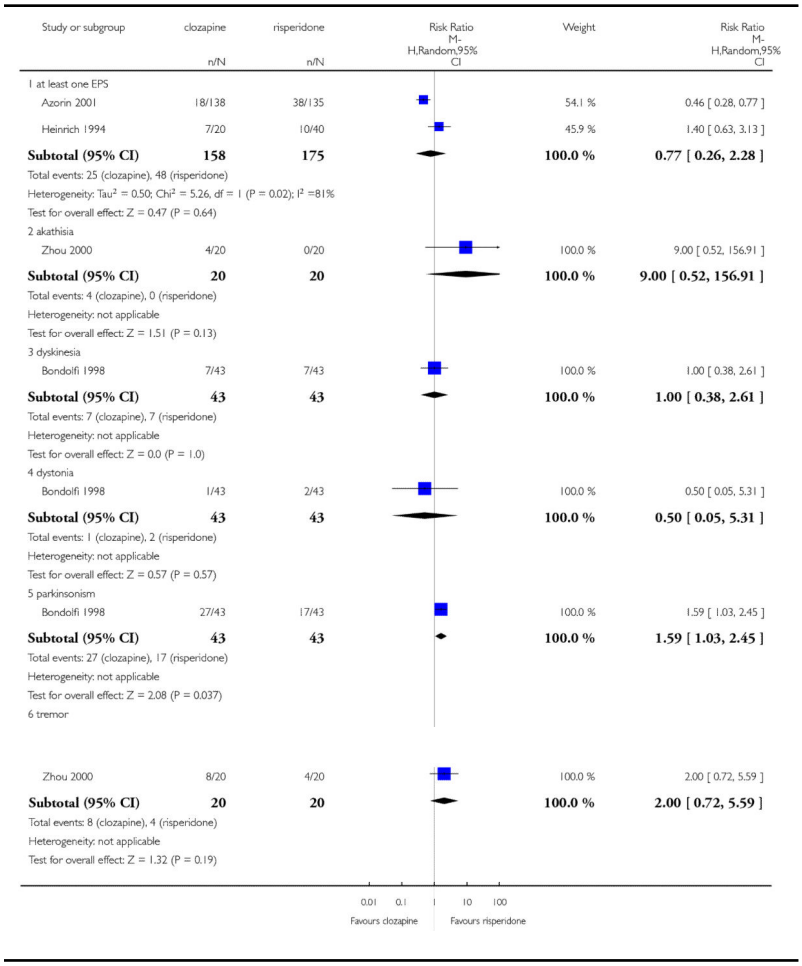
Analysis 5.20

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 20 Adverse effects: 3b. Extrapyramidal: various symptoms - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 20 Adverse effects: 3b. Extrapyramidal: various symptoms - short term



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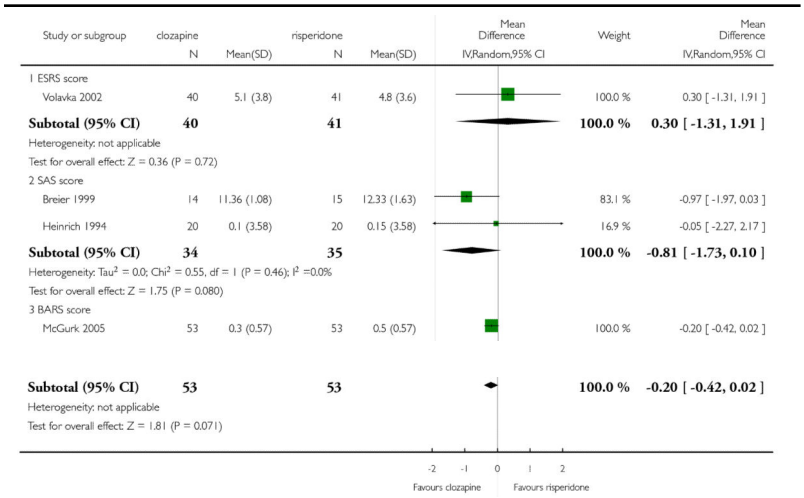
Analysis 5.21

