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Olanzapine versus other atypical antipsychotics for schizophrenia

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Abstract

Background—In many countries of the industrialised world second generation ("atypical") antipsychotics have become the first line drug treatment for people with schizophrenia. The question as to whether, and if so how much, the effects of the various second generation antipsychotics differ is a matter of debate. In this review we examined how the efficacy and tolerability of olanzapine differs from that of other second generation antipsychotics.

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DECLARATIONS OF INTEREST

Katja Komossa: none.
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Objectives—To evaluate the effects of olanzapine compared to other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychosis.

1. Electronic searching: We searched the Cochrane Schizophrenia Group Trials Register (April 2007) which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO.

2. Reference searching: We inspected the reference of all identified studies for more trials.

3. Personal contact: We contacted the first author of each included study for missing information.

4. Drug companies: We contacted the manufacturers of all atypical antipsychotics included for additional data.

Selection criteria—We included all randomised trials that used at least single-blind (rater-blind) design, comparing oral olanzapine with oral forms of amisulpride, aripiprazole, clozapine, quetiapine, risperidone, sertindole, ziprasidone or zotepine in people with schizophrenia or schizophrenia-like psychosis.

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

Main results—The review currently includes 50 studies and 9476 participants which provided data for six comparisons (olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone). The overall attrition from the included studies was considerable (49.2%) leaving the interpretation of results problematic.

Olanzapine improved the general mental state (PANSS total score) more than aripiprazole (2 RCTs, n=794, WMD −4.96 CI −8.06 to −1.85), quetiapine (10 RCTs, n=1449, WMD −3.66 CI −5.39 to −1.93), risperidone (15 RCTs, n=2390, WMD −1.94 CI −3.31 to −0.58) and ziprasidone (4 RCTs, n=1291, WMD −8.32 CI −10.99 to −5.64), but not more than amisulpride or clozapine. This somewhat better efficacy was confirmed by fewer participants in the olanzapine groups leaving the studies early due to inefficacy of treatment compared to quetiapine (8 RCTs, n=1563, RR 0.56 CI 0.44 to 0.70, NNT 11 CI 6 to 50), risperidone (14 RCTs, n=2744, RR 0.78 CI 0.62 to 0.98, NNT 50 CI 17 to 100) and ziprasidone (5 RCTs, n=1937, RR 0.64 CI 0.51 to 0.79, NNT 17, CI 11 to 33).

Fewer participants in the olanzapine group than in the quetiapine (2 RCTs, n=876, RR 0.56 CI 0.41 to 0.77, NNT 11 CI 7 to 25) and ziprasidone (2 RCTs, n=766, RR 0.65 CI 0.45 to 0.93, NNT 17 CI 9 to 100) treatment groups, but not in the clozapine group (1 RCT, n=980, RR 1.28 CI 1.02 to 1.61, NNH not estimable), had to be re-hospitalised in the trials.

Except for clozapine, all comparators induced less weight gain than olanzapine (olanzapine compared to amisulpride: 3 RCTs, n=671, WMD 2.11kg CI 1.29kg to 2.94kg; aripiprazole: 1 RCT, n=90, WMD 5.60kg CI 2.15kg to 9.05kg; quetiapine: 7 RCTs, n=1173, WMD 2.68kg CI 1.10kg to 4.26kg; risperidone: 13 RCTs, n=2116, WMD 2.61kg CI 1.48kg to 3.74kg; ziprasidone: 5 RCTs, n=1659, WMD 3.82kg CI 2.96kg to 4.69kg). Associated problems such as glucose and cholesterol increase were usually also more frequent in the olanzapine group.

Other differences in adverse effects were less well documented. Nevertheless, olanzapine may be associated with slightly more extrapyramidal side effects than quetiapine (use of antiparkinson medication (6 RCTs, n=1090, RR 2.05 CI 1.26 to 3.32, NNH 25 CI 14 to 100), but less than risperidone (use of antiparkinson medication 13 RCTs, n=2599, RR 0.78 CI 0.65 to 0.95, NNH 17 CI 9 to 100) and ziprasidone (use of antiparkinson medication 4 RCTs, n=1732, RR 0.70 CI 0.50 to 0.97, NNH not estimable). It may also increase prolactin somewhat more than aripiprazole, clozapine and quetiapine, but clearly less so than risperidone (6 RCTs, n=1291, WMD −22.84 CI −27.98 to −17.69).

Authors' conclusions—Olanzapine may be a somewhat more efficacious drug than some other second generation antipsychotic drugs. This small superiority in efficacy needs to be weighed against a larger weight gain and associated metabolic problems than most other second generation antipsychotic drugs, except clozapine. These conclusions are tentative due to the large number of people leaving the studies early which possibly limits the validity of the findings. Further large, well-designed trials are necessary to establish the relative effects of different second generation antipsychotic drugs.

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Benzodiazepines [*therapeutic use]; Clozapine [therapeutic use]; Dibenzothiazepines [therapeutic use]; Piperazines [therapeutic use]; Quinolones [therapeutic use]; Risperidone [therapeutic use]; Schizophrenia [*drug therapy]; Sulpiride [analogs & derivatives; therapeutic use]; Thiazoles [therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Schizophrenia is usually a chronic and disabling psychiatric disorder which afflicts approximately one per cent of the population world-wide with little gender differences. The annual incidence of schizophrenia averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7%. (Tandon 2008). Its typical manifestations are positive symptoms such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations) plus negative symptoms such as apathy and lack of drive, disorganisation of behaviour and thought, and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994). The degree of suffering and disability is considerable with 80% - 90% not working (Marvaha 2004) and up to 10% dying (Tsuang 1978). In the age group of 15-44 years, schizophrenia is among the top ten leading causes of disease-related disability in the world (WHO 2001).

Description of the intervention

Conventional antipsychotic drugs such as chlorpromazine and haloperidol have traditionally been used as first line antipsychotics for people with schizophrenia (Kane 1993). The

introduction of clozapine in the United States of America in 1990 and a finding that clozapine was more efficacious and associated with fewer movement disorders than chlorpromazine (Kane 1988) has boosted the development of so-called “atypical ” or second generation antipsychotics (SGA). There is no good definition of what an “atypical” or second generation antipsychotic is, but they were initially said to differ from typical antipsychotics in that they do not cause movement disorders (catalepsy) in rats at clinically effective doses (Arnt 1998). The terms “new” or “second generation” antipsychotics are not much better, because clozapine is a very old drug. According to treatment guidelines (APA 2004, Gaebel 2006) second generation antipsychotics include drugs such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine, although it is unclear whether some old and cheap compounds such as sulpiride or perazine have similar properties (Möller 2000). The second generation antipsychotics raised major hopes of superior effects in a number of areas such as compliance, cognitive functioning, negative symptoms, movement disorders, quality of life and the treatment of people with treatment resistant schizophrenia.

How the intervention might work

Technical background—Olanzapine, a thienobenzodiazepine derivative, is an ‘atypical’ antipsychotic showing affinity at D1-D5, serotinergic (5HT2, 3, 6), muscarinic (subtypes 1-5), adrenergic (alpha 1-2) and histaminergic (H1) binding sites (Conley 1998, Tollefson 1997, Reus 1997, Anonymous 1997). It is structurally similar to clozapine but has a slightly different binding site affinity. It is weaker than clozapine as an alpha-1 and alpha-2 adrenergic agonist relative to D2, D4 or 5HT2a antagonism.

Why it is important to do this review

The debate as to how far the SGA improve these outcomes compared to conventional antipsychotics continues (Duggan 2005, El-Sayeh 2006) and the results from recent studies were sobering (Liebermann 2005, Jones 2006). Nevertheless, in some parts of the world, especially in the highly industrialised countries, second generation antipsychotics have become the mainstay of treatment. The second generation antipsychotics also differ in terms of their costs; while amisulpride and risperidone are already generic in many countries and olanzapine is generic in India other antipsychotics such as aripiprazole and ziprasidone are still not. Therefore the question as to whether they differ from each other in their clinical effects becomes increasingly important. In this review we aim to summarise evidence from randomised controlled trials that compared olanzapine with other second generation antipsychotics.

OBJECTIVES

To review the effects of olanzapine compared to other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychosis.

METHODS

Criteria for considering studies for this review

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

We included randomised cross-over studies, but only data up to the point of first cross-over because of the instability of the problem behaviours and the likely carry-over effects of all treatments.

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

Types of interventions

1. Olanzapine: any oral form of application, any dose
2. Other atypical antipsychotic drugs: amisulpride, aripiprazole, clozapine, quetiapine, risperidone, sertindole, ziprasidone, zotepine: any oral form of application, any dose.

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

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

Secondary outcomes

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

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3.2 Average endpoint general mental state score

3.3 Average change in general mental state score

3.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)

3.5 Average endpoint specific symptom score

3.6 Average change in specific symptom score

4 General functioning

4.1 No clinically important change in general functioning

4.2 Average endpoint general functioning score

4.3 Average change in general functioning score

5 Quality of life/satisfaction with treatment

5.1 No clinically important change in general quality of life

5.2 Average endpoint general quality of life score

5.3 Average change in general quality of life score

6 Cognitive functioning

6.1 No clinically important change in overall cognitive functioning

6.2 Average endpoint of overall cognitive functioning score

6.3 Average change of overall cognitive functioning score

7 Service use

7.1 Numbers hospitalised

8 Adverse effects

8.1 Number of participants with at least one adverse effect

8.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders, prolactin increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count)

8.3 Average endpoint in specific adverse effects

8.4 Average change in specific adverse effects

Search methods for identification of studies

No language restriction was applied within the limitations of the search tools.

Electronic searches—We searched the Cochrane Schizophrenia Group's Specialised Register (April 2007) using the phrase: [((ziprasidon* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR zotepin*)) in title, abstract or index terms of REFERENCE) or ((ziprasidon* AND (amisulprid* OR

aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon * OR zotepin*)) in interventions of STUDY)]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module). The Cochrane Schizophrenia Group Trials Register is maintained on Meerkat 1.5. This version of Meerkat stores references as studies. When an individual reference is selected through a search, all references which have been identified as the same study are also selected.

Searching other resources

1. Reference searching: We inspected the reference lists of all studies identified in the search for more trials.

2. Personal contact: We contacted the first author of each included study for missing information.

3. Drug companies: We contacted the manufacturers of all atypical antipsychotics included for additional data.

Data collection and analysis

Selection of studies—We independently extracted 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, we did not enter data and added the trial to the list of those awaiting assessment.

Data extraction and management

1. Data extraction: We independently extracted 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, we did not enter data and added the trial to the list of those awaiting assessment.

2. Management: We extracted the data onto standard simple forms. Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for olanzapine.

3. Rating scales: A wide range of instruments are available to measure outcomes in mental health studies. These instruments vary in quality and many are not validated, 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.

Assessment of risk of bias in included studies—Again working independently, KK and SL assessed risk of bias using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases.

The risk of bias in each domain and overall were assessed and categorised into:

A. Low risk of bias: plausible bias unlikely to seriously alter the results (categorised as 'Yes' in Risk of Bias table)

B. High risk of bias: plausible bias that seriously weakens confidence in the results (categorised as 'No' in Risk of Bias table)

C. Unclear risk of bias: plausible bias that raises some doubt about the results (categorised as 'Unclear' in Risk of Bias table)

We categorised trials with high risk of bias (defined as at least four out of seven domains) as 'No'. Where allocation was clearly not concealed we did not include these trials in the review. If the initial raters disagreed, the final rating was made by consensus with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors the studies in order to obtain further information. Non-concurrence in quality assessment was reported.

Measures of treatment effect

1. Data types: We assessed outcomes using continuous (for example changes on a behaviour scale), categorical (for example, one of three categories on a behaviour scale, such as "little change";, "moderate change" or "much change") or dichotomous (for example, either "no important changes or "important change" in a person's behaviour) measures. Currently RevMan does not support categorical data so we were unable to analyse this.

2. Dichotomous- yes/no- data: We carried out an intention to treat analysis. Everyone allocated to the intervention were counted, whether they completed the follow up or not. It was assumed that those who dropped out had no change in 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 adverse effects, but we felt that assuming that all those leaving early would have developed side effects would overestimate risk. 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 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 mis-interpretation 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.

3 Continuous data

3.1 Normal distribution of the 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 more 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.
- **d.** The rules explained in a) and b) do not apply to change data.

The reasons 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 ALLSTAT 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. We therefore included change data and did not apply a sensitivity analysis.

3.2 Data synthesis: For continuous outcomes we estimated a weighted mean difference (WMD) between groups. WMDs 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. 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 2008). 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)

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 causes type 1 errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we would have 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 would have seeked 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 had been incorporated into the analysis of primary studies, we would also have presented 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, we would have synthesised these with other studies 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.

3. Studies with multiple treatment groups: Where a study involved more than two treatment groups, if relevant, the additional treatment groups were presented in additional relevant comparisons. Data were not double counted. Where the additional treatment groups were not relevant, these data were not reproduced.

Dealing with missing data—At some degree of loss of follow-up data must lose credibility (Xia 2007). 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).

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^2 statistic

Visual inspection was supplemented using, primarily, the I^2 statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I^2 estimate was greater than or equal to 50% we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003).

Assessment of reporting biases—Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10.1 of the Cochrane Handbook (Higgins 2008). We are aware that funnel plots may be useful in investigating small-study effects but are of limited power to detect such effects when there are few studies. 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. We did not undertake a formal test for funnelplot asymmetry.

Data synthesis—Where possible for both dichotomous and continuous data we used the random-effects model for data synthesis as this takes into account any differences between studies even if there is no statistically significant heterogeneity. We understand that there is no closed argument for preference for use of fixed or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This does seem true to us, however, random-effects does put added weight onto the smaller of the studies - those trials that are most vulnerable to bias.

Subgroup analysis and investigation of heterogeneity—If data are clearly heterogeneous we checked that data are correctly extracted and entered and that we had made no unit of analysis errors. 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.

Sensitivity analysis—In sensitivity analyses 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

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

Results of the search—The search strategy yielded 3620 reports. 193 reports were closely inspected. 110 of them had to be excluded, 50 were included and nine studies are ongoing (Eli Lilly 2003a, Eli Lilly 2003b, Eli Lilly 2004a, Eli Lilly 2004b, Eli Lilly 2006, NCT00001656, Mortimer 2001, N0081052094, N0081121981). No studies are awaiting assessment. For further descriptions please see below and the included, excluded and ongoing studies tables.

The fifty included studies provided data on six comparisons: olanzapine versus amisulpride, olanzapine versus aripiprazole, olanzapine versus clozapine, olanzapine versus quetiapine, olanzapine versus risperidone and olanzapine versus ziprasidone. For the following comparisons no relevant RCTs were identified: olanzapine versus sertindole and olanzapine versus zotepine.

Included studies—The 50 included studies randomised approximately 9100 people. All but eight included studies were double blind. Seventeen studies were sponsored by pharmaceutical companies producing olanzapine and 14 studies were sponsored by pharmaceutical companies marketing the comparing substances,15 studies had a neutral sponsor. Four studies did not provide data on sponsoring.

1 Length of studies: Twenty-eight studies fell in the short-term category (up to twelve weeks). Mori 2004 was the shortest trial with a duration of 4 weeks. Eight studies lasted 6 weeks (Atmaca 2003, CN138003, Ozguven 2004, Simpson 2004, Svestka 2003a, Svestka 2003b, Svestka 2005, Van Nimwegen 2006). Fifteen trials lasted 8 weeks (Canive 2000, Conley 2001, Conley 2003, Dollfus 2005, Dolnak 2001, Jeste 2003, Moresco 2004, Riedel 2007, Sacchetti 2004, Shaw 2006, Sikich 2004, Vanelle 2006, Wagner 2005, Wang 2002, and Wynn 2007) and four studies lasted 12 weeks (Krakowski 2006, Kumra 2007, Sirota 2006, Wang 2006).

Thirteen studies fell into the medium-term category (13-26 weeks) (Bai 2005, Bitter 2004, Kinon 2006a, Kinon 2006b, Lecrubier 2006, McEvoy 2006, McQuade 2004, Mortimer 2004, Naber 2005, Robinson 2006, Stroup 2006, Tollefson 2001, Volavka 2002).

Nine trials (Breier 2005, Gureje 2003, Keefe 2006, Lieberman 2005, McEvoy 2007, Meltzer 2003, Purdon 2000, Tran 1997, and Voruganti 2007) were long-term (more than 26 weeks).

2. Setting: In 22 trials in- and outpatients could be included, sixteen used an inpatient setting and three studies an outpatient setting. Nine study reports did not provide information on the setting.

3. Participants: Most studies used operationalised diagnostic criteria, most frequently on the basis of the Diagnostic and Statistical Manual (DSM-IV, APA 2004, or older). Other diagnostic systems were the International Classification of Diseases (ICD 10 or older). Sikich 2004 used the DSM-IV as well as the Schedule for Affective Disorders and Schizophrenia. Chinese trialists applied the Chinese Classification of Mental Disorders (CCDM, Version 3 or older). All studies included people with schizophrenia, twenty-one studies additionally included those with schizoaffective disorder (Conley 2001, Gureje 2003, Jeste 2003, Keefe 2006, Kinon 2006a, Kinon 2006b, Krakowski 2006, Kumra 2007, McEvoy 2007, Meltzer 2003, Robinson 2006, Sikich 2004, Simpson 2004, Svestka 2003a, Svestka 2003b, Svestka 2005, Tran 1997, Van Nimwegen 2006, Volavka 2002, Wang 2006, Wynn 2007) and seven studies also included people with schizophreniform disorder (Gureje 2003, McEvoy 2007, Mortimer 2004, Robinson 2006, Sikich 2004, Tran 1997, Van Nimwegen 2006).

In most studies there was a preponderance of men but Svestka 2003b included only women.

In most studies the participants were relatively chronic with a median mean age of 37.6 years. However, eight studies included only children and adolescents, participants with a first episode or people in the early stages of the illness (McEvoy 2007, Purdon 2000, Robinson 2006, Sikich 2004, Kumra 2007, Svestka 2003a, Svestka 2003b, Svestka 2005). In contrast, Jeste 2003 randomised only elderly people with schizophrenia aged 60 or older.

Nine studies required suboptimal response to, or intolerance of, at least one previous standard antipsychotic therapy (Bitter 2004, Conley 2003, Kumra 2007, McEvoy 2006, Moresco 2004, Naber 2005, Shaw 2006, Tollefson 2001, and Volavka 2002). The definitions for non-response and treatment resistance, however, differed.

While most studies required a minimum of positive symptoms for inclusion, Lecrubier 2006, Kinon 2006b focused on people with predominant negative symptoms. Dollfus 2005 addressed people with postpsychotic depression, and Kinon 2006a examined participants with predominant depressive symptoms.

4. Study size: Lieberman 2005 was the largest study (1460 participants) whilst Conley 2003 was the smallest study, randomising only 13 people. Eleven studies had fewer than fifty participants, fifteen had 50-100 participants, sixteen studies had 100 to 400 participants and six randomised more than four hundred people. Two studies did not indicate the total number of randomised participants.

5. Interventions

5.1 Olanzapine: The trialists gave olanzapine in a wide range of flexible doses from 2.5 mg/day to 50 mg/day. Only five studies were fixed dose trials (Conley 2003: 50mg/day;

Kinon 2006a three doses: 10, 15, 20 mg/day, Lecrubier 2006: 5 and 20mg/day, Wynn 2007: 15mg/day). In seven reports a dose range was not indicated.

5.2 Comparators: Six other second generation antipsychotic drugs were used as comparators with the following dose ranges: amisulpride (150 mg/day to 800 mg/day), aripiprazole (15 mg/day to 30 mg/day), clozapine (25 mg/day to 900 mg/day), quetiapine (50 mg/day to 826.67 mg/day), risperidone (0.5 mg/day to 16 mg/day) and zisprasidone (40 mg/day to 160 mg/day). Some studies also included additional arms with the typical antipsychotic drugs haloperidol, perospirone, perphenazine as comparators. These results were not considered in the current review.

6 Outcomes

6.1 Leaving the study early: We evaluated numbers leaving early for any reason, for adverse events or for lack of efficacy.

6.2 Response to treatment: The studies rarely reported the response cut off of at least 50% reduction of a scale's baseline value that we considered clinically meaningful. The criteria of at least 50% PANSS total score reduction was used by Bitter 2004, Dollfus 2005, Gureje 2003, Svestka 2003b, Tollefson 2001, Tran 1997 and Wagner 2005. Wang 2002 used 50% BPRS total score reduction. In contrast, Liu 2004 described at least 50% SANS reduction from baseline, Simpson 2004 at least 40% BPRS total score reduction from baseline, Breier 2005 and Zhong 2006 at least 30% PANSS total score reduction from baseline, Conley 2001 at least 20% PANSS total score reduction from baseline, Lecrubier 2006 at least 20% SANS total reduction from baseline in addition to 10% PANSS total score reduction, Ozguven 2004 at least 20% SANS total score reduction from baseline, McQuade 2004, Naber 2005 and Vanelle 2006 at least much improved on CGI, CN138003 a CGI of 3 or less or at least 20% PANSS total reduction, McEvoy 2007 all PANSS items of 3 or less plus a CGI-S item of 3 or less, Sikich 2004 a CGI at least much improved in addition to at least 20% BPRS reduction and Robinson 2006 applied a criterion mild or less on certain SADS-C+PD items plus at least much improved on CGI.

6.3 Relapse: Only three studies (Dollfus 2005, Keefe 2006, Lecrubier 2006) provided data for relapse and used different definitions.

6.4 Service use: Some studies indicated the number of participants re-hospitalised during the trial.

6.5 Outcome scales: Details of scales that provided usable data are shown below. Reasons for exclusion of data from other instruments are given under 'Outcomes' in the Characteristics of included studies table.

6.5.1 Global state scales:

6.5.1.1 Clinical Global Impression Scale - CGI (Guy 1976): This is used to assess both severity of illness and clinical improvement, by comparing the conditions of the person

standardised against other people with the same diagnosis. A seven-point scoring system is usually used with low scores showing decreased severity and/or overall improvement.

6.5.2 Mental state scales:

6.5.2.1 Brief Psychiatric Rating Scale - BPRS (Overall 1962): This is used to assess the severity of abnormal mental state. The original scale has 16 items, but a revised 18-item scale is commonly used. Each item is defined on a seven-point scale varying from 'not present' to 'extremely severe', scoring from 0-6 or 1-7. Scores can range from 0-126, with high scores indicating more severe symptoms.

6.5.2.2 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 1 - absent to 7 - extreme. It can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates lesser severity.

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

6.5.2.4 Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1983): This four-point scale gives a global rating of the following positive symptoms: hallucinations, paranoia, disorganised behaviour and disorganised thinking. Higher scores indicate more symptoms.

6.5.3 General functioning scales:

6.5.3.1 Social and Occupational Functioning Assessment Scale - SOFAS (Goldman 1992): The SOFAS scale focuses on the different levels of social and occupational functioning. Higher scores indicate a higher level of functioning.

6.5.3.2 Global Assessment of Functioning - GAF (APA 2004): This is a rating scale for a participant's overall capacity of psychosocial functioning scoring from 1-100. Higher scores indicate a higher level of functioning.

6.5.4 Quality of life scales:

6.5.4.1 Quality of Life Scale - QLS (Carpenter 1984): This semi-structured interview is administered and rated by trained clinicians. It contains 21 items rated on a seven-point scale based on the interviewers judgement of patient functioning. A total QLS and four sub-scale scores are calculated, with higher scores indicating less impairment.

6.5.4.2 Subjective Well-being under Neuroleptics Scale - SWN (De Haan 2002): The SWN is an instrument to measure the subtle subjective changes, such as restrictions in emotionality, the clarity of thinking and spontaneity, that are frequently referred as 'pharmacogenic depression' or the 'neuroleptic induced deficit syndrome'.

6.5.5 Cognitive functioning scales:

6.5.5.1 Global Cognitive Index (Wagner 2005): For cognitive assessment Wagner 2005 used a global cognitive index that was constructed by summing and averaging the z-scores of various cognitive tests. The tests were grouped into four cognitive domains: attention, executive functions, working memory, and verbal learning and memory.

6.5.5.2 Global Neurocognitive Score (Volavka 2002): This score consists of 15 tests that assess the domains general ability, learning and memory, attention, executive functions, and motor skills. 16 variables were selected from 12 tests. For each test variable, z-scores were computed. This global score was then computed by averaging the z-scores of contributing variables. All z-scores were computed in a way that positive scores indicate better performance.

6.5.5.3 Neurocognitive Composite Score (Keefe 2006): The Neurocognitive Composite score comprises individual cognitive domains (executive function, learning and memory, processing speed, attention/vigilance, verbal working memory, verbal fluency, motor function, and visuospatial ability) measured by various tests that were transformed into a composite score.

6.5.5.4 PANSS cognitive subscore: This score has been derived from the Positive and Negative Syndrome Scale - PANSS (Kay 1986).

6.5.6 Adverse effects scales:

6.5.6.1 Abnormal Involuntary Movement Scale - AIMS (Guy 1976): This has been used to assess tardive dyskinesia, a long-term, drug-induced movement disorder and short-term movement disorders such as tremor.

6.5.6.2 Barnes Akathisia Scale - BAS (Barnes 1989): The scale comprises items rating the observable, restless movements that characterise akathisia, a subjective awareness of restlessness, and any distress associated with the condition. These items are rated from 0 - normal to 3 - severe. In addition, there is an item for rating global severity (from 0 - absent to 5 - severe). A low score indicates low levels of akathisia.

6.5.6.3 Extrapyramidal Symptom Rating Scale - ESRS (Chouinard 1980): This 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.

6.5.6.4 Hillside Akathisia Scale - HAS (Fleischhacker 1989): The Hillside Akathisia Scale has two subjective and three objective items for which anchored rating points are provided.

6.5.6.5 Simpson Angus Scale - SAS (Simpson 1970): This ten-item scale, with a scoring system of 0-4 for each item, measures drug-induced parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of parkinsonism.

Excluded studies—We excluded a total of 110 studies. Of these, 54 were excluded because of open-label treatment, 29 were excluded because of lack of randomisation, and twelve due to pooled-analyses. Nine were excluded because of inappropriate intervention, three because of no usable data and two were excluded because of other aims. One study was excluded because of inadequate diagnosis.

Awaiting assessment: No studies are waiting assessment.

Ongoing studies: Nine RCTs comparing olanzapine with other atypical antipsychotics are considered as ongoing (Eli Lilly 2003a, Eli Lilly 2003b, Eli Lilly 2004a, Eli Lilly 2004b, Eli Lilly 2006, NCT00001656, Mortimer 2001, N0081052094, N0081121981).

Risk of bias in included studies

For details of risk of bias please refer to risk of bias table (Figure 1, Figure 2).

Allocation—All of the included studies were randomised, but only thirteen provided some details about the allocation process: Gureje 2003, Kinon 2006b, Kumra 2007, Mortimer 2004, Naber 2005, Purdon 2000 and Sikich 2004 used a computer-generated randomisation, Shaw 2006 used a random-numbers chart (blocks of four) and Wagner 2005 used medication containers according to a pseudorandom computer algorithm. These studies had a relatively low risk of bias. For all the others information was so little, that it remained unclear, whether there was a risk of bias. Conley 2001 mentioned that randomisation was stratified by site and Krakowski 2006 used block randomisation (block size of three). Stroup 2006 described two steps of randomisation: in phase two the participants were re-randomised to a different medication than in phase one. Wynn 2007 randomly assigned most participants to three different treatment arms (olanzapine, risperidone or haloperidol; blocks of 15) while those participants with a history of haloperidol induced adverse events were randomly assigned to either olanzapine or risperidone. Only two studies (Mortimer 2004, Shaw 2006) provided some information on allocation concealment, whereas the other studies did not report on this.

Blinding—Forty-two of the included studies were described as double-blind and eight as single-blind (Meltzer 2003, Robinson 2006, Bai 2005, Atmaca 2003, Voruganti 2007, Ozguven 2004, Sacchetti 2004 and Sirota 2006). Nine studies (Kinon 2006b, Lieberman 2005, McEvoy 2006, Mortimer 2004, Naber 2005, Shaw 2006, Stroup 2006, Volavka 2002, Wang 2006) described using identical capsules for blinding. No study examined whether blinding was effective. We found that the side-effect profiles of the examined compounds are quite different which may have made blinding difficult. We therefore conclude that the risk of bias for objective outcomes (e.g. death or laboratory values) was low, but there was a risk of bias for subjective outcomes.

Incomplete outcome data—The overall number of participants leaving the study early was high 49.2%. Ten studies did not provide data on leaving the study early (Canive 2000, Dolnak 2001, Mori 2004, Svestka 2003a, Svestka 2003b, Svestka 2005, Van Nimwegen 2006, Wang 2002, Wang 2006, Wynn 2007). The majority of trials that had been published

in peer reviewed journals described the participant disposition well. Most studies applied the last-observation-carried-forward method to account for participants leaving the study early which is an imperfect method. It assumes that a participant who left the study prematurely would not have had a change of his condition if he had stayed in the study. This assumption can be wrong. This may be less of a problem in the studies with low attrition or people leaving close to the end of the trial, but clearly problematic in studies with high attrition.

Selective reporting—In nine studies the reporting on secondary or even primary outcomes was incomplete (Dollfus 2005, Mori 2004, Purdon 2000, Sacchetti 2004, Stroup 2006, Van Nimwegen 2006, Volavka 2002, Wang 2006, Wynn 2007). Some authors only described those treatment emergent adverse events with an incidence of at least 5% or 10%, or only in case of moderate or worse severity, or only if there was a significant difference between groups (Conley 2001, Gureje 2003, Jeste 2003, Keefe 2006, McEvoy 2007, Tran 1997 Zhong 2006). This procedure is problematic, because rare, but potentially serious side-effects may be missed. Only five studies appeared to have a low risk of bias (Atmaca 2003, Purdon 2000, Lieberman 2005, Shaw 2006, Sikich 2004).

Other potential sources of bias—None of the studies was clearly free of other bias. 29 studies were industry sponsored which poses a problem due to an inevitable conflict of interest (Bitter 2004, Breier 2005, Conley 2001, Canive 2000, Conley 2003, Dollfus 2005, Gureje 2003, Jeste 2003, Keefe 2006, Kinon 2006a, Kinon 2006b, Lecrubier 2006, McEvoy 2007, McQuade 2004, Meltzer 2003, Mortimer 2004, Naber 2005, Purdon 2000, Riedel 2007, Sacchetti 2004, Simpson 2004, Sirota 2006, Tollefson 2001, Tran 1997, Vanelle 2006, Voruganti 2007, Wagner 2005, Wang 2006, Wynn 2007). Sponsoring of nine studies remained unclear. There is evidence that pharmaceutical companies sometimes highlight the benefits of their compounds and tend to suppress their disadvantages (Heres 2006).

Other methodological shortcomings of recent antipsychotic drug trials such as short wash-out phases, selected and usually chronic participants, and lack of standardised response criteria also applied here (Leucht 2008).

Effects of interventions

1. Comparison 1. OLANZAPINE versus AMISULPRIDE—Five included studies (Bai 2005, Lecrubier 2006, Mortimer 2004, Vanelle 2006, Wagner 2005) compared olanzapine with amisulpride.

1.1 Global state

1.1.1 Global state - no clinically significant response to treatment - as defined by the original studies: There was no significant difference between olanzapine and amisulpride (4 RCTs, n=724, RR 0.97 CI 0.82 to 1.14).

1.1.2 Global state - no clinically important change: There was no significant difference (3 RCTs, n=514, RR 1.10 CI 0.84 to 1.43).

1.1.3 Global state - relapse - as defined by the original studies: There was no significant difference (1 RCT, n=210, RR 1.07 CI 0.46 to 2.51).

1.2 Leaving the study early: There was no significant difference between groups. More than one third, 38% of the participants in the treatment group and 37% of those in the control group, left the studies early due to any reason (5 RCTs, n=804, RR 0.94 CI 0.79 to 1.11). Due to adverse events 9% of the participants of each groups left the studies early (4 RCTs, n=724, RR 0.84 CI 0.52 to 1.36) and 15% of the participants of each group left the studies early due to inefficacy of treatment (4 RCTs, n=724, RR 0.84 CI 0.50 to 1.40).

1.3 Mental state

1.3.1 General - no clinically important change - less than 50% PANSS total score reduction: There was no significant difference (1 RCT, n=52, RR 1.45 CI 0.85 to 2.50).

1.3.2 General - average score at endpoint - PANSS total: There was no significant difference in the overall analysis (4 RCTs, n=701, WMD −1.57 CI −6.09 to 2.94),

short term (2 RCTs, n=119, WMD 2.86 CI −11.36 to 17.08), medium term (2 RCTs, n=582, WMD −2.53 CI −7.45 to 2.48)

1.3.3 General - no clinically important change - less than 50% BPRS total score reduction: There was no significant difference (1 RCT, n=377, RR 0.92 CI 0.73 to 1.14).

1.3.4 General - average score at endpoint - BPRS total: There was no significant difference analysis (3 RCTs, n=665, WMD −1.26 CI −3.34 to 0.82), as well as in short term data (1 RCT, n=83, WMD −1.40 CI −4.98 to 2.18) and medium term data (2 RCTs, n=582, WMD −1.39 CI −4.83 to 2.04).

1.3.5 Positive symptoms - no clinically important change (less than 50% PANSS positive sub-score reduction): There was no significant difference (1 RCT, n=52, RR 1.44 CI 0.75 to 2.78).

1.3.6 Positive symptom - average score at endpoint - PANSS positive: There was no significant difference (4 RCTs, n=701, WMD −0.66 CI −1.88 to 0.56), as well as in short term data (2 RCTs, n=119, WMD −0.15 CI −2.57 to 2.27) and medium term data (2 RCTs, n=582, WMD −0.98 CI −3.12 to 1.16).

1.3.7 Negative symptoms - average score at endpoint - PANSS negative: There was no significant difference in the overall analysis (4 RCTs, n=701, WMD −0.21 CI −1.10 to 0.69), as well as in short term (2 RCTs, n=119, WMD 0.49 CI −2.05 to 3.02) and medium term data (2 RCTs, n=582, WMD −0.38 CI −1.56 to 0.80).

1.3.8 Negative symptoms - no clinically important change - less than 20% SANS total score reduction: There was no significant difference (1 RCT, n=210, RR 0.88 CI 0.63 to 1.25).

1.3.9 Negative symptoms - average score at endpoint - SANS total: There was no significant difference in the overall analysis (2 RCTs, n=243, WMD 0.00 CI −1.43 to 1.43), as well as in short term (1 RCT, n=33, WMD 8.62 CI −10.45 to 27.69) and medium term data (1 RCT, n=210, WMD −0.05 CI −1.49 to 1.39).

1.4 General functioning - average score at endpoint - SOFAS total - percent change: There was no significant difference (1 RCT, n=359, WMD −0.20 CI −10.94 to 10.54).

1.5 Quality of Life - average score at endpoint - QLS total score: There was no significant difference (2 RCTs, n=510, WMD 0.00 CI −0.22 to 0.22).

1.6 Cognitive functioning

1.6.1 Cognitive functioning: no clinically important change- less than 50% Global Cognitive Index reduction: There was no significant difference (1 RCT, n=52, RR 1.00 CI 0.74 to 1.35).

1.6.2 Global cognitive index - average score at endpoint: There was no significant difference (1 RCT, n=36, WMD 0.13 CI −0.09 to 0.35).

1.7 Adverse effects

1.7.1 Numbers of participants with at least one adverse effect: There was no significant difference (2 RCTs, n=462, RR 0.97 CI 0.82 to 1.15).

1.7.2 Death: There was no significant difference in the number of participants dying due to ‘natural causes’ (1 RCT, n=377, RR 0.34 CI 0.01 to 8.17) or due to suicide (1 RCT, n=377, RR 3.02 CI 0.12 to 73.56). There was also no significant difference in the number of suicide attempts (1 RCT, n=210, RR 1.50 CI 0.16 to 14.16).

1.7.3 Cardiac effects - number of participants with a QTc interval > 500 ms: There was no significant difference (1 RCT, n=377, RR not estimable).

1.7.4 Cardiac effects - mean change of QTc interval from baseline in ms: There was no significant difference (2 RCTs, n=303, WMD −5.25 CI −11.07 to 0.57).

1.7.5 Central nervous system - sedation: There was no significant difference (2 RCTs, n=587, RR 0.82 CI 0.43 to 1.57).

1.7.6 Central nervous system - seizures: There was no significant difference (1 RCT, n=210, RR 1.51 CI 0.06 to 36.61).

1.7.7 Extrapyramidal effects: There was no significant difference in the number of participants with extrapyramidal side effects reported as akathisia (2 RCTs, n=587, RR 1.52 CI 0.82 to 2.81), dyskinesia (1 RCT, n=210, RR 1.51 CI 0.06 to 36.61), dystonia (1 RCT, n=377, RR 0.20 CI 0.01 to 4.16), ‘extrapyramidal symptoms’ (1 RCT, n=210, RR 0.83 CI 0.50 to 1.39), parkinsonism (data are of two studies are presented separately due to heterogeneity, I^2 = 61%, Mortimer 2004: n=377, RR 0.09 CI 0.01 to 0.70 and Lecrubier

2006: n=210, RR 0.75 CI 0.13 to 4.39), tremor (1 RCT, n=210, RR 1.75 CI 0.37 to 8.20), and use of antiparkinson medication (1 RCT, n=377, RR 0.66 CI 0.37 to 1.17).

1.7.8 Extrapyramidal symptoms - scale measured: There was no significant difference between amisulpride and olanzapine in dyskinesia (AIMS: 1 RCT, n=356, WMD 0.40 CI −0.33 to 1.13) and general extrapyramidal side-effects (SAS: 2 RCTs, n= 406, WMD 0.00 CI −0.08 to 0.08).

1.7.9 Haematological - white blood cell count - leukopenia: There was no significant difference in numbers of people with leukopenia (1 RCT, n=210, RR 2.52 CI 0.12 to 51.74).

1.7.10 Prolactin associated side effects: There were no significant differences between olanzapine and amisulpride in the number of participants with amenorrhoea (1 RCT, n=66, RR 0.65 CI 0.12 to 3.61), galactorrhoea (1 RCT, n=66, RR 0.15 CI 0.01 to 3.51) and sexual dysfunction (2 RCTs, n=521, RR 0.74 CI 0.08 to 7.02).

1.7.11 Metabolic - cholesterol - change from baseline in mg/dl: There was no significant difference (1 RCT, n=85, WMD 3.42 CI −5.48 to 12.32).

1.7.12 Metabolic - glucose - number of participants with diabetes mellitus: There was no significant difference between olanzapine and amisulpride (1 RCT, n=377, RR 3.02 CI 0.12 to 73.56).

1.7.13 Metabolic - glucose - mean change from baseline in mg/dl: Amisulpride was associated with significantly less glucose increase than olanzapine (2 RCTs, n=406, WMD 7.30 CI 6.99 to 7.62).

1.7.14 Metabolic - weight gain - number of participants with weight gain: More participants in the olanzapine group than in the amisulpride group gained weight (3 RCTs, n=672, RR 1.83 CI 1.34 to 2.50, NNH 9 CI 6 to 20).

1.7.15 Metabolic - weight gain - change from baseline in kg: On the average olanzapine was associated with more weight gain than amisulpride (3 RCTs, n=671, WMD 2.11 CI 1.29 to 2.94).

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

1.10 Investigation for heterogeneity and sensitivity analysis: The reasons for the preplanned sensitivity analysis did not apply and were therefore not performed.

2. Comparison 2. OLANZAPINE versus ARIPIPRAZOLE—Two included studies (CN138003, McQuade 2004) compared olanzapine with aripiprazole.

2.1 Global state

2.1.1 Global state - no clinically significant response - as defined by the original studies: There was no significant difference (2 RCTs, n=1020, RR 0.95 CI 0.85 to 1.05).

2.1.2 Global state - no clinically important change: There was no significant difference in the overall analysis (2 RCTs, n=1020, RR 0.95 CI 0.85 to 1.05), as well as in the short term (1 RCT, n=703, RR 1.00 CI 0.82 to 1.23) and medium term (1 RCT, n=317, RR 0.93 CI 0.82 to 1.05).

2.2 Leaving the study early: 37% of the participants in the olanzapine group and 43% of the participants in the aripiprazole group left the studies early, a non-significant difference (2 RCTs, n=1020, RR 0.87 CI 0.69 to 1.09). The results were somewhat heterogeneous, I^2 = 62%, but the direction of the effect was the same in both studies (McQuade 2004: n=317, RR 0.94 CI 0.82 to 1.08; CN138003: n=703, RR 0.87 CI 0.69 to 1.09). Only McQuade 2004 provided data on leaving early due to adverse events or inefficacy of treatment, but again there was no significant difference. 19% of the participants in the olanzapine group and 24% of the participants of the aripiprazole group left the study early because of adverse events (n=317, RR 0.79 CI 0.51 to 1.21). 9% of the participants treated with olanzapine and 15% of the participants treated with aripiprazole left the study early due to lack of efficacy of treatment (n=317, RR 0.59 CI 0.32 to 1.10).

2.3 Mental state

2.3.1 General - average score at endpoint - PANSS total: Olanzapine was significantly more efficacious than aripiprazole in the overall analysis (2 RCTs, n=794, WMD −4.96 CI −8.06 to −1.85), which was mainly seen in the short term data analysis (1 RCT, n=703, WMD −5.21 CI −8.51 to −1.91) but not in the medium term data analysis (1 RCT, n=91, WMD 3.00 CI −12.21 to 6.21).

2.4 Adverse effects

2.4.1 Cardiac effects - number of participants with QTc prolongation: There was no significant difference (1 RCT, n=317, RR 2.91 CI 0.60 to 14.18).

2.4.2 Cardiac effects - mean change of QTc interval from baseline in ms: There was no significant difference (1 RCT, n=317, WMD 3.70 CI −2.11 to 9.51).

2.4.3 Central nervous system - sedation: Sedation was significantly less frequent in the aripiprazole group than in the olanzapine group (1 RCT, n=317, RR 2.99 CI 1.62 to 5.51, NNH 7 CI 4 to 13).

2.4.4 Extrapyramidal effects: There was no significant difference in akathisia (1 RCT, n=317, RR 0.54 CI 0.18 to 1.57), ‘extrapyramidal symptoms’ (1 RCT, n=317, RR 0.93 CI 0.56 to 1.54) and parkinsonism (1 RCT, n= 317, RR 1.08 CI 0.58 to 2.01).

2.4.5 Prolactin - numbers of participants with prolactin level increase: Abnormally high prolactin levels were reported by one study indicating a significant difference favouring aripiprazole (1 RCT, n=317, RR 3.74 CI 1.68 to 8.33, NNH 8 CI 5 to 17).

2.4.6 Metabolic - cholesterol - number of participants with cholesterol increase: More participants in the olanzapine group than in the aripiprazole group had a cholesterol increase (1 RCT, n=223, RR 3.15 CI 1.84 to 5.39, NNH 4 CI 3 to 6).

2.4.7 Metabolic - cholesterol - mean change from baseline in mg/dl: Olanzapine was associated with a significantly higher increase of cholesterol levels than aripiprazole (1 RCT, n=223, WMD 17.43 CI 7.65 to 27.21).

2.4.8 Metabolic - glucose - mean change from baseline in mg/dl: There was no significant difference (1 RCT, n=317, WMD 2.00 CI −6.48 to 10.48).

2.4.9 Metabolic - weight gain - number of participants with 7% or more increase of total body weight: More participants in the olanzapine group gained more than 7% of their initial weight (1 RCT, n=317, RR 2.68 CI 1.71 to 4.19, NNH 4 CI 3 to 8).

2.4.10 Metabolic - weight gain - mean change from baseline in kg: Weight gain reported as mean change from baseline indicated a significant difference favouring aripiprazole (1 RCT, n=90, WMD 5.60 CI 2.15 to 9.05).

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

2.6 Investigation for heterogeneity and sensitivity analysis: The reasons for the preplanned sensitivity analysis did not apply and were therefore not performed.

3.Comparison 3. OLANZAPINE versus CLOZAPINE—Twelve included studies (Atmaca 2003, Bitter 2004, Conley 2003, Krakowski 2006, Kumra 2007, Meltzer 2003, Moresco 2004, Naber 2005, Shaw 2006, Tollefson 2001, Volavka 2002, Wang 2002) compared olanzapine with clozapine.

3.1 Global state

3.1.1 Global state - no clinically significant response - as defined by the original studies: There was no statistically significant difference (6 RCTs, n=518, RR 0.99 CI 0.91 to 1.09).

3.1.2 Global state - no clinically important change: There was no significant difference in the overall analysis (5 RCTs, n=505, RR 0.97 CI 0.81 to 1.16), as well as in short term data analysis (2 RCTs, n=44, RR 1.32 CI 0.39 to 4.44) but not in the medium term data analysis (2 RCTs, n=441, WMD 0.92 CI 0.77 to 1.10).

3.2 Leaving the study early: A similar amount of participants in the olanzapine group (38%) and in the clozapine group (40%) left the studies early due to any reason (11 RCTs, n=1702, RR 0.96 CI 0.86 to 1.08). However, significantly fewer participants in the

olanzapine group (7%) than in the clozapine group (11%) left the studies early due to adverse events (10 RCTs, n=1674, RR 0.62 CI 0.43 to 0.92, NNT 20 CI 13 to 100). There was no significant difference in the number of participants leaving early due to lack of efficacy (15% versus 9%, 10 RCTs, n=1674, RR 1.38 CI 0.77 to 2.47).

3.3 Mental state

3.3.1 General - no clinically important change (less than 50% PANSS total score reduction): There was no significant difference (2 RCTs, n=327, RR 1.00 CI 0.91 to 1.09).

3.3.2 General - no clinically important change (less than 50% BPRS total score reduction): There was no significant difference (1 RCT, n=61, RR 0.89 CI 0.49 to 1.59).

3.3.3 General - no clinically important change (less than 20% BPRS total score reduction): There was no significant difference (1 RCT, n=25, RR 1.27 CI 0.80 to 2.02).

3.3.4 General - average score at endpoint - PANSS total: There was no significant difference in the overall analysis (7 RCTs, n=618, WMD −1.97 CI −4.66 to 0.71), as well as in short term data (3 RCTs, n=117, WMD −1.97 CI −5.42 to 1.48) or medium term data (4 RCTs, n=503, WMD −1.99 CI −6.27 to 2.29).

3.3.5 General - average score at endpoint - BPRS total: There was a statistically significant difference favouring the olanzapine (6 RCTs, n=412, WMD −1.47 CI −2.68 to −0.25). Nevertheless, the data of two studies Wang 2002, Kumra 2007 were possibly skewed. Excluding these two studies the difference was no longer significant (4 RCTs, n=312, WMD −1.56 CI −4.53 to 1.40),

3.3.6 Positive symptoms - average score at endpoint - PANSS positive: There was no significant difference in the overall analysis (6 RCTs, n=592, WMD −0.08 CI −1.11 to 0.96),

as well as in the short term data analysis (2 RCTs, n=89, WMD 0.63 CI −1.00 to 2.27) and in the medium term data analysis (4 RCTs, n=503, WMD −0.54 CI −1.87 to 0.78).

3.3.7 Positive symptoms - average score at endpoint - BPRS positive: There was no significant difference in the overall analysis (3 RCTs, n=297, WMD −0.13 CI −1.25 to 1.00)

as well as in short term data analysis (1 RCT, n=13, WMD 1.11 CI −2.10 to 4.32) and medium term data analyis (2 RCTs, n=284, WMD −0.30 CI −1.51 to 0.91).

3.3.8 Positive symptoms - average score at endpoint - SAPS total: There was no significant difference (1 RCT, n=25, WMD 9.00 CI −4.06 to 22.06).

3.3.9 Negative symptoms - average score at endpoint - PANSS negative: There was no significant difference (6 RCTs, n=592, WMD −0.78 CI −1.77 to 0.21), as well as in the short term data analysis (2 RCTs, n=89, WMD −1.32 CI −3.05 to 0.42) and in the medium term data analysis (4 RCTs, n=503, WMD −0.52 CI −1.72 to 0.68).