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 21 Adverse effects: 3c. Extrapyramidal: symptom scales (high = poor)

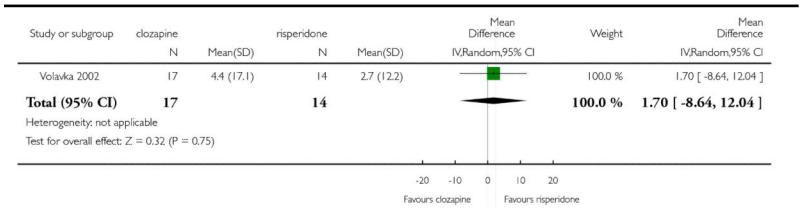
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 21 Adverse effects: 3c. Extrapyramidal: symptom scales (high = poor)



Analysis 5.22

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 22 Adverse effects: 4. Glucose: average change - medium term (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 22 Adverse effects: 4. Glucose: average change - medium term (high = poor)



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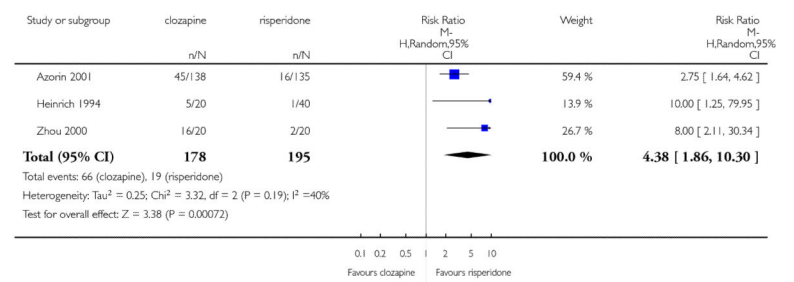
Analysis 5.23

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 23 Adverse effects: 5. Hypersalivation -short term

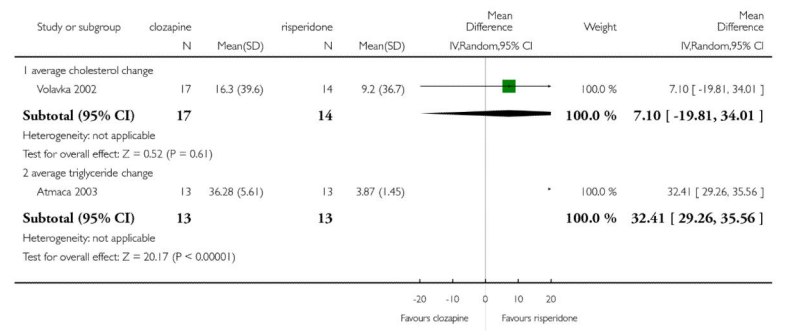
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 23 Adverse effects: 5. Hypersalivation -short term



Analysis 5.24

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 24 Adverse effects: 6. Lipids: average change (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 24 Adverse effects: 6. Lipids: average change (high = poor)



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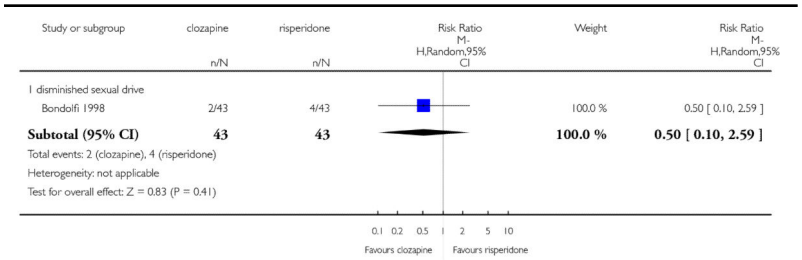
Analysis 5.25

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 25 Adverse effects: 7a. Prolactin: associated side effects - short term

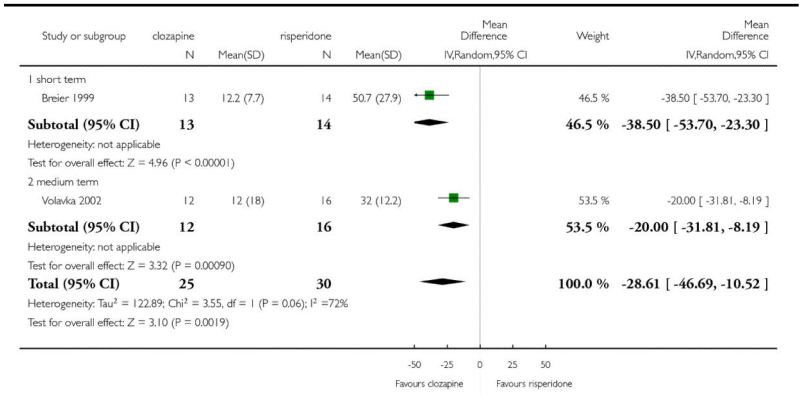
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 25 Adverse effects: 7a. Prolactin: associated side effects - short term



Analysis 5.26

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 26 Adverse effects: 7b. Prolactin: average at endpoint (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 26 Adverse effects: 7b. Prolactin: average at endpoint (high = poor)



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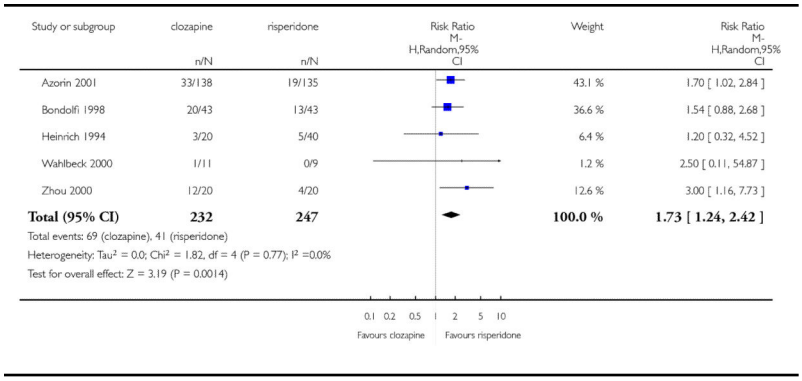
Analysis 5.27

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 27 Adverse effects: 8. Sedation - short term

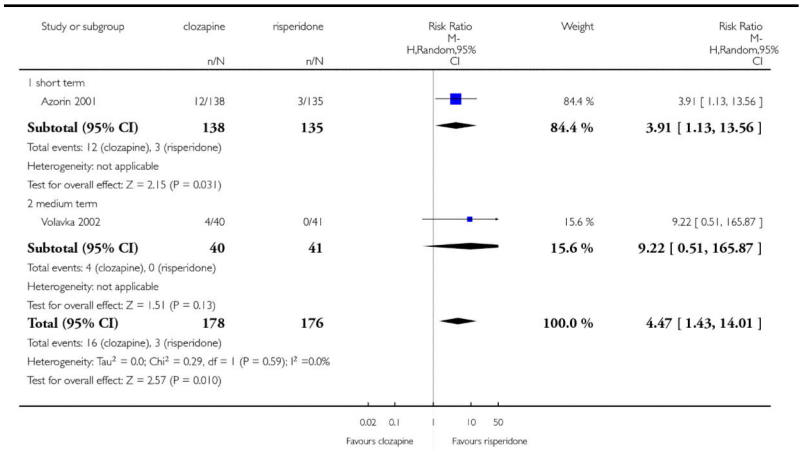
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 27 Adverse effects: 8. Sedation - short term



Analysis 5.28

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 28 Adverse effects: 9. Seizures. Review: Clozapine versus other atypical antipsychotics for schizophreni

Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 28 Adverse effects: 9. Seizures