3.3.10 Negative symptoms - average score at endpoint - BPRS negative: There was no significant difference (3 RCTs, n=297, WMD 0.18 CI −0.44 to 0.80), as well as in short term data analysis (1 RCT, n=13, WMD 0.78 CI −0.23 to 1.79) and medium term data analyis (2 RCTs, n=284, WMD −0.15 CI −0.89 to 0.60).

3.3.11 Negative symptoms - average score at endpoint - SANS total: Overall there was no significant difference (2 RCTs, n=64, WMD 4.81 CI −4.71 to 14.33), but the results were heterogeneous I^2 = 73%. Shaw 2006 found a significant superiority of clozapine (n=25, WMD 11.00 CI 1.10 to 20.90) while in Kumra 2007 there was only a small trend in the same direction (n=39, WMD 1.00 CI −1.60 to 3.60).

3.4 Quality of Life - average score at endpoint - SWN total score: There was no significant difference (1 RCT, n=99, WMD −8.20 CI −21.67 to 5.27).

3.5 Cognitive functioning

3.5.1 Cognitive functioning - no clinically important change - less than half a standard deviation improvement in the global neurocognitive score: Only one study reported data on this outcome and showed a statistically significant superiority of olanzapine (n=79, RR 0.61 CI 0.43 to 0.87, NNT 3 CI 2 to 9).

3.5.2 Global neurocognitive score - average score at endpoint: There was no significant difference (1 RCT, n=50, WMD 0.29 CI −0.08 to 0.66).

3.6 Service use - number of participants rehospitalised: In a single large study (Meltzer 2003) more participants in the olanzapine group had to be rehospitalized than in the clozapine group (1 RCT, n=980, RR 1.28 CI 1.02 to 1.61, NNH not estimable).

3.7 Adverse effects

3.7.1 Number of participants with at least one adverse effect: Data on ‘at least one adverse effect’ showed a statistically significant difference favouring olanzapine (7 RCTs, n=422, RR 0.65 CI 0.45 to 0.94, NNT 5 CI 3 to 33). Although the results were heterogeneous, I^2 = 81%, the trend in all single studies was in favour of olanzapine (Wang 2002: n=61, RR 0.30 CI 0.16 to 0.54, NNH 2 CI 1 to 2; Conley 2003: n=13, RR not estimable; Bitter 2004: n=147, RR 0.61 CI 0.25 to 1.49; Moresco 2004: n=23, RR 0.73 CI 0.28 to 1.91; Naber 2005: n=114, RR 0.85 CI 0.72 to 1.00; Shaw 2006: n=25, RR 0.46 CI 0.19 to 1.14; Kumra 2007: n=39, RR 0.91 CI 0.77 to 1.08).

3.7.2 Death: There was no significant difference on death due to ‘any reason’ (1 RCT, n=980, RR 0.67 CI 0.27 to 1.62) and due to ‘natural causes (2 RCTs, n=193, RR not estimable). Suicide attempts were reported by one study revealing a statistically significant difference favouring the clozapine (Meltzer 2003) (1 RCT, n=980, RR 1.78 CI 1.22 to 2.62, NNH 17 CI 10 to 50) Analysis of data on death due to suicide did not show a statistically significant difference between groups (2 RCTs, n=993, RR 0.60 CI 0.14 to 2.50).

3.7.3 Cardiac effects: There was no significant difference in 'ECG abnormalities' (1 RCT, n=25, RR 0.46 CI 0.05 to 4.46) and 'QTc prolongation' (2 RCTs, n=127, RR 0.33 CI 0.01 to 8.01).

3.7.4 Central nervous system - sedation: Olanzapine was less sedating than clozapine (7 RCTs, n=1445, RR 0.54 CI 0.32 to 0.89, NNT 7 CI 5 to 13). Although the direction of the effect was the same in all studies, there was a high degree of heterogeneity, I^2 = 88%, caused by Kumra 2007. Excluding this single first episode study resolved the heterogeneity and olanzapine was still less sedating than clozapine (6 RCTS, n=1406, RR 0.52 CI 0.43 to 0.62, NNT 5 CI 4 to 12).

3.7.5 Central nervous system - seizures: Fewer participants in the olanzapine groups than in the clozapine groups had seizures (4 RCTs, n=1097, RR 0.15 CI 0.04 to 0.58, NNT 50 CI 25 to 100)

3.7.6 Extrapyramidal effects: There was no significant difference in the number of participants with akathisia (4 RCTs, n=1320, RR 1.37 CI 0.71 to 2.63), dyskinesia (2 RCTs, n=327, RR 2.29 CI 0.81 to 6.45), 'extrapyramidal symptoms' (2 RCTs, n=84, RR not estimable), parkinsonism (2 RCTs, n=327, RR 0.78 CI 0.30 to 2.00), rigor (1 RCT, n=980, RR 6.00 CI 0.73 to 49.65) or use of antiparkinson medication (6 RCTs, n=561, RR 1.14 CI 0.60 to 2.19).

3.7.7 Extrapyramidal effects - scale measured: There was no significant difference in akathisia (BAS: 1 RCT, n=175, WMD 0.10 CI −0.18 to 0.38; Hillside Akathisia Scale: 1 RCT, n=137, WMD 0.40 CI −2.30 to 3.10), dyskinesia (AIMS: 3 RCTs, n=352, WMD −0.13 CI −0.51 to 0.25) or overall extrapyramidal side-effects (ESRS: 1 RCT, n=79, WMD −1.30 CI −2.83 to 0.23; SAS: 6 RCTs, n=481, WMD −0.43 CI −1.30 to 0.45).

3.7.8 Haematological - white blood cells - low white blood cell count: Significantly fewer participants in the olanzapine groups had a low white blood cell count (4 RCTs, n=1264, RR 0.18 CI 0.08 to 0.41, NNT 20 CI 14 to 33).

3.7.9 Prolactin - change from baseline in ng/ml: In three studies olanzapine was associated with more prolactin increase than clozapine, although the amount of the difference varied. One study reported prolactin increase for men and women combined (n=120, WMD 0.57 CI 0.09 to 1.05), two studies for men only (2 RCTs, n=47, WMD 8.65 CI −3.26 to 20.55, I^2 = 63%), and one study for women only (n=18, WMD 54.40 CI 22.06 to 86.74).

3.7.10 Metabolic - cholesterol - number of participants with a cholesterol increase: There was no significant difference (1 RCT, n=25, RR 0.31 CI 0.01 to 6.94).

3.7.11 Metabolic - cholesterol - mean change from baseline in mg/dl: There was no significant difference (3 RCTs, n=89, WMD 1.16 CI −17.52 to 19.85).

3.7.12 Metabolic - glucose - number of participants with diabetes mellitus: There was no significant difference (1 RCT, n=980, RR 1.31 CI 0.69 to 2.48).

3.7.13 Metabolic - glucose - change from baseline in mg/dl: There was no significant difference (3 RCTs, n=89, WMD −2.62 CI −16.34 to 11.09). The results were heterogeneous, because two studies found no difference (Volavka 2002: n=39, WMD 9.90 CI −3.50 to 23.30; Conley 2003: n=12, WMD −7.40 CI −28.15 to 13.35), while a single first episode study found a superiority of olanzapine (Kumra 2007: n=38, WMD −10.10 CI −18.74 to −1.46).

3.7.14 Metabolic - weight gain - number of participants with weight gain: Weight gain was either reported as 'the number of participants with significant weight gain' or as 'weight gain reported as an adverse event'. Overall, there was no significant difference (7 RCTs, n= 1600, RR 1.13 CI 0.70 to 1.81), but the data were heterogeneous I^2 = 73%. When both categories were analysed separately there was no significant difference in 'the number of participants with significant weight gain' (3 RCTs, n=232, RR 0.92 CI 0.40 to 2.13), whereas 'weight gain reported as an adverse event' indicated a significant difference in favour of clozapine (4 RCTs, n=1368, RR 1.67 CI 1.39 to 2.01, NNH not estimable).

3.7.15 Metabolic - weight gain - mean change from baseline in kg: There was no significant difference (7 RCTs, n=581, WMD 0.04 CI −0.97 to 1.06).

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

3.9 Investigation for heterogeneity and sensitivity analyses: After excluding two studies due to possibly skewed data from the analysis of the BPRS total score (Wang 2002, Kumra 2007) the significant superiority of clozapine disappeared. When Kumra 2007 (possibly skewed data) was excluded from the analysis of the SANS total score clozapine was significantly more efficacious than olanzapine.

4. Comparison 4. OLANZAPINE versus QUETIAPINE—Thirteen included studies (Atmaca 2003, Kinon 2006b, Lieberman 2005, McEvoy 2006, McEvoy 2007, Mori 2004, Ozguven 2004, Riedel 2007, Sacchetti 2004, Sirota 2006, Stroup 2006, Svestka 2003b, Voruganti 2007) compared olanzapine with quetiapine.

4.1 Global state

4.1.1 Global state - no clinically significant response - as defined by the original studies: There was no significant difference (3 RCTs, n=339, RR 0.90 CI 0.70 to 1.16).

4.1.2 Global state - no clinically important change: There was no significant difference in the overall analysis (2 RCTs, n=309, RR 0.85 CI 0.64 to 1.13),

as well as in the short term data analysis (1 RCT, n=42, RR 0.73 CI 0.32 to 1.69) and in the medium term data analysis (1 RCT, n=267, RR 0.86 CI 0.64 to 1.17).

4.2 Leaving the study early: Significantly fewer participants in the olanzapine group (57%) than in the quetiapine group (70%) left the studies early due to any reason (10 RCTs, RR 0.82 CI 0.76 to 0.88, NNT 10 CI 6 to 33), as well as due to lack of efficacy (14% versus

25%, 8 RCTs, n=1563, RR 0.56 CI 0.44 to 0.70, NNT 11 CI 6 to 50). There was no significant difference in the number of participants leaving the studies early due to adverse events (8 RCTs, n=1573, RR 1.11 CI 0.85 to 1.46).

4.3 Mental state

4.3.1 General - no clinically important change - less than 50% PANSS total score reduction: There was no significant difference (1 RCT, n=42, RR 1.10 CI 0.65 to 1.86).

4.3.2 General - average endpoint score - PANSS total: Olanzapine improved the general mental state as measured by the PANSS total score more than quetiapine (10 RCTs, n=1449, WMD −3.66 CI −5.39 to −1.93), which was not significant in short term data (4 RCTs, n=142, WMD −2.17 CI −5.85 to −1.51) but in medium (3 RCTs, n=482, WMD −5.57 CI −9.17 to −1.97) and long term data (3 RCTs, n=825, WMD −3.40 CI −5.88 to −0.91) there was a benefit for olanzapine.

4.3.3 Positive symptoms - no clinically important change - less than 20% SAPS total score reduction: Only one study used the SAPS to examine positive symptoms and found only a trend in favour of olanzapine (1 RCT, n=30, RR 0.07 CI 0.00 to 1.07).

4.3.4 Positive symptoms - average score at endpoint - PANSS positive subscore: Olanzapine improved positive symptoms as measured by the PANSS positive subscore significantly better than quetiapine (7 RCTs, n=679, WMD −1.80 CI −2.59 to −1.02), which was not significant in short term data (3 RCTs, n=115, WMD −1.05 CI −2.85 to 0.75) but in medium (3 RCTs, n=483, WMD −2.21 CI −3.52 to −0.90) and long term data (1 RCT, n=81, WMD −1.80 CI −3.21 to −0.39)

4.3.5 Positive symptoms - average score at endpoint - SAPS total score - percent change: There was a significant difference favouring olanzapine (1 RCT, n=30, WMD −40.84 CI −57.71 to −23.97).

4.3.6 Negative symptoms - no clinically important change - less than 20% SANS total score reduction: There was no significant difference (1 RCT, n=30, RR 0.67 CI 0.23 to 1.89).

4.3.7 Negative symptoms - average score at endpoint - PANSS negative: There was no significant difference in the overall analysis (7 RCTs, n=679, WMD −0.41 CI −1.18 to 0.36), as well as in the short term data (3 RCTs, n=115, WMD −0.01 CI −1.73 to 1.72) medium term data

(3 RCTs, n=484, WMD −0.40 CI −1.47 to 0.67) and long term data analysis (1 RCT, n=81, WMD −0.70 CI −2.13 to 0.73)

4.3.8 Negative symptoms - average score at endpoint - SANS total: There was no significant difference (1 RCT, n=335, WMD −3.70 CI −7.88 to 0.48).

4.3.9 Negative symptoms - average score at endpoint - SANS total score - percent change: There was no significant difference (1 RCT, n=30, WMD −2.46 CI −36.82 to 31.90).

4.4 General functioning - average score at endpoint - GAF total score: There was a statistically significant difference favouring olanzapine (1 RCT, n=278, WMD −3.80 CI −6.83 to −0.77).

4.5 Quality of life - average score at endpoint - QLS total: There was no significant difference (1 RCT, n=286, WMD −1.80 CI −6.02 to 2.42).

4.6 Service use - number of participants rehospitalised: There was a statistically significant difference favouring olanzapine (2 RCTs, n=876, RR 0.56 CI 0.41 to 0.77, NNT 11 CI 7 to 25), this tendency was seen in both medium term (1 RCT, n=203, RR 0.56 CI 0.28 to 1.08) and long term data but the difference was significant in the long term data analysis ((1 RCT, n=673, RR 0.56 CI 0.39 to 0.81, NNT 11 CI 7 to 25).

4.7 Adverse effects

4.7.1 Number of participants with at least one adverse effect: There was no significant difference (6 RCTs, n=1269, RR 1.04 CI 0.95 to 1.13).

4.7.2 Death: There was no significant difference in the number of suicides (2 RCT, n=470, RR 0.20 CI 0.01 to 4.16) and suicide attempts (2 RCTs, n=940, RR 2.86 CI 0.44 to 18.71).

4.7.3 Cardiac effects - number of participants with QTc prolongation: There was no significant difference (1 RCT, n=673, RR 0.08 CI 0.00 to 1.36).

4.7.4 Cardiac effects - change of QTc interval from baseline in ms: Quetiapine was associated with a significantly longer mean increase of the QTc interval than olanzapine (3 RCTs, n=643, WMD −4.81 CI −9.28 to −0.34).

4.7.5 Central nervous system - sedation: There was no significant difference (7 RCTs, n=1615, RR 1.01 CI 0.88 to 1.15).

4.7.6 Central nervous system - seizures: There was no significant difference (1 RCT, n=40, RR 0.30 CI 0.01 to 7.02).

4.7.7 Extrapyramidal effects: There was no significant difference in the following extrapyramidal side effects: akathisia (6 RCTs, n=1277, RR 1.03 CI 0.72 to 1.47), akinesia (1 RCT, n=267, RR 0.98 CI 0.64 to 1.49), dystonia (1 RCT, n=42, RR 0.22 CI 0.01 to 4.30), ‘extrapyramidal symptoms’ (2 RCTs, n=245, RR 0.62 CI 0.27 to 1.39), parkinsonism (1 RCT, n=40, RR 1.51 CI 0.42 to 5.48), and tremor (1 RCT, n=42, RR 2.57 CI 0.77 to 8.60). Nevertheless, significantly fewer participants in the quetiapine group received at least one dose of antiparkinson medication (6 RCTs, n=1090, RR 2.05 CI 1.26 to 3.32, NNH 25 CI 14 to 100).

4.7.8 Extrapyramidal effects - scale measured: There was no significant difference of data in akathisia (BAS: 1 RCT, n=50, WMD 0.10 CI −0.38 to 0.58) or general extrapyramidal side effects (ESRS total score: 1 RCT, n=33, WMD 0.00 CI −2.68 to 2.68; SAS: 1 RCT, n=50, WMD −0.60 CI −2.58 to 1.38).

4.7.9 Prolactin associated side effects: There was no significant difference in the number of participants with an abnormally high prolactin value (1 RCT, n=42, RR 9.86 CI 0.56 to 172.33), amenorrhoea (3 RCTs, n=252, RR 1.51 CI 0.83 to 2.76), galactorrhoea (4 RCTs, n=1015, RR 1.52 CI 0.58 to 3.98) and gynaecomastia (1 RCT, n=267, RR 3.02 CI 0.84 to 10.92). Significantly fewer people in the quetiapine group reported sexual dysfunctions (4 RCTs, n=1177, RR 1.25 CI 1.01 to 1.55, NNH 20 CI 10 to 100).

4.7.10 Prolactin - change from baseline in ng/ml: Olanzapine was associated with significantly more prolactin increase than quetiapine (5 RCTs, n=1021, WMD 5.89 CI 0.16 to 11.62). The results were heterogeneous, but the direction of the effect was the same in all single studies. The small first episode study by Svestka 2003b found an especially pronounced difference (n=35, WMD 40.07 CI 16.04 to 64.10).

4.7.11 Metabolic - cholesterol - number of participants with cholesterol increase: There was no significant difference (1 RCT, n=267, RR 1.01 CI 0.60 to 1.70).

4.7.12 Metabolic - cholesterol - mean change from baseline in mg/dl: Overall, there was no significant difference between groups (4 RCTs, n=986, WMD 4.69 CI −4.45 to 13.84).

The results were heterogeneous, because the first episode study by McEvoy 2007 showed a trend in favour of olanzapine, while in all other studies olanzapine was associated with more cholesterol increase than quetiapine. Indeed, excluding McEvoy 2007 there was a significant superiority of quetiapine (3 RCTs, n=905, WMD 7.84 CI 1.57 to 14.12).

4.7.13 Metabolic - glucose - number of participants with abnormally high fasting glucose value: There was no significant difference (1 RCT, n=267, RR 1.41 CI 0.65 to 3.06).

4.7.14 Metabolic - glucose - change from baseline in mg/dl: There was a statistical significant difference favouring quetiapine (4 RCTs, n=986, WMD 9.32 CI 0.82 to 17.82). The data were heterogeneous, because again the first episode study by McEvoy 2007 showed a different direction of the effect than the other three studies. Excluding McEvoy 2007, statistical significance prevailed (3 RCTs, n=905, WMD 14.04 CI 2.44 to 25.65).

4.7.15 Metabolic - weight gain - number of participants with weight gain: Weight gain was reported either as ‘significant weight gain’ (as defined by the original studies)’ or as ‘weight gain reported as an adverse event’. Overall fewer participants in the quetiapine group gained weight (8 RCTs, n=1667, RR 1.47 CI 1.09 to 1.98, NNH not estimable).

4.7.16 Metabolic - weight gain - change from baseline in kg: There was a statistically significant difference favouring quetiapine (7 RCTs, n=1173, WMD 2.68 CI 1.10 to 4.26).

The results were heterogeneous, but all studies consistently favoured quetiapine concerning this outcome.

4.8 Publication bias: The funnel plot for the outcome PANSS total score (10 included studies) did not suggest a publication bias.

4.9 Investigation for heterogeneity and sensitivity analyses: Excluding Mori 2004 from the outcome 'PANSS positive subscore' due to potentially skewed data the results remained significant

5. Comparison 5. OLANZAPINE versus RISPERIDONE—Twenty-three included studies (Atmaca 2003, Canive 2000, Conley 2001, Dollfus 2005, Dolnak 2001, Gureje 2003, Jeste 2003, Keefe 2006, Lieberman 2005, McEvoy 2006, McEvoy 2007, Mori 2004, Purdon 2000, Robinson 2006, Sacchetti 2004, Sikich 2004, Stroup 2006, Svestka 2003a, Tran 1997, Van Nimwegen 2006, Volavka 2002, Wang 2006, Wynn 2007) compared olanzapine with risperidone.

5.1 Global state

5.1.1 Global state - no clinically significant response (as defined by the original studies): There was no statistically significant difference (7 RCTs, n=1376, RR 0.94 CI 0.88 to 1.01)

5.1.2 Global state - no clinically important change: Overall, there was no significant difference (5 RCTs, n=975, RR 1.03 CI 0.92 to 1.14), which was similar for all the time periods (short term data (3 RCTs, n=589, RR 1.00 CI 0.86 to 1.15), medium term data (1 RCT, n=120, RR 1.20 CI 0.87 to 1.66) and long term data (1 RCT, n=266, RR 1.02 CI 0.74 to 1.41)).

5.1.3 Global state - relapse: There was no significant difference (2 RCTs, n=211, RR 0.80 CI 0.37 to 1.75), neither in short term (1 RCT, n=76, RR 1.33 CI 0.44 to 4.00) nor long term data (1 RCT, n=135, RR 0.59 CI 0.27 to 1.27).

5.2 Leaving the study early: Significantly fewer participants in the olanzapine group (48%) than in the risperidone group (56%) left the studies early due to any reason (16 RCTs, n=2738, RR 0.88 CI 0.82 to 0.94, NNT 13 CI 9 to 25).

Leaving the studies early due to adverse events did not differ between groups (12% versus 11%, 13 RCTs, n=2595, RR 1.04 CI 0.77 to 1.42). Fewer participants in the olanzapine group (11%) than in the risperidone group (15%) left the studies early due to inefficacy of treatment (14 RCTs, n=2744, RR 0.78 CI 0.62 to 0.98, NNT 50 CI 17 to 100).

5.3 Mental State

5.3.1 General - no clinically important change - less than 50% PANSS total score reduction: There was a tendency that more participants in the olanzapine group than in the risperidone group responded to treatment (3 RCTs, n=472, RR 0.92 CI 0.85 to 1.00, NNT not estimable), this was rather due to longterm data (2 RCTs, n=401, RR 0.92 CI 0.85 to 1.00, NNT not estimable) than short term data (1 RCT, n=71, RR 2.30 CI 0.22 to 24.26).

5.3.2 General - no clinically important change - less than 20% PANSS total score reduction: There was no significant difference (2 RCTs, n=553, RR 0.98 CI 0.84 to 1.14).

5.3.3 General - average score at endpoint - PANSS total: Olanzapine improved the general mental state as measured by the PANSS total score more than risperidone (15 RCTs, n=2390, WMD −1.94 CI −3.31 to −0.58), which was significantly different in long term data (5 RCTs, n=1431, WMD −2.59 CI −4.98 to −0.20), whereas short term (7 RCTs, n=728, WMD −0.97 CI −3.05 to 1.10) and medium term data (3 RCTs, n=231, WMD −4.11 CI −8.93 to 0.71) indicated the same direction, but did not show a significant difference

5.3.4 General - average score ate endpoint - BPRS total: Again, olanzapine improved the general mental state more than risperidone in the overall analysis (3 RCTs, n=428, WMD −4.16 CI −8.29 to −0.03).

5.3.5 Positive symptoms - no clinically important change (less than 50% PANSS positive subscore reduction): There was no significant difference (1 RCT, n=377, RR 1.02 CI 0.96 to 1.07).

5.3.6 Positive symptoms - average score at endpoint - PANSS positive: There was no significant difference in the overall analysis (13 RCTs, n=1702, WMD −0.46 CI −1.02 to 0.09), short term data (5 RCT, n=661, WMD 0.48 CI −0.57 to 1.53), medium term data (3 RCT, n=231, WMD −1.58 CI −3.20 to 0.03) and long term data (5 RCT, n=810, WMD −0.68 CI −1.40 to 0.04).

5.3.7 Negative symptoms - average score at endpoint - PANSS negative: There was no significant difference (13 RCTs, n=1702, WMD −0.44 CI −0.96 to 0.08), short term data (5 RCT, n=661, WMD −0.19 CI −1.22 to 0.85), medium term data (3 RCT, n=231, WMD −0.00 CI −1.59 to 1.58) and long term data (5 RCT, n=810, WMD −0.81 CI −1.54 to −0.07).

5.3.8 Negative symptoms - average score at endpoint - SANS total: There was a significant difference favouring olanzapine (1 RCT, n=308, WMD −1.40 CI −2.43 to −0.37).

5.4 Quality of life - average score at endpoint - QLS total score: There was a significant difference in favour of olanzapine (2 RCTs, n=296, WMD −5.10 CI −9.10 to −1.09).

5.5 Cognitive functioning

5.5.1 Cognitive functioning - no clinically important change (less than half a standard deviation improvement of the Global Neurocognitive Score): There was no significant difference (1 RCT, n=80, RR 0.77 CI 0.52 to 1.14).

5.5.2 Global neurocognitive score - average score at endpoint: There was no significant difference (1 RCT, n=52, WMD −0.04 CI −0.39 to 0.31).

5.5.3 Neurocognitive composite score - average score at endpoint: There was no significant difference (1 RCT, n=263, WMD −0.01 CI −0.13 to 0.11).

5.6 Service use - number of participants re-hospitalised: There was no significant difference (3 RCTs, n=965, RR 0.75 CI 0.54 to 1.04).

5.7 Adverse effects

5.7.1 Number of participants with at least one adverse effect: There was no significant difference (11 RCTs, n=2576, RR 1.05 CI 0.97 to 1.13).

5.7.2 Death: There was no significant difference in the number of participants dying due to any reason (1 RCT, n=339, RR 0.32 CI 0.01 to 7.89), due to natural causes (2 RCTs, n=252, RR 2.93 CI 0.12 to 71.04) or suicide (4 RCTs, n=730, RR 0.32 CI 0.01 to 7.79). There was also no clear difference in the number of suicide attempts (5 RCTs, n=1724, RR 0.87 CI 0.28 to 2.67).

5.7.3 Cardiac effects: Cardiac effects were reported as 'ECG abnormalities' (2 RCTs, n= 415, RR 2.39 CI 0.43 to 13.14) and 'QTc prolongation'. There were no significant differences. As the results of the latter outcome were heterogeneous I^2 = 74%, we present the results of the two single studies separately (Jeste 2003: n=176, RR 1.30 CI 0.30 to 5.65; Lieberman 2005: n=677, RR 0.07 CI 0.00 to 1.18).

5.7.4 Cardiac effects - mean change of QTc interval from baseline in ms: There was no significant difference (6 RCTs, n=1518, WMD −0.96 CI −4.67 to 2.74).

5.7.5 Central nervous system - sedation: There was no significant difference (11 RCTs, n=2576, RR 1.07 CI 0.96 to 1.19).

5.7.6 Central nervous system - seizures: There was no significant difference (4 RCTs, n=671, RR 3.82 CI 0.43 to 34.35).

5.7.7 Extrapyramidal effects: Significantly fewer participants in the olanzapine group than in the risperidone group suffered from akathisia (8 RCTs, n=1988, RR 0.77 CI 0.60 to 0.98, NNH not estimable) and parkinsonism (4 RCTs, n=776, RR 0.61 CI 0.40 to 0.92, NNH not estimable) or needed antiparkinson medication (13 RCTs, n=2599, RR 0.78 CI 0.65 to 0.95, NNH 17 CI 9 to 100). There was no significant difference in other extrapyramidal side effects such as akinesia (3 RCTs, n=681, RR 0.83 CI 0.56 to 1.23), dyskinesia (3 RCTs, n=580, RR 0.98 CI 0.34 to 2.80), dystonia (3 RCTs, n=591, RR 0.56 CI 0.11 to 2.73), rigor (2 RCTs, n=141, RR 2.44 CI 0.37 to 16.14), and tremor (5 RCTs, n=973, RR 1.15 CI 0.64 to 2.08) or 'extrapyramidal symptoms' (4 RCTs, n=1104, RR 0.75 CI 0.47 to 1.21). The results of the latter outcome were heterogeneous I^2 = 62%, we therefore also present the results of the single studies separately, (Tran 1997: n=339, RR 0.59 CI 0.40 to 0.87, Conley 2001: n=377, RR 0.84 CI 0.57 to 1.23, Jeste 2003: n=176, RR 1.71 CI 0.76 to 3.87 and Stroup 2006: n=212, RR 0.32 CI 0.11 to 0.96).

5.7.8 Extrapyramidal effects - scale measured: There was no significant difference in akathisia (BAS: 2 RCTs, n=353, WMD −0.72 CI −1.81 to 0.36; but the data were extremely heterogeneous, I^2 = 94%; ESRS akathisia subscore: 1 RCT, n=359, WMD 0.00 CI −0.27 to 0.27), dyskinesia (AIMS: 1 RCT, n=302, WMD −0.03 CI −0.78 to 0.72; ESRS dyskinesia

subscore: 3 RCTs, n=572, WMD 0.08 CI −0.60 to 0.76), dystonia (ESRS dystonia subscore: 1 RCT, n=42, WMD 0.09 CI −0.73 to 0.91), overall extrapyramidal symptoms (ESRS total score: 4 RCTs, n= 682, WMD −0.30 CI −0.94 to 0.35; SAS: 5 RCTs, n=522, WMD −0.62 CI −1.33 to 0.08; I^2 = 60%) or parkinsonism (ESRS parkinsonism subscore: 3 RCTs, n=572, WMD −0.24 CI −1.57 to 1.09; I^2 = 58%). It should be noted that several of these results were heterogeneous, but no clear reason for the heterogeneity could be identified.

5.7.9 Haematological - white blood cells - number of participants with low white blood cell count: Overall there was no significant difference (3 RCTs, n=484, RR 1.00 CI 0.09 to 10.59). The results of the three studies were heterogeneous I^2 = 56%, but the single trials did not show significant differences between olanzapine and risperidone either (Tran 1997: n=339, RR 6.80 CI 0.85 to 54.64; Volavka 2002: n=80, RR 0.21 CI 0.01 to 4.24; Gureje 2003: n=65, RR 0.34 CI 0.01 to 8.13).

5.7.10 Prolactin associated side effects: Significantly fewer participants in the olanzapine group suffered from amenorrhoea (7 RCTs, n=565, RR 0.67 CI 0.45 to 0.98, NNH not estimable) and ‘abnormal ejaculation’ (3 RCTs, n=531, RR 0.23 CI 0.08 to 0.67, NNH not estimable). Fewer participants in the olanzapine group had abnormally high prolactin levels, but this result did not reach conventional levels of statistical signifcance (3 RCTs, n=477, RR 0.33 CI 0.11 to 1.01).There were no significant differences in decreased libido (3 RCTs, n=781, RR 0.40 CI 0.12 to 1.30), galactorrhea (7 RCTs, n=547, RR 0.61 CI 0.30 to 1.26), gynaecomastia (5 RCTs, n=1083, RR 0.72 CI 0.36 to 1.42), impotence (3 RCTs, n=531, RR 0.50 CI 0.17 to 1.47), orgastic dysfunction (1 RCT, n=377, RR 0.20 CI 0.01 to 4.12) and sexual dysfunction (7 RCTs, n=1715, RR 0.93 CI 0.78 to 1.11).

5.7.11 Prolactin - mean change from baseline in ng/ml: Olanzapine was associated with significantly less prolactin increase than risperidone (men and women combined: 6 RCTs, n=1291, WMD −22.84 CI −27.98 to −17.69; men only: 2 RCTs, n=70, WMD −19.91 CI −26.18 to −13.64; women only: 1 RCT, n=71, WMD −41.40 CI −53.16 to −29.64). There was some heterogeneity in the degree of the difference, but all studies consistently favoured olanzapine.

5.7.12 Metabolic - cholesterol - number of participants with cholesterol increase: There was no significant difference (1 RCT, n=266, RR 1.28 CI 0.72 to 2.26).

5.7.13 Metabolic - cholesterol - change from baseline in mg/dl: There was a significant difference in favour of risperidone (7 RCTs, n=1391, WMD 10.36 CI 6.28 to 14.43).

5.7.14 Metabolic - glucose - number of participants with abnormally high glucose value: There was no significant difference (3 RCTs, n=670, RR 1.99 CI 0.87 to 4.60).

5.7.15 Metabolic - glucose - mean change from baseline in mg/dl: Risperidone produced significantly less glucose increase than olanzapine (7 RCTs, n=1201, WMD 7.58 CI 3.93 to 11.23).

5.7.16 Metabolic - weight gain - number of participants with weight gain: Significantly fewer participants in the risperidone group than in the olanzapine group suffered from weight gain (11 RCTs, n=2594, RR 1.81 CI 1.39 to 2.35, NNH 9 CI 7 to 14). Again, there was some heterogeneity I^2 = 52% due to the first episode study McEvoy 2007, but overall the trend was very consistent in favour of risperidone.

5.7.17 Metabolic - weight gain - mean change from baseline in kg: Risperidone was associated with significantly less weight gain than olanzapine (13 RCTs, n=2116, WMD 2.61 CI 1.48 to 3.74). The results were heterogeneous I^2 = 83%, because Atmaca 2003 showed an extreme superiority of risperidone. Excluding this study resolved the heterogeneity and risperidone's superiority remained (12 RCTs, n=2116, WMD 2.06 CI 1.37, 2.74).

5.8 Publication bias: The funnel plot of the PANSS total score (>10 included studies) did not suggest a publication bias.

5.9 Investigation for heterogeneity and sensitivity analyses: We identified some heterogeneity, but clear reasons explaining this could not be found. Excluding (Mori 2004) from the outcome 'PANSS positive score' (skewed data) did not change the result. The exclusion of Sikich 2004 (skewed data) from the analysis of the BPRS total score did not have an important impact on the result.

6. Comparison 6. OLANZAPINE versus ZIPRASIDONE—Six included studies (Breier 2005, Kinon 2006a, Lieberman 2005, Simpson 2004, Stroup 2006, Svestka 2005) compared olanzapine with ziprasidone.

6.1 Global state

6.1.1 Global state - no clinically significant response - as defined by the original studies: There was no significant difference (2 RCTs, n=817, RR 0.83 CI 0.64 to 1.09), but the studies were heterogeneous, I^2 = 84%. In Simpson 2004 (maximum olanzapine dose 15mg/day) there was no significant difference (n=269, RR 0.94 CI 0.83 to 1.06), whereas in Breier 2005 (maximum olanzapine dose 20mg/day) olanzapine was superior (n=548, RR 0.73 CI 0.62 to 0.87).

6.1.2 Global state - no clinically important change: There was no significant difference (1 RCT, n=269, RR 0.84 CI 0.65 to 1.09).

6.2 Leaving the study early: Fewer participants in the olanzapine group (53%) than in the ziprasidone group (66%) left the studies early due to any reason (5 RCTs, n=1937, RR 0.79 CI 0.74 to 0.85, NNT 7 CI 5 to 10). Olanzapine was also superior in the number of participants leaving the studies early due to lack of efficacy (12% versus 19%; 5 RCTs, n=1937, RR 0.64 CI 0.51 to 0.79, NNH 17 CI 11 to 33). A similar number of participants left the studies early due to adverse events (12% versus 13%, 5 RCTs, n=1937, RR 0.90 CI 0.62 to 1.29).

6.3 Mental State

6.3.1 General - no clinically important change - less than 30% PANSS total score reduction: There was a significant difference favouring olanzapine (1 RCT, n=548, RR 0.73 CI 0.62 to 0.87, NNH 6 CI 4 to 14).

6.3.2 General - no clinically important change - less than 40% BPRS total score reduction: There was no significant difference (1 RCT, n=269, RR 0.94 CI 0.83 to 1.06)

6.3.3 General - average score at endpoint - PANSS total: Olanzapine improved the general mental state significantly more than ziprasidone in the overall analysis (PANSS total score: 4 RCTs, n=1291, WMD −8.32 CI −10.99 to −5.64). Short term (1 RCT, n=48, WMD −8.37 CI −18.74 to 2.00) medium term (1 RCT, n=201, WMD −6.50 CI −13.07 to 0.07) and long term data (2 RCTs, n=1042, WMD −6.50 CI −13.07 to 0.07) indicated the same direction.

6.3.4 General - average score at endpoint - BPRS total: There was no significant difference (1 RCT, n=251, WMD −0.50 CI −3.85 to 2.85).

6.3.5 Positive symptoms - average score at endpoint - PANSS positive: Olanzapine improved positive symptoms as measured by the PANSS positive subscore significantly better than ziprasidone in the overall analysis (2 RCTs, n=730, WMD −3.11 CI −4.30 to −1.93) as well as in medium term (1 RCT, n=201, WMD −3.60 CI −5.75 to −1.45), and long term data (1 RCT, n=529, WMD −2.90 CI −4.33 to −1.47).

6.3.6 Negative symptoms - average score at endpoint - PANSS negative: There was no significant difference (2 RCTs, n=730, WMD −0.68 CI −3.81 to 2.45), but the results were heterogeneous, I^2 = 87%. Stroup 2006 found no difference between groups (n=201, WMD 1.00 CI −0.91 to 2.91), whereas Breier 2005 significantly favoured olanzapine (1 RCT, n=529, WMD −2.20 CI −3.48 to −0.92).

6.4 General functioning

6.4.1 General functioning - no clinically important change (less than 5 points improvement on GAF total score): More participants in the olanzapine had an improvement of general functioning (1 RCT, n=394, RR 0.83 CI 0.71 to 0.98, NNT 9 CI 5 to 50).

6.4.2 General functioning - average score at endpoint - GAF total: Data on this outcome showed a significant difference in favour of olanzapine (1 RCT, n=326, WMD −3.49 CI −6.34 to −0.64).

6.5 Quality of life - average endpoint score - QLS total (Heinrichs-Carpenter Scale): There was no significant difference (1 RCT, n=393, WMD −3.70 CI −8.61 to 1.21).

6.6 Cognitive functioning - average endpoint score - PANSS cognitive subscore: Olanzapine improved cognitive function more than ziprasidone (1 RCT, n=529, WMD −2.40 CI −3.63 to −1.17).

6.7 Service use - number of participants rehospitalised: There was a significant difference in favour of olanzapine in the overall analysis (2 RCTs, n=766, RR 0.65 CI 0.45 to 0.93, NNT 17 CI 9 to 100), medium term (1 RCT, n=245, RR 0.69 CI 0.36 to 1.33) an and long term data (1 RCT, n=521, RR 0.63 CI 0.41 to 0.98, NNT not estimable).

6.8 Adverse effects

6.8.1 Numbers of participants with at least one adverse effect: Overall there was no significant difference (4 RCTs, n=1583, RR 0.95 CI 0.85 to 1.07). There was some heterogeneity I^2 = 62%, but we did not find obvious reasons for the heterogeneity. In Simpson 2004 olanzapine was superior (n=269, RR 0.84 CI 0.74 to 0.96), whereas Breier 2005 (n=548, RR 0.93 CI 0.85 to 1.02), Lieberman 2005 (n=521, RR 1.09 CI 0.96 to 1.24) and Stroup 2006 (1 RCT, n=245, RR 0.97 CI 0.64 to 1.46) reported no significant differences.

6.8.2 Death: There was no significant difference in the number of suicides (1 RCT, n=245, RR 0.25 CI 0.01 to 5.22) and suicide attempts (1 RCT, n=521, RR 1.10 CI 0.10 to 12.06).

6.8.3 Cardiac effects - number of participants with QTc prolongation: Overall there was no significant difference between olanzapine and ziprasidone (3 RCT, n=521, RR 0.63 CI 0.04 to 9.93). There was some heterogeneity I^2 = 65%, but the single studies did not find a significant difference either (Simpson 2004: n=269, RR not estimable; Lieberman 2005 n=521, RR 0.11 CI 0.01 to 2.29; Kinon 2006a (1 RCT, n=394, RR 1.90 CI 0.48 to 7.49).

6.8.4 Cardiac effects - mean change of QTc interval from baseline in ms: There was no significant difference (4 RCTs, n=1372, WMD −2.19 CI −4.96 to 0.58).

6.8.5 Central nervous system - sedation: There was no significant difference (2 RCTs, n=766, RR 1.56 CI 0.96 to 2.55). The results of the two studies were heterogeneous, I^2 = 63%. Stroup 2006 found a significant superiority of ziprasidone (n=245, RR 2.11 CI 1.25 to 3.58), whereas in Lieberman 2005 the superiority was less pronounced (n=521, RR 1.27 CI 0.94 to 1.72).

6.8.6 Extrapyramidal effects: There was no significant difference in the number of participants suffering from akathisia (2 RCTs, n=766, RR 0.71 CI 0.40 to 1.28), dystonia (1 RCT, n=548, RR 0.08 CI 0.00 to 1.33) or extrapyramidal symptoms (2 RCTs, n=793, RR 0.53 CI 0.21 to 1.31). Nevertheless, fewer participants in the olanzapine groups needed at least one dose of antiparkinson medication (4 RCTs, n= 1732, RR 0.70 CI 0.50 to 0.97, NNH not estimable).

6.8.7 Extrapyramidal effects - scale measured: There was no significant difference in dyskinesia (AIMS: 2 RCTs, n=925, WMD −0.16 CI −0.46 to 0.15), akathisia (BAS: 2 RCTs, n=924, WMD −0.07 CI −0.17 to 0.04) or general EPS (ESRS total score: 1 RCT, n=269, WMD −0.40 CI −1.53 to 0.73; SAS: 2 RCTs, n=922, WMD −0.34 CI −0.81 to 0.13).

6.8.8 Prolactin associated side effects: There was no significant difference in the number of participants with an abnormally high prolactin value (1 RCT, n=394, RR 1.12 CI 0.74 to

1.71), amenorrhoea (1 RCT, n=148, RR 0.84 CI 0.36 to 1.95), galactorrhoea (2 RCTs, n=597, RR 0.64 CI 0.22 to 1.88) or sexual dysfunction (2 RCTs, n=766, RR 1.33 CI 0.99 to 1.79).

6.8.9 Prolactin - change from baseline in ng/ml: There was no significant difference (3 RCTs, n=1079, WMD −0.20 CI −3.72 to 3.33).

6.8.10 Metabolic - cholesterol - number of participants with cholesterol increase: There was no significant difference (1 RCT, n=394, RR 1.43 CI 0.24 to 8.44).

6.8.11 Metabolic - cholesterol - mean change from baseline in mg/dl: Olanzapine was associated with significantly more cholesterol increase than ziprasidone (4 RCTs, n=1502, WMD 15.83 CI 5.95 to 25.72). There was some heterogeneity, I^2 = 87%, in the degree of the difference, but the direction of the effect consistently favoured ziprasidone (Breier 2005: n=418, WMD 7.39 CI 4.35 to 10.43; Lieberman 2005: n=521, WMD 18.90 CI 7.91 to 29.89; Kinon 2006a: n=318, WMD 9.43 CI 2.04 to 16.82; Stroup 2006: n= 245, WMD 30.40 CI 20.97 to 39.83).

6.8.12 Metabolic - glucose - number of participants with abnormally high fasting glucose: There was no significant difference (1 RCT, n=394, RR 0.95 CI 0.14 to 6.68).

6.8.13 Metabolic - glucose - change from baseline in mg/dl: Olanzapine was associated with significantly more glucose increase than ziprasidone (4 RCTs, n=1420, WMD 8.25 CI 2.77 to 13.72).

6.8.14 Metabolic - weight gain - number of participants with weight gain: More participants in the olanzapine group than in the ziprasidone group had weight gain (4 RCTs, n=1708, RR 4.90 CI 3.38 to 7.12, NNH 6 CI 5 to 10).

6.8.15 Metabolic - weight gain - mean change from baseline in kg: Olanzapine produced significantly more weight gain than ziprasidone (5 RCTs, n=1659, WMD 3.82 CI 2.96 to 4.69). There was some heterogeneity, I^2 = 59%, in the degree of weight gain, but the direction of the effect was the same in all single studies (Simpson 2004: n=238, WMD 2.62 CI 1.32 to 3.92; Breier 2005: n=529, WMD 4.18 CI 3.18 to 5.18; Lieberman 2005: n=468, WMD 5.00 CI 3.75 to 6.25; Svestka 2005: n=48, WMD 2.12 CI −0.12 to 4.36; Kinon 2006a: n=376, WMD 4.18 CI 3.26 to 5.10).

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

6.10 Investigation for heterogeneity and sensitivity analyses: The reasons for the preplanned sensitivity analyses did not apply and were therefore not performed.

DISCUSSION

Summary of main results

1. General—In the last years the number of randomised olanzapine trials has dramatically increased. A previous Cochrane review comparing olanzapine with any other treatment included 55 studies (Duggan 2005). The current review includes 50 RCTs, although we included only comparisons of olanzapine with other second generation antipsychotic drugs and we excluded open RCTs. Nevertheless, the many problems that were identified by the previous review have not been solved.

The number of participants leaving schizophrenia trials prematurely remain high (Wahlbeck 2001). The overall attrition of 49% in the included studies is a threat to the validity of the findings. Often adverse events were only reported if they had a frequency of 10% or greater. This procedure results in underreporting of rare but important adverse effects. We suggest to abandon the >10% frequency rule for reporting of adverse effects and suggest that all adverse events should be reported instead, for example as online supplements, that are nowadays made available by most journals. Most trials provide data on leaving the studies early and overall efficacy. Outcomes that are possibly more important for daily life such as general functioning or satisfaction with treatment are rarely presented. Authors keep using different criteria for 'response to treatment' making comparisons difficult, although validated suggestions for the presentation of response to treatment are available (Van Os 2006, Leucht 2005a, Leucht 2005b).

Half of the fifty included trials were categorised as 'short term' studies and only nine 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.

Thirty-one studies were sponsored by pharmaceutical companies producing either olanzapine or its comparator drugs, whereas only fifteen studies had a neutral sponsor. Due to the inevitable conflict of interest, industry sponsorship is a concern (Heres 2006).

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

2. Comparison 1. OLANZAPINE versus AMISULPRIDE

2.1 Efficacy outcomes (global state, overall and specific mental state): Efficacy related outcomes that were measured with the Clinical Global Impression Scale, the PANSS total score and its positive and negative symptoms subscores, the BPRS total score and the SANS total score showed no significant difference between groups. Olanzapine and amisulpride may thus be similarly efficacious. Nevertheless, this finding should be cautiously interpreted, because all studies were sponsored by the manufacturers of either olanzapine or amisulpride.

2.2 Leaving the studies early: There was no significant difference between olanzapine and amisulpride in the number of participants leaving the studies early, neither due to any

reason, nor due to adverse events or inefficacy of treatment. This suggests that both compounds may be similarly acceptable for people with schizophrenia, at least within the confines of a trial. Nevertheless, the high discontinuation rate in the five trials of overall 37.2% calls the validity of other findings into question, because the results must be estimated by statistical modelling.

2.3 General functioning and quality of life: Only two studies reported on general functioning and on overall quality of life and found no significant difference between groups. It is disappointing that no more data on these important outcomes are available.

2.4 Cognitive functioning: Only Wagner 2005 examined cognitive function and found no difference between olanzapine and amisulpride. Further studies are needed. Such studies should also try to find out whether differences in cognitive effects are associated with better general functioning, such as an improved ability to work.

2.5 Adverse effects: The reporting of adverse effects was incomplete and usually based on only one or two studies. Some data on extrapyramidal symptoms, cardiac effects, cholesterol, death, glucose, prolactin associated side effects, weight gain, white blood cell count, sedation and seizures are available. Among these olanzapine was associated with significantly more weight gain and increase of glucose levels than amisulpride. Amisulpride may therefore be a preferable drug for people at risk to develop diabetes or metabolic syndrome. It was surprising that prolactin increase has not been reported in the publications, although this is a well known side effect of amisulpride. Nevertheless, the few available data did not show a significant difference in prolactin associated adverse events.

3. Comparison 2. OLANZAPINE versus ARIPIPRAZOLE—Only two studies that presented very limited data could be in included in this comparison. One of the studies had only been presented on the internet (CN138003). It only provided data for the outcomes leaving the study early due to any reason and general mental state.

3.1 Efficacy outcomes (global state, overall and specific mental state): Olanzapine improved the general mental state (PANSS total score) more than aripiprazole. This finding was not confirmed by dichotomous data on response to treatment. Results on specific symptoms of schizophrenia, namely positive and negative symptoms, have not been reported.

3.2 Leaving the studies early: There was no significant difference between groups but the overall rate of participants leaving the two studies early of 40.1% was considerable. It should be noted that one of the two studies (CN138003) did not present data on the specific reasons for leaving the study early. This limited the statistical power to detect significant differences.

3.3 Adverse effects: One study provided some data on extrapyramidal symptoms, cardiac effects, cholesterol, prolactin levels and associated side effects, weight gain and sedation. Among these aripiprazole produced less prolactin increase, weight gain, cholesterol increase and sedation than olanzapine. Therefore, the overall tolerability profile of aripiprazole seems

to be better than that of olanzapine, but it must be kept in mind that this result is based on only one study. Replications are needed.