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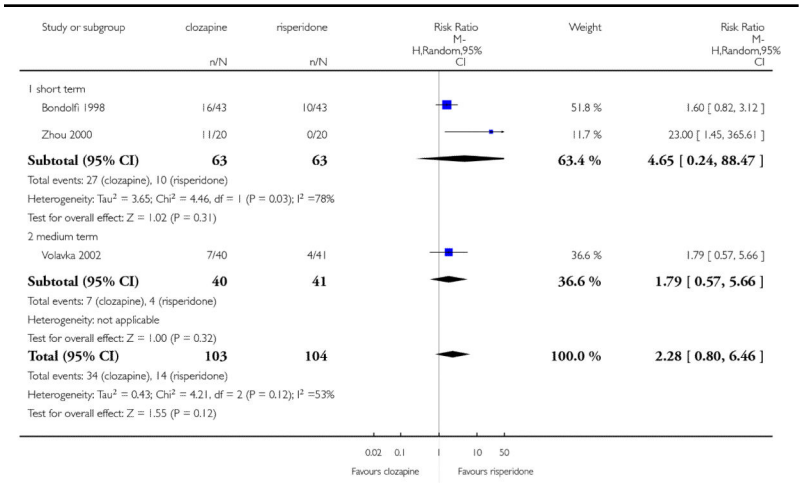
Analysis 5.29

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 29 Adverse effects: 10a. Weight: number of participants with weight gain

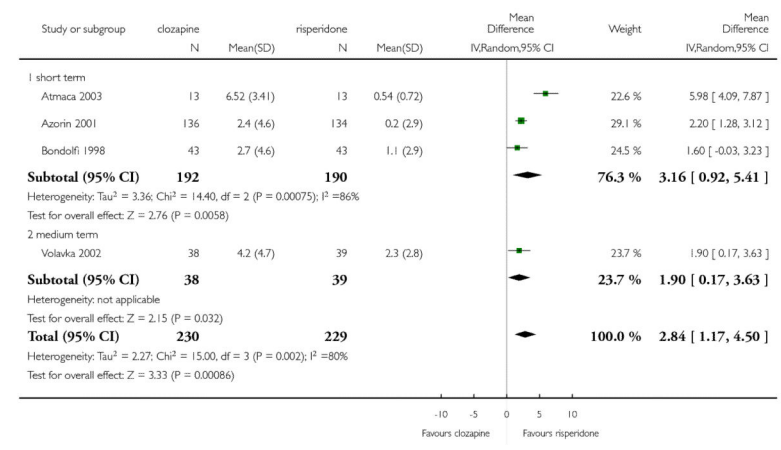
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 29 Adverse effects: 10a. Weight: number of participants with weight gain



Analysis 5.30

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 30 Adverse effects: 10b. Weight: average weight change (high=poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 30 Adverse effects: 10b. Weight: average weight change (high=poor)



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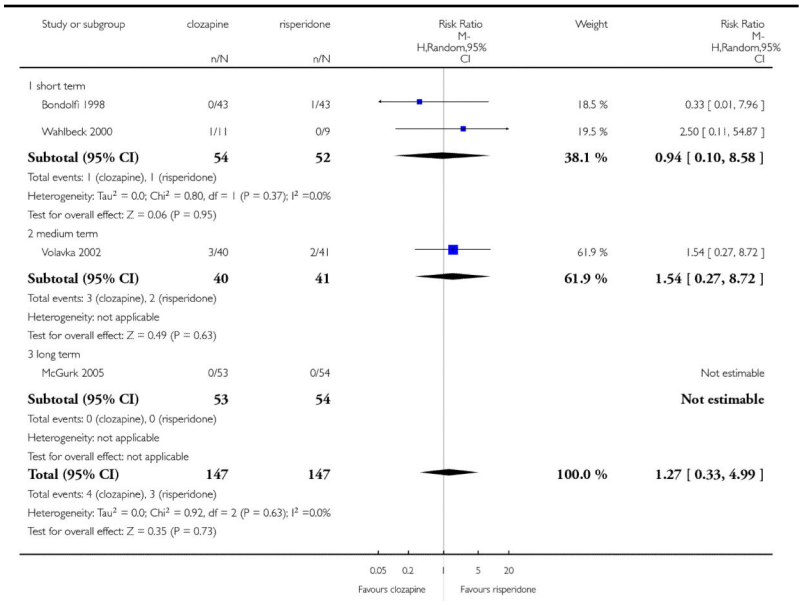
Analysis 5.31