4. Comparison 3. OLANZAPINE versus CLOZAPINE

4.1 Efficacy outcomes (global state, overall and specific mental state): Although a number of different efficacy domains were addressed there was no clear difference in efficacy between olanzapine and clozapine. This finding was surprising, because clozapine is generally considered to be the most efficacious antipsychotic drug available. This superiority has recently been confirmed by the industry independent studies CATIE II (McEvoy 2006) and CUtLASS (Lewis 2006), which could not be included here. The clozapine group of CATIE II was a non-blinded study arm and CUtLASS compared clozapine with a number of second generation antipsychotics as a group. Almost all studies described including treatment resistant participants, but the criteria of refractoriness varied. Hardly any studies had a run-in phase to confirm refractoriness. A possible explanation for the failure to find clozapine superiorioty may be relatively low clozapine doses. The mean doses in two pivotal studies demonstrating clozapine's superiority to first generation antipsychotic drugs were 600mg/day (Kane 1988) and 523mg/day (Rosenheck 1997). A randomised, blinded dose finding study found that a clozapine dose of 600mg/day was more efficacious than lower doses (Simpson 1999). In contrast, of the 12 trials included in this review only two studies had mean clozapine doses higher than 500mg/day (Volavka 2002: 526mg/day; Krakowski 2006: 565mg/day) and several trials limited the upper clozapine dose range to 400mg/day.

4.2 Leaving the studies early: A similar number of participants in the olanzapine and the clozapine group left the studies early due to any reason, suggesting a similar overall acceptability of treatment of both compounds. The fact that clozapine was associated with somewhat more premature discontinuations due to adverse events was not surprising. Clozapine induces many side-effects such as agranulocytosis, seizures, sedation and weight gain (see below).

4.3 Quality of life: Only a single study (Naber 2005) reported on quality of life and found no difference between olanzapine and clozapine. This finding is certainly not conclusive. It is disappointing that so few data on this important outcome are available.

4.4 Cognitive functioning: Again only one out of twelve included studies reported on cognitive function and used a global cognitive score for this outcome (Volavka 2002). The results are equivocal, because dichotomous data (number of participants with improvement of at least half a standard deviation of the baseline score) suggested a superiority of olanzapine, while the mean change from baseline of the same cognitive score yielded no difference.

4.5 Service use: In a single large study (Meltzer 2003) more participants in the olanzapine group than in the clozapine group had to be re-hospitalised. The difference was small and the NNH could not be calculated, because the risk difference was not significant. No firm conclusion can be drawn.

4.6 Adverse effects: There were no differences in cardiac effects, cholesterol, death, diabetes mellitus, glucose, extrapyramidal side effects and weight gain, but the often small number of trials contributing data to these outcomes must be kept in mind.

Nevertheless, significantly fewer participants in the olanzapine group had 'at least one adverse effect', suffered from sedation, had seizures, and had a low white blood cell count. These are well known side effects of clozapine. It is reassuring that the review was able to document these expected differences in tolerability between olanzapine and clozapine.

On the other hand clozapine was associated with less prolactin increase. Clozapine's very low propensity to increase prolactin levels can be important in specific patients, e.g. women with a history of breast cancer.

There is a theory that clozapine reduces suicide attempts in schizophrenia. This hypothesis has to date been confirmed by only one large RCT (Meltzer 2003), which formed the basis of our review and recorded fewer suicide attempts in the clozapine group.

5. Comparison 4. OLANZAPINE versus QUETIAPINE

5.1 Efficacy outcomes (global state, overall and specific mental state): Olanzapine was more efficacious than quetiapine in a number of measures of the general mental state and positive symptoms. There was no difference in global state, but the interpretation is limited, because only three studies contributed to this outcome. More robust data of seven RCTs suggest that there may be no difference in efficacy for negative symptoms between olanzapine and quetiapine.

5.2 Leaving the study early: Fewer participants in the olanzapine group than in the quetiapine group left the studies early due to any reason. This better acceptability of treatment of olanzapine may be mainly explained by a better efficacy, because olanzapine was also significantly superior in the number of people leaving early due to inefficacy of treatment, whereas there was no difference in the outcome leaving early due to adverse events. This somewhat better efficacy of olanzapine is also supported by other efficacy parameters such as the general mental state (PANSS total score, see below). Nevertheless, the high overall discontinuation rate of 63.2% needs to be highlighted. It is an important threat to the validity of the findings, because a large amount of data must be estimated by statistical modelling.

5.3 General functioning / Quality of life: Only one study (Kinon 2006b) reported on general functioning (GAF total score) and showed a superiority of olanzapine. The same trial examined quality of life and found no difference between groups. It is disappointing that so few data on these important outcomes are available.

5.4 Service use: Fewer participants in the olanzapine group than in the quetiapine group had to be re-hospitalised. Although based on only two studies, this is an important finding for policy makers, because in many industrialised countries hospital costs are the main cost factor in the treatment of schizophrenia.

5.5 Adverse effects: Limited data on cardiac effects, cholesterol, death, extrapyramidal side effects, glucose, prolactin increase and associated side effects (amenorrhoea, galactorrhoea, gynaecomastia, sexual dysfunction), sedation and seizures were available.

Among these, quetiapine was associated with fewer EPS (use of antiparkinson medication), prolactin increase, sexual adverse events, weight gain and glucose increase. These results suggest that the overall tolerability profile of quetiapine may be better than that of olanzapine. Especially the marked weight gain and glucose increase associated with olanzapine is a major concern, because it may lead to diabetes, metabolic syndrome and cardiac problems in the long run. Only QTc prolongation was less pronounced in the olanzapine group than in the quetiapine group. This side effect may make olanzapine a preferable antipsychotic drug in people with cardiac arrhythmias.

6. Comparison 5. OLANZAPINE versus RISPERIDONE

6.1 Efficacy outcomes (global state, overall and specific mental state): Most data were available for the general mental state (PANSS total score, 15 RCTs) and positive and negative symptoms of schizophrenia (PANSS positive and negative subscore, 13 RCTs). Olanzapine was superior in the improvement of the general mental state, but not of specific symptoms of schizophrenia. Most other efficacy related outcomes were equivocal.

6.2 Leaving the study early: The high overall rate of participants leaving the studies early (52%) is a source of concern. The field must urgently find ways to decrease the amount of attrition in schizophrenia trials, because the typically high discontinuation rates make the validity of the results questionable. Olanzapine may be a somewhat more acceptable treatment than risperidone for people with schizophrenia, because fewer participants in the olanzapine group left the studies early due to any reason. In addition, fewer olanzapine treated participants left the studies early due to inefficacy of treatment. This may reflect a somewhat better efficacy of olanzapine which is also supported by a stronger improvement of the participants' general mental state (see below). Leaving the studies early due to adverse events showed no difference between groups suggesting a similar overall tolerability of olanzapine and risperidone.

6.3 Quality of life: The results suggested a better quality of life of participants treated with olanzapine compared to risperidone. Since only two studies provided data on this outcome, any recommendation would be premature.

6.4 Cognitive functioning: Only two studies compared the cognitive effects of olanzapine and risperidone and found no significant difference between groups.

6.5 Service use: In three trials a similar number of participants in the olanzapine and risperidone groups had to be re-hospitalised. This lack of a difference suggest a similar efficacy of both compounds. Or possible efficacy differences are so small that they do not translate to more global outcomes such as re-hospitalisation.

6.6 Adverse effects: The adverse effects that occurred in a statistically significantly different frequency can be grouped into three categories.

Olanzapine was associated with more weight gain and associated metabolic problems such as cholesterol and glucose increase. Therefore, olanzapine might not be an appropriate treatment for people at risk to develop a metabolic syndrome, overweight people, individuals suffering from diabetes or those with high cholesterol levels.

Risperidone produced some extrapyramidal side effects more frequently than olanzapine. Namely, the participants in the risperidone group used more antiparkinson medication and suffered more frequently from akathisia and parkinsonism. Although the number needed to treat for use of antiparkinson medication was relatively high (NNT 17), movement disorders are very unpleasant side effects and should be avoided.

Risperidone was also associated with clearly more prolactin increase and related sexual dysfunctions such as abnormal ejaculation in men and amenorrhoea in women. Clinicians and people with schizophrenia may consider these different tolerability profiles of both compounds in their drug choice.

7. Comparison 6. OLANZAPINE versus ZIPRASIDONE

7.1 Efficacy outcomes (global state, overall and specific mental state): Most data were available for the general mental state (PANSS total score, 4 RCT), which showed a superiority of olanzapine. All other efficacy outcomes were reported less consistently, but there was also some superiority of olanzapine in positive symptoms and negative symptoms. A single study applied the BPRS instead of the PANSS and found no significant difference between groups (Simpson 2004). It is a limitation of this study that it restricted the upper olanzapine dose range to 15mg/day, although the registered maximum olanzapine dose is 20mg/day.

7.2 Leaving the studies early: As in most other comparisons the overall number of participants leaving the studies early was very high (59.1%). Such high attrition rates call into question the validity of all other outcomes beyond leaving the study early.

Fewer participants in the olanzapine group than in the ziprasidone group left the studies early due to any reason. This better acceptability of treatment of olanzapine was mainly due to better efficacy, because olanzapine was also significantly superior in the number of people leaving early due to inefficacy of treatment, whereas there was no difference in the outcome leaving early due to adverse events. Other efficacy parameters such as the general mental state or positive symptoms suggested a somewhat better efficacy of olanzapine, as well (see below).

7.3 General functioning: In one study the participants' general functioning (GAF score) improved more than in the ziprasidone group (Kinon 2006a). The small evidence base is not sufficient for this important outcome.

7.4 Cognitive functioning: Only one study reported on cognitive function and found a superiority of olanzapine (Breier 2005). Nevertheless, this result was based on the PANSS cognition score which is not really a cognitive test. More data on this outcome would be

desirable because cognitive function could be an important component of a person's daily functioning, including the ability to work.

7.5 Service use: Fewer people in the olanzapine had to be re-hospitalised during the studies. This result may again reflect a better efficacy of olanzapine. Furthermore, the result may be important for policy makers, because in many industrialised countries hospitalisation is the main cost factor in the treatment of schizophrenia.

7.6 Adverse effects: The studies reported some data on the following adverse effects: cardiac effects, cholesterol, death, extrapyramidal side effects, prolactin increase, sedation and weight gain. Olanzapine was associated with somewhat fewer extrapyramidal side effects than ziprasidone in terms of antiparkinson medication. On the other hand olanzapine clearly induced more weight gain, plus glucose and cholesterol increase than ziprasidone. This high propensity of olanzapine to induce these potentially dangerous metabolic side effects limits its use in daily practice.

8. Summary—The review currently includes 50 studies and 9476 participants, which provided data for six comparisons (olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone). For two comparisons - olanzapine versus sertindole and olanzapine versus zotepine - RCTs are not available. The overall attrition from the included studies was considerable (49.2%). This high attrition makes the interpretation of the results problematic, because half of the results must be estimated by statistical modelling.

Olanzapine improved the general mental state somewhat more than some other second generation antipsychotic drugs, namely aripiprazole, quetiapine, risperidone, and ziprasidone. A difference in efficacy compared to amisulpride and clozapine has not been documented. This somewhat better efficacy was confirmed by fewer participants in the olanzapine groups leaving the studies early due to inefficacy of treatment compared to quetiapine, risperidone and ziprasidone. Furthermore, fewer participants in the olanzapine group than in the quetiapine and ziprasidone treatment groups, but not in the clozapine group, had to be re-hospitalised in the trials.

It is a major concern that olanzapine induced more weight gain than all other second generation antipsychotic drugs, except clozapine. This more pronounced weight gain of olanzapine was usually accompanied by more glucose and cholesterol increase compared to the other second generation antipsychotic drugs.

Other differences in adverse effects were less well documented. Nevertheless, olanzapine may be associated with slightly more extrapyramidal side effects than quetiapine, but less than risperidone and ziprasidone. It may also increase prolactin somewhat more than aripiprazole, clozapine and quetiapine, but clearly less so than risperidone.

Overall completeness and applicability of evidence

The amount of RCTs comparing olanzapine with the other second generation antipsychotic drugs varied substantially. A high number of studies compared olanzapine with risperidone

(N=23). A reasonable amount of trials comparing olanzapine with clozapine (N=12) and quetiapine (N=13) were available. In contrast, relatively few trials compared olanzapine with ziprasidone (N=6), amisulpride (N=5) and aripiprazole (N=2). We did not identify any randomised controlled trial comparing olanzapine with sertindole or zotepine. Therefore the evidence is incomplete. Furthermore, it is also obvious that most of the studies reported on leaving the studies early due to any reason and overall symptoms of schizophrenia. All other outcomes were usually based on much smaller numbers. Very little information is available on general functioning, satisfaction with care or cognition. These outcomes may be more important for people suffering from schizophrenia than the improvement of symptoms. Only three included studies reported on service use, although such data would be very important for policy makers. Most of the included studies had tight inclusion criteria, thus limiting external validity. Further effectiveness studies are needed. The high attrition in the studies also limits the applicability of the evidence to daily practice.

Quality of the evidence

A major threat for the quality of the evidence is the high overall attrition of 49.2% in the studies. It is questionable whether even a sophisticated statistical method can account for such a high percentage of participants leaving the studies before their end. All included studies were stated to be randomised and all but eight studies were double-blind. The remaining eight trials used blinded raters. Nevertheless, the randomisation and blinding methods were rarely described. The study authors did also not make attempts to verify whether blinding was successful. The majority of the trials fell in the short term category which is problematic in a chronic disease such as schizophrenia. All these factors limit the overall quality of the evidence.

Potential biases in the review process

We are not aware of obvious flaws in our review process. Nevertheless, we admit that we present only a selection of outcomes. Although these outcomes were defined a priori in the protocols, and although we think that we made a meaningful selection, other people may have different opinions.

Agreements and disagreements with other studies or reviews

A previous Cochrane review examined the effects of olanzapine compared to placebo, first generation antipsychotic drugs and second generation antipsychotic drugs for schizophrenia (Duggan 2005). The results can not be directly compared with our findings, because the previous review pooled all other second generation antipsychotic drugs together and compared them as a group with olanzapine. Nevertheless, Duggan 2005 also found that olanzapine produces more weight gain than other second generation antipsychotic drugs.

Another Cochrane review compared olanzapine with risperidone (Jayaram 2006) The authors describe a high attrition rate in the trials and little differences between both comparators, except for side effects where olanzapine was associated with more weight gain. They also found more people in the risperidone group required more medication to alleviate extrapyramidal symptoms.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—Olanzapine may be a slightly more efficacious antipsychotic drug than aripiprazole, quetiapine, risperidone and ziprasidone. On the other hand, olanzapine is associated with more weight gain than any other second generation antipsychotic drug included in this review, except for clozapine. This weight gain is a source of major concern, because in the long run it can lead to diabetes and cardiovascular problems. Differences in other adverse effects are less clear, but olanzapine may be associated with slightly more movement disorders than quetiapine, but less than risperidone and ziprasidone. It may also increase prolactin somewhat more than aripiprazole, clozapine and quetiapine, but clearly less so than risperidone.

2. For clinicians—The great attrition makes recommendations difficult. 49.2% of the participants discontinued the trials prematurely meaning that almost half of the results had to be estimated by statistical modelling. Olanzapine was more efficacious than some other second generation antipsychotic drugs in terms of the general mental state and in terms of the number of participants leaving the studies early due to inefficacy. The major disadvantage of olanzapine is its weight gain and the associated metabolic problems. There is no clear evidence on the question as to whether people treated with olanzapine will have a better quality of life or will be more satisfied by olanzapine than by other second generation antipsychotic drugs.

3. For managers/policy makers—Unfortunately, there is very little information to guide the decisions of managers and policy makers. Service use was reported by only three of the fifty included studies. Fewer people in the olanzapine groups had to be hospitalised than those treated with quetiapine, risperidone or ziprasidone, but more than those treated with clozapine. The evidence base is too limited for making any recommendation.

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—Comparisons of olanzapine with some second generation antipsychotic drugs are completely lacking, and the number of available trials for some other ones is small. These gaps need to be filled by future trials (Table 1).

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CHARACTERISTICS OF STUDIES

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

Atmaca 2003

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: single centre. Country: Turkey.
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). Sex: 24 M, 29 F (3 not reported). 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. Setting: not described, probably inpatient.
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: EPS (use of antiparkinson medication), weight gain (BMI), laboratory (serum leptin, triglyceride levels)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.

Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Low risk	Three subjects in the control groups left the study early (5.4%). Reason for dropout were not assessed, only completer data were presented. But due to the very low rate we do not think that there was a risk of bias
Free of selective reporting?	Low risk	Probably free of bias. The study focused on serum leptin and triglyceride levels which were adequately described
Free of other bias?	Unclear risk	Data on the allowed dose range have not been presented. Furthermore, the pre-study treatment was quite heterogeneous as 19 participants had never taken any psychotropic drugs while most other participants had a long history of previous treatment. Sponsorship was neutral

Bai 2005

Methods	Allocation: random, no further details. Blindness: single, no further details. Duration: 24 weeks. Design: parallel. Location: not described. Country: not reported.	
Participants	Diagnosis: chronic schizophrenia. N=80. Age: mean ~ 50.2 years, range not described. Sex: 39M, 41F. History: duration illness not described, age of onset not described. Setting: not described.	
Interventions	**1** Amisulpride: dose range not described, mean dose not described, fixed/flexible dose not described. N=40. **2** Olanzapine: dose range not described, mean dose not described, fixed/flexible dose not described. N=40	
Outcomes	Leaving the study early: any reason. Cognitive functioning: Wisconsin card sorting test. Unable to use - Mental state: BPRS change (no data). Adverse effects: BAS, SAS, UKU (no data).	
Notes	There are control groups without further details provided.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Single, 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

Incomplete outcome data addressed? All outcomes	Low risk	The rate of leaving the study early was low (5%), data on reasons for drop-out were provided. All data were analysed on an intent to treat basis with the last-observation-carried forward-method. This method is not perfect, but due to the very low attrition, the risk of bias was low
Free of selective reporting?	High risk	The study is only available as an abstract. Data on BPRS and EPS scales were not available
Free of other bias?	Unclear risk	Insufficient data to judge on baseline imbalance or industry sponsoring

Bitter 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 18 weeks. Design: parallel. Location: multicentre. Countries: Hungary, South Africa.
Participants	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of, standard antipsychotic therapy, BPRS of 42 or more. N=147. Age: 18-65 years (mean=37.6). Sex: 88 M, 59 F. History: duration ill not reported, age at onset not reported. Setting: inpatient.
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 subscore, PANSS negative subscore. Adverse effects: open interviews, cardiac effects (ECG), EPS (akathisia, dyskinesia, parkinsonism, use of antiparkinson medication, AIMS, Hillside Akathisia Scale, SAS), sedation, headache, back pain, asthenia, flu syndrome, dizziness, hypersalivation, postural hypertension, weight, laboratory (liver enzymes, hematology, urine analysis) Unable to use - Leukopenia (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition was high (42.1%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of

		his condition if he had remained in the study. This assumption might be wrong, especially in case of high attrition
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 5% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Breier 2005

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 28 weeks. Design: parallel. Location: multicentre. Countries: not reported. (Continents: Europe, North - South America)
Participants	Diagnosis: (DSM-IV) schizophrenia, BPRS of 42 or more, CGI-S of 4 or more. N=548. Age: 18-75 years (mean olanzapine=40.1 years, mean ziprasidone=38.2 years). Sex: 352 M, 196 F. History: duration ill not reported, age at onset mean olanzapine=23.9 years, mean ziprasidone=22.8 years. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose, allowed dose range: 10-20 mg/day, mean dose=15.27 mg/day. N=277. **2** Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=115.96 mg/day. N=271
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, PANSS cognition subscore, depression MADRS, HAMD. Quality of life: Heinrichs - Carpenter Scale. Adverse effects: open interviews, EPS (use of antiparkinson medication, dystonia, extrapyramidal symptoms, AIMS, BAS, SAS), cardiac effects (ECG), weight gain, laboratory (prolactin, glucose, lipids). Unable to use - Prolactin (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details
Blinding? Objective outcomes	Low risk	Double, no further details. Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition was high (48.9%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. Additionally mixed models analysis was performed but it is unclear whether

		any statistical method can account for such high numbers of leaving the study early
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Canive 2000

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 16 weeks (first 8 weeks observed). Design: cross-over. Location: not reported. Country: not reported.
Participants	Diagnosis: schizophrenia. N=8. Age: not reported. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Olanzapine: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported **2** Risperidone: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported
Outcomes	Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore depression Calgary depression scale Unable to use - Global state: CGI (no usable data). Mental State: (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not available.
Free of selective reporting?	High risk	Data were only presented as a poster, data on primary outcomes were missing
Free of other bias?	High risk	The study was sponsored by the manufacturers of olanzapine.

CN138003

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 52 weeks (first 6 weeks observed). Design: parallel. Location: multicentre. Countries: Argentina, Brazil, Canada, Mexico, USA.
Participants	Diagnosis: (DSM-IV) acute schizophrenia, PANSS of 60 or more. N=703. Age: not reported. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Aripiprazole: flexible dose. Allowed dose range: 15-30 mg/day. Mean dose: not reported. N=355. **2** Olanzapine: flexible dose. Allowed dose range: 10-20mg/day. Mean dose: not reported. N=348
Outcomes	Leaving the study early: any reason. Global state: CGI. Mental state: PANSS total score, depression MADRS. Quality of life/satisfaction with treatment: Quality of Life Enjoyment and Satisfaction Questionnaire, Medication adherence scale. Adverse effects: open interviews, EPS (SAS, AIMS, BAS), cardiac effects (ECG), weight gain (BMI) Unable to use - Adverse effects: (no data, interim report).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate within the first six weeks was 25% overall, but data on reason for leaving the study early were not available. The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	High risk	Data for the predefined primary outcome are available but secondary outcome measures like 30% PANSS total reduction are missing in the six weeks interim report. Treatment emergent adverse events were hardly addressed in the interim report
Free of other bias?	High risk	The study was sponsored by the manufacturer of aripiprazole.

Conley 2001

Methods	Allocation: random, stratified by site.

	Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) schizophrenia (n=325) paranoid (n=213) or schizoaffective disorder (n=52), PANSS between 60 and 120. N=377. Age: 18-64 years (mean=40.0 years). Sex: 274 M, 103 F. History: duration ill mean olanzapine=15.4 years, mean risperidone=16.5 years, age at onset mean olanzapine=23.6 years, mean risperidone=24.5 years. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 13.1 mg/day. N=189. **2** Risperidone: flexible dose. Allowed dose range: 2-6 mg/day. Mean dose: 4.7 mg/day. N=188
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: open interviews, cardiac effects (ECG), death (suicide attempt), EPS (use of antiparkinson medication, ESRS), prolactin associated side effects (abnormal ejaculation, amenorrhoea, decreased libido, galactorrhoea, gynaecomastia, impotence, orgastic dysfunction, sexual dysfunction) depression, insomnia, dry mouth, agitation, rhinitis, dizziness, anxiety, vision abnormalities, sedation, weight gain, laboratory (liver enzymes, lipids)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	The attrition rate was possibly acceptable (25.5%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of risperidone. Total number of participants was very low (n=13), which may limit the validity of results

Conley 2003

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 16 weeks (first 8 weeks observed). Design: cross-over. Location: not reported. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia, resistance to previous treatment, BPRS of 45 or more, CGI of 4 or more. N=13. Age: mean=37.58 years. Sex: 8 M, 5 F. History: duration ill not reported, age at onset not reported. Setting: not reported.
Interventions	**1** Clozapine: fixed dose: 450 mg/day. N=5. **2** Olanzapine: fixed dose: 50 mg/day. N=8.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: BPRS total score, BPRS positive subscore, BPRS negative subscore. Adverse effects: open interviews, cardiac effects (ECG), death (natural causes, suicide) , EPS (akathisia, use of antiparkinson medication, SAS), sedation, dry mouth, blurry vision, urinary hesitancy, constipation, tachycardia, diarrhoea, dyspepsia, headache, lethargy, myoclonus, stuttering, sialorrhoea, sweating, urinary frequency, dysphagia, orthostasis, dizziness increased appetite. Seizures, Weight change, laboratory (cholesterol, glucose, liver enzymes)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	The attrition rate was possibly acceptable (23%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The fixed dose of olanzapine was rather high (50mg/day), and the total number of participants were rather low (N=13). The study had a neutral sponsor

Dollfus 2005

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Country: France.
Participants	Diagnosis: (DSM-IV) schizophrenia with post-psychotic depression, PANSS positive subscore of 28 or less and MADRS score of 16 or more. N=76. Age: 18-65 years (mean olanzapine=39 years, mean risperidone=39.6 years). Sex: 53 M, 23 F. History: duration ill mean olanzapine=13.7 years, mean risperidone=13.1 years, age at onset not reported. Setting: not reported.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 5-15 mg/day. Mean dose: not reported. N=36. **2** Risperidone: flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: not reported. N=40
Outcomes	Global state: relapse. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, depression MADRS. Service use: number of participants re-hospitalised. Adverse effects: open interviews, cardiac effects (ECG), death (natural causes, suicide) , EPS (akathisia, akinesia, dystonia, parkinsonism, rigor, tremor, use of antiparkinson medication, continuous: ESRS total score), prolactin associated side effects (abnormally high prolactin value, amenorrhoea, sexual dysfunction), sedation, seizures, weight gain. Weight: (change from baseline in kg). Unable to use- White blood cell count (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not published separately for each group, the overall attrition was possibly acceptable (25%). (Data on both treatment attrition rates were provided from contact of the author)
Free of selective reporting?	High risk	Data on efficacy outcomes were incompletely reported.
Free of other bias?	High risk	The study was sponsored by the manufacturers of olanzapine.

Dolnak 2001

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: not reported. Country: not reported.	
Participants	Diagnosis: (DSM-IV) schizophrenia. N=40. Age: 18-65 years. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: not reported.	
Interventions	**1**	Olanzapine: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=20.
	2	Risperidone: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=20
Outcomes	General functioning: Scale of functioning.	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	No data on leaving the study early available.
Free of selective reporting?	Unclear risk	Insufficient data.
Free of other bias?	Unclear risk	Insufficient data. Sponsorship unclear.

Gureje 2003

Methods	Allocation: random, computer-generated randomisation. Blindness: double, double-dummy design. Duration: 30 weeks. Design: parallel. Location: multicentre. Countries: Australia, New Zealand.	
Participants	Diagnosis: (DSM-IV) schizophrenia, schizoaffective disorder or schizophreniform disorder, BPRS total score of 36 or more. N=65. Age: 18 years or more (mean olanzapine=35.6 years, mean risperidone=34.8 years). Sex: 38 M, 27 F. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.	
Interventions	**1**	Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 17.2 mg/day. N=32.

	2 Risperidone: flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 6.6 mg/day. N=33
Outcomes	Leaving the study early: any reason, inefficacy. Global state: CGI-S. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, PANSS negative subscore. Quality of life: QLS, SF-36. Adverse effects: open interviews, death (suicide attempt), cardiac effects (ECG), EPS (akathisia, dyskinesia, parkinsonism, rigor, tremor, use of antiparkinson medication), prolactin associated side effects (abnormal ejaculation, decreased libido, gynaecomastia, impotence), sedation, Weight change, laboratory (glucose, leukopenia). Unable to use: Cardiac effects (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, double-dummy design. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	The overall attrition was high (55. 4%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Jeste 2003

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Countries: USA, Israel, Poland, Norway, Netherlands, Austria
Participants	Diagnosis: (DSM-IV) schizophrenia (n=149) or schizoaffective disorder (n=26), PANSS between 50 and 120. N=176. Age: 60 years or more (mean olanzapine=71.4 years, mean risperidone=70.9 years) (of intent-to-treat population). Sex: 62 M, 113 F (of intent-to-treat population). History: duration ill mean=36.5 years, age at onset mean olanzapine=33.4 years, mean risperidone=36.0 years (of intent-to-treat population). Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 11.1 mg/day. N=89.

	2 Risperidone: flexible dose. Allowed dose range: 1-3 mg/day. Mean dose: 1.9 mg/day. N=87
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: open interviews, cardiac effects (ECG), death (natural causes, suicide) EPS (akinesia, dystonia, extrapyramidal symptoms, parkinsonism, tremor, use of antiparkinson medication, ESRS), sedation, seizures, weight change, laboratory (cholesterol, glucose, prolactin)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	Number of participants leaving the study early was possibly acceptable (23. 9%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of risperidone. The mean age of included subjects was about 71 years. Probably due to this reason the upper dose range limit of risperidone was rather low (3mg/day) compared with olanzapine (20mg/day)

Keefe 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Countries: USA, Canada.
Participants	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder. N=414. Age: 18-55 years (mean=39 years). Sex: 282 M, 132 F. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Haloperidol: flexible dose. Allowed dose range: 2-19 mg/day. Mean dose: 8.2 mg/day. N=97. **2** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 12.3 mg/day. N=159.

	3 Risperidone: flexible dose. Allowed dose range: 2-10 mg/day. Mean dose: 5.2 mg/day. N=158
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: relapse. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, depression (MADRS), anxiety (Hamilton anxiety scale). Cognitive Functioning: Neurocognitive Composite Score. Adverse effects: open interviews, EPS (akathisia, tremor, use of antiparkinson medication, AIMS, BAS, SAS), sedation, weight change, laboratory (cholesterol, prolactin, urine analysis)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (62.8%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 10% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Kinon 2006a

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 24 weeks. Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder, dominant depressive symptoms, MADRS of 16 or more. N=394. Age: 18-60 years. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Olanzapine: fixed dose: 10, 15 or 20 mg/day. N=202. **2** Ziprasidone: fixed dose: 80, 120 or 160 mg/day. N=192.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, depression MADRS, Calgary depression scale for schizophrenia. General Functioning: GAF.

	Adverse effects: open interviews, EPS (use of antiparkinson medication, AIMS, BAS, SAS), cardiac effects (ECG), weight gain, laboratory (prolactin, glucose, lipids) Unable to use - PANSS (no data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (62.7%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	High risk	Secondary outcomes were not fully reported.
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Kinon 2006b

Methods	Allocation: random, computer-generated randomisation. Blindness: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia (n=230), schizoaffective disorder (n=116), prominent negative symptoms. N=346. Age: mean olanzapine=41.67 years, mean quetiapine=40.45 years. Sex: 228 M, 118 F. History: duration ill mean olanzapine=17.57 years, quetiapine=17.78 years, age at onset mean olanzapine=24.16 years, quetiapine=22.59 years. Setting: outpatient.
Interventions	**1** Olanzapine flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.6 mg/day. N=171. **2** Quetiapine flexible dose. Allowed dose range: 300-700 mg/day. Mean dose: 455.8 mg/day. N=175
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, SANS total score, depression (Calgary Depression Scale). General functioning: GAF, Case Manager Rating Scale, Patient Functioning Rating Scale. Quality of life: QLS total score. Adverse effects: Sedation, weight gain, laboratory (hematology, uric acid) Unable to use - Leukopenia (no useable data). Use of antiparkinson medication (no data).

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, 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
Incomplete outcome data addressed? All outcomes	High risk	The drop-out rate was high (54.9%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong, especially in case of high attrition
Free of selective reporting?	High risk	Numbers of participants with antiparkinson medication or leukopenia were not indicated
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Krakowski 2006

Methods	Allocation: random, block randomisation (block size of 3). Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Country: not reported. (probably USA).
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 olanzapine=35.6 years). Sex: 90 M, 20 F. History: duration ill mean clozapine=15.7 years, mean haloperidol=13.9 years, mean olanzapine=16.8 years, age at onset not reported. Setting: inpatient.
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.5 mg/day (at the end of the last 6 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 6 weeks). N=36. **3** Olanzapine: flexible dose. Allowed dose range: 10-35 mg/day. Mean dose: 24.7 mg/day (at the end of the last 6 weeks). N=37
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, modified overt aggression scale

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, block randomisation (block size of 3).

Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Number of participants leaving the study early was considerable (33.3%)
Free of selective reporting?	High risk	Data on adverse effects or use of antiparkinson medication were not presented
Free of other bias?	High risk	There was no wash-out period, pre study antipsychotic medication was gradually discontinued during the first six weeks leading to an overlap of medications. Sponsorship was neutral

Kumra 2007

Methods	Allocation: random, computer-generated randomisation. Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: single centre. Country: not reported (probably USA).
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, BPRS of 35 or more. N=40. Age: 10-18 years (mean=15.6 years). Sex: 21 M, 18 F (of intent-to-treat population). History: duration ill not reported, age at onset mean clozapine=12.7 years, mean olanzapine=11.7 years (of intent-to-treat population). Setting: in- and outpatient.
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: open interviews, cholesterol (change from baseline in mg/dl). EPS (AIMS, Simpson-Angus), sedation, weight change, laboratory (glucose, prolactin, hematology) Unable to use - Extrapyramidal symptoms (no data). Diabetes mellitus (no data). Hyperglycaemia (no data). Neutropenia (no data).
Notes	One subject was excluded owing to withdrawal of parental consent after randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.

Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	Number of participants leaving the study early were moderate (28.2%). The statistical analysis was based on mixed effects model. It is unclear whether this led to bias
Free of selective reporting?	High risk	Data on adverse effects were incompletely reported.
Free of other bias?	Unclear risk	The age range of participants included was 10 to 18 years. Sponsorship was neutral

Lecrubier 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 26 weeks. Design: parallel. Location: multicentre. Countries: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia catatonic (n=11), disorganised (n=102) or residual (n=131) (of intent-to-treat population), SANS severity score of 10 or more (excluding the item attention). N=245. Age: mean amisulpride=37.8 years, mean olanzapine (5 mg/day)=38.1 years, mean olanzapine (20 mg/day)=36.4 years, mean placebo=38.2 years. Sex: 167 M, 78 F. History: duration ill mean amisulpride=12.33 years, mean olanzapine (5 mg/day)=10. 08 years, mean olanzapine (20 mg/day)=11.08 years, mean placebo=15.42 years, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Amisulpride: fixed dose: 150 mg/day. N=70. **2** Olanzapine: fixed dose: 5 mg/day. N=70. **3** Olanzapine: fixed dose: 20 mg/day. N=70.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI, relapse, Patient's global impression. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, PANSS negative subscore, SANS total score, Psychotic depression Scale. Quality of life: Carpenters QLS total score. Adverse effects: EPS (akathisia, akinesia, parkinsonism, tremor), prolactin associated side effects, sedation, seizures, weight, laboratory (leukopenia)
Notes	There is a placebo group (n=35), which is not relevant for this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The rate of leaving the study early was high (57.6%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong and poses problem given the high attrition
Free of selective reporting?	High risk	Only those adverse events were reported that occurred with an incidence of at least 10%, therefore rare but important side effects may have been missed by this procedure
Free of other bias?	High risk	The study was industry sponsored by the manufacturer of olanzapine and one of the authors is employee of that company. A fixed dose regimen was used where it might be difficult to decide which comparator doses are appropriate

Lieberman 2005

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Country: USA.	
Participants	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Age: 18-65 years (mean=40.6 years). Sex: 1080 M, 380 F. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.	
Interventions	**1**	Olanzapine: flexible dose, allowed dose range: 7.5-30 mg/day, mean dose=20.1 mg/day. N=336.
	2	Perphenazine: flexible dose, allowed dose range: 8-32 mg/day, mean dose=20.8 mg/day. N=261.
	3	Quetiapine: flexible dose, allowed dose range: 200-800 mg/day, mean dose=543.4 mg/day. N=337.
	4	Risperidone: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean dose=3.9 mg/day. N=341.
	5	Ziprasidone: flexible dose, allowed dose range: 40-160 mg/day, mean dose=112.8 mg/day. N=185
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI-S. Mental State: PANSS total score. Service use: number of participants re-hospitalised. Death: suicide attempt. Adverse effects: open interviews, EPS (use of antiparkinson medication, akathisia), cardiac effects (ECG), prolactin-associated side-effects, sedation, weight gain, laboratory (prolactin, lipids, glucose) Unable to use - Withdrawal due to “extrapyramidal effects” (no usable data).	
Notes	Note: 33 participants were excluded before analysis.	
Risk of bias		
Bias	**Authors’ judgement**	**Support for judgement**

Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, 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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (75%), and it is unclear whether any statistical method can account for such a high drop-out rate. Efficacy outcomes were evaluated based on mixed effects model analysis
Free of selective reporting?	Low risk	There was no evidence of selective reporting.
Free of other bias?	Unclear risk	Dose ranges were quite different, the upper dose range of olanzapine was 30 mg whereas risperidone could only be titrated up to 6mg /day. There was no wash-out period. An overlap in the administration of formerly given antipsychotics was permitted for the first four weeks after randomisation. Allocation to ziprasidone treatment was not possible from the start of the study due to later availability of ziprasidone. Sponsorship was neutral

McEvoy 2006

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 52 weeks (26 weeks observed, because of small group sizes). Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) schizophrenia, inadequate efficacy in previous study, clozapine treatment (n=49) was open-label. N=99, (observed N=50). Age: 18-65 years (mean=39.7 years). Sex: 80 M, 19 F. History: duration ill, age at onset, not reported. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 23.4 mg/day. N=19. **2** Quetiapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 642.9 mg/day. N=15. **3** Risperidone: flexible dose. Allowed dose range: 1.5-6 mg/day. Mean dose: 4.8 mg/day. N=16
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: open interviews, amenorrhoea, galactorrhoea, sexual dysfunction, sedation, laboratory (lipids, glucose, prolactin, haemoglobin A1C level), weight gain Unable to use - Global state CGI: no data.
Notes	
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	The overall attrition rate was high (74%). It is doubtful that the validity of the results was unaffected
Free of selective reporting?	High risk	Due to small numbers and the very high attrition only data on 26 weeks treatment (rather than 52 weeks) were presented
Free of other bias?	Unclear risk	Dose ranges were quite different, the upper dose range of olanzapine was 30 mg whereas risperidone could only be titrated up to 6mg /day. Patients had a history of former inefficacy to one of the medications. It was excluded that the same medication could be given again but still this might implicate a risk of bias due to baseline imbalance in terms of former treatment. There was no wash out period. Sponsorship was neutral

McEvoy 2007

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia (n=231), schizophreniform disorder (n=115) or schizoaffective disorder (n=54), first episode, psychotic symptoms for 1 month to 5 years, PANSS psychosis and CGI-S score of 4 or more. N=400. Age: 16-40 years (mean=24.5 years). Sex: 292 M, 108 F. History: duration ill mean=1.08 years, age at onset 23.5 years. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 11.7 mg/day. N=133. **2** Quetiapine: flexible dose. Allowed dose range: 100-800 mg/day. Mean dose: 506 mg/day. N=134. **3** Risperidone: flexible dose. Allowed dose range: 0.5-4 mg/day. Mean dose: 2.4 mg/day. N=133
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total, PANSS positive subscore, PANSS negative subscore, depression Calgary depression scale. Adverse effects: open interviews, death (suicide attempt, suicide, EPS (akathisia, akinesia, use of antiparkinson medication, laboratory (cholesterol, fasting glucose, prolactin) , prolactin associated side effects (amenorrhoea, galactorrhoea, gynaecomastia, sexual dysfunction), sedation, insomnia, dry mouth, orthostatic faintness, constipation, sialorrhoea, skin rash, gynaecomastia, urinary hesitancy, incontinence, weight gain (BMI, waist circumference)
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (70.3.%). Analysis was based on mixed effects model and secondary on last-observation-carried forward and observed cases. It is unclear whether any statistical method can account for such a high drop-out rate
Free of selective reporting?	High risk	Adverse events were presented only in case of moderate or worse severity
Free of other bias?	High risk	The study was sponsored by the manufacturer of quetiapine.

McQuade 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 26 weeks. Design: parallel. Location: multicentre. Country: USA, Canada, Argentina, Brazil, Mexico.
Participants	Diagnosis: (DSM-IV) schizophrenia disorganised (n=17), paranoid (n=271), residual (n=3) or undifferentiated (n=26), in acute relapse and hospitalised. PANSS total score of 60 or more. N=317. Age: >17 years (mean=38.4 years). Sex: 229 M, 88 F. History: duration ill not reported, age at first hospitalisation mean=24.50 years. Setting: originally inpatient.
Interventions	**1** Aripiprazole: flexible dose. Allowed dose range: 15-30 mg/day. Mean dose: 25.1 mg/day. N=156. **2** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 16.5 mg/day. N=161
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: PANSS total score. Adverse effects: cardiac effects (ECG, QTc abnormalities in ms), extrapyramidal side-effects (akathisia, extrapyramidal symptoms, parkinsonism), laboratory (lipids, glucose (change from baseline in mg/dl, prolactin - increase of prolactin level above upper limit (males >20 ng/ml, females >27 ng/ml)), sedation, weight gain Unable to use - Adverse effects: use of antiparkinson medication (no data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.

Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by lack of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Quote: " Because of the high number of participants who discontinued the study (72%) results of analysis by time point are described on the observed case (OC) basis (except for primary outcome), as the last observation-carried-forward analysis would have included a large amount of data carried forward from patients who discontinued the study." For the reason of the high number of participants leaving the study early, the validity is definitely limited
Free of selective reporting?	High risk	Although inclusion criteria required participants in acute relapse, no data on the PANSS positive subscore were available. Data on use of antiparkinson medication were missing
Free of other bias?	High risk	The study was industry sponsored by the manufacturer of aripiprazole

Meltzer 2003

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 104 weeks. Design: parallel. Location: multicentre. Countries: USA, Canada, France, Italy, UK, Czech Republic, Hungary, Croatia, South Africa, Argentina, Chile	
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). Sex: 602 M, 378 F. History: duration ill not reported, age at onset mean=24.7 years. Setting: in- and outpatient.	
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	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI - of suicide severity. Mental State: depression Calgary depression scale, anxiety Covi anxiety scale. General functioning: scale of functioning. Service use: number of participants re-hospitalised. Adverse effects: death (any reason, suicide attempt, suicide, scale of suicidal thinking), cardiomyopathy, EPS (akathisia, rigor), sedation, seizures, weight gain, suicide ideation, depression, insomnia, dysarthria, salivary hypersecretion, dry mouth, drug abuse, alcoholism, laboratory (glucose, hematology). Unable to use - ESRS (no data)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	The number of participants leaving the study early was high (38.7%). It is unclear whether any statistical method can account for such a high attrition rate. Quote: “every effort was made to follow patients for study end points for the two years of evaluation, even after they formally discontinued using the study drug. Such information from retrieved drop-outs was included in the intent-to-treat analysis”. Numbers on “retrieved drop-outs” were not indicated
Free of selective reporting?	High risk	Data on ESRS scales were not available.
Free of other bias?	High risk	The study was sponsored by the manufacturer of clozapine. Quote: “patients were allowed to reenter the study if they desired”. Comment: The study is not free of other bias.

Moresco 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre. Country: Italy.	
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). Sex: 16 M, 7 F. History: duration ill not reported, age at onset not reported. Setting: inpatient.	
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 subscore, PANSS negative subscore. Receptor occupancy measures ([18F]FESP/PET). Adverse effects: open interviews, EPS (SAS, AIMS). Unable to use - AIMS (no useable data).	
Notes		
Risk of bias		
Bias	**Authors’ judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.

Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Numbers of leaving the study early were high (34.8%). The statistical analysis was based on completer data
Free of selective reporting?	High risk	Data on EPS scales were incompletely reported.
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Mori 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks (last 4 weeks observed). Design: parallel. Location: single centre. Country: Japan.
Participants	Diagnosis: (DSM-IV) schizophrenia disorganised (n=23), paranoid (n=10), undifferentiated (n=34). N=77. Age: 28-84 years (mean=59.9 years). Sex: 39 M, 38 F. History: duration ill mean=34.51 years, age at onset, not reported. Setting: inpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 16.5 mg/day. N=20. **2** Perospirone: flexible dose. Allowed dose range: 4-48 mg/day. Mean dose: 37.3 mg/day. N=18. **3** Quetiapine: flexible dose. Allowed dose range: 50-750 mg/day. Mean dose: 432.5 mg/day. N=20. **4** Risperidone: flexible dose. Allowed dose range: 1-12 mg/day. Mean dose: 7.37 mg/day. N=19
Outcomes	Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Cognitive functioning: digit span distractibility test.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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

Incomplete outcome data addressed? All outcomes	High risk	There were no data on attrition available.
Free of selective reporting?	High risk	Adverse events were not reported. Numbers on use of antiparkinson medication have not been presented
Free of other bias?	High risk	There was no wash-out period. The previous antipsychotic treatment was gradually tapered over four weeks. Thus, during a period of 4 weeks the participants were on two drugs. Sponsorship is not reported.

Mortimer 2004

Methods	Allocation: random, computer-generated randomisation. Blindness: double, identical capsules. Duration: 24 weeks. Design: parallel. Location: multicentre. Countries: Belgium, Czech Republic, Denmark, France, Hungary, Morocco, Portugal, UK, Switzerland, Tunisia
Participants	Diagnosis: (DSM-IV) schizophrenia disorganised (n=33), paranoid (n=260) or undifferentiated (n=76) or schizophreniform disorder (n=8), dominant positive symptoms, BPRS of 36 or more, PANSS positive score higher than PANSS negative score. N=377. Age: 18-65 years (mean amisulpride=38.2 years, mean olanzapine=37.4 years). Sex: 245 M, 132 F. History: duration ill mean amisulpride=9.56 years, mean olanzapine=8.12 years, age at onset, not described. Setting: in- and outpatient.
Interventions	**1** Amisulpride: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 504 mg/day. N=189 **2** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 13 mg/day. N=188
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, PANSS negative subscore, Depression MADRS. General Functioning: SOFAS total score. Quality of life: QLS total score. Adverse effects: open interviews, cardiac effects (ECG), death (natural causes, suicide) EPS (akathisia, dystonia, parkinsonism, use of antiparkinson medication, AIMS, Simpson-Angus), glucose, sedation, weight Unable to use - Amenorrhoea (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Low risk	Computer generated randomisation list was prepared and kept outside the study centre. Quote: Patient numbers were assigned in strict chronological order in each centre
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Quote: "to permit dose adjustment whilst maintaining the double-blind, blister

		packs corresponding to a low and a high dosage were provided". Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	The rate of leaving the study early was high (35.8%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	High risk	Only those adverse events that occurred in at least 5% of the participants were reported. This procedure can miss rare, but important adverse events
Free of other bias?	High risk	The study was sponsored by the manufacturer of amisulpride.

Naber 2005

Methods	Allocation: random, computer-generated randomisation. Blindness: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre. Country: not reported.	
Participants	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of, standard antipsychotic therapy, BPRS of 24 or more. N=114. Age: 18-65 years (mean=34.0 years). Sex: 69 M, 45 F. History: duration ill not reported, age at onset 26.9 years. Setting: in- and outpatient, initially inpatient.	
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 subscore, BPRS positive subscore, PANSS negative subscore, BPRS negative subscore. Quality of life: Munich dimension list, subject well-being under neuroleptic treatment. Cognitive functioning: Wisconsin card sorting test. Adverse effects: open interviews, cardiac effects (ECG), EPS (use of antiparkinson medication, Simpson-Angus), dizziness, increased salivation, constipation, weight change Unable to use - Glucose elevation (non fasting): no data.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding

Blinding? Subjective outcomes	Low risk	Double, identical capsules. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (62.3%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong, given the high number of attrition. Completer data were also available
Free of selective reporting?	High risk	Adverse effects data were not fully addressed (data on non fastening blood glucose level were not presented)
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Ozguven 2004

Methods	Allocation: random, no further details. Blindness: single, no further details. Duration: 6 weeks. Design: parallel. Location: not reported. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia. N=30. Age: mean=35.3 years. Sex:: 8 M, 22 F. History: duration ill, age at onset, not reported. Setting: not reported.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: Mean dose: 23.0 mg/day. N=15. **2** Quetiapine: flexible dose. Allowed dose range: Mean dose: 826.67 mg/day. N=15.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global state: CGI. Mental state: SAPS total score, SANS total score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Low risk	The attrition rate was rather low (13%), there was no further explanation on the statistical method that was used, but due to the low attrition the risk of bias is rather low
Free of selective reporting?	High risk	The data were only published as an abstract.

		Data was only available in percent change
Free of other bias?	Unclear risk	Unclear due to insufficient information. Sponsorship: unclear.

Purdon 2000

Methods	Allocation: random, computer-generated randomisation. Blindness: double, no further details. Duration: 54 weeks. Design: parallel. Location: multicentre. Country: Canada.
Participants	Diagnosis: (DSM-IV) schizophrenia, in early phase. N=65. Age: 18-65 years (mean haloperidol=28.83 years, mean olanzapine=26.01 years, mean risperidone=31.77 years). Sex: 46 M, 19 F. History: duration ill mean haloperidol=2.45 years, mean olanzapine=2.79 years, mean risperidone=2.67 years, age at onset mean haloperidol=24.25 years, mean olanzapine=23.37 years, mean risperidone=28.86 years. Setting: outpatient.
Interventions	**1** Haloperidol: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 9.70 mg/day. N=23. **2** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 11.00 mg/day. N=21. **3** Risperidone: flexible dose. Allowed dose range: 4-10 mg/day. Mean dose: 6.00 mg/day. N=21
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental state: PANSS positive subscore, PANSS negative subscore. Cognitive functioning: Cognitive test battery (finger tapping, digit span, Peabody picture vocabulary test, trail making test). Adverse effects: EPS (use of antiparkinson medication, ESRS) Unable to use - Cognitive Functioning (no overall score).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (54.8%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	Low risk	The study focused on neuropsychological changes, data for efficacy and EPS scales were also presented, probably ok

Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Riedel 2007

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre. Country: Germany.
Participants	Diagnosis: (DSM-IV) schizophrenia, acute episode, CGI of more than 4, PANSS total score of more than 60. N=52. Age: 18-65 years (mean olanzapine=34.47 years, mean quetiapine=36.69 years) (of completers). Sex: 21 M, 12 F (of completers, here defined as participants who completed cognitive assessments at two or more time points out of three (baseline, week 4, weeks 8)). History: duration ill mean olanzapine=4.71 years, mean quetiapine=8.44 years (of completers), age at onset mean olanzapine=29.76 years, mean quetiapine=28.25 years (of completers). Setting: inpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.82 mg/day. N=26. **2** Quetiapine: flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 586.86 mg/day. N=26
Outcomes	Leaving the study early: any reason, adverse events. Global state: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: open interviews, UKU, EPS (akathisia, use of antiparkinson medication, BAS, ESRS), sedation, headache, dizziness, obstipation, weight gain Unable to use - Global state: no data. BAS: no data.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding? Subjective outcomes	Unclear risk	Double, no further details. Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (61.5%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong, given the high number of attrition
Free of selective reporting?	High risk	Data on global state have not been presented.
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

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Robinson 2006

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 16 weeks. Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) first episode schizophrenia (n=84), schizophreniform disorder (n= 19) or schizoaffective disorder (n=9) (of intent-to-treat population). N=120. Age: 16-40 years (mean=23.3 years) (of intent-to-treat population). Sex: 78 M, 34 F (of intent-to-treat population). History: duration ill mean=2.2 years (of intent-to-treat population), age at onset mean= 20.7 years (of intent-to-treat population). Setting: not reported.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 11.8 mg/day. N=60. **2** Risperidone: flexible dose. Allowed dose range: 1-6 mg/day. Mean dose: 3.9 mg/day. N=60
Outcomes	Leaving the study early: inefficacy. Global State. Adverse effects: EPS (parkinsonism, use of antiparkinson medication, Simpson-Angus) , weight gain Unable to use - Leaving the study early (incomplete data). Weight gain (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Single-blind, rater-blinded. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	Unclear risk	Data on leaving the study early is incomplete. The overall attrition is moderate (28%). Eight patients were excluded from the analysis for various reasons. Analysis was based on mixed effects model
Free of selective reporting?	High risk	The study included first episode schizophrenic patients but data on PANSS change were not presented. Available data for adverse effects were incomplete. Data on weight gain were missing
Free of other bias?	Unclear risk	Quote:" .. the study was designed to detect differences in our primary analysis at alpha=0.05 with 80% power based upon 130 subjects, the stability analysis included only 47 subjects and therefore might lack adequate power". Comment: risk of other bias is unclear.

Sacchetti 2004

Methods	Allocation: random, no further details. Blindness: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia, PANSS total score of 70 or more, PANSS positive subscore of 4 or more on at least 2 items. N=75. Age: 18-65 years. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: inpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 14.6 mg/day. N=25. **2** Quetiapine: flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 602.4 mg/day. N=25. **3** Risperidone: flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 4.3 mg/day. N=25
Outcomes	Leaving the study early: any reason. Mental State: BPRS hostility cluster score. Adverse effects: EPS (BAS, SAS), weight gain. Unable to use- Mental State - PANSS total score, PANSS positive subscore, PANSS negative subscore (no usable data)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Unclear risk	The attrition rate was moderate (18. 6%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	High risk	Efficacy data (PANSS) were only presented as per cent change, without indications of standard deviations, standard errors, p-values or ranges. Only interim data after half the patients had been recruited have been presented
Free of other bias?	High risk	The study was sponsored by the manufacturer of quetiapine.

Shaw 2006

Methods	Allocation: random, random-numbers chart, blocks of 4. Blindness: double, identical capsules. Duration: 8 weeks. Design: parallel. Location: not reported. Country: not reported.
Participants	Diagnosis: (DSM-IV) schizophrenia, treatment resistant to two previous antipsychotics, IQ of 70 or more. N=25. Age: 7-16 years (mean clozapine=11.7 years, mean olanzapine=12.8 years). Sex: 15 M, 10 F. History: duration ill mean clozapine=3.1 years, mean olanzapine=3.3 years, age at onset mean clozapine=8.6 years, mean olanzapine=9.5 years. Setting: inpatient.
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 150-500 mg/day. Mean dose: 327 mg/day. N=12. **2** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 18.1 mg/day. N=13
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental state: SAPS total subscore, SANS total score. Adverse effects: open interviews, cardiac effects (ECG), sedation, seizures, weight change, laboratory (cholesterol, white blood cell count)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, random-numbers chart, blocks of 4.
Allocation concealment?	Low risk	Quote: Numbered containers were used to implement the random allocation sequence
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	Low risk	Only one subject left the study early (4%) . The attrition rate was very low, therefore a risk of bias is rather not expected
Free of selective reporting?	Low risk	Review authors do not believe this will introduce bias.
Free of other bias?	Unclear risk	Upper dose limit of clozapine was 500mg/day. The low age of included participants and the small number of included subjects also has to be taken into account. Sponsorship was neutral

Sikich 2004

Methods	Allocation: random, computer-generated randomisation. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Country: not reported.

Participants	Diagnosis: Children and adolescents with (K-SADS-P or DSM-IV) schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, major depression with psychotic features or bipolar affective disorder with psychotic features, schizophrenia spectrum (n=26), affective disorders (n=24) subjects selected because of prominent positive psychotic symptoms (of intent-to-treat population). N=51. Age: 8-19 years (mean=14.8 years). Sex: 30 M, 21 F. History: duration ill not reported, age at onset mean=12.4 years. Setting: in- and outpatient.
Interventions	**1** Haloperidol : flexible dose. Allowed dose range: 1-8 mg/day. Mean dose: 5.0 mg/day. N=15. **2** Olanzapine: flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 12.3 mg/day. N=16. **3** Risperidone: flexible dose. Allowed dose range: 0.5-6 mg/day. Mean dose: 4.0 mg/day. N=20
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: BPRS-C total score, CPRS. Adverse effects: open interviews, cardiac effects (QTc, vital signs), EPS (akathisia, use of antiparkinson medication, Simpson-Angus), prolactin associated side effects (amenorrhoea, galactorrhoea, gynaecomastia), sedation, gastrointestinal malfunction, weight (BMI), laboratory (glucose, prolactin)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Random, computer-generated randomisation.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was rather high (33. 3%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. It is unclear whether this led to bias
Free of selective reporting?	Low risk	No evidence for selective reporting.
Free of other bias?	High risk	Quote: "….this ..study has a number of limitations including limited sample size, differences in the diagnosis of participants, use of co-comitant medication, variations in age and perpetual status". Comment: Probably not free of bias.

Simpson 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel. Location: multicentre. Country: not reported.

Participants	Diagnosis: (DSM-IV) acute schizophrenia (n=170) or schizoaffective disorder (n=99), CGI-S score of 4 or more, CGI-I score of 3 or more. N=269. Age: 18-55 years (mean olanzapine=37.6 years, mean ziprasidone=37.7 years). Sex: 176 M, 93 F. History: duration ill mean olanzapine=14.0, mean risperidone=15.4, age at onset mean olanzapine=23.7 years, mean ziprasidone=22.2 years. Setting: inpatient.
Interventions	**1** Olanzapine: flexibledose, allowed dose range: 5-15 mg/day, mean dose=11.3 mg/day. N=133. **2** Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=129.9 mg/day. N=136
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: BPRS total score, depression Calgary depression scale for schizophrenia. Adverse effects: open interviews, EPS (use of antiparkinson medication, ESRS) cardiac effects (ECG), weight gain, laboratory Unable to use - Laboratory (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The overall attrition rate was high (42.8%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong
Free of selective reporting?	High risk	The study focused on acutely ill schizophrenic or schizoaffective patients but data on positive symptoms were not provided
Free of other bias?	High risk	The study was sponsored by the manufacturer of ziprasidone. Upper dose limit of olanzapine was 15 mg/day, which is below the maximum dose for this medication

Sirota 2006

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 12 weeks. Design: parallel. Location: single centre. Country: Israel.
Participants	Diagnosis: (DSM-IV) schizophrenia, PANSS negative subscore of more than 15, SANS total score more than 60. N=40.

	Age: 21-64 years (mean olanzapine=36.2 years, mean quetiapine=38.3 years). Sex: 32 M, 8 F. History: duration ill mean olanzapine=13.3 years, mean quetiapine=15.9 years, age at onset not reported. Setting: inpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 16.0 mg/day. N=21. **2** Quetiapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 637.2 mg/day. N=19
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental State: PANSS total score, SANS. Adverse effects: open interviews, cardiac effects (ECG), EPS (akathisia, parkinsonism, use of antiparkinson medication, SAS, AIMS, BAS), sedation, insomnia, abdominal pain, fever, rhinitis, conjunctivitis, seizures, weight gain Unable to use - Mental State - PANSS total score (median change). Negative Symptoms - SANS (median change). EPS scales (no data). Cardiac effects (no data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Low risk	The attrition rate was quite low (12%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong. For the reason of low attrition the risk of bias can be considered as low
Free of selective reporting?	High risk	Efficacy data (PANSS, SANS) were only presented as median change. There were no data on EPS and cardiac effects
Free of other bias?	High risk	The study was sponsored by the manufacturer of quetiapine.

Stroup 2006

Methods	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blindness: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) chronic schizophrenia. N=444.

	Age: 18-65 years (mean olanzapine=40.0 years, mean quetiapine=40.1 years, mean risperidone=41.8 years, mean ziprasidone=41.3 years). Sex: 308 M, 136 F. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose, allowed dose range: 7.5-30 mg/day, mean dose=20.5 mg/day. N=108. **2** Quetiapine: flexible dose, allowed dose range: 200-800 mg/day, mean dose=565.2 mg/day. N=95. **3** Risperidone: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean dose=4.1 mg/day. N=104. **4** Ziprasidone: flexible dose, allowed dose range: 40-160 mg/day, mean dose=115.9 mg/day. N=137
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score. Death: suicide. Adverse effects: open interviews, EPS (akathisia), cardiac effects (ECG), prolactin-associated side-effects, weight gain, laboratory (prolactin, glucose, cholesterol)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, 2 steps of randomisation before and after the availability of ziprasidone, subjects were re-randomised to other medication than in phase 1
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, 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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (72.5%). Efficacy data analysis was based on mixed effect models. It is unclear whether any statistical method can account for such high rates of leaving the study early
Free of selective reporting?	High risk	Use of antiparkinson medication was permitted but data on this was not available
Free of other bias?	Unclear risk	Patients had a history of former intolerance to atypical antipsychotic treatment but baseline data on this was not provided

Svestka 2003a

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel. Location: not reported. Country: Czech Republic.
Participants	Diagnosis: schizophrenia or schizoaffective disorder, first episode. N=42. Age: not reported. Sex: not reported.

	History: duration ill not reported, age at onset not reported. Setting: inpatient.
Interventions	**1** Olanzapine: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=21. **2** Risperidone: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=21
Outcomes	Mental State: PANSS total score.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on subjects leaving the study early were not available.
Free of selective reporting?	High risk	Allowed study medication dose ranges were not indicated. A publication was not available
Free of other bias?	Unclear risk	Insufficient information. Sponsorship was neutral.

Svestka 2003b

Methods	Allocation: random, no further details. Blindness:double, no further details. Duration: 6 weeks. Design: parallel. Location: not reported. Country: Czech Republic.
Participants	Diagnosis: (ICD-10) acute schizophrenia (n=32) or schizoaffective disorder (n=10), first episode. N=42. Age: mean=35.78 years. Sex: 42 females. History: duration ill mean=7.05 years, age at onset not reported. Setting: inpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 19.5 mg/day. N=20. **2** Quetiapine: flexible dose. Allowed dose range: 50-700 mg/day. Mean dose: 677.3 mg/day. N=22

Outcomes	Leaving the study early: inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: cardiac effects (QTc), EPS (akathisia, dystonia, extrapyramidal symptoms, tremor), weight gain, laboratory (cholesterol, glucose, prolactin) Unable to use - Cholesterol (no data). Glucose (no data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on the overall attrition rate were not available.
Free of selective reporting?	High risk	For some metabolic parameters there were no data available.
Free of other bias?	Unclear risk	There was a certain baseline imbalance in terms of mean age, which was not statistically significant. Sponsorship was neutral

Svestka 2005

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel. Location: not reported. Country: Czech Republic.
Participants	Diagnosis: (ICD-10) acute schizophrenia or schizoaffective disorder, first episode. N=48. Age: not reported. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: inpatient.
Interventions	**1** Olanzapine: fixed/flexible dose: not reported, allowed dose range: not reported, mean dose: not reported. N=24. **2** Ziprasidone: fixed/flexible dose: not reported, allowed dose range: not reported, mean dose: not reported. N=24
Outcomes	Mental State: PANSS total score. Adverse effects: EPS (akathisia, parkinsonism, dystonia). Unable to use - EPS (no data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on subjects leaving the study early were not available.
Free of selective reporting?	High risk	Allowed study medication dose ranges were not indicated. A publication was not available
Free of other bias?	Unclear risk	Insufficient information. Sponsorship was neutral.

Tollefson 2001

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 18 weeks. Design: parallel. Location: multicentre. Countries: Belgium, Denmark, Finland, France, Germany, Italy, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Great Britain, Ireland
Participants	Diagnosis: (DSM-IV) schizophrenia catatonic (n=3), disorganised (n=34), paranoid (n= 101), residual (n=8) or undifferentiated (n=34), previous treatment resistance, BPRS of 45 or more. N=180. Age: 18-70 years (mean=38.6 years). Sex: 115 M, 65 F. History: duration ill not reported, age at onset mean=22.8 years. Setting: in- and outpatient.
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. Global State: CGI-S. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, BPRS positive subscore, PANSS negative subscore, BPRS negative subscore. Adverse effects: EPS (akathisia, akinesia, parkinsonism, use of antiparkinson medication, AIMS, BAS, SAS), death (natural cause), sedation, weight gain, laboratory (prolactin, white blood cell count)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding

Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (40.1%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong, given the rather high number of attrition
Free of selective reporting?	High risk	Adverse events had to occur with an incidence of more than 5% or with a statistically significant difference of $p<0.05$ for being reported. Important side effects may have been missed by this procedure
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Tran 1997

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 28 weeks. Design: parallel. Location: multicentre. Countries: Belgium, France, Germany, The Netherlands, South Africa, Spain, Switzerland, UK, USA
Participants	Diagnosis: (DSM-IV) schizophrenia (n=277), schizophreniform disorder or schizoaffective disorder, BPRS score of 42 or more. N=339. Age: 18-65 years (mean=36.21 years). Sex: 220 M, 119 F. History: duration ill not reported, age at onset mean=23.7 years. Setting: in- and outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 17.2 mg/day. N=172. **2** Risperidone: flexible dose. Allowed dose range: 4-12 mg/day. Mean dose: 7.2 mg/day. N=167
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, PANSS negative subscore, SANS total score. Quality of life: QLS total score. Adverse effects: open interviews, cardiac effects (ECG), death (any reason, suicide attempt), EPS (akathisia, akinesia, dyskinesia, dystonia, extrapyramidal symptoms, parkinsonism, tremor, use of antiparkinson medication), Prolactin associated side effects (abnormal ejaculation, abnormally high prolactin value, amenorrhoea, decreased libido, galactorrhoea, gynaecomastia, impotence), sedation, backache, blurred vision, breathing difficulties, early wakening, nightmares, seizures, weight gain, laboratory (glucose, white blood cell count)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding

Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (47.5 %). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong, given the rather high number of attrition
Free of selective reporting?	High risk	Adverse effects were only reported in the case of a significant difference between groups, therefore important side effects may have been missed by this procedure
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Van Nimwegen 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel. Location: not reported. Country: The Netherlands.
Participants	Diagnosis: (DSM-IV) schizophrenia, schizophreniform disorder or schizoaffective disorder, cannabis positive last month olanzapine (n=20), risperidone (n=23). N=131. Age: mean olanzapine=24.4 years, mean risperidone=25.1 years. Sex: 106 M, 25 F. History: duration ill not reported, age at onset not reported. Setting: not reported.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 10.95 mg/day. N=64. **2** Risperidone: flexible dose. Allowed dose range: 1-5 mg/day. Mean dose: 2.96 mg/day. N=67
Outcomes	Quality of life: Subject well being. Adverse effects: EPS (BAS). Cannabis use.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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

Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not provided.
Free of selective reporting?	High risk	Outcome reporting was incomplete, standard deviation values were not published
Free of other bias?	Unclear risk	Additional usage of cannabis.

Vanelle 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Countries: France, Italy, Tunisia.
Participants	Diagnosis: (DSM-IV) schizophrenia and comorbid depression, disorganised (n=26), paranoid (n=32), residual (n=4) or undifferentiated (n=23) . N=85. Age: 18-65 years (mean=34 years). Sex: 54 M, 31 F. History: duration ill not reported, age at onset not reported. Setting: in- and outpatient.
Interventions	**1** Amisulpride: flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 471 mg/day. N=45. **2** Olanzapine: flexible dose. Allowed dose range: 5-15 mg/day. Mean dose: 11.4 mg/day. N=40
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State. Mental State: PANSS total score, BPRS total score, PANSS positive subscore, PANSS negative subscore, Calgary depression scale. Adverse effects: open interviews, cardiac effects (QTc), EPS (tremor), weight, laboratory (cholesterol, glucose) Unable to use - Tremor: (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	Low risk	The rate of participants leaving the study early was 16.5% and reasons for leaving the study early were provided. The analysis was based on the last-observation carried forward method with two people being excluded due to no exploitable outcome data. In addition there was a per protocol population which excluded subjects with a major protocol deviation. As two different methods with similar results were applied and as the overall attrition was low we do not think that there was a bias
Free of selective reporting?	High risk	Data on extrapyramidal symptoms were not provided.

Free of other bias?	High risk	The study was sponsored by the manufacturer of amisulpride. Additionally there was a relatively high number of subjects (18) with major protocol deviations

Volavka 2002

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 14 weeks. Design: parallel. Location: multicentre. Country: USA.
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). Sex: 133 M, 24 F (of intent-to-treat population). History: duration ill mean=19.5 years (of intent-to-treat population), age at onset not reported. Setting: inpatient.
Interventions	**1** Clozapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 526.6 mg/day (at the end of the last 6 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 6 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 6 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 6 weeks). N=41
Outcomes	Leaving the study early. any reason, adverse events, inefficacy. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Quality of life: Quality of life scale, Nurses'observation scale for inpatient evaluation. Cognitive Functioning: Global Neurocognitive Score. Adverse effects: EPS (use of antiparkinson medication, ESRS), seizures, weight gain, laboratory (cholesterol, glucose, prolactin, white blood cell count) Unable to use - Quality of life scale (no data).
Notes	The two participants with neutropenia (clozapine) are additional participants to the one with agranulocytosis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	The attrition rate was high (41.7%). The last-observation-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This

		assumption can obviously be wrong, given the rather high number of attrition
Free of selective reporting?	High risk	Some outcomes were reported on subgroup from the entire sample. Quality of life scale data is not provided
Free of other bias?	High risk	Quote: “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.”

Voruganti 2007

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 52 weeks. Design: parallel. Location: multi-centre. Country: Canada.
Participants	Diagnosis: schizophrenia. N=86. Age: not reported. Sex: not reported. History: duration ill not reported, age at onset not reported. Setting: not reported.
Interventions	**1** Olanzapine: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: 17.2 mg/day. N=42. **2** Quetiapine: fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: 612.8 mg/day. N=43
Outcomes	Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. General functioning: GAF. Cognitive functioning: PANSS cognitive cluster, Wisconsin card sorting test. Adverse effects: UKU, EPS (SAS, AIMS, BAS), weight gain, number of dysglycaemics Unable to use - At the time the publication was available the update search was finished, therefore most of the data except for PANSS total, could not be considered
Notes	

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	There is a discrepancy between the abstract in the text. While according to the abstract there were fewer participants leaving the study early in the olanzapine group, this finding was no longer mentioned in the text according to which the overall attrition was only 1.2%
Free of selective reporting?	High risk	Use of antiparkinson medication was permitted but data were not presented

Free of other bias?	High risk	The study was sponsored by the manufacturer of quetiapine. There was no wash-out period

Wagner 2005

Methods	Allocation: random, medication containers according to a pseudo-random computer algorithm. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre. Country: Germany.
Participants	Diagnosis: (DSM-IV and ICD-10) schizophrenia, CGI of 4 or more, PANSS of 61 or more. N=52. Age: 18-65 years (mean amisulpride=38.3 years, mean olanzapine=34.3 years). Sex: 23 M, 13 F (of subjects with neuropsychological data, n=36). History: duration ill mean=8.4 years (of subjects with neuropsychological data, n=36), age at onset 27.9 years (of subjects with neuropsychological data, n=36). Setting: inpatient.
Interventions	**1** Amisulpride: flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 511.1 mg/day. N=26. **2** Olanzapine: flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.0 mg/day. N=26
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, SANS total score. Cognitive Functioning: Global Cognitive Index total score, trail making test A & B, continuos performance test, seld ordered pointing task, Rey auditory verbal learni g test. Adverse effects: EPS (SAS).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, medication containers according to a pseudo-random computer algorithm
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	The rate of participants leaving the study early was high (50%). The last-observa-tion-carried-forward method was used to account for people leaving the study early. It assumes that a participant who discontinued the study would not have had a change of his condition if he had remained in the study. This assumption can obviously be wrong and lead to bias in cases of high attrition
Free of selective reporting?	High risk	Additional treatment with biperiden up to 4mg/day was permitted, but data on use of antiparkinson medication was not available
Free of other bias?	High risk	The study was sponsored by the manufacturer of olanzapine.

Wang 2002

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre. Country: China.
Participants	Diagnosis:(CCMD-3) schizophrenia. N=61. Age: mean clozapine=30 years, mean olanzapine=25.8 years. Sex: 29 M, 32 F. History: duration ill mean=4.2 years, age at onset not reported. Setting: in- and outpatient.
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	Leaving the study early: adverse events. Mental State: BPRS total score. Adverse effects: open interviews, cardiac effects (palpitation, blood pressure), EPS, sedation, dry mouth, congestion, weight gain, laboratory (leukopenia) Unable to use - Leaving the study early - adverse events (no usable data). Leukopenia (no usable data).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not provided.
Free of selective reporting?	High risk	Data were not available for all of the predefined adverse effect outcomes
Free of other bias?	High risk	The sponsor was unclear. The upper dose range limit of clozapine was 400mg/day which was reached rather quickly (10 days), which could mean a disadvantage for clozapine in terms of side effects

Wang 2006

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 22 weeks (last 12 weeks observed). Design: parallel. Location: multicentre. Country: USA.

Participants	Diagnosis: (DSM-IV) schizophrenia (n=24) or schizoaffective disorder (n=12). N=36. Age: mean=47.0 years. Sex: 17 M, 19 F. History: duration ill not reported, age at onset not reported. Setting: outpatient.
Interventions	**1** Olanzapine: flexible dose. Allowed dose range: not reported. Mean dose: 13.8 mg/day. N=17. **2** Risperidone: flexible dose. Allowed dose range: not reported. Mean dose: 5.3 mg/day. N=19
Outcomes	Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: EPS (SAS), weight gain. Unable to use - Leaving the study early (no data).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not available.
Free of selective reporting?	High risk	Standard deviations for the primary outcome were not available
Free of other bias?	High risk	Dose ranges were not indicated. The study was sponsored by the manufacturer of risperidone

Wynn 2007

Methods	Allocation: random, 33 participants were assigned to a three-arm randomisation (1:1:1, blocks of 15) and 18 participants with a history of adverse experiences with haloperidol were assigned to a two-arm randomisation (1:1) for risperidone and olanzapine only. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Country: USA.
Participants	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder. N=51. Age: 18-60 years (mean=48.8 years). Sex: 43 M, 8 F. History: duration ill not reported, age at onset not reported. Setting: not reported.
Interventions	**1** Haloperidol: fixed dose: 8 mg/day. N=11. **2** Olanzapine: fixed dose: 15 mg/day. N=21.

3 Risperidone: fixed dose: 4 mg/day. N=19.

Outcomes	Neurological functioning: pre pulse inhibition, EMG.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Random, 33 participants were assigned to a three-arm randomisation (1:1:1, blocks of 15) and 18 participants with a history of adverse experiences with haloperidol were assigned to a two-arm randomisation (1:1) for risperidone and olanzapine only
Allocation concealment?	Unclear risk	No further details.
Blinding? Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Blinding? Subjective outcomes	Unclear risk	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
Incomplete outcome data addressed? All outcomes	High risk	Data on leaving the study early were not available.
Free of selective reporting?	High risk	Efficacy outcomes as change of PANSS score were not reported
Free of other bias?	High risk	The study was sponsored by the manufacturer of risperidone.

Diagnostic tool

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

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

BMI - Body Mass Index.

Rating Scales:

Global rating scales:

CGI - Clinical Global Impressions.

CGI-S - Clinical Global Impression-Severity.

CGI-I - Clinical Global Impression-Improvement.

Mental state:

BPRS - Brief Psychiatric Rating Scale.

MADRS - Montgomery-Asberg Depression Rating Scale.

MMSE - Wiing Mini Mental State Examination.

PANSS - Positive and Negative Syndrome Scale.

SANS - Scale for the Assessment of Negative Symptoms.

Side effects:

AIMS - Abnormal Involuntary Movement Scale.

BAS - Barnes Akathisia Scale.

BMI - Body mass index.

EPS- Extrapyramidal Symptoms

ESRS - Extrapyramidal Syndrome Rating Scale.

HAS - Hillside Akathisia Scale.

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

UKU - Udvalg for kliniske ndersogelser Side Effect Rating Scale -side effect rating scale.

Quality of Life:

QoL - Quality of Life Scale.

SWN -Subjective Well-being List.

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

Study	Reason for exclusion
Almond 1999	Allocation: randomised. Blindness: open-label.
Alvarez 2006	Allocation: randomised. Blindness: open-label.
Alvarez-Jimenez 2006	Allocation: pooled analysis.
Antonova 2005	Allocation: randomised, Blindness: single-blind (rater-blinded). Participants: people with schizophrenia. Interventions: olanzapine, risperidone and quetiapine versus conventional antipsychotics. Outcomes: no usable data.
Apiquian 2003	Allocation: randomised. Blindness: open-label.
Aquila 2000	Allocation: randomised. Blindness: open-label.
Ascher-Svanum 2006	Allocation: not randomised, cohort study.
Baloescu 2006	Allocation: not randomised, controlled-trial.
Basson 2001	Allocation: pooled analysis.
Beasley 2001	Allocation: pooled analysis.
Beasley 2003a	Allocation: randomised. Blindness: open-label.
Beasley 2003b	Allocation: randomised. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Bera 2001	Allocation: randomised. Blindness: open-label.
Beuzen 2005	Allocation: randomised. Blindness: open-label.
Bitter 2005	Allocation: not randomised, cohort study.
Blonde 2004	Allocation: randomised. Blindness: open-label.
Boylan 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Briken 2002	Allocation: randomised. Blindness: open-label.
Cao 2005	Allocation: randomised. Blindness: open-label.
Casey 2003	Allocation: pooled analysis.
Chaudhry 2006	Allocation: randomised. Blindness open-label.
Chen 2003	Allocation: randomised. Blindness: open-label.

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Study	Reason for exclusion
Chen 2005	Allocation: randomised. Blindness: open-label.
Chrzanowski 2006	Allocation: randomised. Blindness: open-label.
Citrome 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Ciudad 2004	Allocation: randomised. Blindness: open-label.
Conley 1999	Allocation: randomised. Blindness: open-label.
Cornblatt 2002	Allocation: randomised. Blindness: open-label.
Crespo-Facorro 2006	Allocation: randomised. Blindness: open-label.
Czekalla 2001	Allocation: randomised. Blindness: open-label.
Dai 2004a	Allocation: randomised. Blindness: open-label.
Dai 2004b	Allocation: randomised. Blindness: open-label.
Dakhale 2005	Allocation: randomised, double-blind. Participants: people with schizophrenia. Interventions: inappropriate intervention.
David 2000a	Allocation: pooled analysis.
David 2000b	Allocation: pooled analysis.
De Haan 2002	Allocation: randomised. Blindness: open-label.
Deng 2000	Allocation: randomised. Blindness: open-label.
Dossenbach 2005	Allocation: not randomised, cohort study.
Ertugrul 2006	Allocation: not randomised, controlled-trial.
Fleischhacker 2005	Allocation: randomised. Blindness: open-label.
Garcia 2006	Allocation: not randomised, case series.
Goldberg 2000	Allocation: not randomised, controlled-trial.
Harrigan 2004	Allocation: randomised. Blindness: open-label.
Harrison 2004	Allocation: randomised, double-blind. Participants: people with schizophrenia. Intervention: olanzapine versus ziprasidone. Outcomes: no usable data.
Heresco-Levy 2005	Allocation: randomisation not mentioned. Blindness: double-blind. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Hrdlicka 2001	Allocation: not randomised, cohort study.
Huber 2004	Allocation: randomised. Blindness: open-label. Intervention: other aims.
Karow 2002	Allocation: pooled analysis.

Study	Reason for exclusion
Keks 2006	Allocation: randomised. Blindness: open-label.
Kelemen 2006	Allocation: not randomised, controlled-trial.
Kern 2006	Allocation: randomised. Blindness: open-label.
Kim 2004	Allocation: not randomised, controlled-trial.
Kinon 2001	Allocation: randomised. Blindness: double-blind. Participants: people with schizophrenia or schizoaffective or schiozophreniform disorder. Interventions: inappropriate intervention.
Kolff 2000	Allocation: randomised. Blindness: open-label.
Kores 2003	Allocation: pooled analysis.
Kropp 2004	Allocation: not randomised, case series.
Lee 2006	Allocation: not randomised, cohort study.
Lin 2005	Allocation: not randomised, case series.
Lipkovich 2005	Allocation: pooled analysis.
Littrell 1999	Allocation: randomised. Blindness: open-label.
Liu 2004	Allocation: randomised. Blindness: open-label.
Loza 2005	Allocation: randomised. Blindness: open-label.
Malla 2004	Allocation: not randomised, controlled-trial.
Malyarov 1999	Allocation: not randomised.
Mazurek 2003	Allocation: randomised. Blindness: open-label.
Meltzer 2002	Allocation: randomised. Blindness: open-label.
Moritz 2002	Allocation: not randomised, case series.
Mortimer 2002	Allocation: randomised. Blindness: open-label.
Musil 2006	Allocation: not randomised.
Naber 2001	Allocation: not randomised, review.
Naber 2002	Allocation: pooled analysis.
Newcomer 2006	Allocation: pooled analysis.
Oliemeulen 2000	Allocation: randomised. Blindness: open-label.
Opjordsmoen 2000	Allocation: not randomised.
Ortega-Soto 1997	Allocation: randomised. Blindness: double-blind. Participants: people with schizophrenia. Intervention: olanzapine versus risperidone. Outcomes: no usable data.
Pan 2006	Allocation: randomised. Blindness: open-label.
Perro 1999	Allocation: randomised. Blindness: open-label.

Study	Reason for exclusion
Peuskens 2004	Allocation: not randomised, controlled-trial.
Rabinowitz 2005	Allocation: randomised. Participants: people with schizophrenia. Intervention: inappropriate intervention.
Ray 2004	Allocation: not randomised, cohort study.
Reznik 2004	Allocation: randomised. Blindness: open-label.
Roerig 2004	Allocation: randomised. Blindness: open-label. Intervention: inadequate diagnosis.
Ryu 2006	Allocation: not randomised.
Sanchez 2006	Allocation: randomised. Blindness: open-label.
Sharma 2003	Allocation: not randomised, controlled-trial.
Sowell 2002	Allocation: randomised. Blindness: open-label.
Su 2005	Allocation: not randomised, controlled-trial.
Swanson 2006	Allocation: randomised. Blindness: open-label.
Tudor 2006	Allocation: not randomised, controlled-trial.
Tunis 2006	Allocation: randomised. Blindness: open-label.
Van Bruggen 2003	Allocation: randomised. Blindness: open-label.
Vaughan 2000	Allocation: randomised. Blindness: open-label. Intervention: other aims.
Wang 2003	Allocation: randomised. Blindness: open-label.
Wang 2004a	Allocation: randomised. Blindness: open-label.
Wang 2004b	Allocation: randomised. Blindness: open-label.
Wang 2005	Allocation: randomised. Blindness: open-label.
Weickert 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Wolf 2002	Allocation: randomised. Blindness: open-label.
Wolf 2005	Allocation: randomised. Blindness: open-label.
Wu 2006	Allocation: randomised. Blindness: open-label.
Wyszogrodzka-Kuchars 2006	Allocation: not randomised, controlled-trial.
Yagdiran 2000	Allocation: not randomised.
Yamashita 2005	Allocation: not randomised.
Yang 2003	Allocation: randomised. Blindness: open-label.

Study	Reason for exclusion
Yu 2002	Allocation: randomised. Blindness: open-label.
Zelaschi 2006	Allocation: not randomised, cohort study.
Zhang 2004	Allocation: randomised. Blindness: open-label.
Zheng 2001	Allocation: randomised. Blindness: open-label.
Zhong 2006	Allocation: randomised. Blindness: open-label.
Zoccali 2003	Allocation: randomisation not mentioned. Participants: people with chronic schizophrenia. Interventions: inappropriate intervention.

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

Eli Lilly 2003a

Trial name or title	Trial 8047 F1D-MC-HGLB
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 28 weeks. Design: parallel. Location: not reported. Setting: in- and outpatient.
Participants	Diagnosis: schizophrenia. N=not reported. Sex: not reported M, not reported F. Age: 18-65 years. History: duration ill not reported, age at onset not reported
Interventions	1. Aripiprazole: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Long-time effectiveness and tolerability. Global state (CGI, PG-I). General Mental State (PANSS). Depression (MADRS). Quality of life (SWN-S, SF-36). Cognitive functioning (MOS). Sexual functioning (GISF). Health resource utilisation and resource utilisation costs, hospitalisation time. Treatment-emergent adverse events, EPS (SAS, BAS, AIMS). Laboratory values. Vital signs.
Starting date	October 2003.
Contact information	Eli Lilly and Company.
Notes	

Eli Lilly 2003b

Trial name or title	Trial 5296 F1D-MC-S014
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: not reported. Setting: not reported.
Participants	Diagnosis: schizophrenia or schizoaffective disorder. N=not reported. Sex: not reported M, not reported F. Age: 18-65 years. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Risperidone: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Global state (CGI-S). General Mental State (BPRS). EPS (AIMS, BAS, SAS). Eating Behavior Assessment Scale. Insuline sensitivity index, weight, BMI, waist circumference, visceral fat area, subcutaneous fat area, ratio of visceral fat area to subcutaneous fat area
Starting date	October 2003
Contact information	Eli Lilly and Company.
Notes	

Eli Lilly 2004a

Trial name or title	Trial 8928 F1D-US-HGLS
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: not reported. Design: parallel. Location: not reported. Setting: initially inpatient.
Participants	Diagnosis: schizophrenia, schizoaffective disorder or schizophreniform disorder, acute phase. N=not reported. Sex: not reported. Age: 18-55 years. History: duration ill not reported, age at onset not reported
Interventions	1. Aripiprazole: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Efficacy, safety, side effects.

Starting date	July 2004
Contact information	Eli Lilly and Company.
Notes	

Eli Lilly 2004b

Trial name or title	Trial 8894 F1D-US-HGLR.
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 26 weeks. Design: parallel. Location: not reported. Setting: not reported.
Participants	Diagnosis: schizophrenia or schizoaffective disorder. N=not reported. Sex: not reported M, not reported F. Age: 18-75 years. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-20 mg/day. Mean dose: not reported. N=not reported. 2. Quetiapine: Flexible dose. Allowed dose range: 300-800 mg/day. Mean dose: not reported. N=not reported.
Outcomes	Discontinuation for any reason, lack of efficacy or worsening of psychiatric syndromes. Global state (CGI, PG-I). General Mental State (PANSS). Response. Global functioning (DAI-10, GAF). Depression (MADRS). Quality of life (SF-36). Treatment-emergent adverse events, Extrapyramidal symptoms (Simpson-Angus, Barnes, AIMS). Fasting laboratory analytes Vital signs. Fasting glucose, haemoglobin A1c, lipids, insulin. Weight, waist circumference, BMI, appetite, metabolic syndrome
Starting date	July 2004
Contact information	Eli Lilly and company.
Notes	

Eli Lilly 2006

Trial name or title	Trial 10769 F1D-US-HGMN
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: not reported. Setting: not reported.

Participants	Diagnosis: schizophrenia or schizoaffective disorder or schizophreniform disorder. N=not reported. Sex: not reportednM, not reported F. Age: 18-65 years. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Risperidone: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Response. Remission. Psychiatric hospitalisations. General Mental State (PANSS). Safety.
Starting date	June 2006
Contact information	not reported.
Notes	

Mortimer 2001

Trial name or title	A1281014
Methods	Allocation: random, no further details. Blindness: double, double-dummy. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: not reported.
Participants	Diagnosis: schizophrenia or schizoaffective disorder. N=not reported. Sex: not reported. Age: not reported. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Ziprasidone: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	not reported.
Starting date	6 October 2000.
Contact information	Prof Ann Mortimer Coniston House East Riding Campus Willerby HU10 6NS UK Telephone: 01482 466700 A.M.Mortimer@medschool.hull.ac.uk
Notes	

N0081052094

Trial name or title	RIS-INT-45
Methods	Allocation: random, using a central randomisation procedure. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.
Participants	Diagnosis: (DSM-IV) schizophrenia, PANSS between 60 and 120. N=not reported. Sex: not reported. Age: 18-65 years. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Risperidone: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Safety and efficacy. Cognitive performance. Sleepiness, weight gain.
Starting date	1 April 1997
Contact information	Professor Michael Reveley Department of Psychiatry Clinical Sciences Building University of Leicester Leicester Royal Infirmary PO BOX 65 LE2 7LX United Kingdom Telephone: 0116 252 3242
Notes	

N0081121981

Trial name or title	MREC/00/147
Methods	Allocation: random, no further details. Blindness: double, double-dummy. Duration: not reported. Design: parallel. Location: multicentre. Setting: not reported.
Participants	Diagnosis: schizophrenia or schizoaffective disorder. N=not reported. Sex: not reported M, not reported F. Age: 18-70 years. History: duration ill not reported, age at onset not reported
Interventions	1. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Ziprasidone: Fixed/flexible dose: not reported.

	Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	Global state (CGI). General Mental State (PANSS). Quality of life (QLS). Health of the nation outcome scale (HoNOS). Drug attitude inventory (DAI). Resource utilization questionnaire. Treatment costs.
Starting date	1 May 2001
Contact information	Professor Michael Reveley Department of Psychiatry Section of Neuropsychiatry & Psychopharmacology Leicester General Hospital Leicester LE5 4PW United Kingdom Telephone: 0116 225 7924 reveleym@leicspart.nhs.uk
Notes	

NCT00001656

Trial name or title	Treatment of childhood onset psychotic disorder with olanzapine or clozapine
Methods	Allocation: randomisation not mentioned. Blindness: double, no further details. Duration: not reported. Design: parallel. Location: not reported. Setting: not reported.
Participants	Diagnosis: (DSM-III-R or DSM-IV) schizophrenia or schizoaffective disorder or psychotic disorders not otherwise specified. N=not reported. Sex: not reported. Age: 6-18 years. History: duration ill not reported.
Interventions	1. Clozapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported. 2. Olanzapine: Fixed/flexible dose: not reported. Allowed dose range: not reported. Mean dose: not reported. N=not reported.
Outcomes	not reported.
Starting date	not reported.
Contact information	not reported.
Notes	

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DATA AND ANALYSES

Comparison 1
OLANZAPINE versus AMISULPRIDE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. No clinically significant response (as defined by the original studies)	4	724	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.14]
2 Global State: 1b. No clinically important change (as defined by the original studies)	3	514	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.84, 1.43]
2.1 short term	2	137	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.94, 1.82]
2.2 medium term	1	377	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.20]
3 Global State: 1c. Relapse - medium term (as defined by the original studies)	1	210	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.46, 2.51]
4 Leaving the study early	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 due to any reason	5	804	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.11]
4.2 due to adverse events	4	724	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.36]
4.3 due to inefficacy	4	724	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.50, 1.40]
5 Mental State: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)	1	52	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.85, 2.50]
6 Mental State: 1b. General - average endpoint score (PANSS total, high=poor)	4	701	Mean Difference (IV, Random, 95% CI)	−1.57 [−6.09, 2.94]
6.1 short term	2	119	Mean Difference (IV, Random, 95% CI)	2.86 [−11.36, 17.08]
6.2 medium term	2	582	Mean Difference (IV, Random, 95% CI)	−2.53 [−7.54, 2.48]
7 Mental State: 1c. General - no clinically important change - medium term (less than 50% BPRS total score reduction)	1	377	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.73, 1.14]
8 Mental State: 1d. General - average endpoint score (BPRS total, high=poor)	3	665	Mean Difference (IV, Random, 95% CI)	−1.26 [−3.34, 0.82]
8.1 short term	1	83	Mean Difference (IV, Random, 95% CI)	−1.40 [−4.98, 2.18]
8.2 medium term	2	582	Mean Difference (IV, Random, 95% CI)	−1.39 [−4.83, 2.04]
9 Mental State: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)	1	52	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.75, 2.78]
10 Mental State: 2b. Positive symptoms - average endpoint	4	701	Mean Difference (IV, Random, 95% CI)	−0.66 [−1.88, 0.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
score (PANSS positive, high=poor)				
10.1 short term	2	119	Mean Difference (IV, Random, 95% CI)	−0.15 [−2.57, 2.27]
10.2 medium term	2	582	Mean Difference (IV, Random, 95% CI)	−0.98 [−3.12, 1.16]
11 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)	4	701	Mean Difference (IV, Random, 95% CI)	−0.21 [−1.10, 0.69]
11.1 short term	2	119	Mean Difference (IV, Random, 95% CI)	0.49 [−2.05, 3.02]
11.2 medium term	2	582	Mean Difference (IV, Random, 95% CI)	−0.38 [−1.56, 0.80]
12 Mental State: 3b. Negative symptoms - no clinically important change - medium term (less than 20% SANS total plus 10% PANSS total reduction)	1	210	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.25]
13 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)	2	243	Mean Difference (IV, Random, 95% CI)	−0.00 [−1.43, 1.43]
13.1 short term	1	33	Mean Difference (IV, Random, 95% CI)	8.62 [−10.45, 27.69]
13.2 medium term	1	210	Mean Difference (IV, Random, 95% CI)	−0.05 [−1.49, 1.39]
14 General functioning: General - average endpoint score - medium term (SOFAS total - percent change, high=poor)	1	359	Mean Difference (IV, Random, 95% CI)	−0.20 [−10.94, 10. 54]
15 Quality of Life: General - average endpoint score - medium term (QLS total, high=poor)	2	510	Mean Difference (IV, Random, 95% CI)	−0.00 [−0.22, 0.22]
16 Cognitive Functioning: 1a. General - no clinically important change - short term (less than 50% Global Cognitive Index reduction)	1	52	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.74, 1.35]
17 Cognitive Functioning: 1b. General - average endpoint score - short term (global cognitive index, high=poor)	1	36	Mean Difference (IV, Random, 95% CI)	0.13 [−0.09, 0.35]
18 Adverse effects: 1. General - at least one adverse effect	2	462	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.15]
19 Adverse effects: 2. Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 natural causes	1	377	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.17]
19.2 suicide attempt	1	210	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.16, 14.16]
19.3 suicide	1	377	Risk Ratio (M-H, Random, 95% CI)	3.02 [0.12, 73.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Adverse effects: 3a. Cardiac effects - QTc interval of >500 ms	1	377	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	2	303	Mean Difference (IV, Random, 95% CI)	−5.25 [−11.07, 0.57]
22 Adverse effects: 4a. Central nervous system - sedation	2	587	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.43, 1.57]
23 Adverse effects: 4b. Central nervous system - seizures	1	210	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.06, 36.61]
24 Adverse effects: 5a. Extrapyramidal effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 akathisia	2	587	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.82, 2.81]
24.2 dyskinesia	1	210	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.06, 36.61]
24.3 dystonia	1	377	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.16]
24.4 extrapyramidal symptoms	1	210	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.50, 1.39]
24.5 parkinsonism	2	587	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.40]
24.6 tremor	1	210	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.37, 8.20]
24.7 use of antiparkinson medication	1	377	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.37, 1.17]
25 Adverse effects: 5b. Extrapyramidal side effects-scale measured	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 abnormal involuntary movement: AIMS (high=poor)	1	356	Mean Difference (IV, Random, 95% CI)	0.4 [−0.33, 1.13]
25.2 extrapyramidal symptoms: SAS (high=poor)	2	406	Mean Difference (IV, Random, 95% CI)	−5.54 [−0.08, 0.08]
26 Adverse effects: 6. Haematological - white blood cell count - leukopenia	1	210	Risk Ratio (M-H, Random, 95% CI)	2.52 [0.12, 51.74]
27 Adverse effects: 7. Prolactin associated side effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 amenorrhoea	1	66	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.12, 3.61]
27.2 galactorrhoea	1	66	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 3.51]
27.3 sexual dysfunction	2	521	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.08, 7.02]
28 Adverse effects: 8a. Metabolic - cholesterol - change from baseline in mg/dl	1	85	Mean Difference (IV, Random, 95% CI)	3.42 [−5.48, 12.32]
29 Adverse effects: 8b. Metabolic - glucose - diabetes mellitus	1	377	Risk Ratio (M-H, Random, 95% CI)	3.02 [0.12, 73.56]
30 Adverse effects: 8c. Metabolic - glucose - change from baseline in mg/dl	2	406	Mean Difference (IV, Random, 95% CI)	7.30 [6.99, 7.62]
31 Adverse effects: 8d. Metabolic - weight gain	3	672	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.34, 2.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.1 weight gain of 7% or more of total body weight	1	377	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.21, 2.39]
31.2 as “weight gain” reported adverse event	2	295	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.23, 5.79]
32 Adverse effects: 8e. Metabolic - weight gain - change from baseline in kg	3	671	Mean Difference (IV, Random, 95% CI)	2.11 [1.29, 2.94]