Comparison 5 CLOZAPINE versus RISPERIDONE, Outcome 31 Adverse effects: 11.White blood cell count: number of participants with a decrease

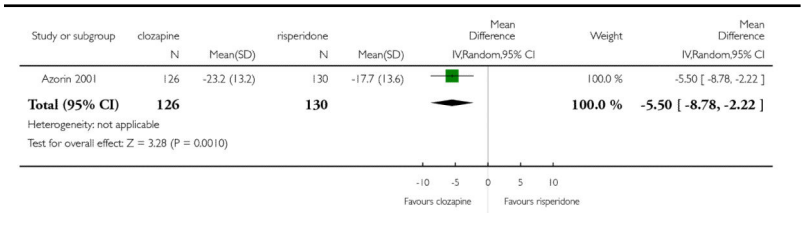
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 CLOZAPINE versus RISPERIDONE
Outcome: 31 Adverse effects: 11. White blood cell count: number of participants with a decrease



Analysis 6.1

Comparison 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis, Outcome 1 Mental state: 1. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis
Outcome: 1 Mental state: 1. BPRS-18 (1-7) total score, excluding possibly skewed data (high = poor)



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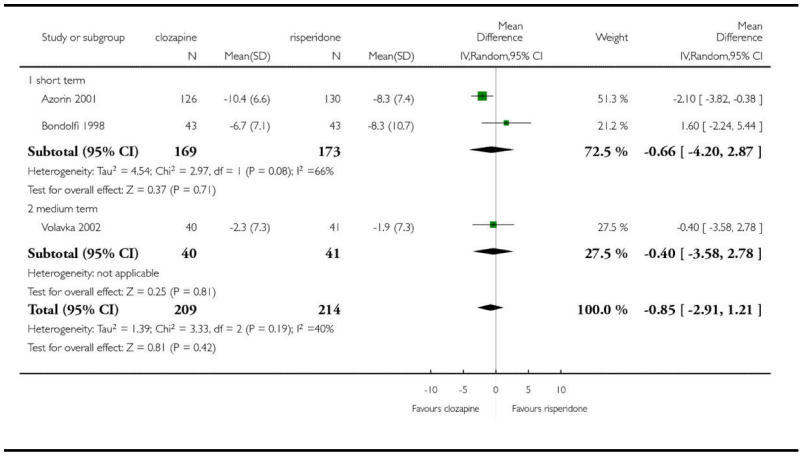
Analysis 6.2

Comparison 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis, Outcome 2 Mental state: 2. PANSS positive subscore, excluding possibly skewed data (high = poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis
Outcome: 2 Mental state: 2. PANSS positive subscore, excluding possibly skewed data (high = poor)



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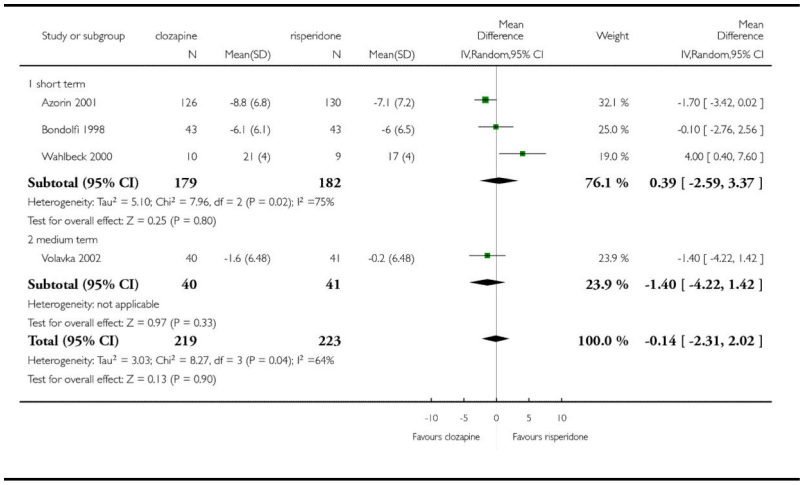
Analysis 6.3