Comparison 2
OLANZAPINE versus ARIPIPRAZOLE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. No clinically significant response (as defined by the original studies)	2	1020	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.05]
2 Global State: 1b. No clinically important change (as defined by the original studies)	2	1020	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.05]
2.1 short term	1	703	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.23]
2.2 medium term	1	317	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
3 Leaving the study early	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 due to any reason	2	1020	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.69, 1.09]
3.2 due to adverse events	1	317	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.51, 1.21]
3.3 due to inefficacy	1	317	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.32, 1.10]
4 Mental State: General - average endpoint score (PANSS total, high=poor)	2	794	Mean Difference (IV, Random, 95% CI)	−4.96 [−8.06, −1.85]
4.1 short term	1	703	Mean Difference (IV, Random, 95% CI)	−5.21 [−8.51,−1.91]
4.2 medium term	1	91	Mean Difference (IV, Random, 95% CI)	−3.0 [−12.21, 6.21]
5 Adverse effects: 1a. Cardiac effects - QTc prolongation	1	317	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.60, 14.18]
6 Adverse effects: 1b. Cardiac effects - QTc abnormalities - change from baseline in ms	1	317	Mean Difference (IV, Random, 95% CI)	3.70 [−2.11, 9.51]
7 Adverse effects: 2. Central nervous system - sedation	1	317	Risk Ratio (M-H, Random, 95% CI)	2.99 [1.62, 5.51]
8 Adverse effects: 3. Extrapyramidal effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 akathisia	1	317	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.18, 1.57]
8.2 extrapyramidal symptoms	1	317	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.56, 1.54]
8.3 parkinsonism	1	317	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.58, 2.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Adverse effects: 4. Prolactin associated side effects - abnormally high prolactin value	1	317	Risk Ratio (M-H, Random, 95% CI)	3.74 [1.68, 8.33]
10 Adverse effects: 5a. Metabolic - cholesterol - significant cholesterol increase	1	223	Risk Ratio (M-H, Random, 95% CI)	3.15 [1.84, 5.39]
11 Adverse effects: 5b. Metabolic - cholesterol - change from baseline in mg/dl	1	223	Mean Difference (IV, Random, 95% CI)	17.43 [7.65, 27.21]
12 Adverse effects: 5c. Metabolic - glucose - change from baseline in mg/dl	1	317	Mean Difference (IV, Random, 95% CI)	2.0 [−6.48, 10.48]
13 Adverse effects: 5d. Metabolic - weight gain of 7% or more of total body weight	1	317	Risk Ratio (M-H, Random, 95% CI)	2.68 [1.71, 4.19]
14 Adverse effects: 5e. Metabolic - weight gain - change from baseline in kg	1	90	Mean Difference (IV, Random, 95% CI)	5.60 [2.15, 9.05]

Comparison 3
OLANZAPINE versus CLOZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. no clinically significant response (as defined by the original studies)	6	518	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
2 Global State: no clinically important change (as defined by the original studies)	5	505	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.16]
2.1 short term	2	64	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.39, 4.44]
2.2 medium term	3	441	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.10]
3 Leaving the study early	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 due to any reason	11	1702	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
3.2 due to adverse events	10	1674	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.43, 0.92]
3.3 due to inefficacy	10	1674	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.77, 2.47]
4 Mental State: 1a. General - no clinically important change - medium term (less than 50% PANSS total score reduction)	2	327	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.09]
5 Mental State: 1b. General - no clinically important change - short term (less than 50% BPRS total score reduction)	1	61	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.49, 1.59]
6 Mental State: 1c. General - no clinically important change - short term (less than 20% BPRS total score reduction)	1	25	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.80, 2.02]
7 Mental State: 1d. General - average endpoint score (PANSS total, high=poor)	7	618	Mean Difference (IV, Random, 95% CI)	−1.97 [−4.66, 0.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	−1.97 [−5.42, 1.48]
7.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	−1.99 [−6.27, 2.29]
8 Mental State: 1e. General - average endpoint score (BPRS total, high=poor)	6	412	Mean Difference (IV, Random, 95% CI)	−1.47 [−2.68, −0.25]
8.1 short term	4	128	Mean Difference (IV, Random, 95% CI)	−0.89 [−3.79, 2.02]
8.2 medium term	2	284	Mean Difference (IV, Random, 95% CI)	−1.64 [−5.24, 1.96]
9 Mental State: 2a. Positive symptoms - average endpoint score (PANSS positive, high=poor)	6	592	Mean Difference (IV, Random, 95% CI)	−0.08 [−1.11, 0.96]
9.1 short term	2	89	Mean Difference (IV, Random, 95% CI)	0.63 [−1.00, 2.27]
9.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	−0.54 [−1.87, 0.78]
10 Mental State: 2b. Positive symptoms - average endpoint score (BPRS positive, high=poor)	3	297	Mean Difference (IV, Random, 95% CI)	−0.13 [−1.25, 1.00]
10.1 short term	1	13	Mean Difference (IV, Random, 95% CI)	1.11 [−2.10, 4.32]
10.2 medium term	2	284	Mean Difference (IV, Random, 95% CI)	−0.30 [−1.51, 0.91]
11 Mental State: 2c. Positive symptoms - average endpoint score (SAPS total, high=poor)	1	25	Mean Difference (IV, Random, 95% CI)	9.0 [−4.06, 22.06]
12 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)	6	592	Mean Difference (IV, Random, 95% CI)	−0.78 [−1.77, 0.21]
12.1 short term	2	89	Mean Difference (IV, Random, 95% CI)	−1.32 [−3.05, 0.42]
12.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	−0.52 [−1.72, 0.68]
13 Mental State: 3b. Negative symptoms - average endpoint score (BPRS negative, high=poor)	3	297	Mean Difference (IV, Random, 95% CI)	0.18 [−0.44, 0.80]
13.1 short term	1	13	Mean Difference (IV, Random, 95% CI)	0.78 [−0.23, 1.79]
13.2 medium term	2	284	Mean Difference (IV, Random, 95% CI)	−0.15 [−0.89, 0.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)	2	64	Mean Difference (IV, Random, 95% CI)	4.81 [−4.71, 14.33]
15 Quality of Life: General - average endpoint score - medium term (SWN total, high=poor)	1	99	Mean Difference (IV, Random, 95% CI)	−8.2 [−21.67, 5.27]
16 Cognitive functioning: 1a. General - no clinically important change - medium term (less than V SD in global neurocognitive score improved)	1	79	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.43, 0.87]
17 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)	1	50	Mean Difference (IV, Random, 95% CI)	0.29 [−0.08, 0.66]
18 Service use: Number of patients re-hospitalised - long term	1	980	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.02, 1.61]
19 Adverse effects: 1. General - at least one adverse effect	7	422	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.53, 0.97]
20 Adverse effects: 2. Death	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 any reason	1	980	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.27, 1.62]
20.2 natural causes	2	193	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.3 suicide attempt	1	980	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.22, 2.62]
20.4 suicide	2	993	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.14, 2.50]
21 Adverse effects: 3. Cardiac effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 ECG abnormalities	1	25	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.05, 4.46]
21.2 QTc prolongation	2	127	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.01]
22 Adverse effects: 4a. Central nervous system - sedation	7	1445	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.39, 0.95]
23 Adverse effects: 4b. Central nervous system - seizures	4	1097	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.58]
24 Adverse effects: 5a. Extrapyramidal effects	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 akathisia	4	1320	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.71, 2.63]
24.2 dyskinesia	2	327	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.81, 6.45]
24.3 extrapyramidal symptoms	2	84	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.4 parkinsonism	2	327	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.30, 2.00]
24.5 rigor	1	980	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.73, 49.65]
24.6 use of antiparkinson medication	6	561	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.60, 2.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Adverse effects: 5b. Extrapyramidal effects - scale measured	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 abnormal involuntary movements: AIMS (high=poor)	3	352	Mean Difference (IV, Random, 95% CI)	−0.13 [−0.51, 0.25]
25.2 akathisia: BAS (high=poor)	1	175	Mean Difference (IV, Random, 95% CI)	0.10 [−0.18, 0.38]
25.3 akathisia: HAS (high=poor)	1	137	Mean Difference (IV, Random, 95% CI)	0.40 [−2.30, 3.10]
25.4 extrapyramidal symptoms: ESRS (high=poor)	1	79	Mean Difference (IV, Random, 95% CI)	−1.30 [−2.83, 0.23]
25.5 extrapyramidal symptoms: SAS (high=poor)	6	481	Mean Difference (IV, Random, 95% CI)	−0.43 [−1.30, 0.45]
26 Adverse effects: 6. Haematological - significant low white blood cell count (as def. by the original studies)	4	1264	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.08, 0.41]
27 Adverse effects: 7. Prolactin - change from baseline in ng/ml	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
27.1 change from baseline in ng/ml	1	120	Mean Difference (IV, Random, 95% CI)	0.57 [0.09, 1.05]
27.2 change from baseline in ng/ml - of men only	2	47	Mean Difference (IV, Random, 95% CI)	8.65 [−3.26, 20.55]
27.3 change from baseline in ng/ml - of women only	1	18	Mean Difference (IV, Random, 95% CI)	54.4 [22.06, 86.74]
28 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase	1	25	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 6.94]
29 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl	3	89	Mean Difference (IV, Random, 95% CI)	1.16 [−17.52, 19.85]
30 Adverse effects: 8c. Metabolic - glucose - diabetes mellitus	1	980	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.69, 2.48]
31 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl	3	89	Mean Difference (IV, Random, 95% CI)	−2.62 [−16.34, 11. 09]
32 Adverse effects: 8e. Metabolic - weight gain	7	1600	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.70, 1.81]
32.1 significant weight gain (as defined by the original studies)	3	232	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.40, 2.13]
32.2 as “weight gain” reported adverse event	4	1368	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.39, 2.01]
33 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg	7	581	Mean Difference (IV, Random, 95% CI)	0.04 [−0.97, 1.06]

Comparison 4
OLANZAPINE versus QUETIAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. No clinically significant response (as defined by the original studies)	3	339	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.70, 1.16]
2 Global state: 1b. No clinically important change (as defined by the original studies)	2	309	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
2.1 short term	1	42	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.32, 1.69]
2.2 long term	1	267	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.17]
3 Leaving the study early	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 due to any reason	10	1651	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.76, 0.88]
3.2 due to adverse events	8	1573	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.85, 1.46]
3.3 due to inefficacy	8	1563	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.44, 0.70]
4 Mental state: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)	1	42	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.65, 1.86]
5 Mental state: 1b. General - average endpoint score (PANSS total, high=poor)	10	1449	Mean Difference (IV, Random, 95% CI)	−3.66 [−5.39,−1.93]
5.1 short term	4	142	Mean Difference (IV, Random, 95% CI)	−2.17 [−5.85, 1.51]
5.2 medium term	3	482	Mean Difference (IV, Random, 95% CI)	−5.57 [−9.17,−1.97]
5.3 long term	3	825	Mean Difference (IV, Random, 95% CI)	−3.40 [−5.88, −0.91]
6 Mental state: 2a. Positive symptoms - no clinically important change-short term (less than 20% SAPS total score reduction)	1	30	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.07]
7 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)	7	679	Mean Difference (IV, Random, 95% CI)	−1.80 [−2.59, −1.02]
7.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	−1.05 [−2.85, 0.75]
7.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	−2.21 [−3.52, −0.90]
7.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	−1.80 [−3.21, −0.39]
8 Mental state: 2c. Positive symptoms - SAPS total score -	1	30	Mean Difference (IV, Random, 95% CI)	−40.84 [−57.71, −23 97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
percent change-short term (high=poor)				
9 Mental state: 3a. Negative symptoms - no clinically important change-short term (less than 20% SANS total score reduction)	1	30	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.23, 1.89]
10 Mental state: 3b. Negative symptoms - average endpoint score (PANSS negative subscore, high=poor)	7	679	Mean Difference (IV, Random, 95% CI)	−0.41 [−1.18, 0.36]
10.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	−0.01 [−1.73, 1.72]
10.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	−0.40 [−1.47, 0.67]
10.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	−0.70 [−2.13, 0.73]
11 Mental state: 3c. Negative symptoms - average endpoint score-medium term (SANS total score, high=poor)	1	335	Mean Difference (IV, Random, 95% CI)	−3.70 [−7.88, 0.48]
12 Mental state: 3d. Negative symptoms - average endpoint score-short term (SANS total score-percent change, high=poor)	1	30	Mean Difference (IV, Random, 95% CI)	−2.46 [−36.82, 31. 90]
13 General functioning: average endpoint score-medium term (GAF total score, high=poor)	1	278	Mean Difference (IV, Random, 95% CI)	−3.80 [−6.83, −0.77]
14 Quality of life: General - average endpoint score-medium term (QLS total score, high=poor)	1	286	Mean Difference (IV, Random, 95% CI)	−1.80 [−6.02, 2.42]
15 Service use - number of patients re-hospitalised	2	876	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
15.1 medium term	1	203	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.28, 1.08]
15.2 long term	1	673	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.39, 0.81]
16 Adverse effects: 1. General - at least one adverse effect	6	1269	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.13]
17 Adverse effects: 2. Death	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
17.1 suicide attempt	2	940	Risk Ratio (M-H, Random, 95% CI)	2.86 [0.44, 18.71]
17.2 suicide	2	470	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.16]
18 Adverse effects: 3a. Cardiac effects - QTc prolongation	1	673	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.36]
19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms 2	3	643	Mean Difference (IV, Random, 95% CI)	−4.81 [−9.28, −0.34]
20 Adverse effects: 4a. Central nervous system - sedation	7	1615	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.15]
21 Adverse effects: 4b. Central nervous system - seizures	1	40	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Adverse effects: 5a. Extrapyramidal effects	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 akathisia	6	1277	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.71, 1.47]
22.2 akinesia	1	267	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.64, 1.49]
22.3 dystonia	1	42	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.30]
22.4 extrapyramidal symptoms	2	245	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.39]
22.5 parkinsonism	1	40	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.42, 5.48]
22.6 tremor	1	42	Risk Ratio (M-H, Random, 95% CI)	2.57 [0.77, 8.60]
22.7 use of antiparkinson medication	6	1090	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.26, 3.32]
23 Adverse effects: 5b. Extrapyramidal effects - scale measured	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 akathisia: BAS (high=poor)	1	50	Mean Difference (IV, Random, 95% CI)	0.10 [−0.38, 0.58]
23.2 extrapyramidal symptoms: ESRS (high=poor)	1	33	Mean Difference (IV, Random, 95% CI)	0.0 [−2.68, 2.68]
23.3 extrapyramidal symptoms: SAS (high=poor)	1	50	Mean Difference (IV, Random, 95% CI)	−0.6 [−2.58, 1.38]
24 Adverse effects: 6a. Prolactin associated side effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 abnormally high prolactin value	1	42	Risk Ratio (M-H, Random, 95% CI)	9.86 [0.56, 172.33]
24.2 amenorrhoea	3	252	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.83, 2.76]
24.3 galactorrhoea	4	1025	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.58, 3.98]
24.4 gynaecomastia	1	267	Risk Ratio (M-H, Random, 95% CI)	3.02 [0.84, 10.92]
24.5 sexual dysfunction	4	1177	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.01, 1.55]
25 Adverse effects: 6b. Prolactin - change from baseline in ng/ml	5	1021	Mean Difference (IV, Random, 95% CI)	5.89 [0.16, 11.62]
26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase	1	267	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.60, 1.70]
27 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl	4	986	Mean Difference (IV, Random, 95% CI)	4.69 [−4.45, 13.84]
28 Adverse effects: 7c. Metabolic - glucose - abnormally high fasting glucose value	1	267	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.65, 3.06]
29 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl	4	986	Mean Difference (IV, Random, 95% CI)	9.32 [0.82, 17.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 Adverse effects: 7e. Metabolic - weight gain	8	1667	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.09, 1.98]
30.1 significant weight gain (as defined by the original studies)	7	1321	Risk Ratio (M-H, Random, 95% CI)	1.44 [1.05, 1.98]
30.2 as “weight gain” reported adverse event	1	346	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.19, 22.36]
31 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg	7	1173	Mean Difference (IV, Random, 95% CI)	2.68 [1.10, 4.26]

Comparison 5
OLANZAPINE versus RISPERIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. No clinically significant response (as defined by the original studies)	7	1376	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.01]
2 Global state: 1b. No clinically important change (as defined by the original studies)	5	975	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.92, 1.14]
2.1 short term	3	589	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.15]
2.2 medium term	1	120	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.87, 1.66]
2.3 long term	1	266	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.74, 1.41]
3 Global state: 1c. Relapse (as defined by the original studies)	2	211	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.37, 1.75]
3.1 short term	1	76	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.44, 4.00]
3.2 long term	1	135	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.27, 1.27]
4 Leaving the study early	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 due to any reason	16	2738	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.82, 0.94]
4.2 due to adverse events	13	2595	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.77, 1.42]
4.3 due to inefficacy	14	2744	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.98]
5 Mental state: 1a. General - no clinically important change (less than 50% PANSS total score reduction)	3	472	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]
5.1 short term	1	71	Risk Ratio (M-H, Random, 95% CI)	2.30 [0.22, 24.26]
5.2 long term	2	401	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]
6 Mental state: 1b. General - no clinically important change - short term (less than 20% PANSS total score reduction)	2	553	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.14]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)	15	2390	Mean Difference (IV, Random, 95% CI)	−1.94 [−3.31,−0.58]
7.1 short term	7	728	Mean Difference (IV, Random, 95% CI)	−0.97 [−3.05, 1.10]
7.2 medium term	3	231	Mean Difference (IV, Random, 95% CI)	−4.11 [−8.93, 0.71]
7.3 long term	5	1431	Mean Difference (IV, Random, 95% CI)	−2.59 [−4.98, −0.20]
8 Mental state: 1d. General - average endpoint score (BPRS total score, high=poor)	3	428	Mean Difference (IV, Random, 95% CI)	−4.16 [−8.29, −0.03]
8.1 short term	1	35	Mean Difference (IV, Random, 95% CI)	−5.0 [−15.74, 5.74]
8.2 long term	2	393	Mean Difference (IV, Random, 95% CI)	−4.28 [−9.91, 1.34]
9 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)	1	377	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.07]
10 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive, high=poor)	13	1702	Mean Difference (IV, Random, 95% CI)	−0.46 [−1.02, 0.09]
10.1 short term	5	661	Mean Difference (IV, Random, 95% CI)	0.48 [−0.57, 1.53]
10.2 medium term	3	231	Mean Difference (IV, Random, 95% CI)	−1.58 [−3.20, 0.03]
10.3 long term	5	810	Mean Difference (IV, Random, 95% CI)	−0.68 [−1.40, 0.04]
11 Mental state: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)	13	1702	Mean Difference (IV, Random, 95% CI)	−0.44 [−0.96, 0.08]
11.1 short term	5	661	Mean Difference (IV, Random, 95% CI)	−0.19 [−1.22, 0.85]
11.2 medium term	3	231	Mean Difference (IV, Random, 95% CI)	−0.00 [−1.59, 1.58]
11.3 long term	5	810	Mean Difference (IV, Random, 95% CI)	−0.81 [−1.54, −0.07]
12 Mental state: 3b. Negative symptoms - average endpoint score - long term (SANS total, high=poor)	1	308	Mean Difference (IV, Random, 95% CI)	−1.4 [−2.43, −0.37]
13 Quality of life: General - average endpoint score - long term (QLS total score, high=poor)	2	296	Mean Difference (IV, Random, 95% CI)	−5.10 [−9.10, −1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Cognitive functioning: 1a.General - no clinically important change - medium term (less than V SD in Global Neurocognitive Score improved)	1	80	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.52, 1.14]
15 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)	1	52	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.39, 0.31]
16 Cognitive functioning: 1c. General - average endpoint score - long term (neurocognitive composite score, high=poor)	1	263	Mean Difference (IV, Random, 95% CI)	−0.01 [−0.13, 0.11]
17 Service use - number of patients re-hospitalised	3	965	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.54, 1.04]
17.1 short term	1	76	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.23, 2.42]
17.2 medium term	1	212	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.45]
17.3 long term	1	677	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.12]
18 Adverse effects: 1. General - at least one adverse effect	11	2576	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.13]
19 Adverse effects: 2. Death	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 any reason	1	339	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.89]
19.2 natural causes	2	252	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.12, 71.04]
19.3 suicide attempt	5	1724	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.28, 2.67]
19.4 suicide	4	730	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.79]
20 Adverse effects: 3a. Cardiac effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 ECG abnormalities	2	415	Risk Ratio (M-H, Random, 95% CI)	2.39 [0.43, 13.14]
20.2 QTc prolongation	2	853	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 8.30]
21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	6	1518	Mean Difference (IV, Random, 95% CI)	−0.96 [−4.67, 2.74]
22 Adverse effects: 4a. Central nervous system - sedation	11	2576	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.96, 1.19]
23 Adverse effects: 4b. Central nervous system - seizures	4	671	Risk Ratio (M-H, Random, 95% CI)	3.82 [0.43, 34.35]
24 Adverse effects: 5a. Extrapyramidal effects	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 akathisia	8	1988	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.60, 0.98]
24.2 akinesia	3	681	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.56, 1.23]
24.3 dyskinesia	3	580	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.34, 2.80]
24.4 dystonia	3	591	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.11, 2.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.5 extrapyramidal symptoms	4	1104	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.21]
24.6 parkinsonism	5	776	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.92]
24.7 rigor	2	141	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.37, 16.14]
24.8 tremor	5	973	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.64, 2.08]
24.9 use of antiparkinson medication	13	2599	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.95]
25 Adverse effects: 5b. Extrapyramidal effects - scale measured	10		Mean Difference (IV, Random, 95% CI)	Subtotals only
25.1 abnormal involuntary movement: AIMS (high=poor)	1	302	Mean Difference (IV, Random, 95% CI)	−0.03 [−0.78, 0.72]
25.2 akathisia: BAS (high=poor)	2	353	Mean Difference (IV, Random, 95% CI)	−0.72 [−1.81, 0.36]
25.3 akathisia: ESRS subscore for akathisia (high=poor)	1	359	Mean Difference (IV, Random, 95% CI)	0.0 [−0.27, 0.27]
25.4 dyskinesia: ESRS subscore for dyskinesia (high=poor)	3	572	Mean Difference (IV, Random, 95% CI)	0.08 [−0.60, 0.76]
25.5 dystonia: ESRS subscore for dystonia (high=poor)	1	42	Mean Difference (IV, Random, 95% CI)	0.09 [−0.73, 0.91]
25.6 extrapyramidal symptoms: ESRS total score (high=poor)	4	682	Mean Difference (IV, Random, 95% CI)	−0.30 [−0.94, 0.35]
25.7 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	5	522	Mean Difference (IV, Random, 95% CI)	−0.62 [−1.33, 0.08]
25.8 parkinsonism: ESRS subscore for parkinsonism (high=poor)	3	572	Mean Difference (IV, Random, 95% CI)	−0.24 [−1.57, 1.09]
26 Adverse effects: 6. Haematological: white blood cells - significant low white blood cell count (as def. by the original studies)	3	484	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.09, 10.59]
27 Adverse effects: 7a. Prolactin associated side effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 abnormal ejaculation	3	531	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.08, 0.67]
27.2 abnormally high prolactin value	3	477	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 1.01]
27.3 amenorrhoea	7	565	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.98]
27.4 decreased libido	3	781	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.12, 1.30]
27.5 galactorrhoea	7	1272	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.30, 1.11]
27.6 gynaecomastia	5	1083	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.36, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.7 impotence	3	531	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.17, 1.47]
27.8 orgastic dysfunction	1	377	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.12]
27.9 sexual dysfunction	7	1715	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.11]
28 Adverse effects: 7b. Prolactin - change from baseline in ng/ml	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
28.1 change from baseline in ng/ml	6	1291	Mean Difference (IV, Random, 95% CI)	−22.84 [−27.98, −17. 69]
28.2 change from baseline in ng/ml - of men only	2	70	Mean Difference (IV, Random, 95% CI)	−19.91 [−26.18, −13. 64]
28.3 change from baseline in ng/ml - of women only	1	71	Mean Difference (IV, Random, 95% CI)	−41.4 [−53.16, −29. 64]
29 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase	1	266	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.72, 2.26]
30 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl	7	1391	Mean Difference (IV, Random, 95% CI)	10.36 [6.28, 14.43]
31 Adverse effects: 8c. Metabolic - glucose - abnormally high fasting glucose value	3	670	Risk Ratio (M-H, Random, 95% CI)	1.99 [0.87, 4.60]
32 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl	7	1201	Mean Difference (IV, Random, 95% CI)	7.58 [3.93, 11.23]
33 Adverse effects: 8e. Metabolic - weight gain	11	2594	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.39, 2.35]
33.1 significant weight gain (as defined by the original studies)	8	1873	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.32, 2.58]
33.2 as “weight gain” reported adverse event	3	721	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.11, 2.53]
34 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg	13	2116	Mean Difference (IV, Random, 95% CI)	2.61 [1.48, 3.74]

Comparison 6
OLANZAPINE versus ZIPRASIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global state: 1a. General - no clinically significant response (as defined by the original studies)	2	817	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.09]
2 Global state: 1b. General - no clinically important change (as defined by the original studies)	1	269	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.09]
3 Leaving the study early	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 due to any reason	5	1937	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.74, 0.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 due to adverse events	5	1937	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.62, 1.29]
3.3 due to inefficacy	5	1937	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.51, 0.79]
4 Mental state: 1a. General - no clinically important change - long term (less than 30% PANSS total score reduction)	1	548	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.62, 0.87]
5 Mental state: 1b. General - no clinically important change - short term (less than 40% BPRS total score reduction)	1	269	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.06]
6 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)	4	1291	Mean Difference (IV, Random, 95% CI)	−8.32 [−10.99, −5.64]
6.1 short term	1	48	Mean Difference (IV, Random, 95% CI)	−8.37 [−18.74, 2.00]
6.2 medium term	1	201	Mean Difference (IV, Random, 95% CI)	−6.50 [−13.07, 0.07]
6.3 long term	2	1042	Mean Difference (IV, Random, 95% CI)	−8.71 [−11.76, −5.66]
7 Mental state: 1d. General - average endpoint score - short term (BPRS total, high=poor)	1	251	Mean Difference (IV, Random, 95% CI)	−0.5 [−3.85, 2.85]
8 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive, high=poor)	2	730	Mean Difference (IV, Random, 95% CI)	−3.11 [−4.30,−1.93]
8.1 medium term	1	201	Mean Difference (IV, Random, 95% CI)	−3.6 [−5.75, −1.45]
8.2 long term	1	529	Mean Difference (IV, Random, 95% CI)	−2.90 [−4.33,−1.47]
9 Mental state: 3. Negative symptoms - average endpoint score (PANSS negative, high=poor)	2	730	Mean Difference (IV, Random, 95% CI)	−0.68 [−3.81, 2.45]
9.1 medium term	1	201	Mean Difference (IV, Random, 95% CI)	1.00 [−0.91, 2.91]
9.2 long term	1	529	Mean Difference (IV, Random, 95% CI)	−2.2 [−3.48, −0.92]
10 General functioning: 1a. General - no clinically important change - medium term (less than 5 points improvement on GAF total score)	1	394	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.98]
11 General functioning: 1b. General - average endpoint score - medium term (GAF total, high=poor)	1	326	Mean Difference (IV, Random, 95% CI)	−3.49 [−6.34, −0.64]
12 Quality of life: General - average endpoint score - long term (QLS total, Heinrichs-Carpenter, high=poor)	1	393	Mean Difference (IV, Random, 95% CI)	−3.70 [−8.61, 1.21]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Cognitive functioning: General - average endpoint score - long term(PANSS cognitive subscore, high=poor)	1	529	Mean Difference (IV, Random, 95% CI)	−2.40 [−3.63, −1.17]
14 Service use - number of patients re-hospitalised	2	766	Risk Difference (M-H, Random, 95% CI)	−0.06 [−0.11, −0.01]
14.1 medium term	1	245	Risk Difference (M-H, Random, 95% CI)	−0.05 [−0.13, 0.04]
14.2 long term	1	521	Risk Difference (M-H, Random, 95% CI)	−0.07 [−0.13, −5.53]
15 Adverse effects: 1. General - at least one adverse effect	4	1583	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.07]
16 Adverse effects: 2. Death	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 suicide attempt	1	521	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.10, 12.06]
16.2 suicide	1	245	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.22]
17 Adverse effects: 3a. Cardiac effects - QTc prolongation	3	1184	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.04, 9.93]
18 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	4	1372	Mean Difference (IV, Random, 95% CI)	−2.19 [−4.96, 0.58]
19 Adverse effects: 4. Central nervous system - sedation	2	766	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.96, 2.55]
20 Adverse effects: 5a. Extrapyramidal effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 akathisia	2	766	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.40, 1.28]
20.2 dystonia	1	548	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.33]
20.3 extrapyramidal symptoms	2	793	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.21, 1.31]
20.4 use of antiparkinson medication	4	1732	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.50, 0.97]
21 Adverse effects: 5b. Extrapyramidal symptoms scales	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
21.1 abnormal involuntary movement: AIMS (high=poor)	2	925	Mean Difference (IV, Random, 95% CI)	−0.16 [−0.46, 0.15]
21.2 akathisia: Barnes Akathisia Scale (high=poor)	2	924	Mean Difference (IV, Random, 95% CI)	−0.07 [−0.17, 0.04]
21.3 extrapyramidal symptoms: ESRS total score (high=poor)	1	269	Mean Difference (IV, Random, 95% CI)	−0.40 [−1.53, 0.73]
21.4 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	2	922	Mean Difference (IV, Random, 95% CI)	−0.34 [−0.81, 0.13]
22 Adverse effects: 6a Prolactin associated side effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 abnormally high prolactin value	1	394	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.74, 1.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 amenorrhoea	1	148	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.36, 1.95]
22.3 galactorrhoea	2	597	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.22, 1.88]
22.4 sexual dysfunction	2	766	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.99, 1.79]
23 Adverse effects: 6b. Prolactin - change from baseline in ng/ml	3	1079	Mean Difference (IV, Random, 95% CI)	−0.20 [−3.72, 3.33]
24 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase	1	394	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.24, 8.44]
25 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl	4	1502	Mean Difference (IV, Random, 95% CI)	15.83 [5.95, 25.72]
26 Adverse effects: 7c Metabolic - glucose - abnormally high fasting glucose value	1	394	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.14, 6.68]
27 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl	4	1420	Mean Difference (IV, Random, 95% CI)	8.25 [2.77, 13.72]
28 Adverse effects: 7e. Metabolic - weight gain	4	1708	Risk Ratio (M-H, Random, 95% CI)	4.90 [3.38, 7.12]
28.1 weight gain of 7% or more of total body weight	3	1160	Risk Ratio (M-H, Random, 95% CI)	4.59 [3.05, 6.90]
28.2 as “weight gain” reported adverse event	1	548	Risk Ratio (M-H, Random, 95% CI)	6.85 [2.72, 17.22]
29 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg	5	1659	Mean Difference (IV, Random, 95% CI)	3.82 [2.96, 4.69]

Comparison 7
OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1a. General - average endpoint score (PANSS total, high=poor)	6	603	Mean Difference (IV, Random, 95% CI)	−2.17 [−4.88, 0.54]
1.1 short term	2	100	Mean Difference (IV, Random, 95% CI)	−2.30 [−5.80, 1.20]
1.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	−1.99 [−6.27, 2.29]
2 Mental state: 1b. General - average endpoint score(BPRS total, high=poor)	4	312	Mean Difference (IV, Random, 95% CI)	−1.56 [−4.53, 1.40]
2.1 short term	2	28	Mean Difference (IV, Random, 95% CI)	−0.32 [−9.38, 8.74]
2.2 medium term	2	284	Mean Difference (IV, Random, 95% CI)	−1.64 [−5.24, 1.96]
3 Mental state: 2a. Positive symptoms - average endpoint score -	5	577	Mean Difference (IV, Random, 95% CI)	−0.34 [−1.44, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
(PANSS positive, high=poor)				
3.1 short term	1	74	Mean Difference (IV, Random, 95% CI)	0.13 [−1.86, 2.12]
3.2 medium term	4	503	Mean Difference (IV, Random, 95% CI)	−0.54 [−1.87, 0.78]
4 Mental state: 2b. Positive symptoms - average endpoint score - (BPRS positive, high=poor)	2	121	Mean Difference (IV, Random, 95% CI)	0.01 [−1.66, 1.69]
4.1 short term	1	13	Mean Difference (IV, Random, 95% CI)	1.11 [−2.10, 4.32]
4.2 medium term	1	108	Mean Difference (IV, Random, 95% CI)	−0.40 [−2.37, 1.57]
5 Mental state: 3a. Negative symptoms - average endpoint score (BPRS negative, high=poor)	2	121	Mean Difference (IV, Random, 95% CI)	0.45 [−0.46, 1.36]
5.1 short term	1	13	Mean Difference (IV, Random, 95% CI)	0.78 [−0.23, 1.79]
5.2 medium term	1	108	Mean Difference (IV, Random, 95% CI)	−0.20 [−1.69, 1.29]
6 Mental state: 6. Negative symptoms - average endpoint score - short term (SANS total, high=poor)	1	25	Mean Difference (IV, Random, 95% CI)	11.0 [1.10, 20.90]
7 Adverse effects: 1. Extrapyramidal symptoms - scale measured	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 abnormal involuntary movement: AIMS (high=poor)	2	314	Mean Difference (IV, Random, 95% CI)	0.05 [−0.49, 0.60]
7.2 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	4	428	Mean Difference (IV, Random, 95% CI)	−0.76 [−1.84, 0.32]

Comparison 8
OLANZAPINE versus QUETIAPINE - sensitivity analysis (skewed data excluded)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. Positive symptoms - average endpoint score (PANSS positive, high=poor)	7	679	Mean Difference (IV, Random, 95% CI)	−1.80 [−2.59, −1.02]
1.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	−1.05 [−2.85, 0.75]
1.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	−2.21 [−3.52, −0.90]
1.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	−1.80 [−3.21, −0.39]

Comparison 9
OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)

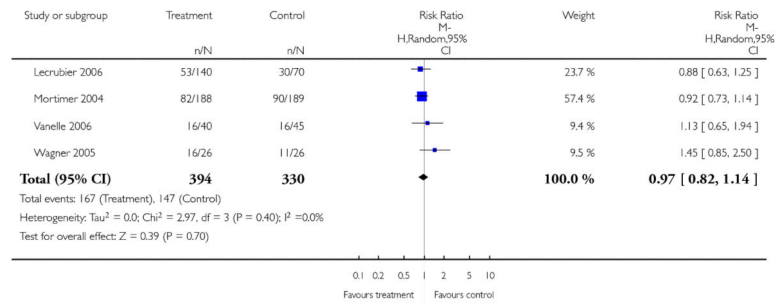
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. General - average endpoint score (PANSS total, high=poor)	14	2348	Mean Difference (IV, Random, 95% CI)	−1.99 [−3.37,−0.60]
1.1 short term	6	686	Mean Difference (IV, Random, 95% CI)	−1.02 [−3.15, 1.11]
1.2 medium term	3	231	Mean Difference (IV, Random, 95% CI)	−4.11 [−8.93, 0.71]
1.3 long term	5	1431	Mean Difference (IV, Random, 95% CI)	−2.59 [−4.98, −0.20]
2 Mental state: 2. General - average endpoint score - long term (BPRS total, high=poor)	2	393	Mean Difference (IV, Random, 95% CI)	−4.28 [−9.91, 1.34]
3 Mental state: 3. Positive symptoms - average endpoint score (PANSS positive, high=poor)	12	1663	Mean Difference (IV, Random, 95% CI)	−0.62 [−1.21, −0.03]
3.1 short term	4	622	Mean Difference (IV, Random, 95% CI)	0.28 [−1.07, 1.62]
3.2 medium term	3	231	Mean Difference (IV, Random, 95% CI)	−1.58 [−3.20, 0.03]
3.3 long term	5	810	Mean Difference (IV, Random, 95% CI)	−0.68 [−1.40, 0.04]
4 Adverse effects: 1. Extrapyramidal symptoms - scale measured	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 dyskinesia: ESRS subscore for dyskinesia (high=poor)	2	401	Mean Difference (IV, Random, 95% CI)	−0.10 [−0.62, 0.42]
4.2 extrapyramidal symptoms: ESRS total score (high=poor)	2	530	Mean Difference (IV, Random, 95% CI)	−0.16 [−0.90, 0.58]
4.3 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	4	487	Mean Difference (IV, Random, 95% CI)	−0.75 [−1.59, 0.10]
4.4 parkinsonism: ESRS subscore for parkinsonism (high=poor)	2	401	Mean Difference (IV, Random, 95% CI)	−1.06 [−3.42, 1.31]
5 Adverse effects: 2. Prolactin - change from baseline in ng/ml	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Change from baseline in ng/ml	5	1256	Mean Difference (IV, Random, 95% CI)	−24.70 [−28.33, −21.08]

Comparison 10
OLANZAPINE versus ZIPRASIDONE - sensitivity analysis (skewed data excluded)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental State: 1. General - average endpoint score (PANSS total, high=poor)	3	1243	Mean Difference (IV, Random, 95% CI)	−8.32 [−11.08, −5.55]
1.1 medium term	1	201	Mean Difference (IV, Random, 95% CI)	−6.50 [−13.07, 0.07]
1.2 long term	2	1042	Mean Difference (IV, Random, 95% CI)	−8.71 [−11.76, −5.66]

Analysis 1.1
Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

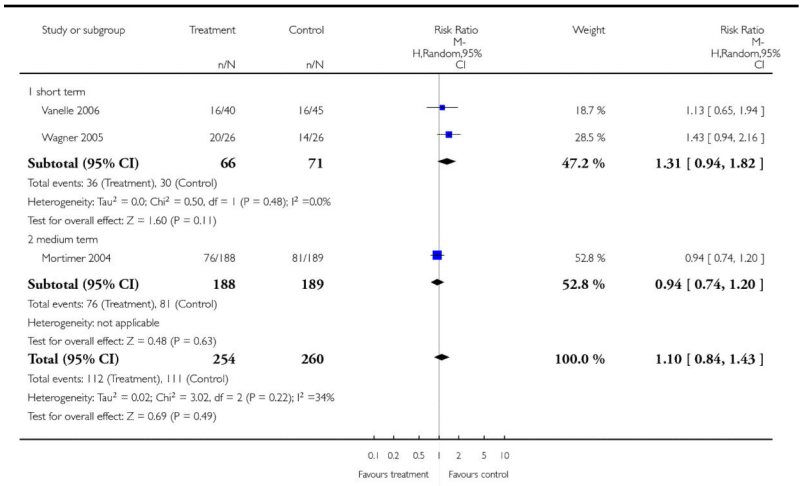
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 1 Global state: 1a. No clinically significant response (as defined by the original studies)



Analysis 1.2

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 2 Global State: 1b. No clinically important change (as defined by the original studies)

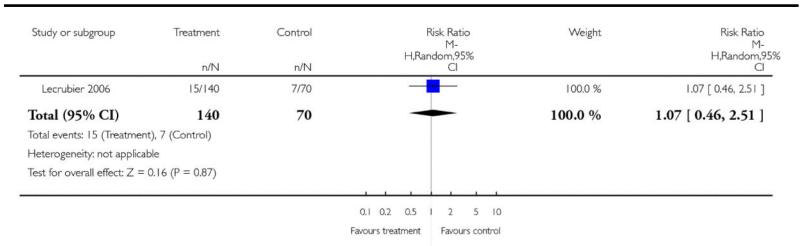
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 2 Global State: 1b. No clinically important change (as defined by the original studies)



Analysis 1.3

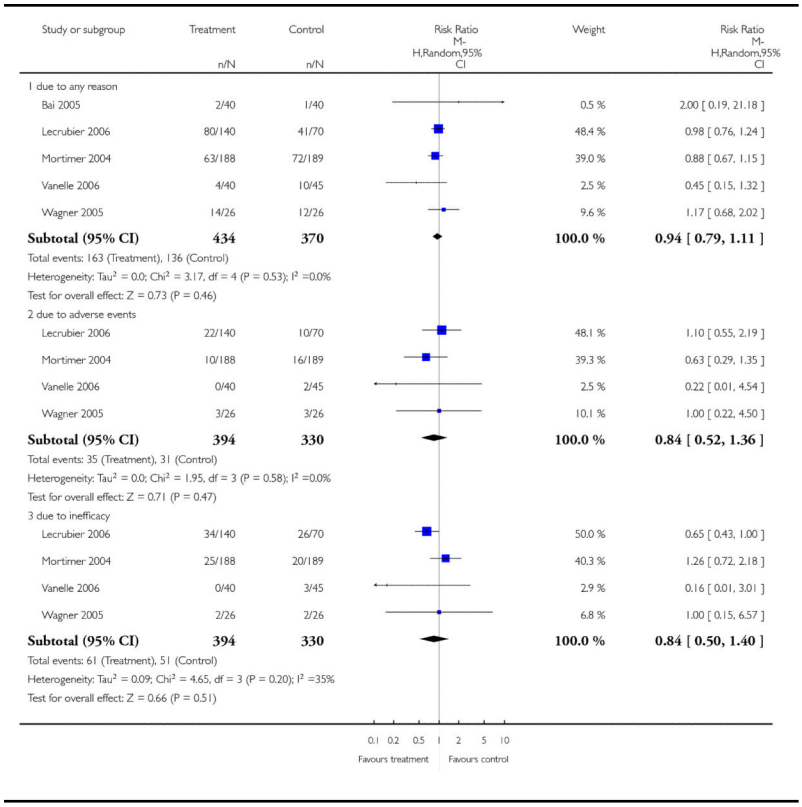
Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 3 Global State: 1c. Relapse - medium term (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 3 Global State: 1c. Relapse - medium term (as defined by the original studies)



Analysis 1.4
Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 4 Leaving the study early

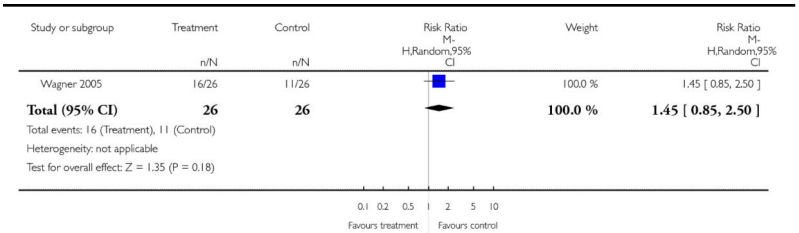
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 4 Leaving the study early



Analysis 1.5

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 5 Mental State: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)

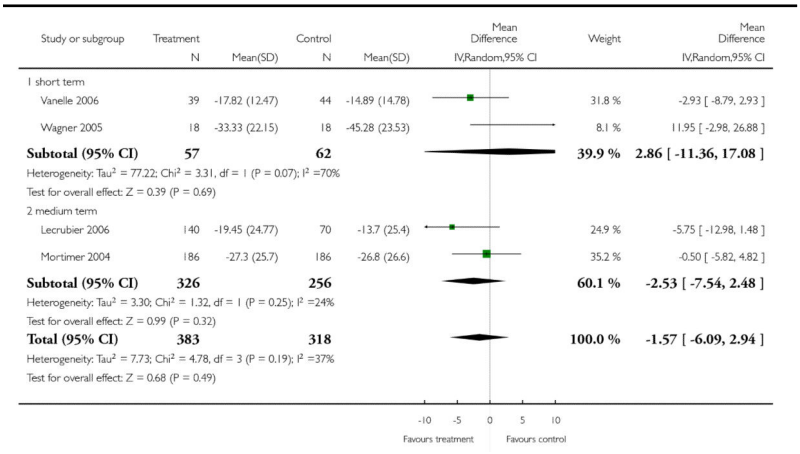
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 5 Mental State: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)



Analysis 1.6

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 6 Mental State: 1b. General - average endpoint score (PANSS total, high=poor)

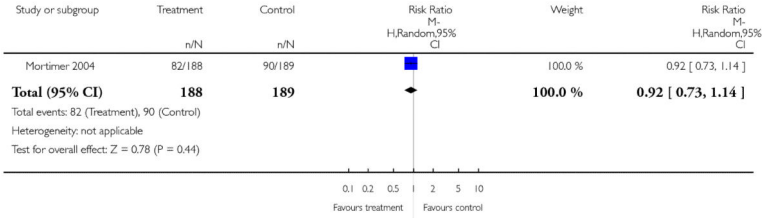
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 6 Mental State: 1b. General - average endpoint score (PANSS total, high=poor)



Analysis 1.7

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 7 Mental State: 1c. General - no clinically important change - medium term (less than 50% BPRS total score reduction)

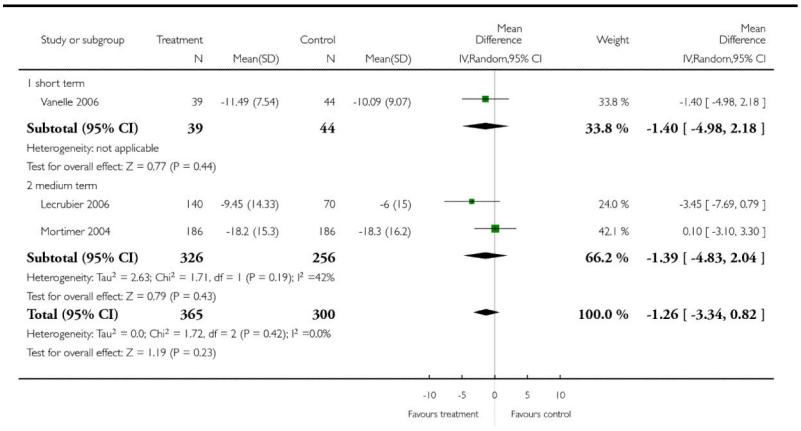
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 7 Mental State: 1c. General - no clinically important change - medium term (less than 50% BPRS total score reduction)



Analysis 1.8

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 8 Mental State: 1d. General - average endpoint score (BPRS total, high=poor)

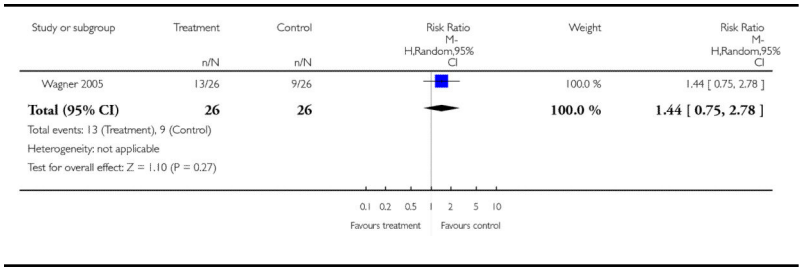
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 8 Mental State: 1d. General - average endpoint score (BPRS total, high=poor)



Analysis 1.9

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 9 Mental State: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)

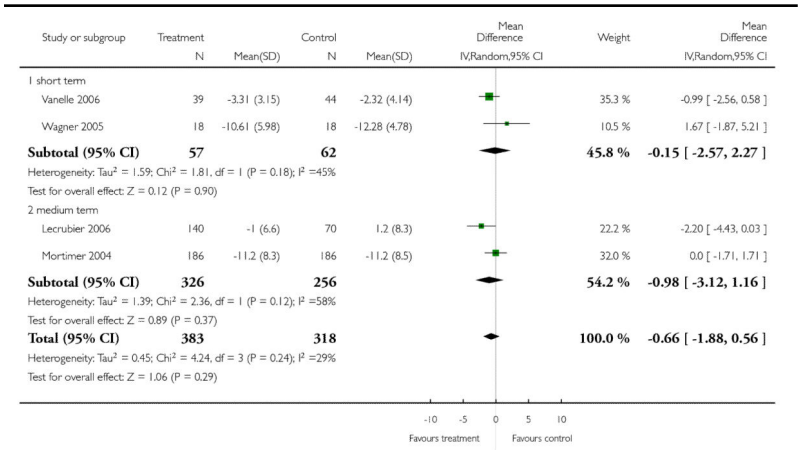
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 9 Mental State: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)



Analysis 1.10

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 10 Mental State: 2b. Positive symptoms - average endpoint score (PANSS positive, high=poor)

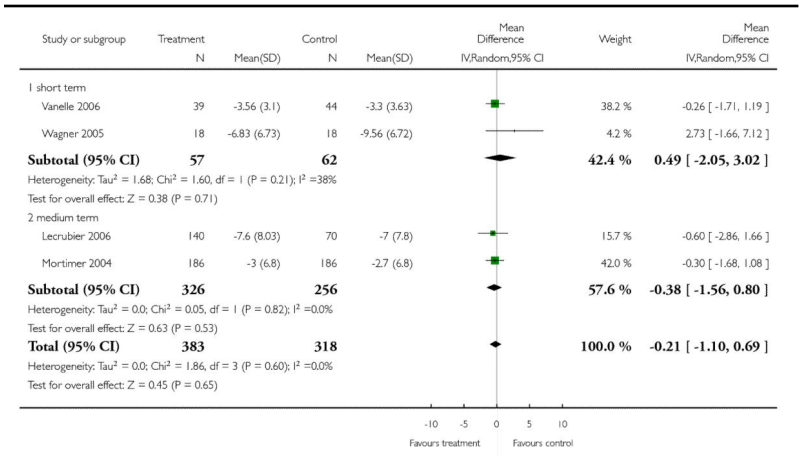
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 10 Mental State: 2b. Positive symptoms - average endpoint score (PANSS positive, high=poor)



Analysis 1.11

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 11 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)

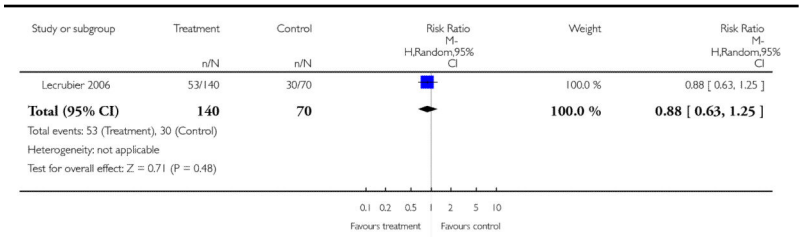
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 11 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)



Analysis 1.12

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 12 Mental State: 3b. Negative symptoms - no clinically important change - medium term (less than 20% SANS total plus 10% PANSS total reduction)

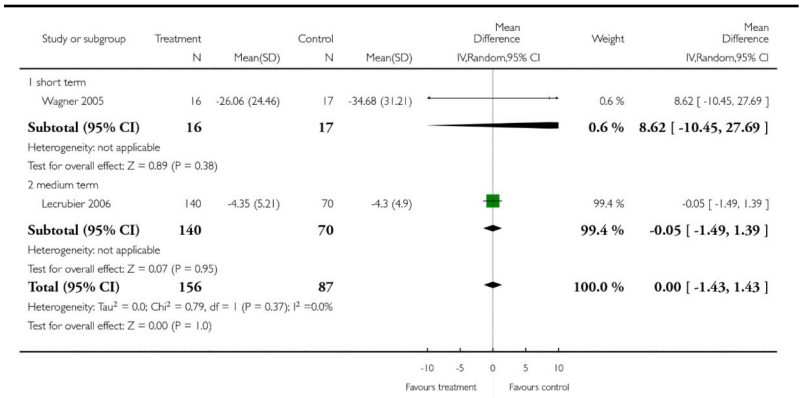
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 12 Mental State: 3b. Negative symptoms - no clinically important change - medium term (less than 20% SANS total plus 10% PANSS total reduction)



Analysis 1.13

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 13 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)

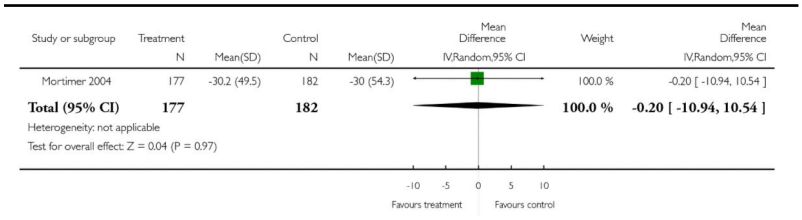
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 13 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)



Analysis 1.14

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 14 General functioning: General - average endpoint score - medium term (SOFAS total - percent change, high=poor)

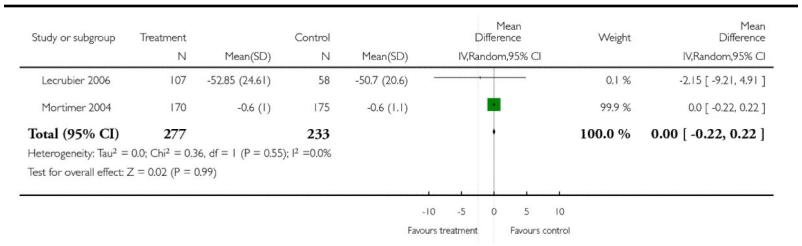
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 14 General functioning: General - average endpoint score - medium term (SOFAS total - percent change, high=poor)



Analysis 1.15

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 15 Quality of Life: General - average endpoint score - medium term (QLS total, high=poor)

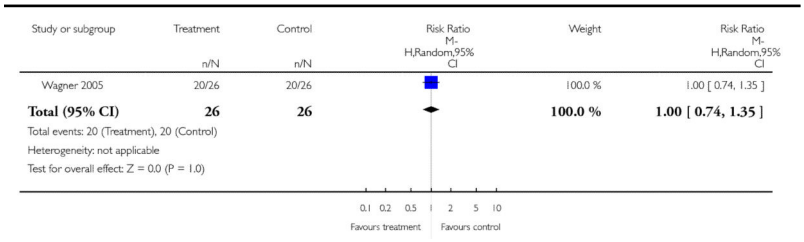
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 15 Quality of Life: General - average endpoint score - medium term (QLS total, high=poor)



Analysis 1.16

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 16 Cognitive Functioning: 1a. General - no clinically important change - short term (less than 50% Global Cognitive Index reduction)

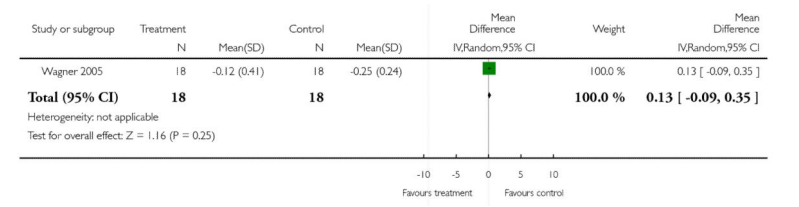
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 16 Cognitive Functioning: 1a. General - no clinically important change - short term (less than 50% Global Cognitive Index reduction)



Analysis 1.17

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 17 Cognitive Functioning: 1b. General - average endpoint score - short term (global cognitive index, high=poor)

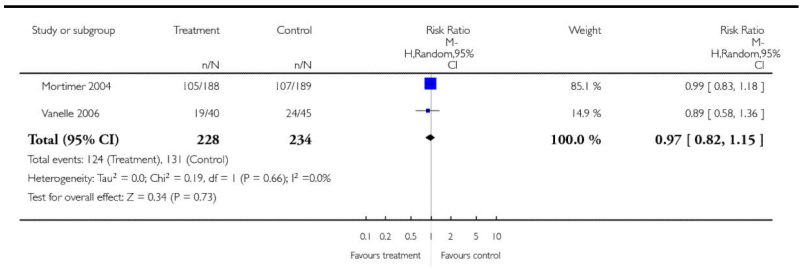
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 17 Cognitive Functioning: 1b. General - average endpoint score - short term (global cognitive index, high=poor)



Analysis 1.18

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 18 Adverse effects: 1. General - at least one adverse effect

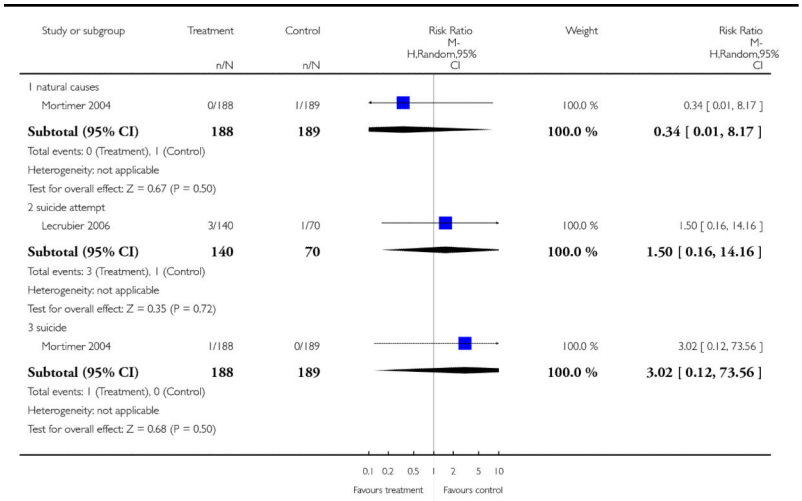
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 18 Adverse effects: 1. General - at least one adverse effect



Analysis 1.19

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 19 Adverse effects: 2. Death

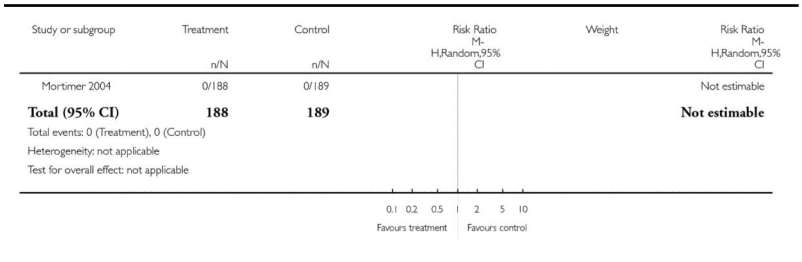
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 19 Adverse effects: 2. Death



Analysis 1.20

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 20 Adverse effects: 3a. Cardiac effects - QTc interval of >500 ms

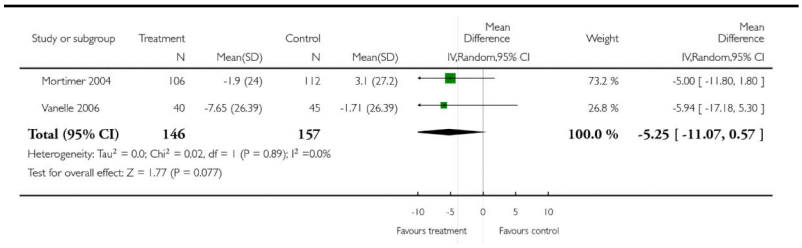
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 20 Adverse effects: 3a. Cardiac effects - QTc interval of >500 ms



Analysis 1.21

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

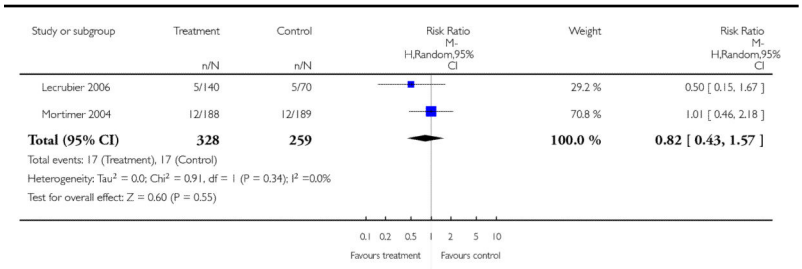
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms



Analysis 1.22

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 22 Adverse effects: 4a. Central nervous system - sedation

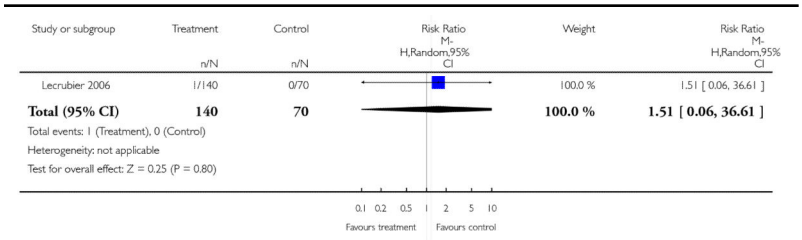
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 22 Adverse effects: 4a. Central nervous system - sedation



Analysis 1.23

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 23 Adverse effects: 4b. Central nervous system - seizures

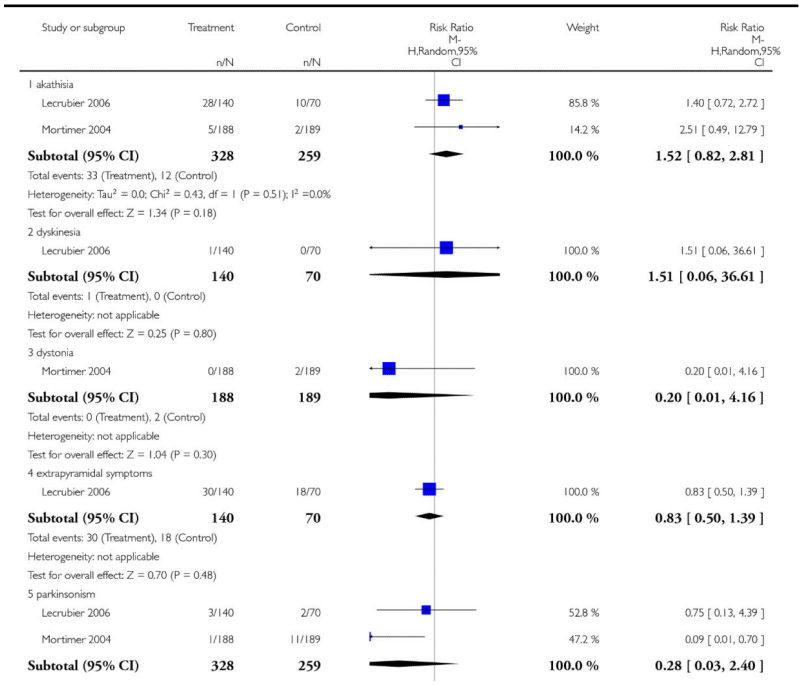
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 23 Adverse effects: 4b. Central nervous system - seizures

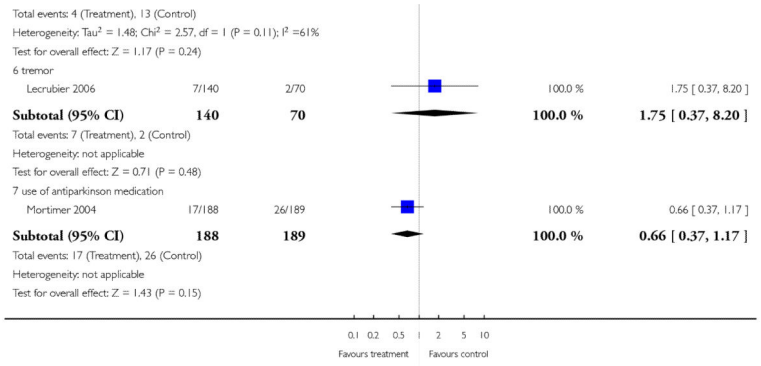


Analysis 1.24

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 24 Adverse effects: 5a. Extrapyramidal effects

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 24 Adverse effects: 5a. Extrapyramidal effects





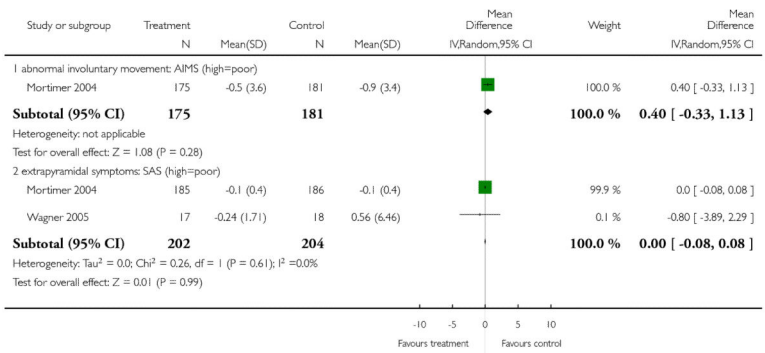
Analysis 1.25

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 25 Adverse effects: 5b. Extrapyramidal side effects- scale measured

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 1 OLANZAPINE versus AMISULPRIDE

Outcome: 25 Adverse effects: 5b. Extrapyramidal side effects- scale measured



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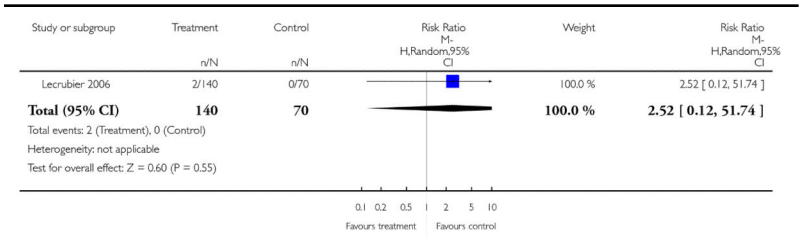
Analysis 1.26

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 26 Adverse effects: 6. Haematological - white blood cell count - leukopenia

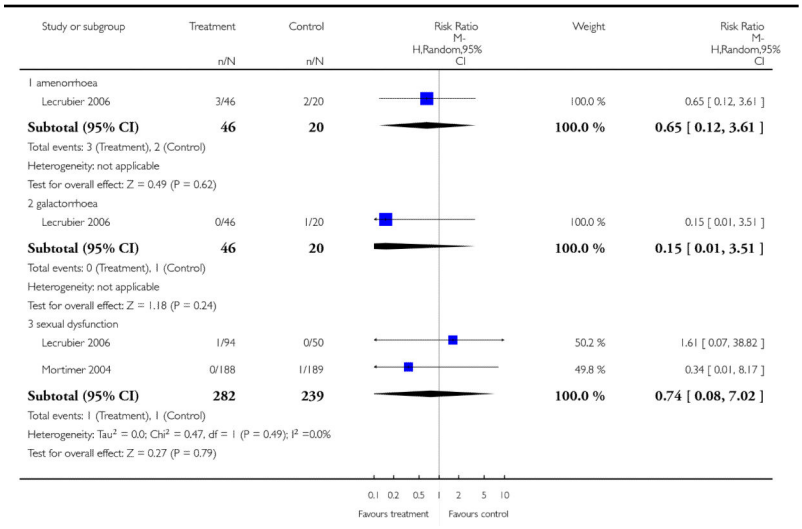
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 26 Adverse effects: 6. Haematological - white blood cell count - leukopenia



Analysis 1.27

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 27 Adverse effects: 7. Prolactin associated side effects

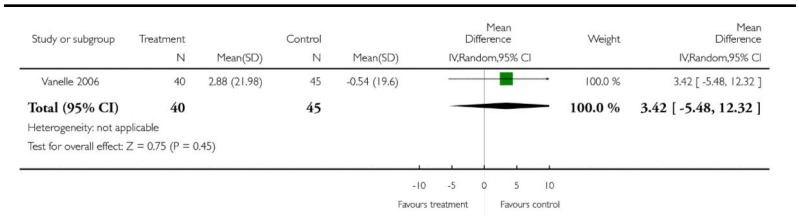
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 27 Adverse effects: 7. Prolactin associated side effects



Analysis 1.28

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 28 Adverse effects: 8a. Metabolic - cholesterol - change from baseline in mg/dl

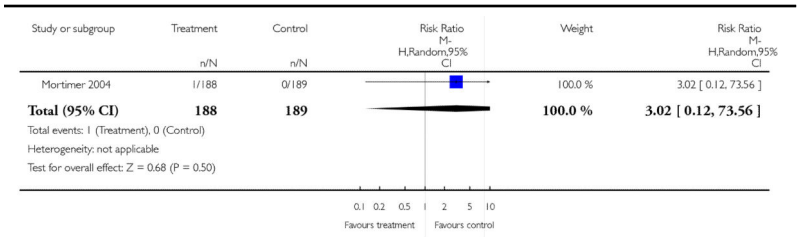
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 28 Adverse effects: 8a. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 1.29

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 29 Adverse effects: 8b. Metabolic - glucose - diabetes mellitus

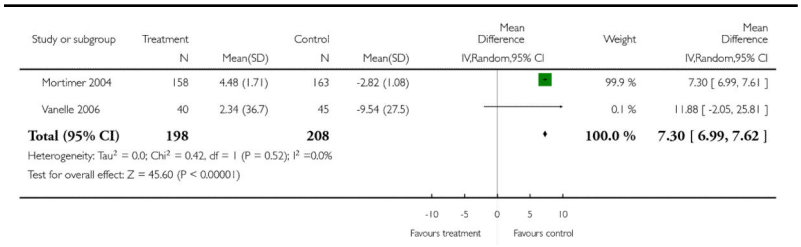
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 29 Adverse effects: 8b. Metabolic - glucose - diabetes mellitus



Analysis 1.30

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 30 Adverse effects: 8c. Metabolic - glucose - change from baseline in mg/dl

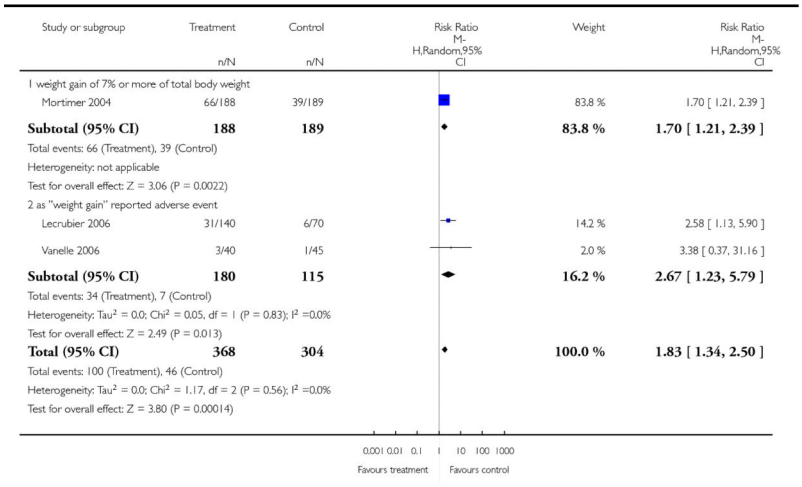
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 30 Adverse effects: 8c. Metabolic - glucose - change from baseline in mg/dl



Analysis 1.31

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 31 Adverse effects: 8d. Metabolic - weight gain

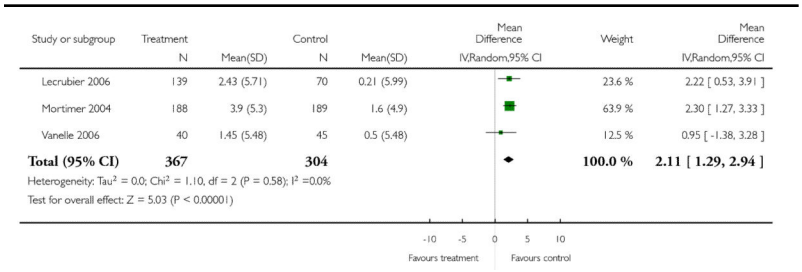
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 31 Adverse effects: 8d. Metabolic - weight gain



Analysis 1.32

Comparison 1 OLANZAPINE versus AMISULPRIDE, Outcome 32 Adverse effects: 8e. Metabolic - weight gain - change from baseline in kg

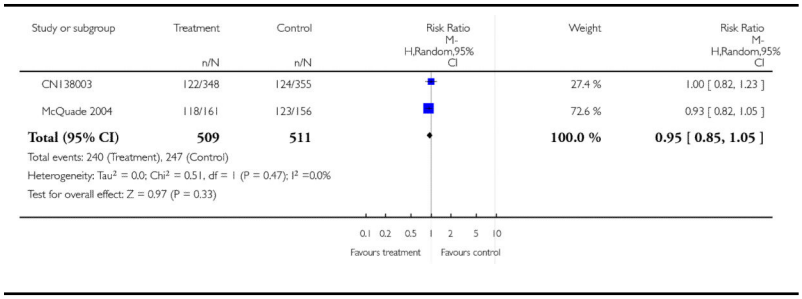
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 1 OLANZAPINE versus AMISULPRIDE
Outcome: 32 Adverse effects: 8e. Metabolic - weight gain - change from baseline in kg



Analysis 2.1

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

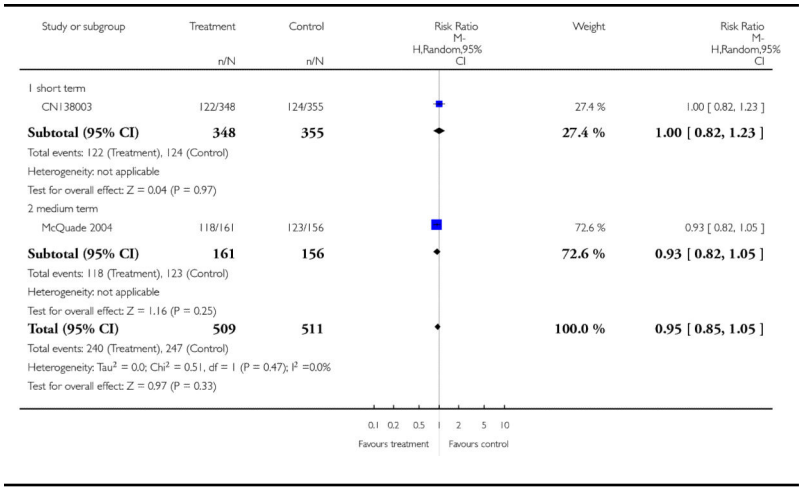
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 1 Global state: 1a. No clinically significant response (as defined by the original studies)



Analysis 2.2

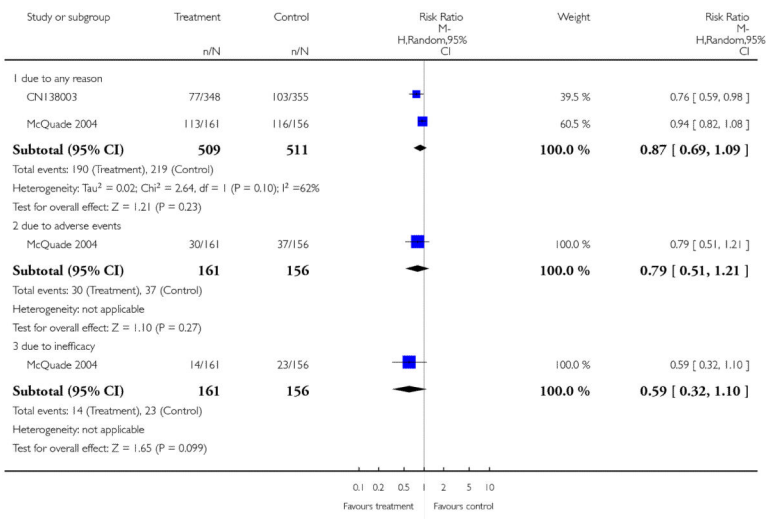
Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 2 Global State: 1b. No clinically important change (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 2 Global State: 1b. No clinically important change (as defined by the original studies)



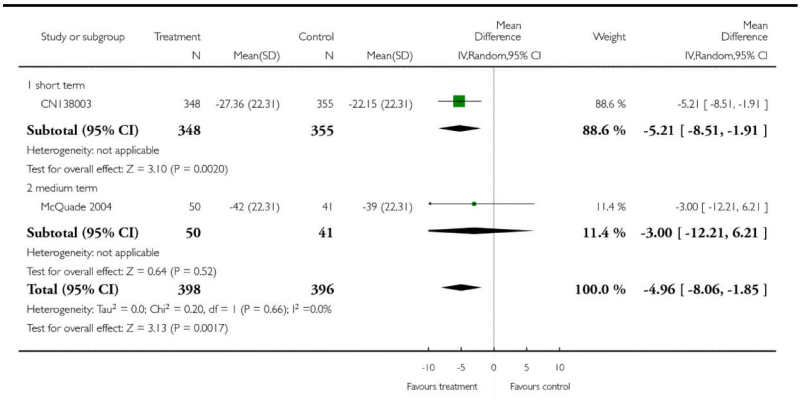
Analysis 2.3
Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 3 Leaving the study early

Review: Olanzapine versus other atypical antipsychotics for schizophreni
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 3 Leaving the study early



Analysis 2.4
Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 4 Mental State: General - average endpoint score (PANSS total, high=poor)

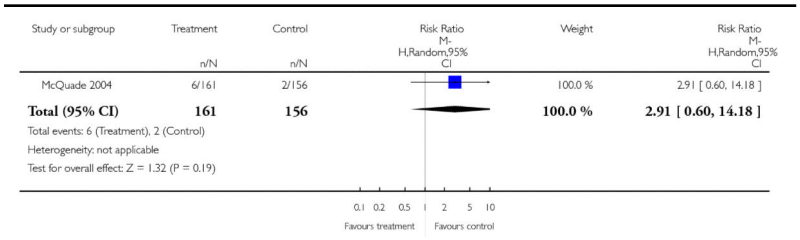
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 4 Mental State: General - average endpoint score (PANSS total, high=poor)



Analysis 2.5

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 5 Adverse effects: 1a. Cardiac effects - QTc prolongation

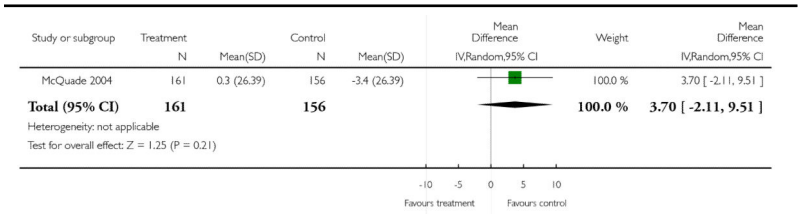
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 5 Adverse effects: 1a. Cardiac effects - QTc prolongation



Analysis 2.6

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 6 Adverse effects: 1b. Cardiac effects - QTc abnormalities - change from baseline in ms

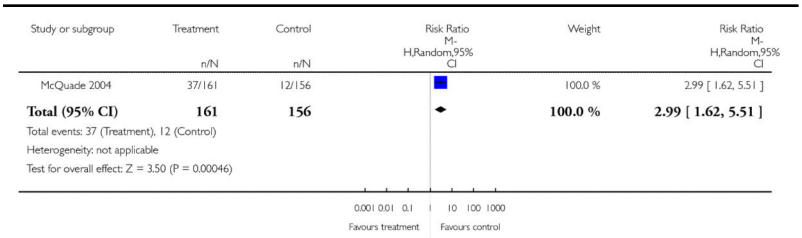
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 6 Adverse effects: 1b. Cardiac effects - QTc abnormalities - change from baseline in ms



Analysis 2.7

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 7 Adverse effects: 2. Central nervous system - sedation

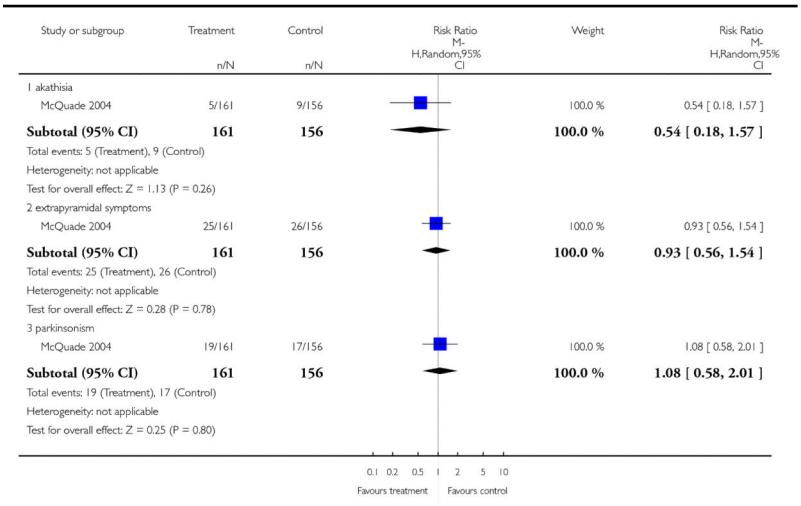
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 7 Adverse effects: 2. Central nervous system - sedation



Analysis 2.8

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 8 Adverse effects: 3. Extrapyramidal effects

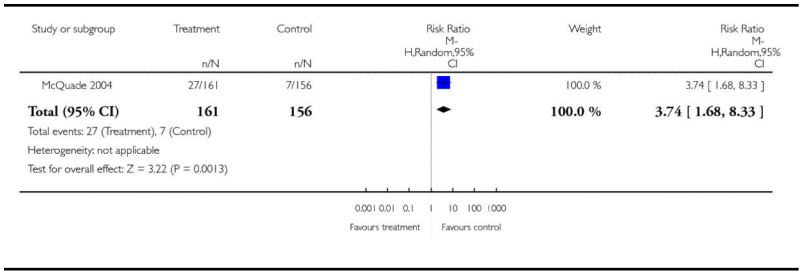
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 8 Adverse effects: 3. Extrapyramidal effects



Analysis 2.9

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 9 Adverse effects: 4. Prolactin associated side effects - abnormally high prolactin value

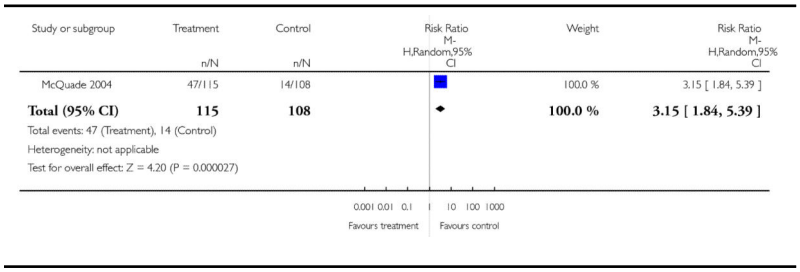
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 9 Adverse effects: 4. Prolactin associated side effects - abnormally high prolactin value



Analysis 2.10

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 10 Adverse effects: 5a. Metabolic - cholesterol - significant cholesterol increase

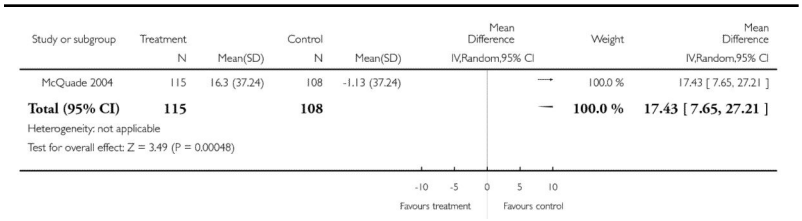
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 10 Adverse effects: 5a. Metabolic - cholesterol - significant cholesterol increase



Analysis 2.11

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 11 Adverse effects: 5b. Metabolic - cholesterol - change from baseline in mg/dl

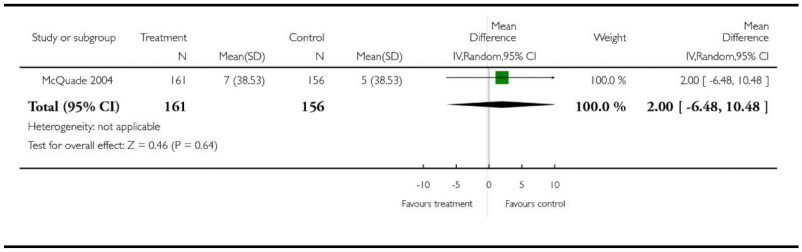
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 11 Adverse effects: 5b. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 2.12

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 12 Adverse effects: 5c. Metabolic - glucose - change from baseline in mg/dl

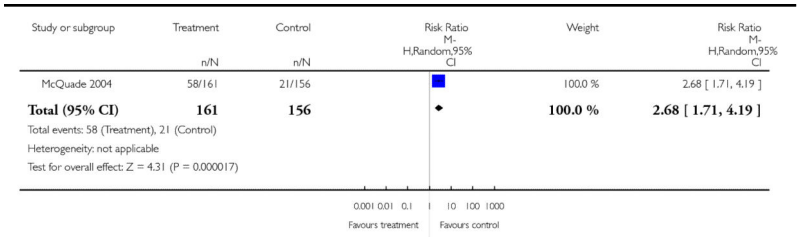
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 12 Adverse effects: 5c. Metabolic - glucose - change from baseline in mg/dl



Analysis 2.13

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 13 Adverse effects: 5d. Metabolic - weight gain of 7% or more of total body weight

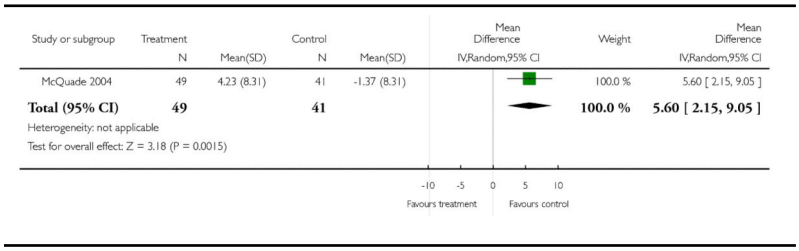
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 13 Adverse effects: 5d. Metabolic - weight gain of 7% or more of total body weight



Analysis 2.14

Comparison 2 OLANZAPINE versus ARIPIPRAZOLE, Outcome 14 Adverse effects: 5e. Metabolic - weight gain - change from baseline in kg

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 2 OLANZAPINE versus ARIPIPRAZOLE
Outcome: 14 Adverse effects: 5e. Metabolic - weight gain - change from baseline in kg



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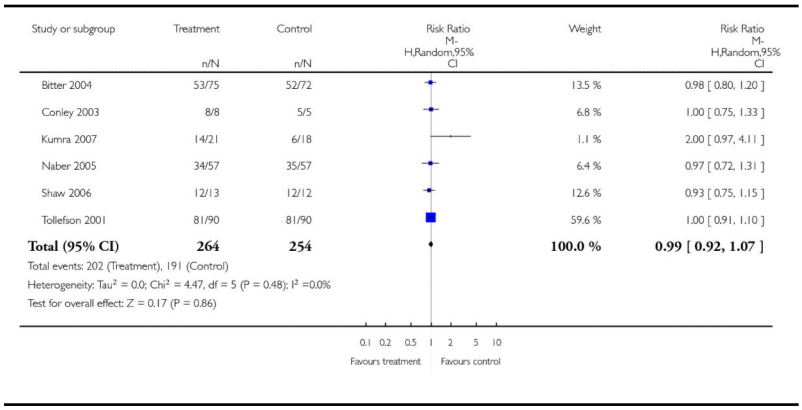
Analysis 3.1

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 1 Global state: 1a. no clinically significant response (as defined by the original studies)

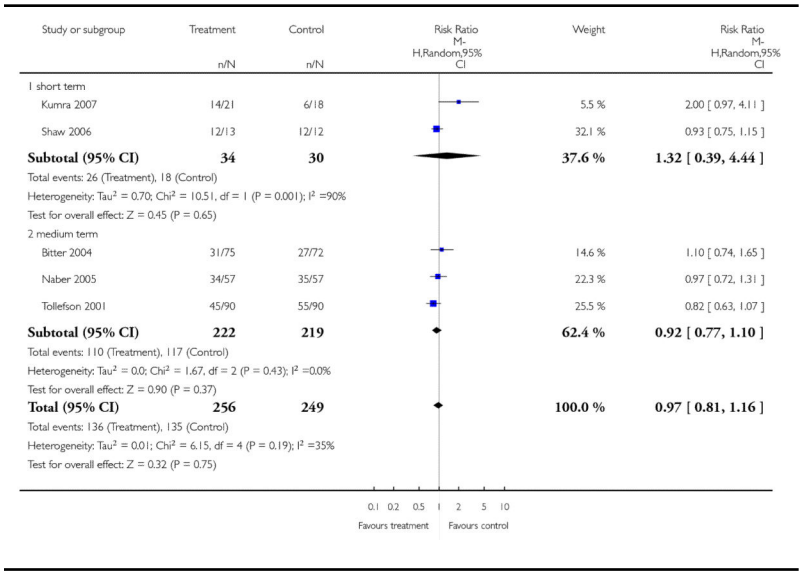
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 1 Global state: 1a. no clinically significant response (as defined by the original studies)



Analysis 3.2

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 2 Global State: no clinically important change (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 2 Global State: no clinically important change (as defined by the original studies)



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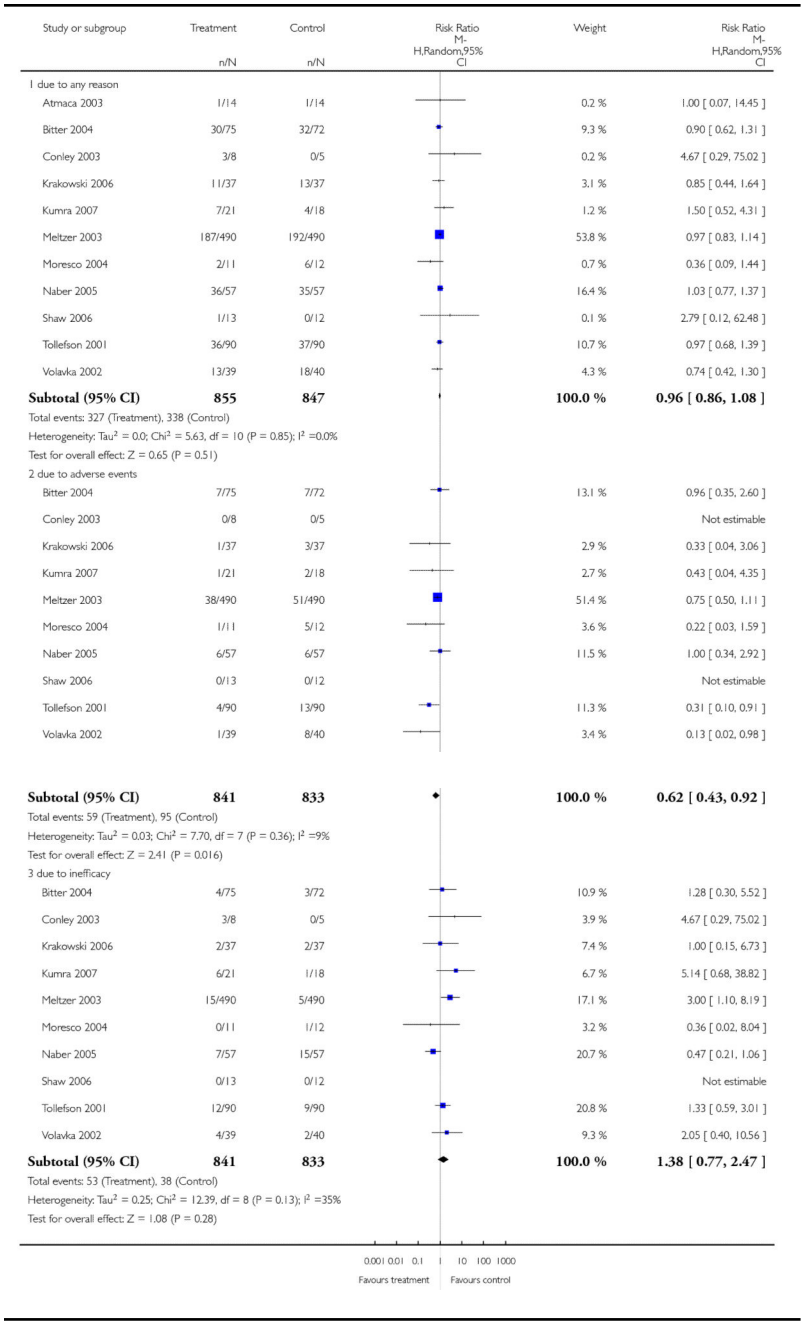
Analysis 3.3
Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 3 Leaving the study early

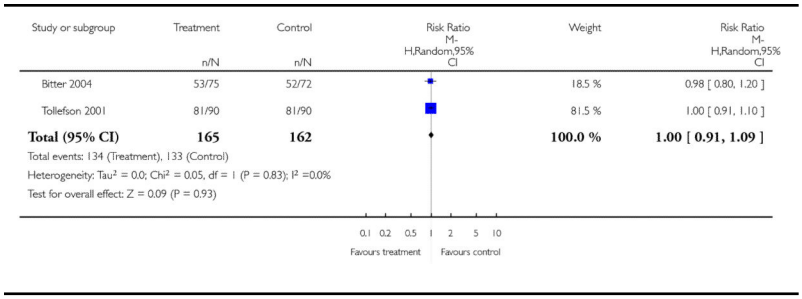
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 3 Leaving the study early



Analysis 3.4

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 4 Mental State: 1a. General - no clinically important change - medium term (less than 50% PANSS total score reduction)

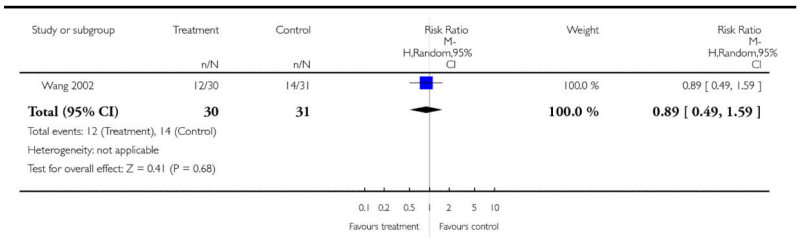
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 4 Mental State: 1a. General - no clinically important change - medium term (less than 50% PANSS total score reduction)



Analysis 3.5

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 5 Mental State: 1b. General - no clinically important change - short term (less than 50% BPRS total score reduction)

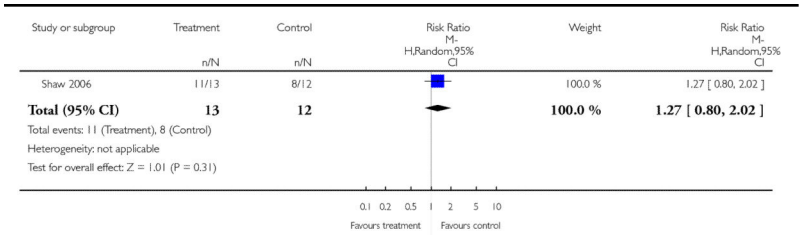
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 5 Mental State: 1b. General - no clinically important change - short term (less than 50% BPRS total score reduction)



Analysis 3.6

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 6 Mental State: 1c. General - no clinically important change - short term (less than 20% BPRS total score reduction)

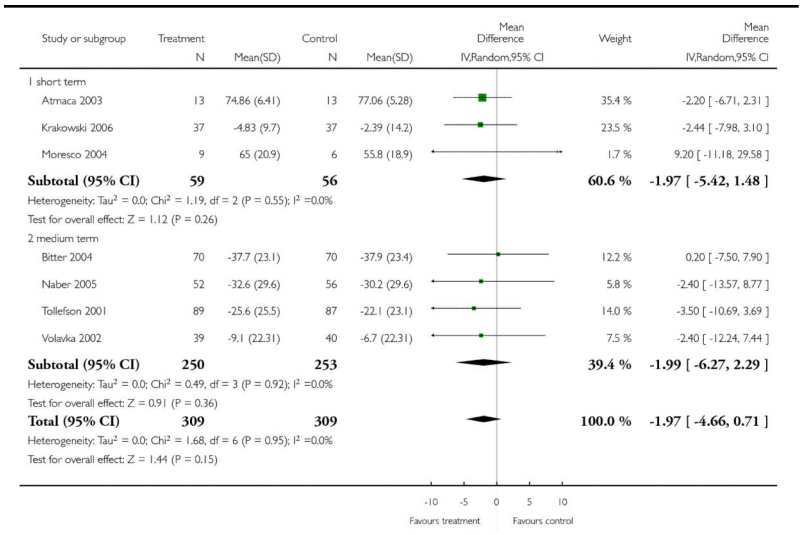
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 6 Mental State: 1c. General - no clinically important change - short term (less than 20% BPRS total score reduction)



Analysis 3.7

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 7 Mental State: 1d. General - average endpoint score (PANSS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 7 Mental State: 1d. General - average endpoint score (PANSS total, high=poor)