Comparison 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis, Outcome 3 Mental state: 3. PANSS negative subscore, excluding possibly skewed data (high = poor)

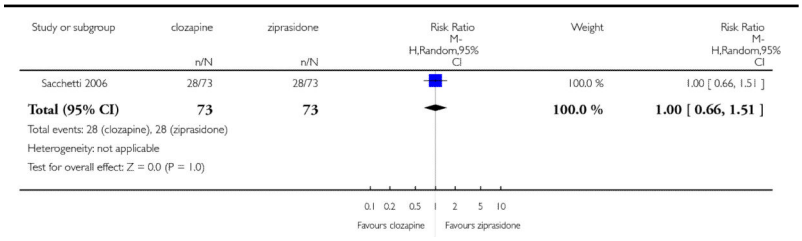
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 CLOZAPINE vs. RISPERIDONE - Sensitivity Analysis
Outcome: 3 Mental state: 3. PANSS negative subscore, excluding possibly skewed data (high = poor)



Analysis 7.1

Comparison 7 CLOZAPINE versus ZIPRASIDONE, Outcome 1 Leaving the study early: any reason - medium term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 CLOZAPINE versus ZIPRASIDONE
Outcome: 1 Leaving the study early: any reason - medium term



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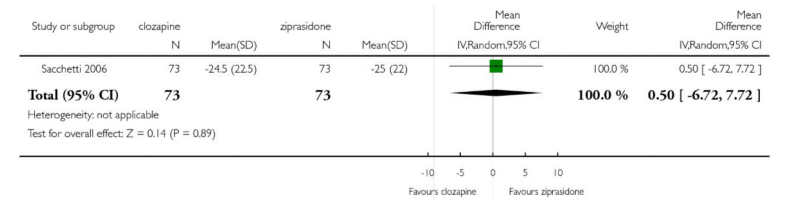
Analysis 7.2

Comparison 7 CLOZAPINE versus ZIPRASIDONE, Outcome 2 Mental state: PANSS total score - medium term (high = poor)

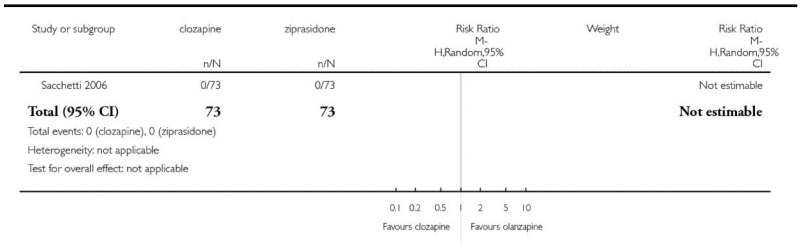
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 CLOZAPINE versus ZIPRASIDONE
Outcome: 2 Mental state: PANSS total score - medium term (high = poor)



Analysis 7.3

Comparison 7 CLOZAPINE versus ZIPRASIDONE, Outcome 3 Adverse effects: 1. Cardiac problems

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 CLOZAPINE versus ZIPRASIDONE
Outcome: 3 Adverse effects: 1. Cardiac problems



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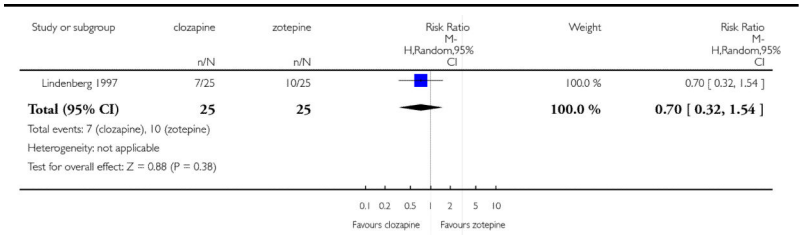
Analysis 8.1

Comparison 8 CLOZAPINE versus ZOTEPINE, Outcome 1 Leaving the study early: any reason