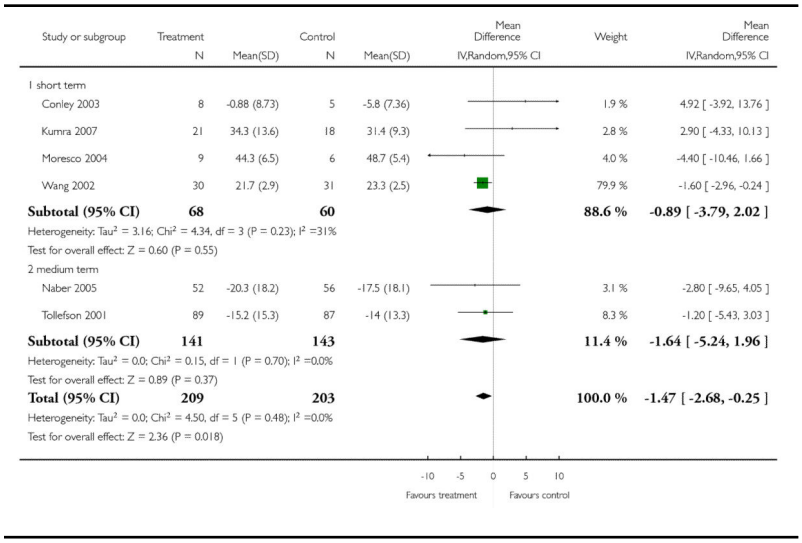
Analysis 3.8

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 8 Mental State: 1e. General - average endpoint score (BPRS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 3 OLANZAPINE versus CLOZAPINE

Outcome: 8 Mental State: 1e. General - average endpoint score (BPRS total, high=poor)



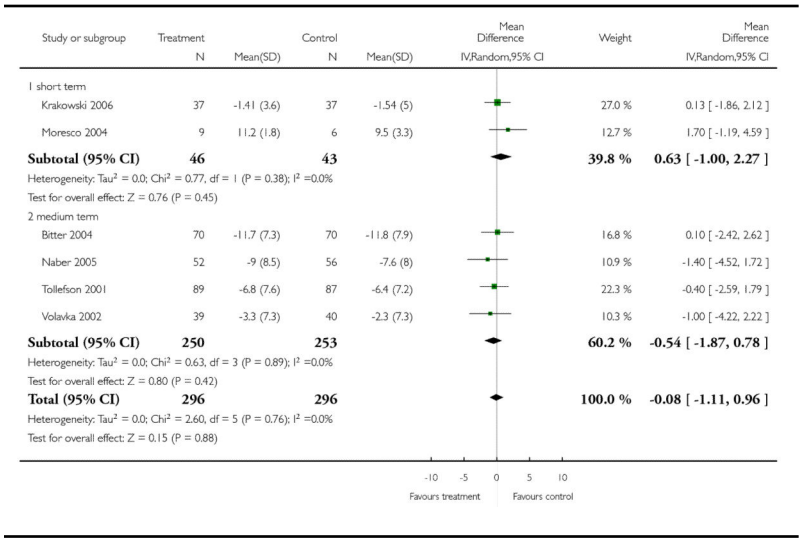
Analysis 3.9

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 9 Mental State: 2a. Positive symptoms - average endpoint score (PANSS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 3 OLANZAPINE versus CLOZAPINE

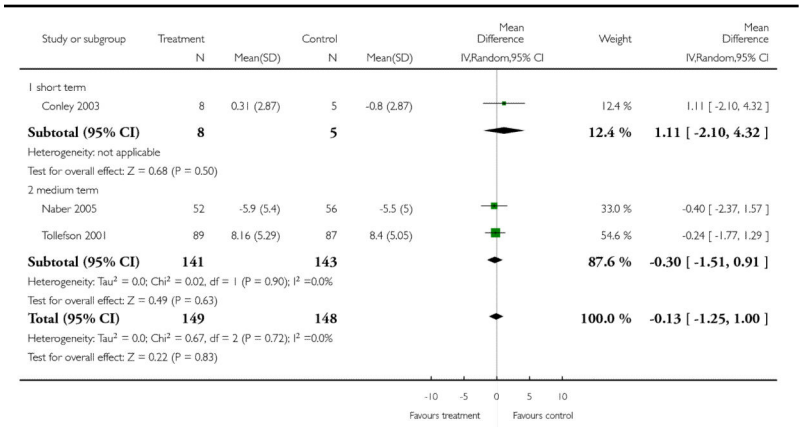
Outcome: 9 Mental State: 2a. Positive symptoms - average endpoint score (PANSS positive, high=poor)



Analysis 3.10

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 10 Mental State: 2b. Positive symptoms - average endpoint score (BPRS positive, high=poor)

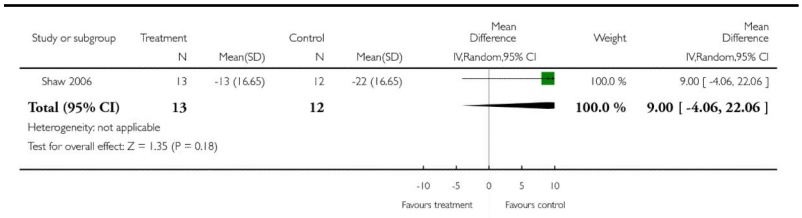
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 10 Mental State: 2b. Positive symptoms - average endpoint score (BPRS positive, high=poor)



Analysis 3.11

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 11 Mental State: 2c. Positive symptoms - average endpoint score (SAPS total, high=poor)

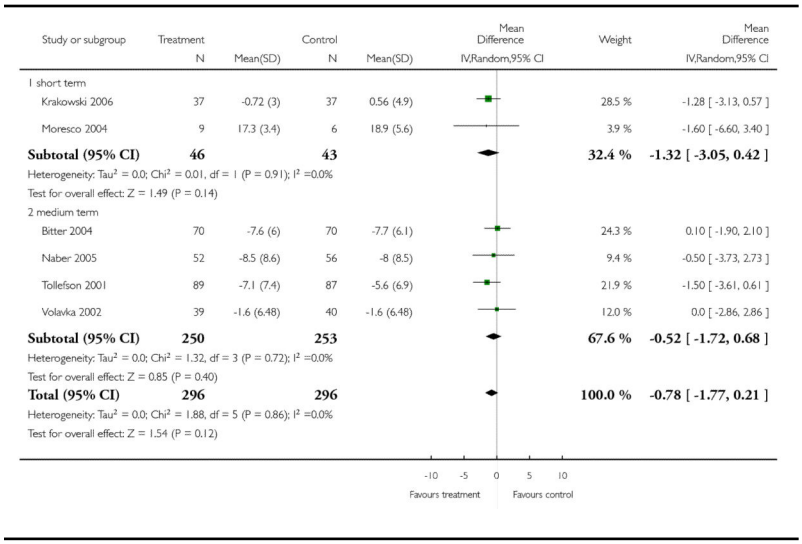
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 11 Mental State: 2c. Positive symptoms - average endpoint score (SAPS total, high=poor)



Analysis 3.12

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 12 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)

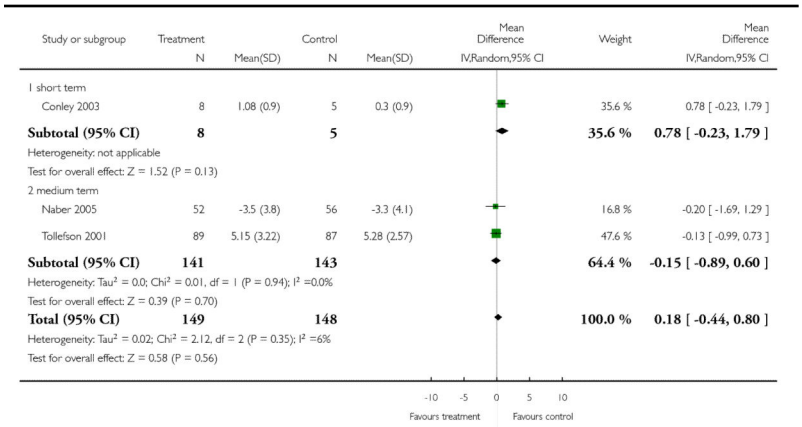
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 12 Mental State: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)



Analysis 3.13

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 13 Mental State: 3b. Negative symptoms - average endpoint score (BPRS negative, high=poor)

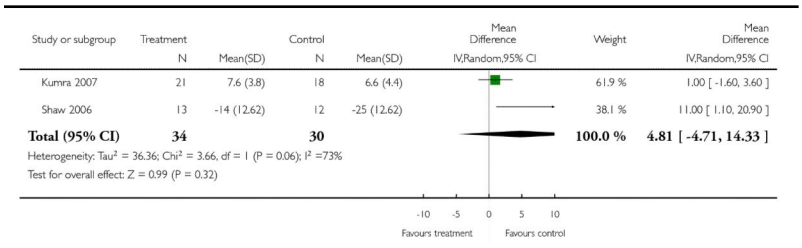
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 13 Mental State: 3b. Negative symptoms - average endpoint score (BPRS negative, high=poor)



Analysis 3.14

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 14 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)

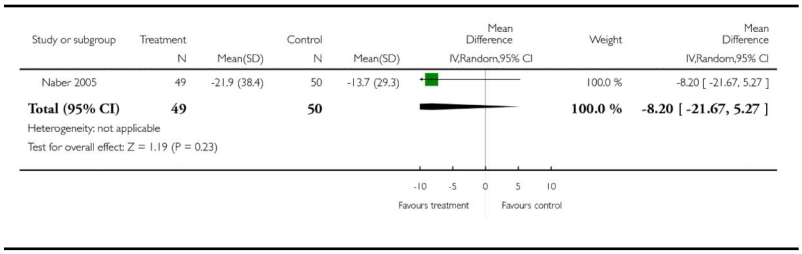
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 14 Mental State: 3c. Negative symptoms - average endpoint score (SANS total, high=poor)



Analysis 3.15

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 15 Quality of Life: General - average endpoint score - medium term (SWN total, high=poor)

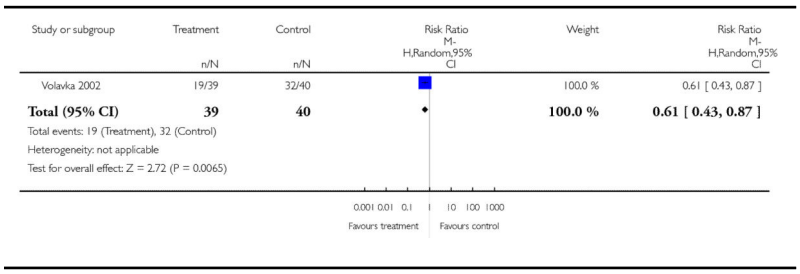
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 15 Quality of Life: General - average endpoint score - medium term (SWN total, high=poor)



Analysis 3.16

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 16 Cognitive functioning: 1a. General - no clinically important change - medium term (less than ½ SD in global neurocognitive score improved)

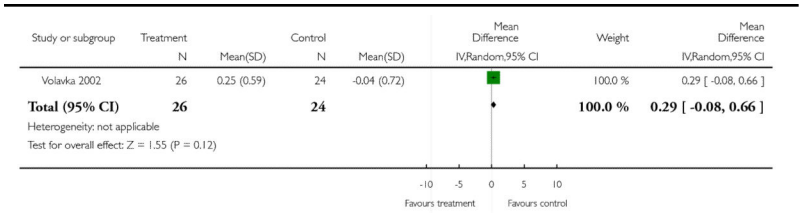
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 16 Cognitive functioning: 1a. General - no clinically important change - medium term (less than SD in global neurocognitive score improved)



Analysis 3.17

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 17 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)

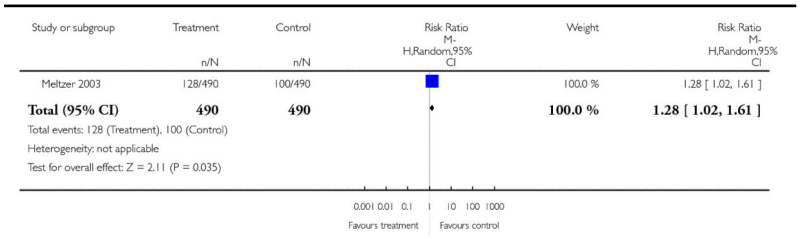
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 17 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)



Analysis 3.18

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 18 Service use: Number of patients re-hospitalised - long term

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 18 Service use: Number of patients re-hospitalised - long term



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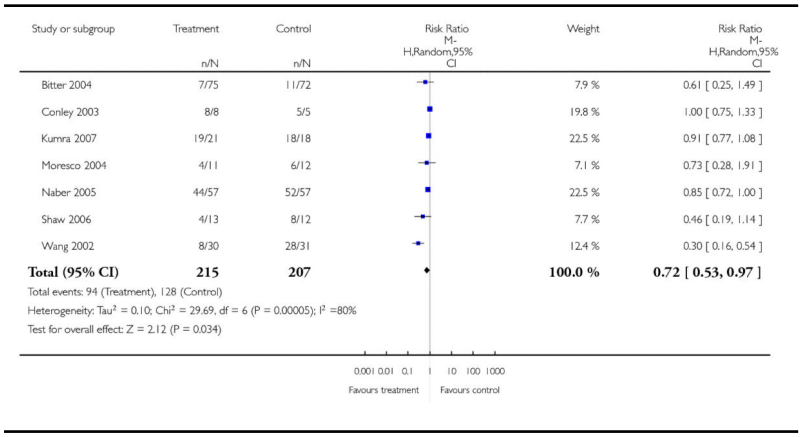
Analysis 3.19

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 19 Adverse effects: 1. General - at least one adverse effect

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 19 Adverse effects: 1. General - at least one adverse effect



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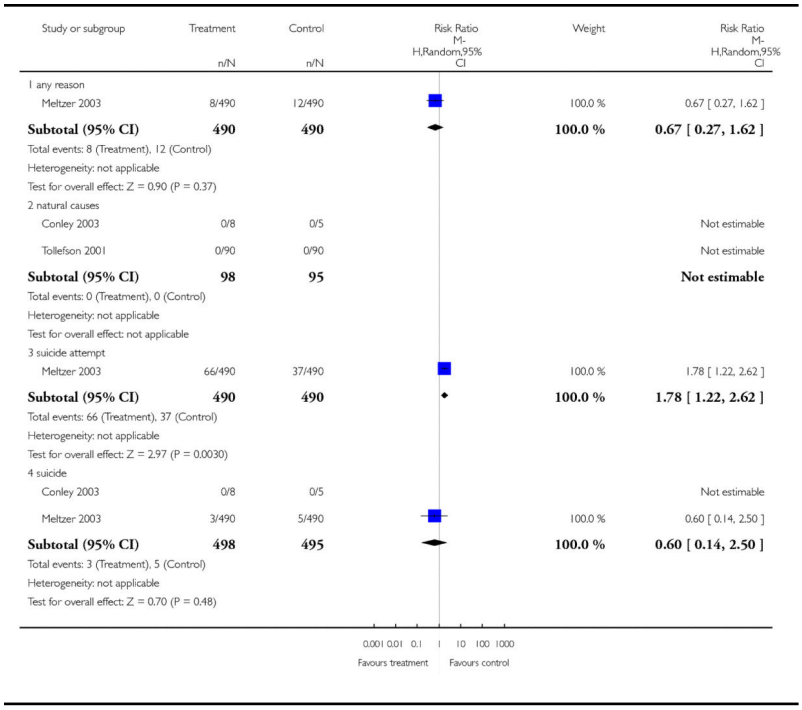
Analysis 3.20
Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 20 Adverse effects: 2. Death

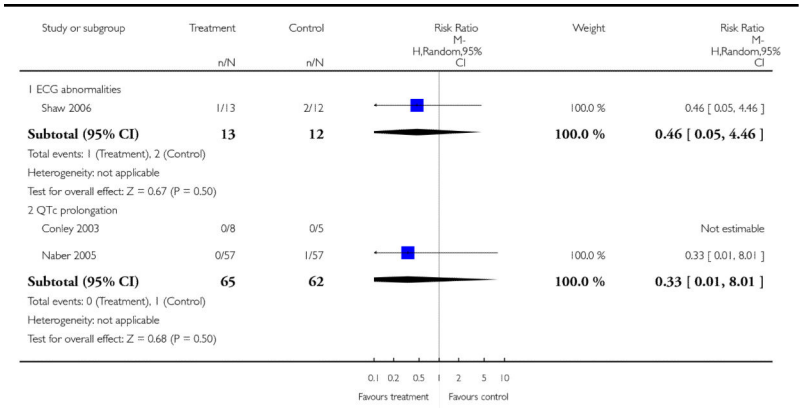
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 20 Adverse effects: 2. Death



Analysis 3.21

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 21 Adverse effects: 3. Cardiac effects

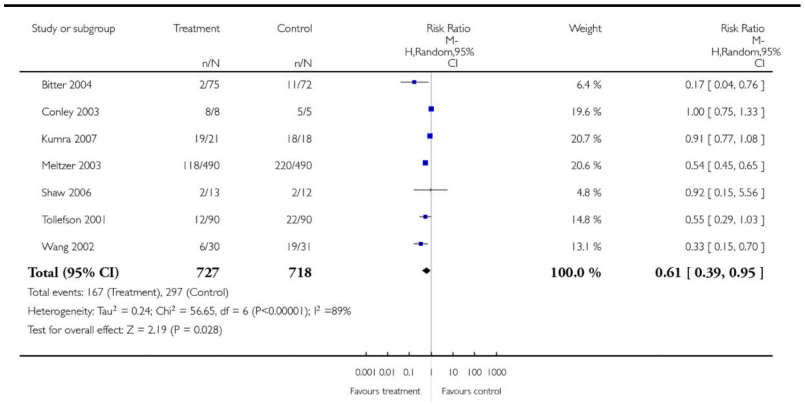
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 21 Adverse effects: 3. Cardiac effects



Analysis 3.22

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 22 Adverse effects: 4a. Central nervous system - sedation

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 22 Adverse effects: 4a. Central nervous system - sedation



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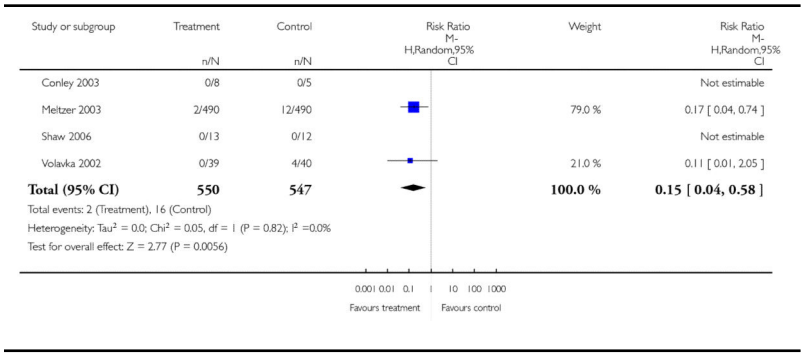
Analysis 3.23

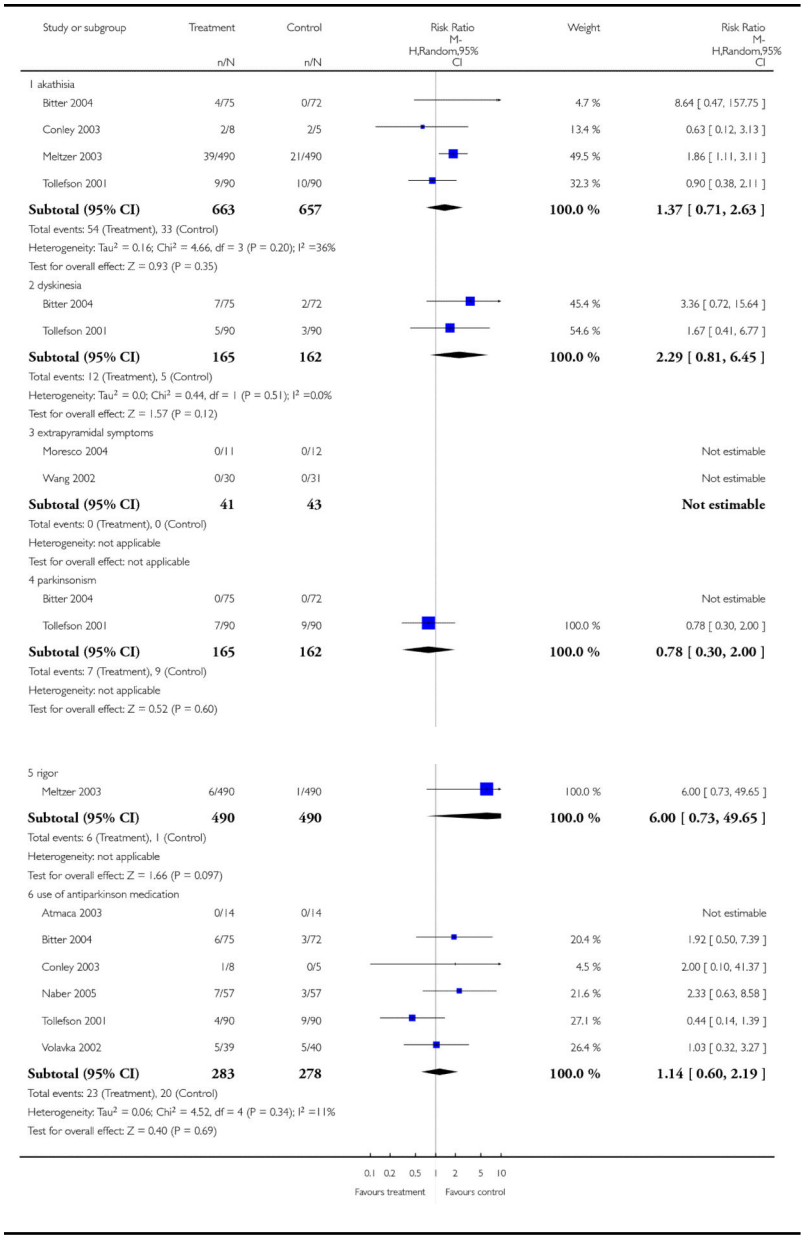
Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 23 Adverse effects: 4b. Central nervous system - seizures

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 23 Adverse effects: 4b. Central nervous system - seizures



Analysis 3.24
Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 24 Adverse effects: 5a. Extrapyramidal effects

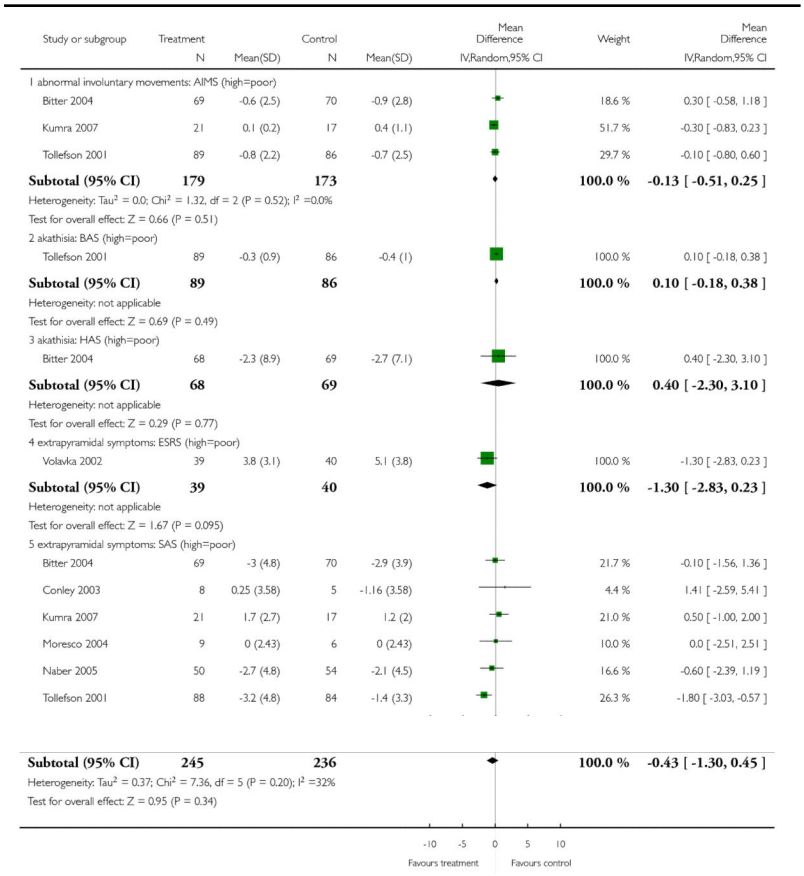
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 24 Adverse effects: 5a. Extrapyramidal effects



Analysis 3.25

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 25 Adverse effects: 5b. Extrapyramidal effects - scale measured

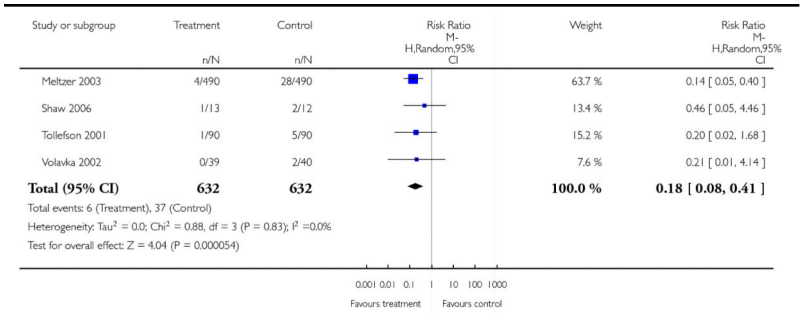
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 25 Adverse effects: 5b. Extrapyramidal effects - scale measured



Analysis 3.26

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 26 Adverse effects: 6. Haematological - significant low white blood cell count (as def. by the original studies)

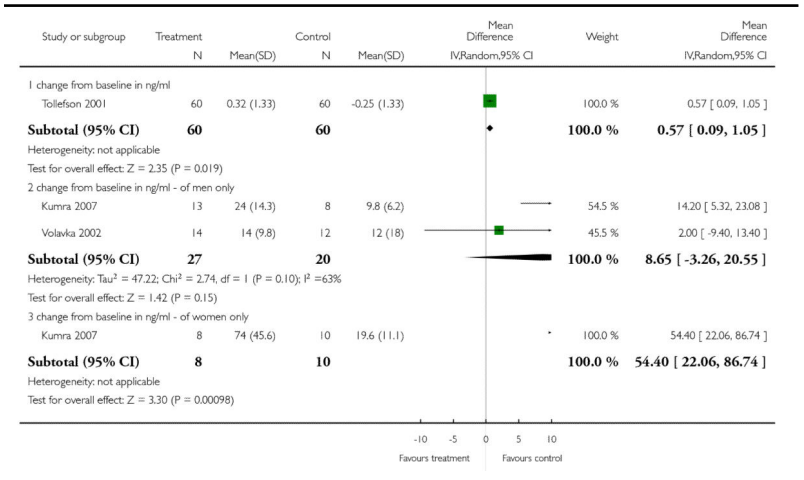
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 26 Adverse effects: 6. Haematological - significant low white blood cell count (as def. by the original studies)



Analysis 3.27

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 27 Adverse effects: 7. Prolactin - change from baseline in ng/ml

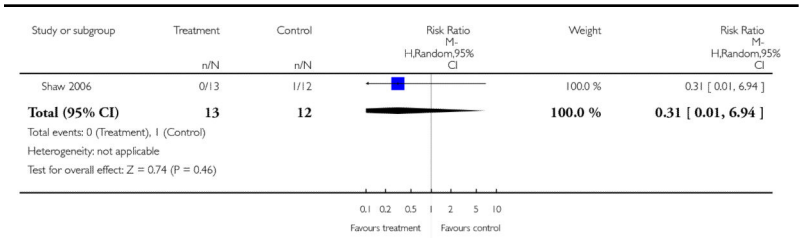
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 27 Adverse effects: 7. Prolactin - change from baseline in ng/ml



Analysis 3.28

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 28 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase

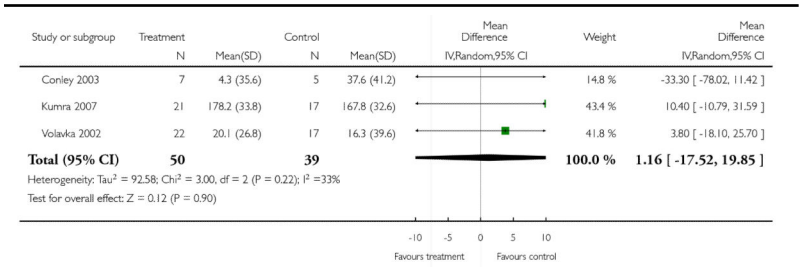
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 28 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase



Analysis 3.29

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 29 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl

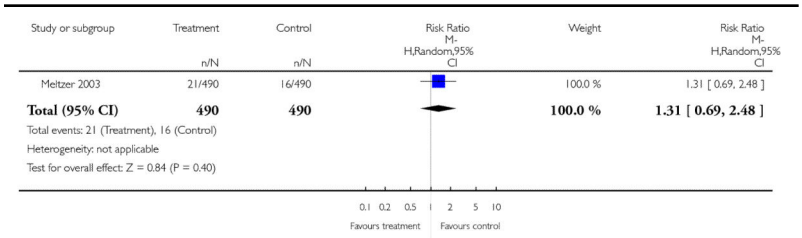
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 29 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 3.30

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 30 Adverse effects: 8c. Metabolic - glucose - diabetes mellitus

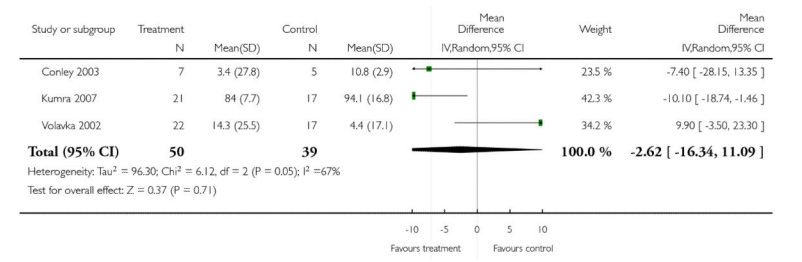
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 30 Adverse effects: 8c. Metabolic - glucose - diabetes mellitus



Analysis 3.31

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 31 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl

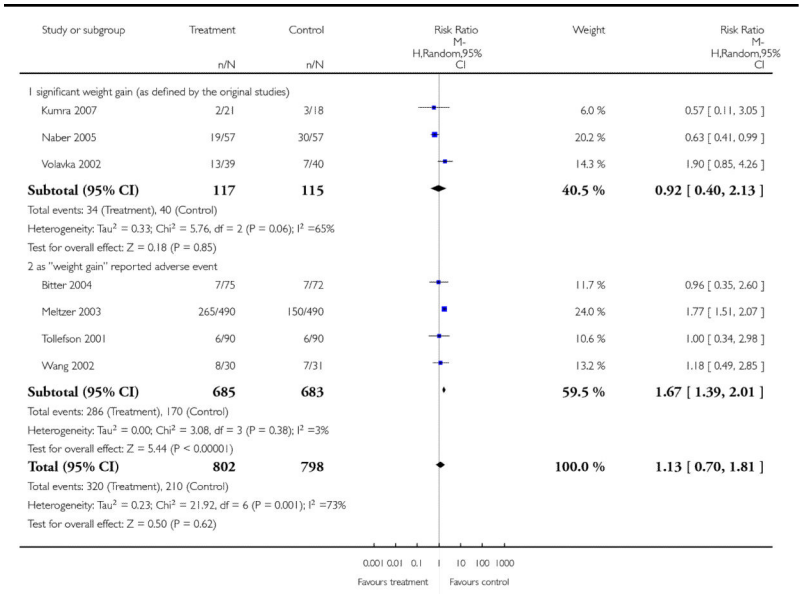
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 31 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl



Analysis 3.32

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 32 Adverse effects: 8e. Metabolic - weight gain

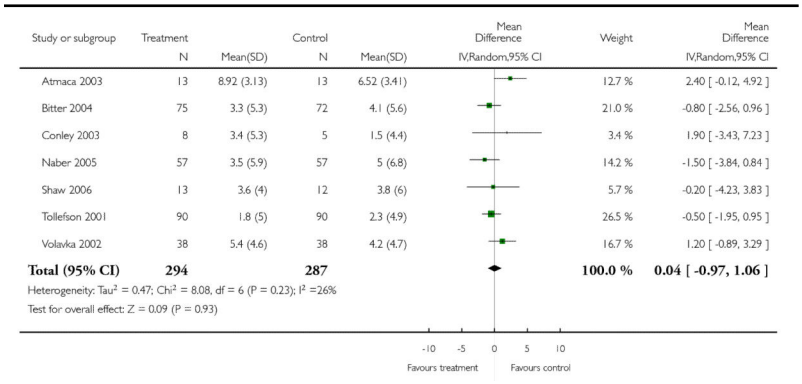
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 32 Adverse effects: 8e. Metabolic - weight gain



Analysis 3.33

Comparison 3 OLANZAPINE versus CLOZAPINE, Outcome 33 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg

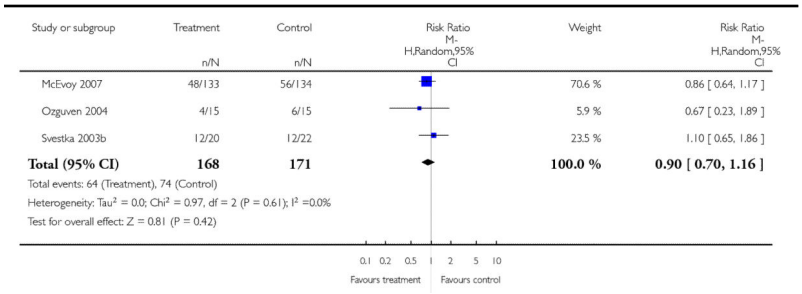
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 3 OLANZAPINE versus CLOZAPINE
Outcome: 33 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg



Analysis 4.1

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

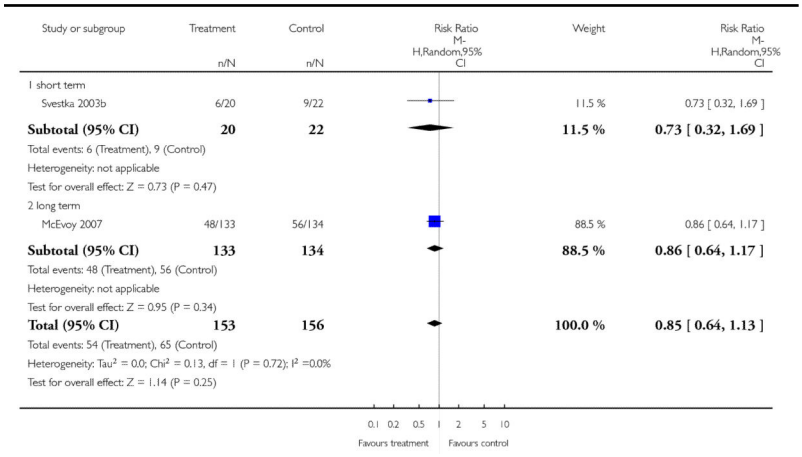
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 1 Global state: 1a. No clinically significant response (as defined by the original studies)



Analysis 4.2

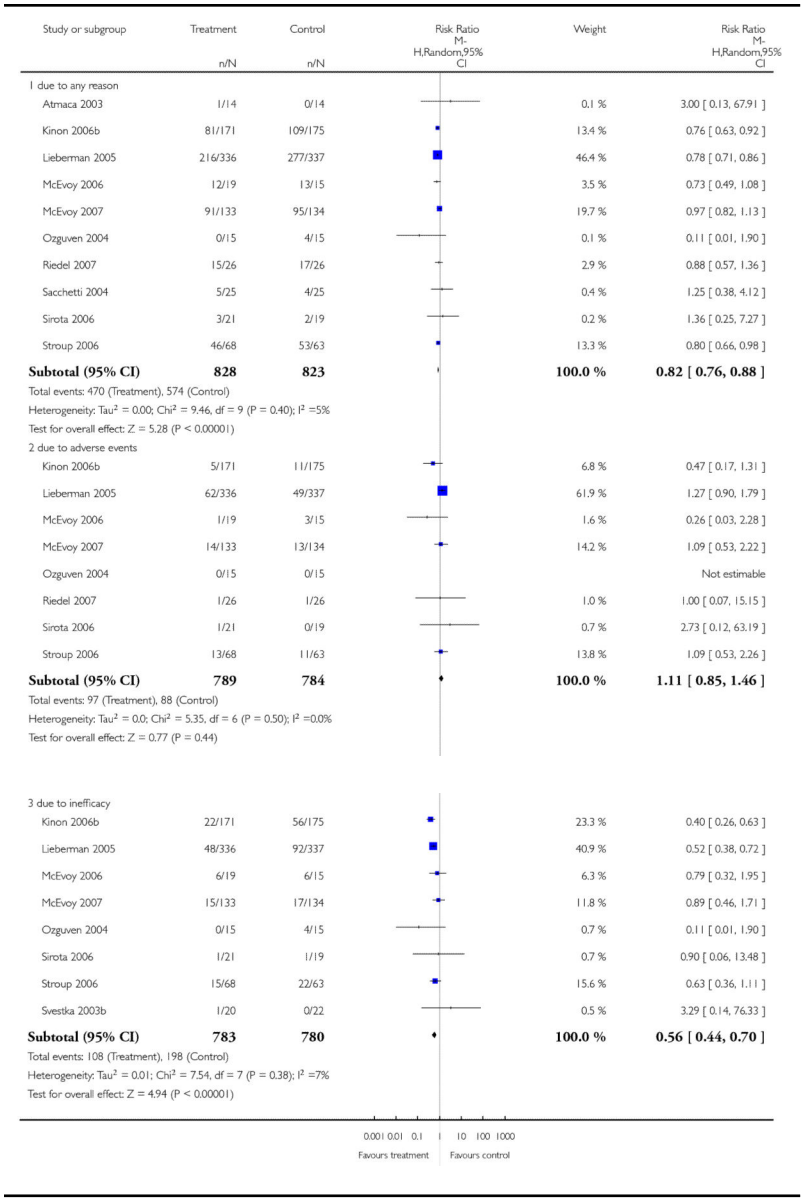
Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 2 Global state: 1b. No clinically important change (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 2 Global state: 1b. No clinically important change (as defined by the original studies)



Analysis 4.3
Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 3 Leaving the study early

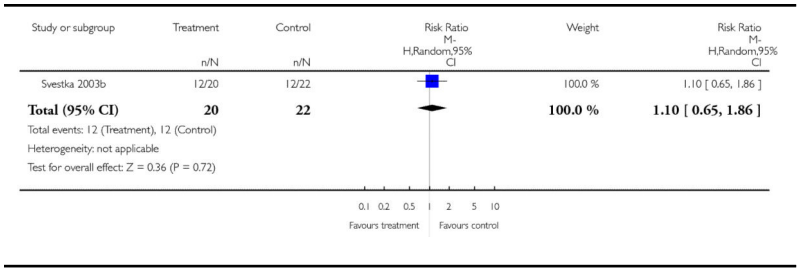
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 3 Leaving the study early



Analysis 4.4

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 4 Mental state: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 4 Mental state: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)



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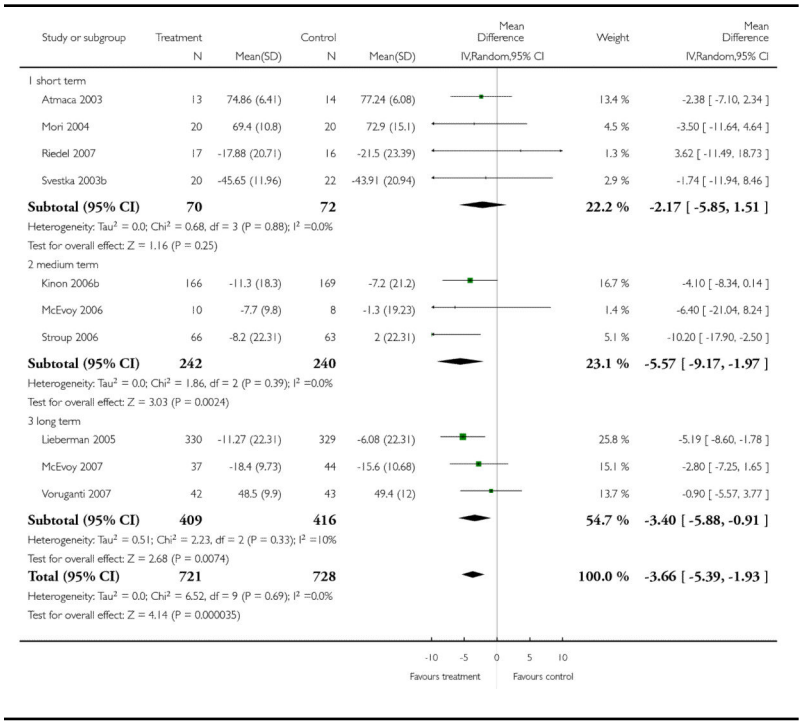
Analysis 4.5

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 5 Mental state: 1b. General - average endpoint score (PANSS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 4 OLANZAPINE versus QUETIAPINE

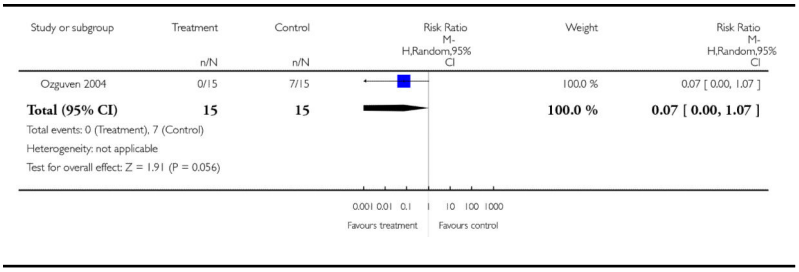
Outcome: 5 Mental state: 1b. General - average endpoint score (PANSS total, high=poor)



Analysis 4.6

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 6 Mental state: 2a. Positive symptoms - no clinically important change-short term (less than 20% SAPS total score reduction)

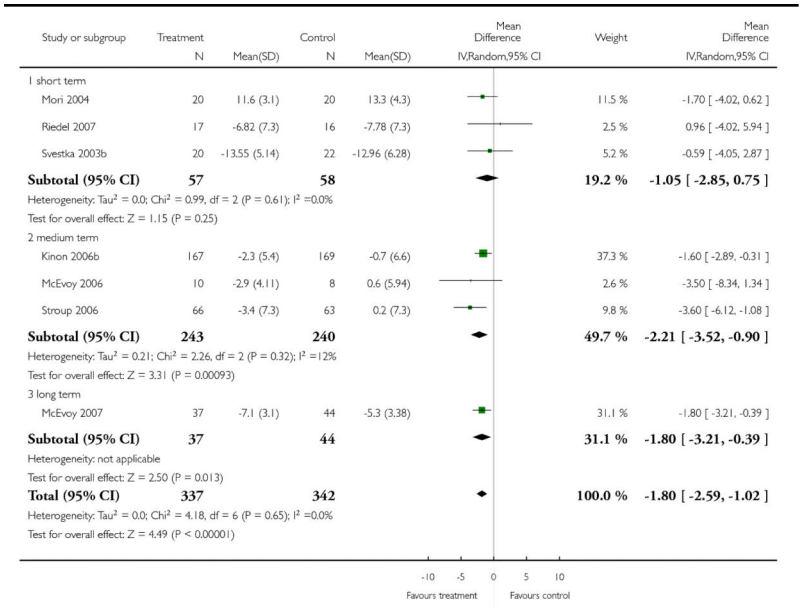
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 6 Mental state: 2a. Positive symptoms - no clinically important change-short term (less than 20% SAPS total score reduction)



Analysis 4.7

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 7 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)

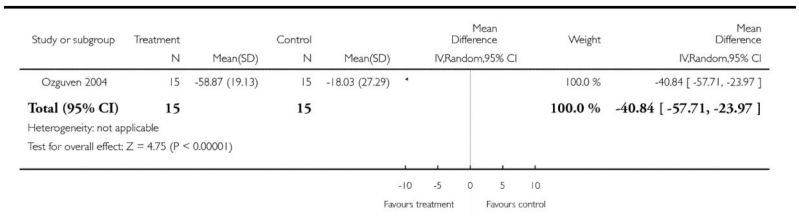
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 7 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)



Analysis 4.8

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 8 Mental state: 2c. Positive symptoms - SAPS total score - percent change-short term (high=poor)

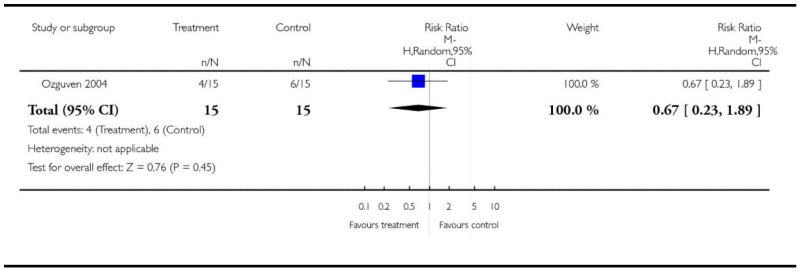
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 8 Mental state: 2c. Positive symptoms - SAPS total score - percent change-short term (high=poor)



Analysis 4.9

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 9 Mental state: 3a. Negative symptoms - no clinically important change-short term (less than 20% SANS total score reduction)

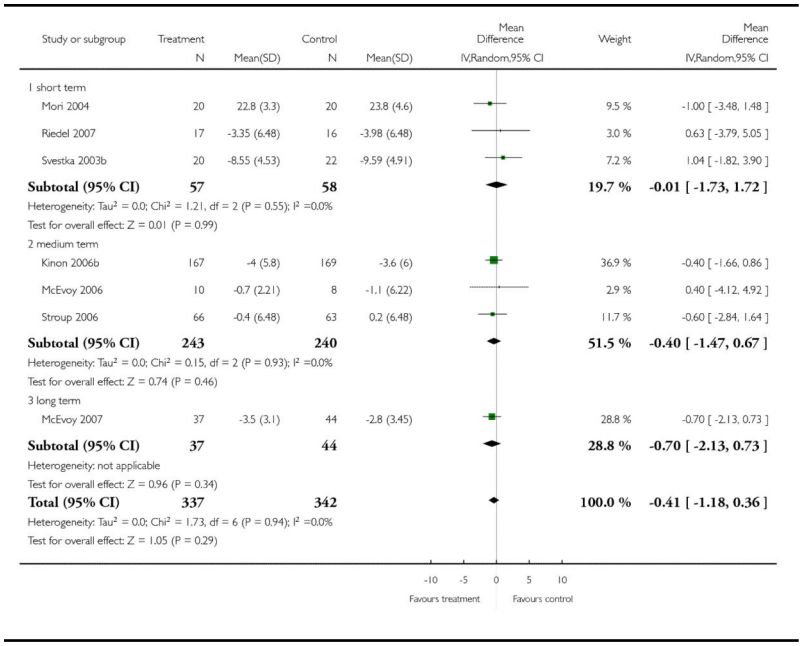
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 9 Mental state: 3a. Negative symptoms - no clinically important change-short term (less than 20% SANS total score reduction)



Analysis 4.10

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 10 Mental state: 3b. Negative symptoms - average endpoint score (PANSS negative subscore, high=poor)

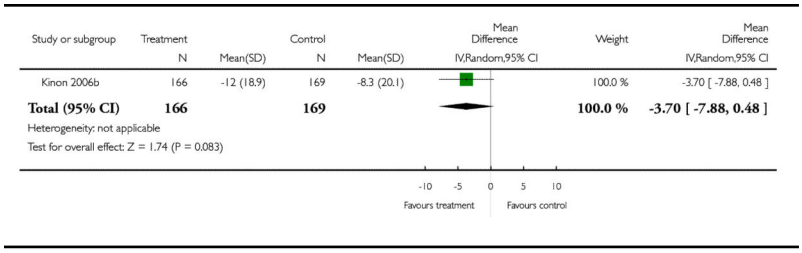
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 10 Mental state: 3b. Negative symptoms - average endpoint score (PANSS negative subscore, high=poor)



Analysis 4.11

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 11 Mental state: 3c. Negative symptoms - average endpoint score-medium term (SANS total score, high=poor)