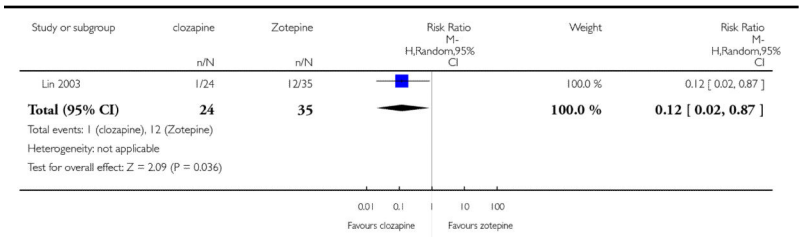
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 8 CLOZAPINE versus ZOTEPINE
Outcome: 1 Leaving the study early: any reason



Analysis 8.2

Comparison 8 CLOZAPINE versus ZOTEPINE, Outcome 2 Global state: no clinically important change - less than successfully and no increase on CGI-S - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 8 CLOZAPINE versus ZOTEPINE
Outcome: 2 Global state: no clinically important change - less than successfully and no increase on CGI-S - short term



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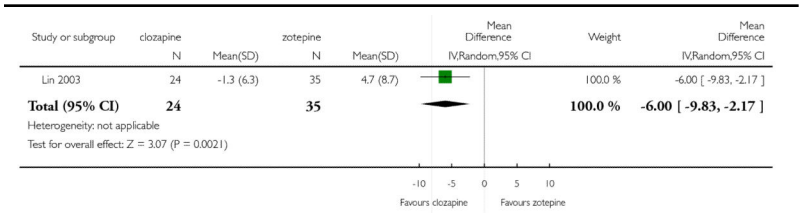
Analysis 8.3

Comparison 8 CLOZAPINE versus ZOTEPINE, Outcome 3 Mental state: BPRS-18 total score - short term (high=poor)

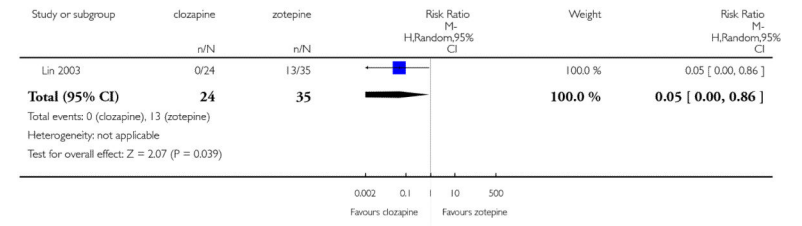
Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 8 CLOZAPINE versus ZOTEPINE
Outcome: 3 Mental state: BPRS-18 total score - short term (high=poor)



Analysis 8.4

Comparison 8 CLOZAPINE versus ZOTEPINE, Outcome 4 Adverse effects: 1. Extrapyramidal: antiparkinson medication use - short term

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 8 CLOZAPINE versus ZOTEPINE
Outcome: 4 Adverse effects: 1. Extrapyramidal: antiparkinson medication use - short term



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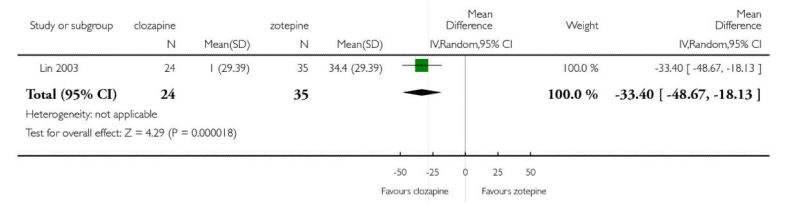
Analysis 8.5

Comparison 8 CLOZAPINE versus ZOTEPINE, Outcome 5 Adverse effects: 2. Prolactin: average change - short term (high=poor)

Review: Clozapine versus other atypical antipsychotics for schizophrenia
Comparison: 8 CLOZAPINE versus ZOTEPINE
Outcome: 5 Adverse effects: 2. Prolactin: average change - short term (high=poor)



ADDITIONAL TABLES

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	**1**	Clozapine: dose ~ 300-800 mg/day. N=300.
	2	Amisulpride: dose ~ 400-800 mg/day. N=300.
	3	Aripiprazole: dose ~ 10-30 mg/day. N=300.
	4	Olanzapine: dose ~ 10-20 mg/day. N=300.
	5	Quetiapine: dose ~300-800 mg/day. N=300.
	6	Risperidone: dose ~ 4-8 mg/day. N=300.
	7	Sertindole: dose ~ 12-24 mg/day. N=300.
	8	Ziprasidone: dose ~ 120-160 mg/day. N=300.
	9	Zotepine: dose ~ 100-300 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: PANSS. 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.

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WHAT'S NEW

Last assessed as up-to-date: 14 October 2008.

Date	Event	Description
10 November 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 11, 2010

Date	Event	Description
6 October 2010	New citation required and conclusions have changed	This review is an update of the review "Newer atypical antipsychotic medication vs. clozapine" which compared clozapine with all other atypical antipsychotics pooled into one group. Since the atypical antipsychotics are a heterogenous group with quite different pharmacological profile and the amount of data published on this topic has grown enormously during the last few years, it is now possible to explore atypical comparisons with clozapine separately. For this reason, the title and the review protocol have been modified
15 October 2008	Amended	Converted to new format

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was adapted to new functions and formatting available in Review Manager 5, notably the risk of bias tables.

References to studies included in this review

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Clozapine versus other atypical antipsychotics for schizophrenia

This review compared the clinical effects of clozapine with the other atypical antipsychotics. Twenty-seven studies fulfilled the review's criteria and provided data to compare clozapine with antipsychotics such as olanzapine, quetiapine, risperidone, ziprasidone and zotepine. Clozapine was somewhat more efficacious than zotepine. Also, inefficacy of treatment led more frequently to leaving the studies early in the risperidone group suggesting a certain higher efficacy of clozapine. The principal drawback of clozapine were its adverse effects which lead to significantly higher numbers of participants leaving the studies early compared to olanzapine and risperidone. Clozapine was associated with more sedation and hypersalivation than olanzapine, quetiapine and risperidone and with more seizures than olanzapine and risperidone. There was a higher incidence of white blood cell decrease in clozapine groups than olanzapine and more weight gain than in risperidone groups. On the other hand clozapine produced fewer movement disorder than risperidone and less prolactin increase than olanzapine, quetiapine and zotepine.

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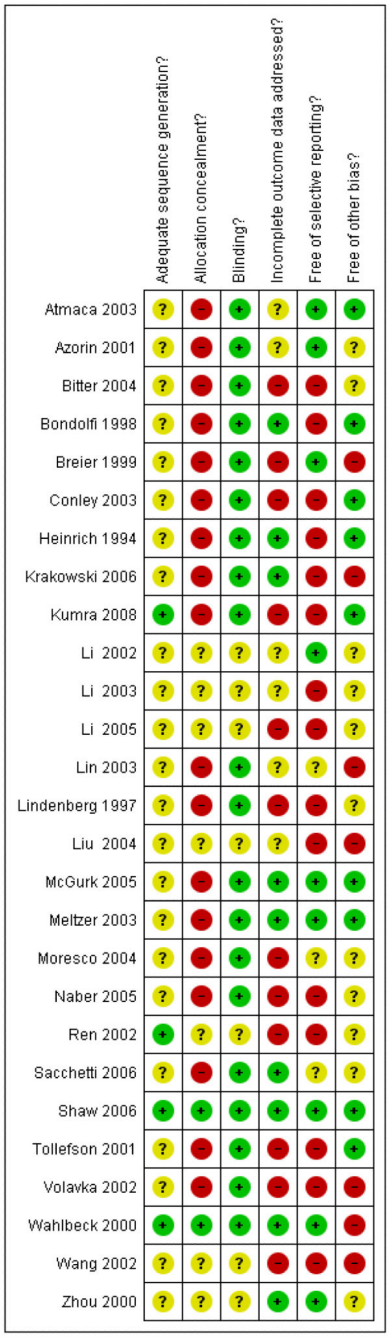

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study