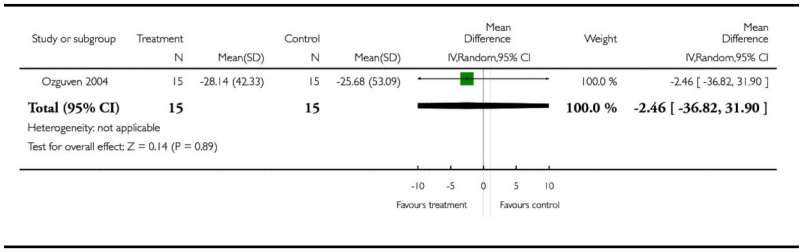
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 11 Mental state: 3c. Negative symptoms - average endpoint score-medium term (SANS total score, high=poor)



Analysis 4.12

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 12 Mental state: 3d. Negative symptoms - average endpoint score-short term (SANS total score-percent change, high=poor)

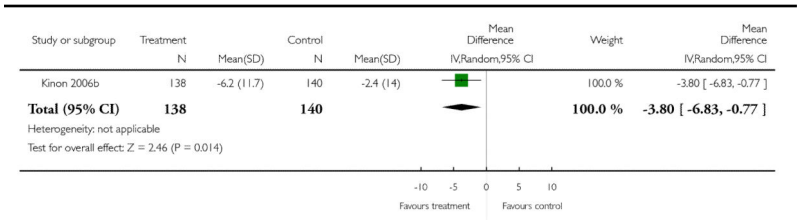
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 12 Mental state: 3d. Negative symptoms - average endpoint score-short term (SANS total score- percent change, high=poor)



Analysis 4.13

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 13 General functioning: average endpoint score-medium term (GAF total score, high=poor)

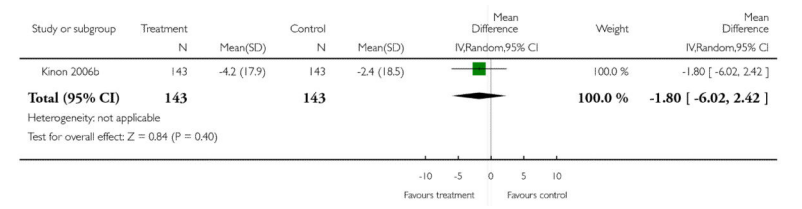
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 13 General functioning: average endpoint score-medium term (GAF total score, high=poor)



Analysis 4.14

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 14 Quality of life: General - average endpoint score-medium term (QLS total score, high=poor)

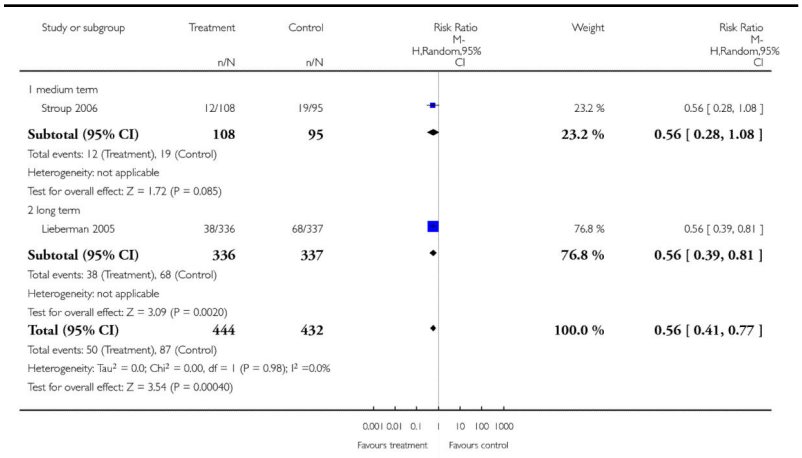
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 14 Quality of life: General - average endpoint score-medium term (QLS total score, high=poor)



Analysis 4.15

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 15 Service use - number of patients re-hospitalised

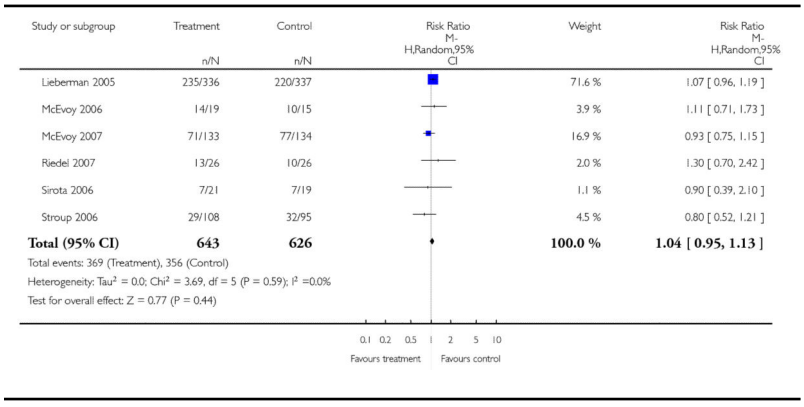
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 15 Service use - number of patients re-hospitalised



Analysis 4.16

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 16 Adverse effects: 1. General - at least one adverse effect

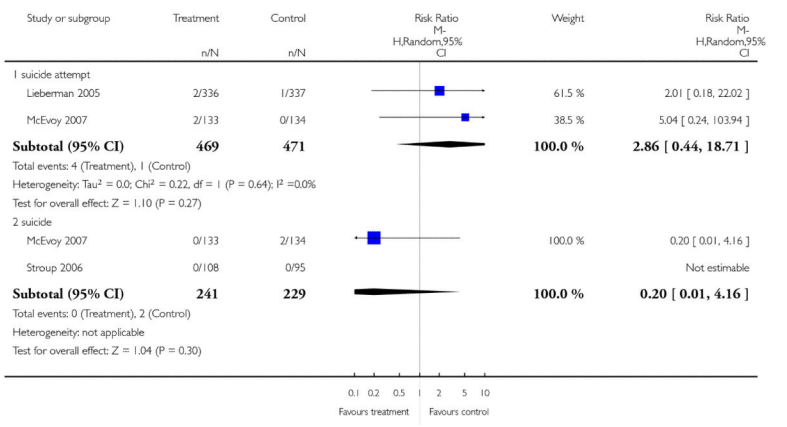
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 16 Adverse effects: 1. General - at least one adverse effect



Analysis 4.17

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 17 Adverse effects: 2. Death

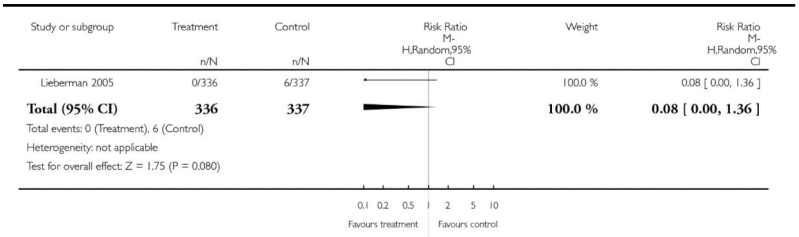
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 17 Adverse effects: 2. Death



Analysis 4.18

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 18 Adverse effects: 3a. Cardiac effects - QTc prolongation

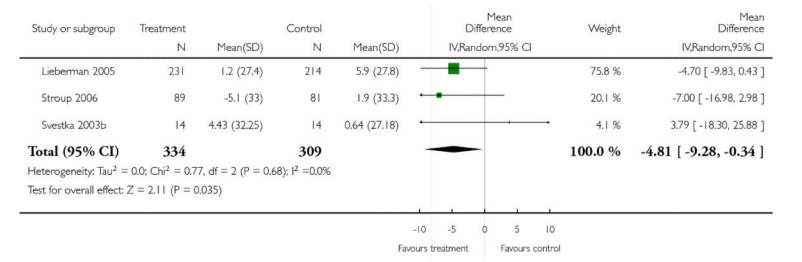
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 18 Adverse effects: 3a. Cardiac effects - QTc prolongation



Analysis 4.19

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

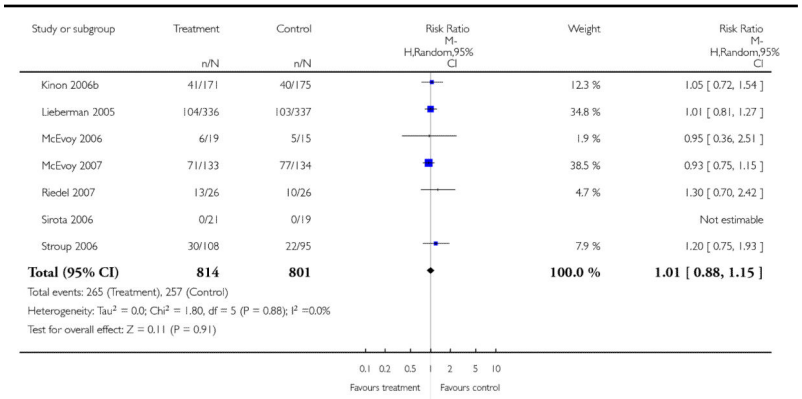
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms



Analysis 4.20

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 20 Adverse effects: 4a. Central nervous system - sedation

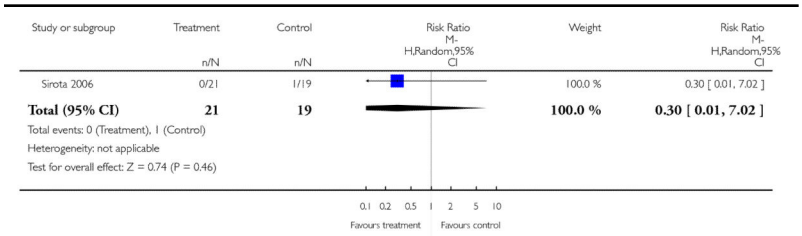
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 20 Adverse effects: 4a. Central nervous system - sedation



Analysis 4.21

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 21 Adverse effects: 4b. Central nervous system - seizures

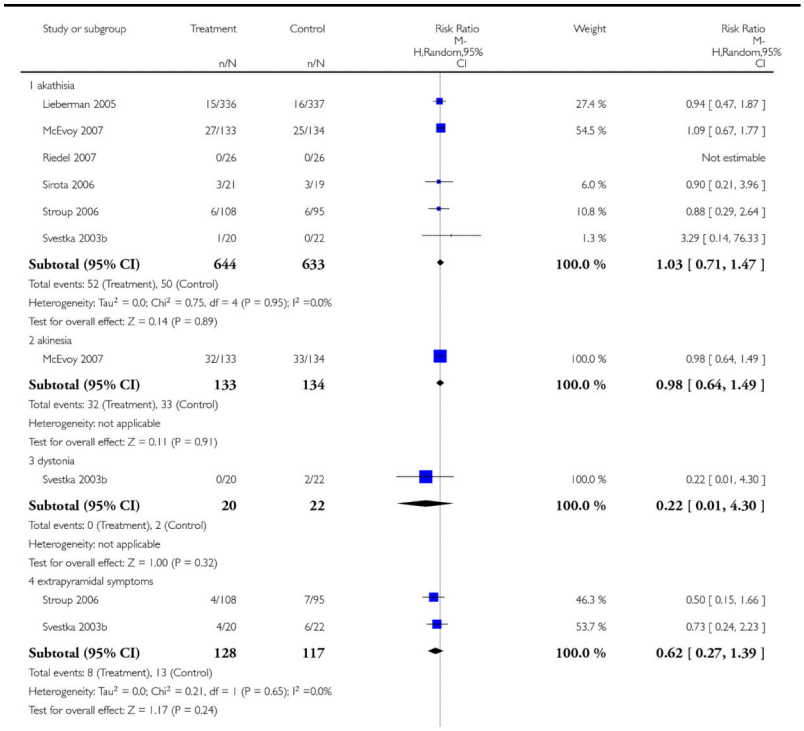
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 21 Adverse effects: 4b. Central nervous system - seizures

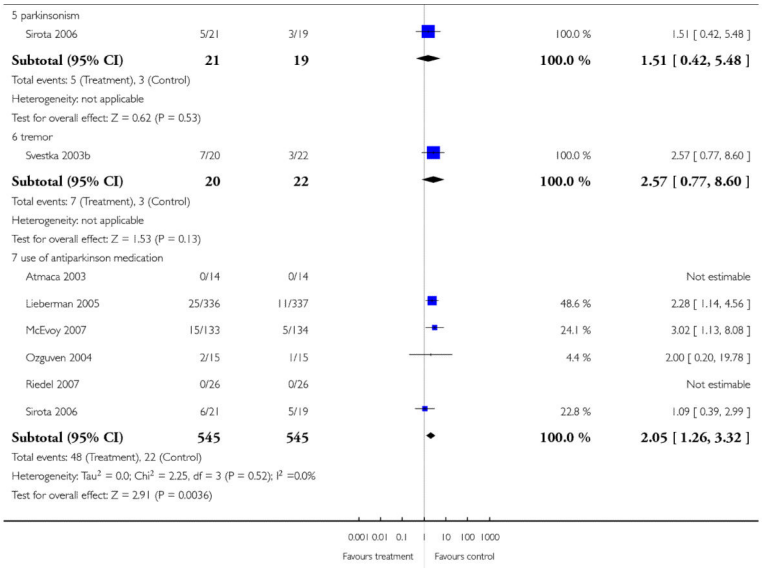


Analysis 4.22

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 22 Adverse effects: 5a. Extrapyramidal effects

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 22 Adverse effects: 5a. Extrapyramidal effects





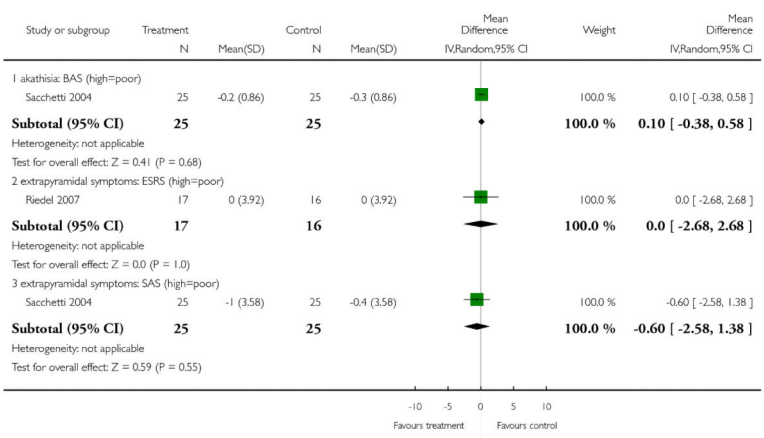
Analysis 4.23

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 23 Adverse effects: 5b. Extrapyramidal effects - scale measured

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 4 OLANZAPINE versus QUETIAPINE

Outcome: 23 Adverse effects: 5b. Extrapyramidal effects - scale measured



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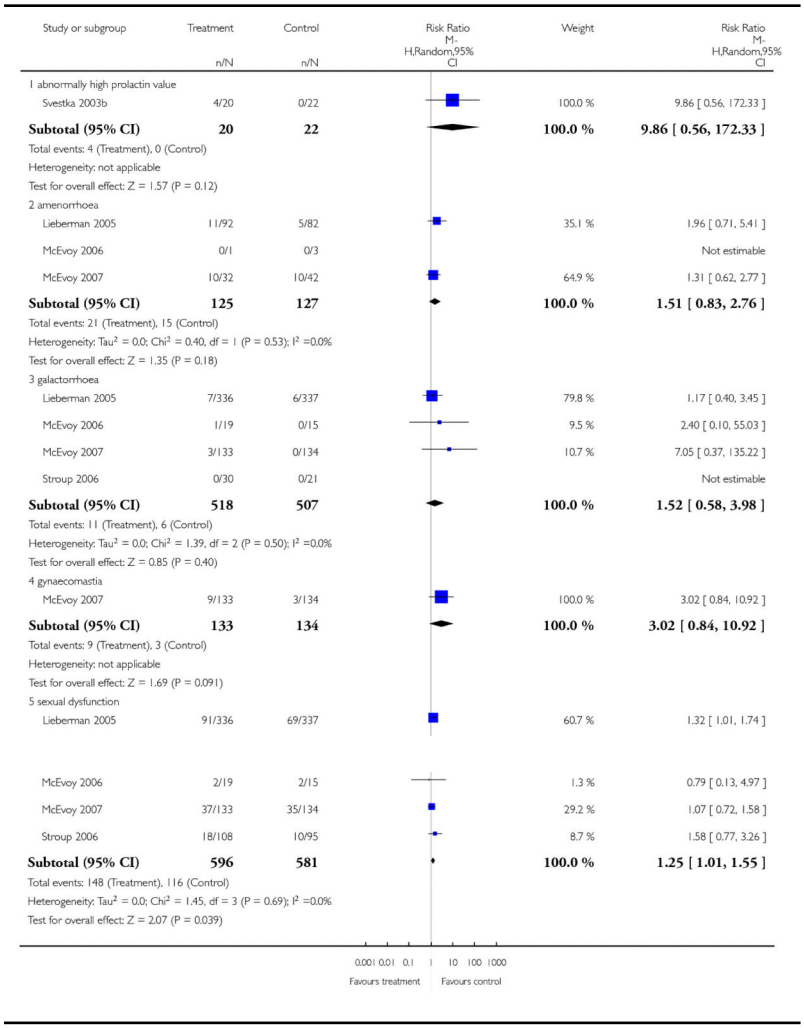
Analysis 4.24

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 24 Adverse effects: 6a. Prolactin associated side effects

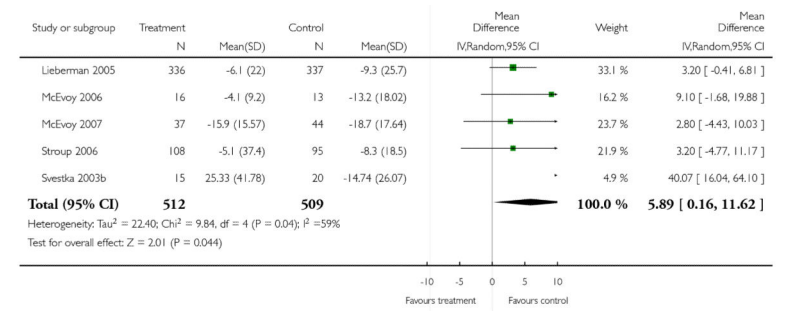
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 24 Adverse effects: 6a. Prolactin associated side effects



Analysis 4.25

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 25 Adverse effects: 6b. Prolactin - change from baseline in ng/ml

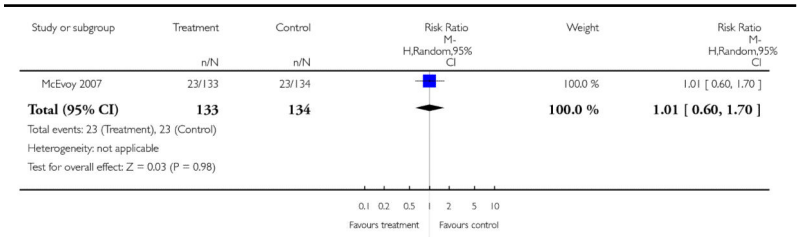
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 25 Adverse effects: 6b. Prolactin - change from baseline in ng/ml



Analysis 4.26

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase

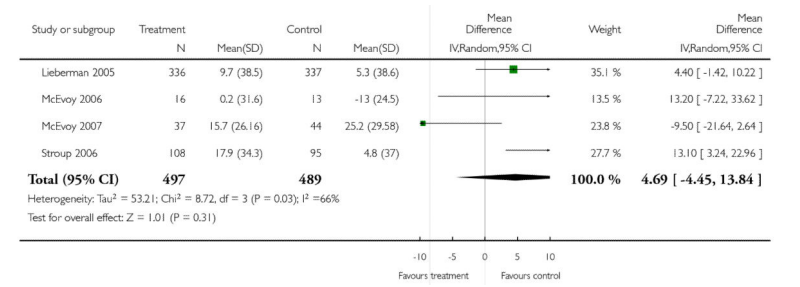
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase



Analysis 4.27

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 27 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl

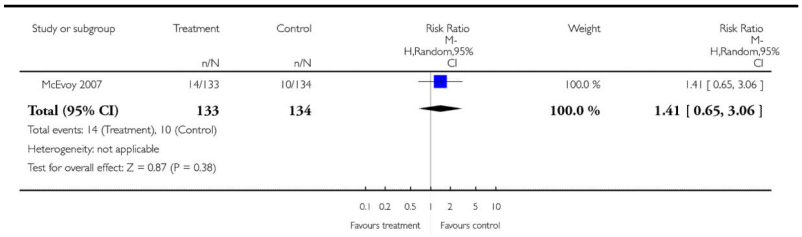
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 27 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 4.28

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 28 Adverse effects: 7c. Metabolic - glucose - abnormally high fasting glucose value

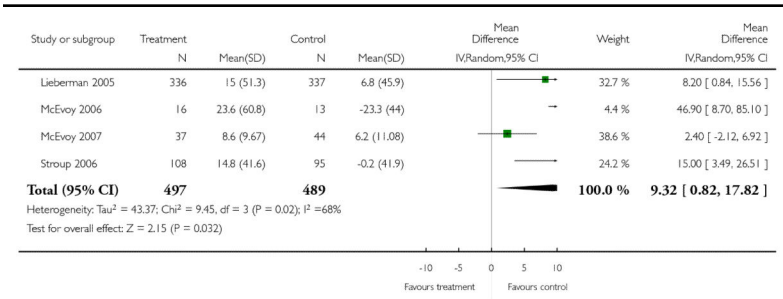
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 28 Adverse effects: 7c. Metabolic - glucose - abnormally high fasting glucose value



Analysis 4.29

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 29 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl

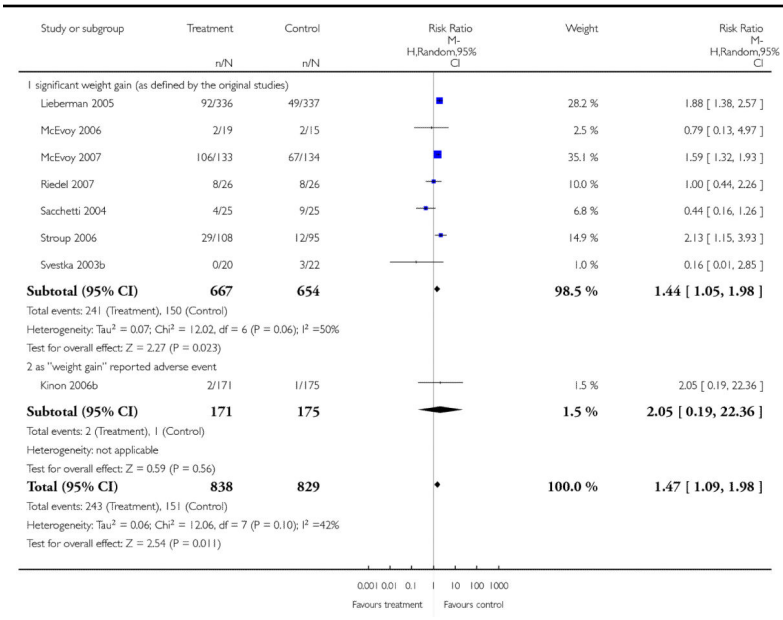
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 29 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl



Analysis 4.30

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 30 Adverse effects: 7e. Metabolic - weight gain

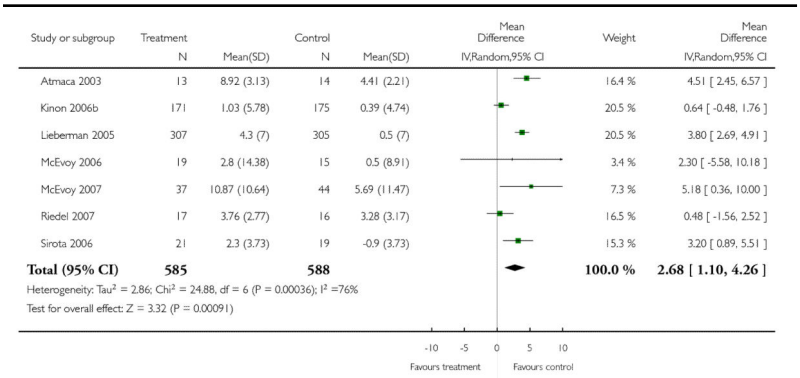
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 30 Adverse effects: 7e. Metabolic - weight gain



Analysis 4.31

Comparison 4 OLANZAPINE versus QUETIAPINE, Outcome 31 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg

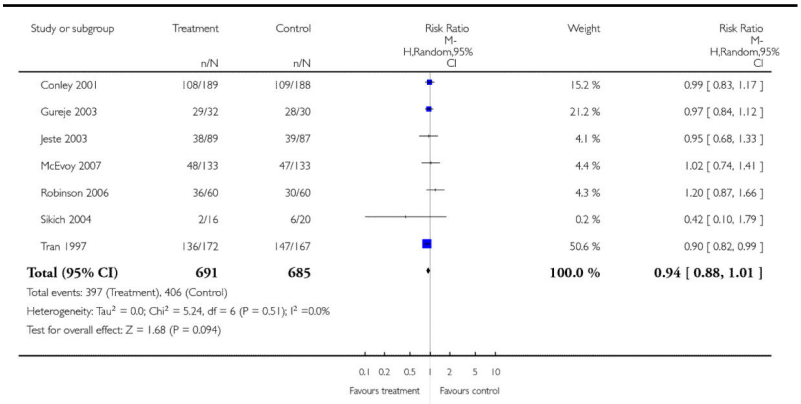
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 4 OLANZAPINE versus QUETIAPINE
Outcome: 31 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg



Analysis 5.1

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 1 Global state: 1a. No clinically significant response (as defined by the original studies)



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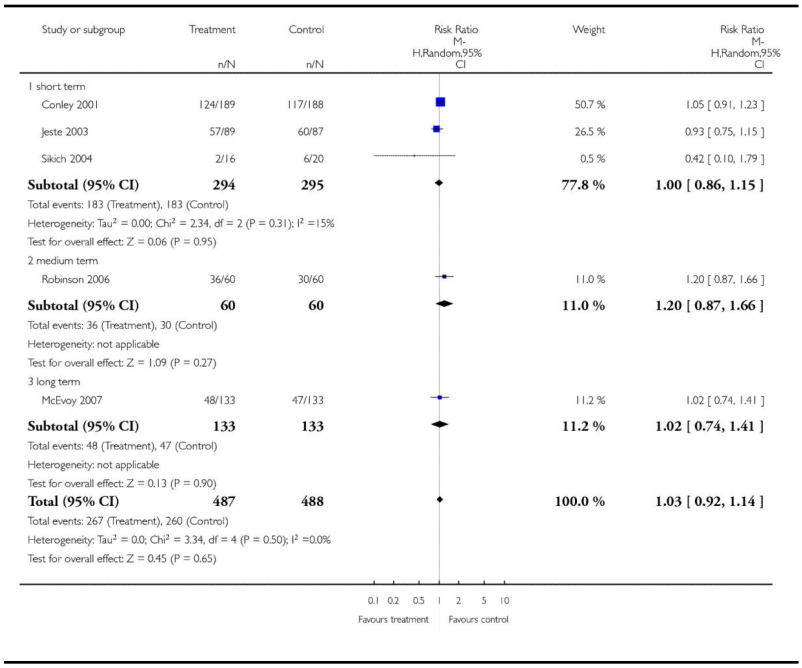
Analysis 5.2

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 2 Global state: 1b. No clinically important change (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 2 Global state: 1b. No clinically important change (as defined by the original studies)



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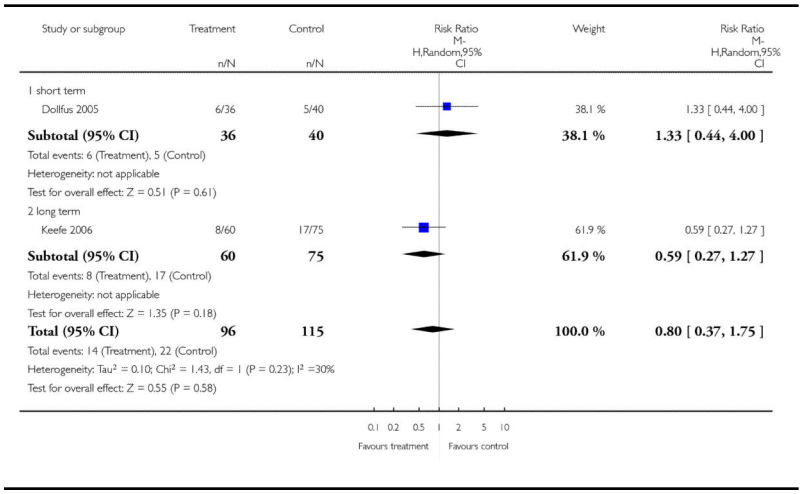
Analysis 5.3

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 3 Global state: 1c. Relapse (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 3 Global state: 1c. Relapse (as defined by the original studies)



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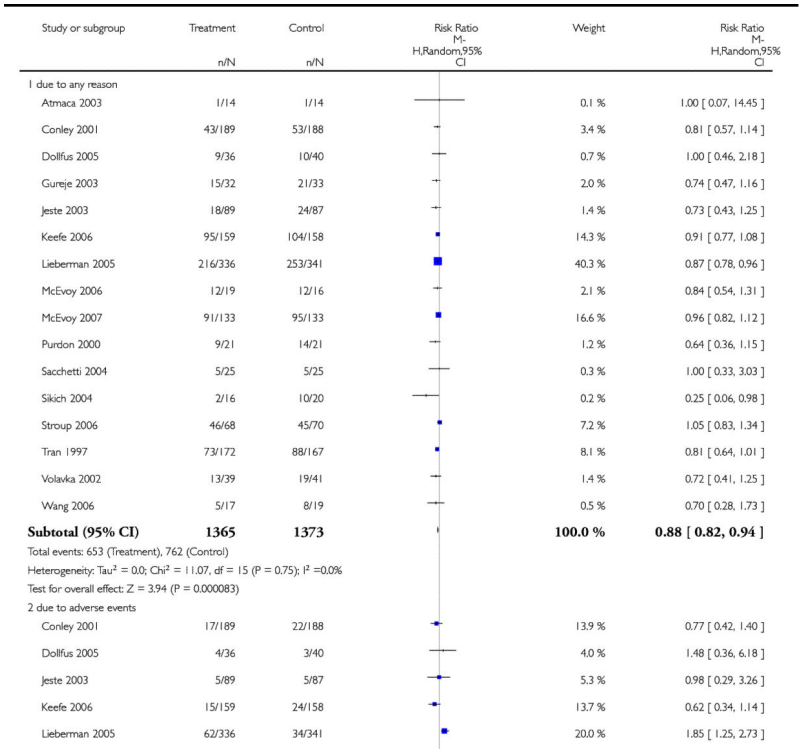
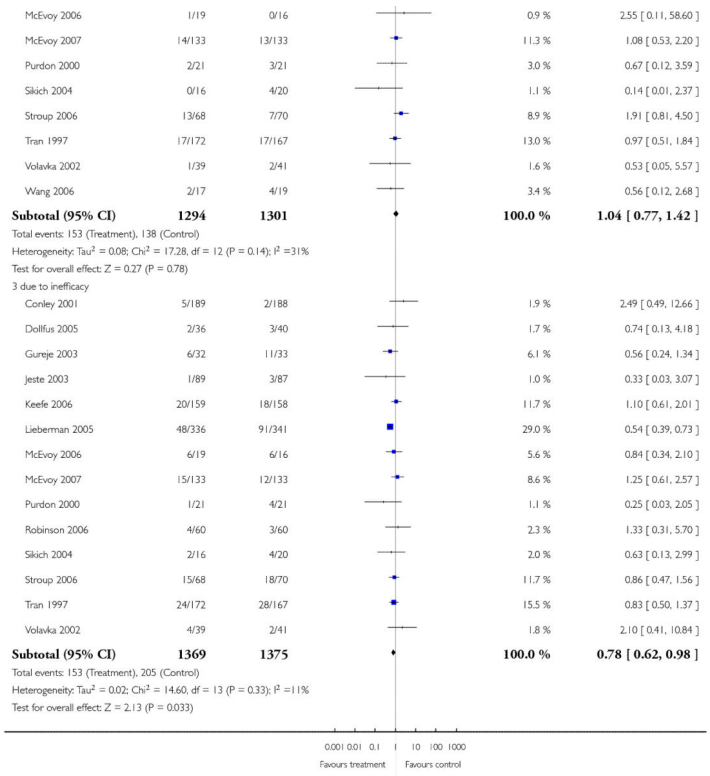
Analysis 5.4
Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 4 Leaving the study early

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 4 Leaving the study early



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 due to any reason					
Atmaca 2003	1/14	1/14		0.1 %	1.00 [0.07, 14.45]
Conley 2001	43/189	53/188		3.4 %	0.81 [0.57, 1.14]
Dollfus 2005	9/36	10/40		0.7 %	1.00 [0.46, 2.18]
Gureje 2003	15/32	21/33		2.0 %	0.74 [0.47, 1.16]
Jeste 2003	18/89	24/87		1.4 %	0.73 [0.43, 1.25]
Keefe 2006	95/159	104/158		14.3 %	0.91 [0.77, 1.08]
Lieberman 2005	216/336	253/341		40.3 %	0.87 [0.78, 0.96]
McEvoy 2006	12/19	12/16		2.1 %	0.84 [0.54, 1.31]
McEvoy 2007	91/133	95/133		16.6 %	0.96 [0.82, 1.12]
Purdon 2000	9/21	14/21		1.2 %	0.64 [0.36, 1.15]
Sacchetti 2004	5/25	5/25		0.3 %	1.00 [0.33, 3.03]
Sikich 2004	2/16	10/20		0.2 %	0.25 [0.06, 0.98]
Stroup 2006	46/68	45/70		7.2 %	1.05 [0.83, 1.34]
Tran 1997	73/172	88/167		8.1 %	0.81 [0.64, 1.01]
Volavka 2002	13/39	19/41		1.4 %	0.72 [0.41, 1.25]
Wang 2006	5/17	8/19		0.5 %	0.70 [0.28, 1.73]
Subtotal (95% CI)	**1365**	**1373**		**100.0 %**	**0.88 [0.82, 0.94]**
Total events: 653 (Treatment), 762 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.07$, df = 15 (P = 0.75); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.94 (P = 0.000083)					
2 due to adverse events					
Conley 2001	17/189	22/188		13.9 %	0.77 [0.42, 1.40]
Dollfus 2005	4/36	3/40		4.0 %	1.48 [0.36, 6.18]
Jeste 2003	5/89	5/87		5.3 %	0.98 [0.29, 3.26]
Keefe 2006	15/159	24/158		13.7 %	0.62 [0.34, 1.14]
Lieberman 2005	62/336	34/341		20.0 %	1.85 [1.25, 2.73]



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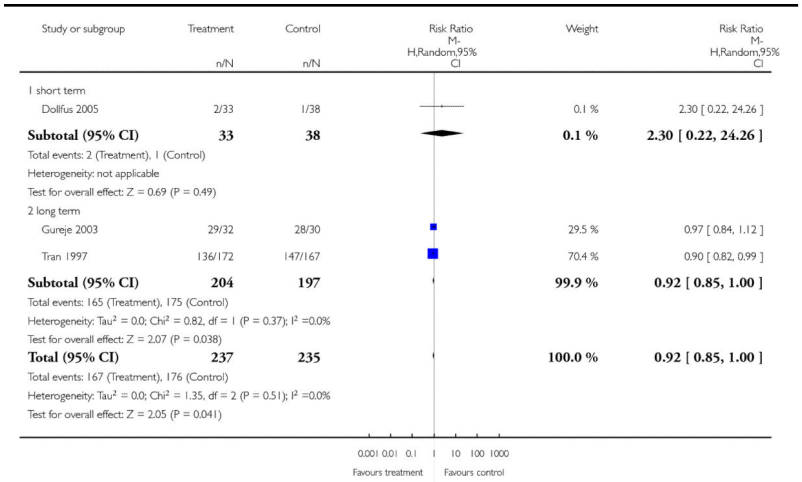
Analysis 5.5

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 5 Mental state: 1a. General - no clinically important change (less than 50% PANSS total score reduction)

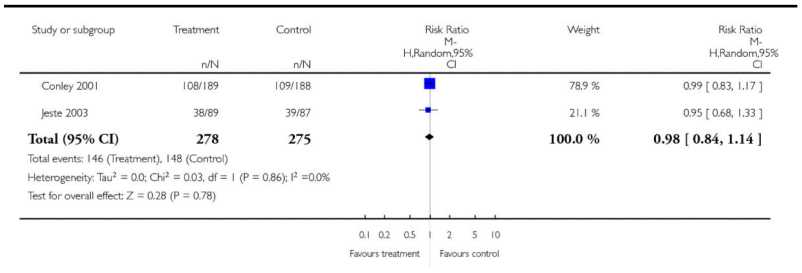
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 5 Mental state: 1a. General - no clinically important change (less than 50% PANSS total score reduction)



Analysis 5.6

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 6 Mental state: 1b. General - no clinically important change - short term (less than 20% PANSS total score reduction)

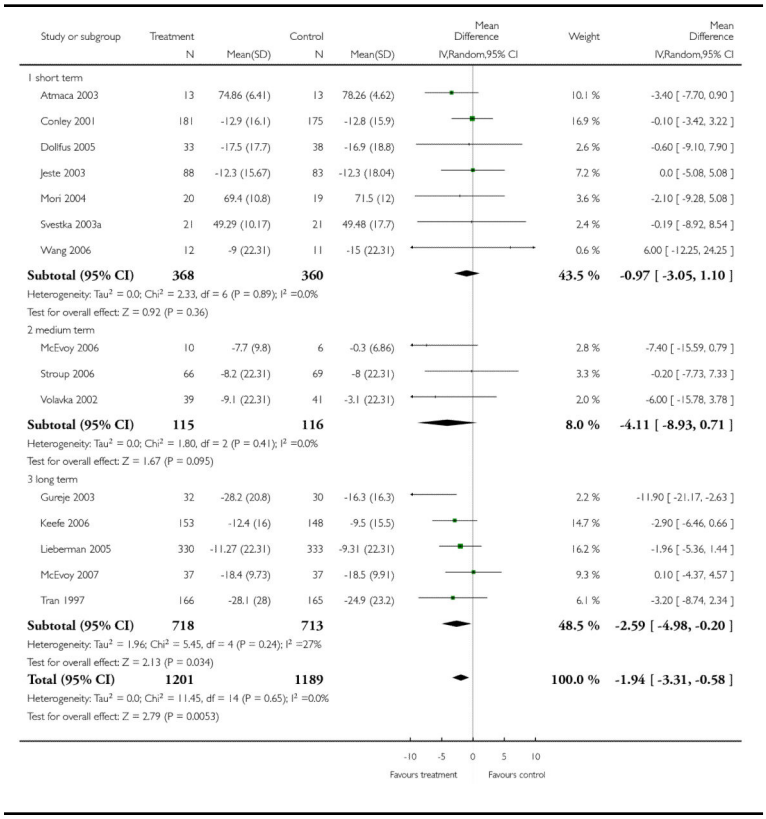
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 6 Mental state: 1b. General - no clinically important change - short term (less than 20% PANSS total score reduction)



Analysis 5.7

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 7 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)

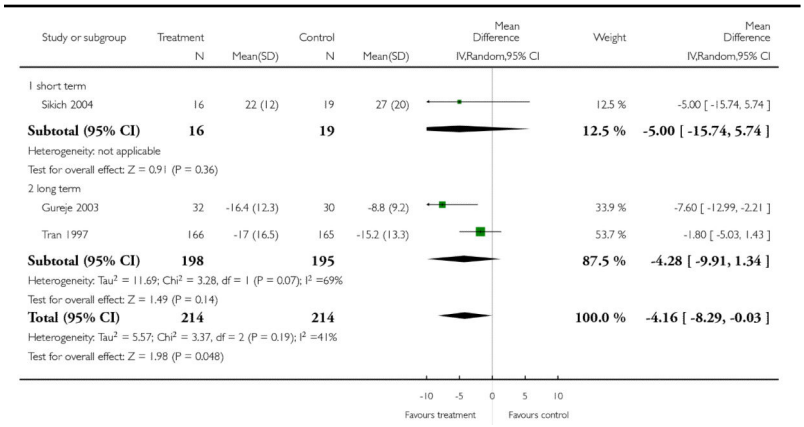
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 7 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)



Analysis 5.8

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 8 Mental state: 1d. General - average endpoint score (BPRS total score, high=poor)

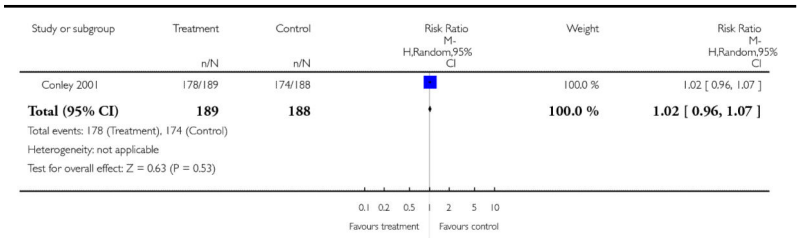
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 8 Mental state: 1d. General - average endpoint score (BPRS total score, high=poor)



Analysis 5.9

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 9 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 9 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 50% PANSS positive subscore reduction)



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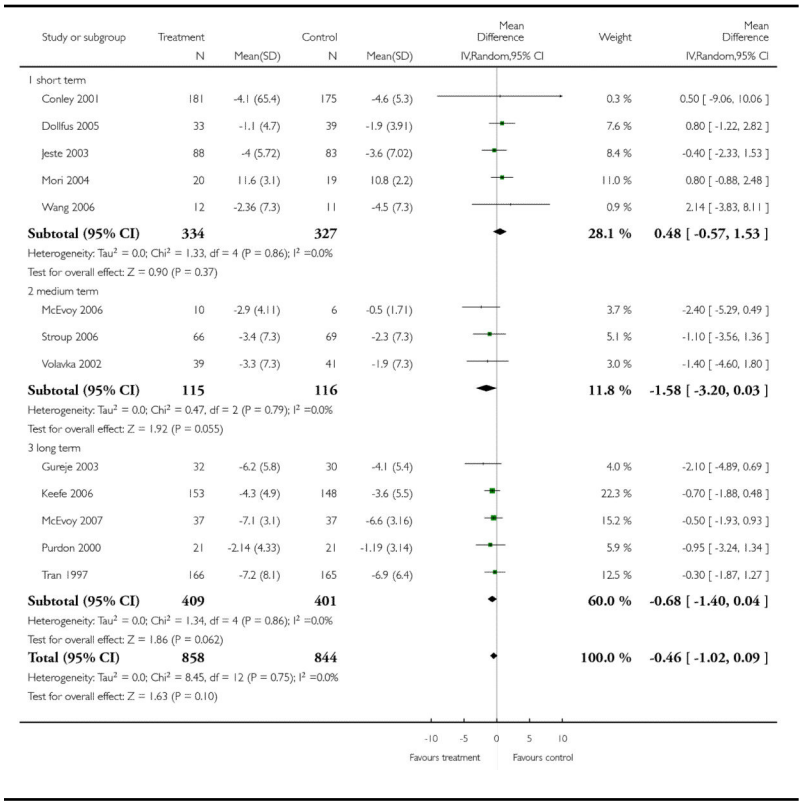
Analysis 5.10

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 10 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 10 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive, high=poor)



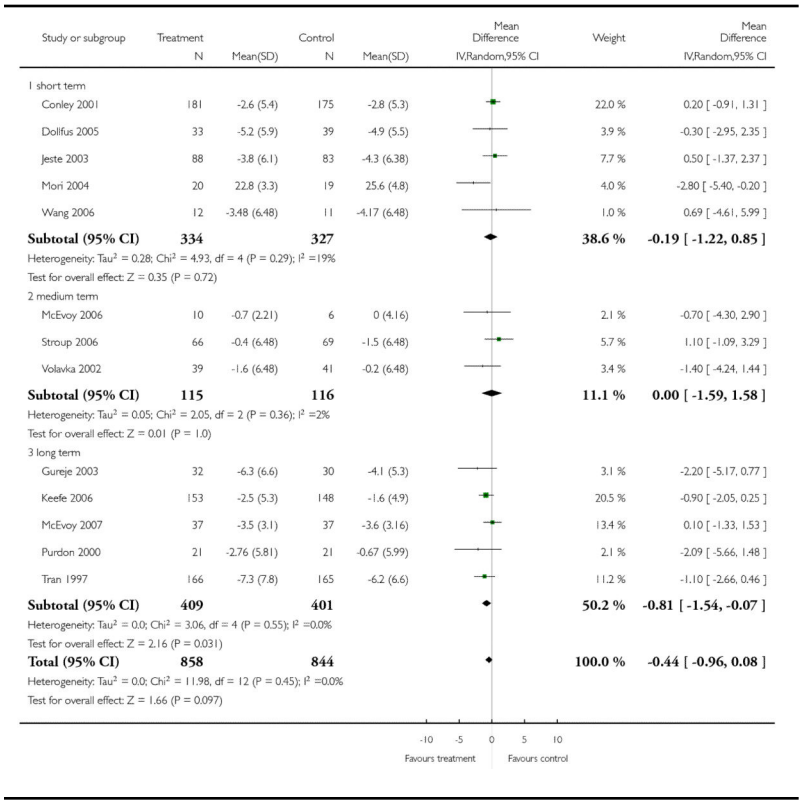
Analysis 5.11

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 11 Mental state: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 5 OLANZAPINE versus RISPERIDONE

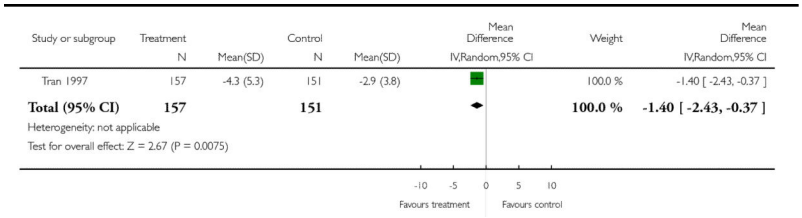
Outcome: 11 Mental state: 3a. Negative symptoms - average endpoint score (PANSS negative, high=poor)



Analysis 5.12

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 12 Mental state: 3b. Negative symptoms - average endpoint score - long term (SANS total, high=poor)

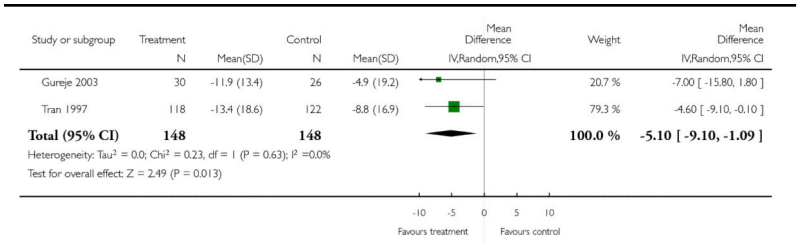
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 12 Mental state: 3b. Negative symptoms - average endpoint score - long term (SANS total, high=poor)



Analysis 5.13

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 13 Quality of life: General - average endpoint score - long term (QLS total score, high=poor)

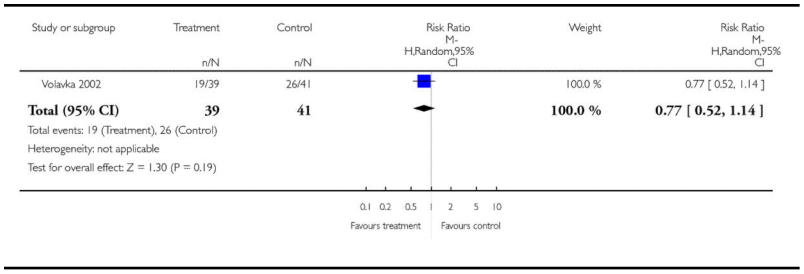
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 13 Quality of life: General - average endpoint score - long term (QLS total score, high=poor)



Analysis 5.14

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 14 Cognitive functioning: 1a.General - no clinically important change - medium term (less than ½ SD in Global Neurocognitive Score improved)

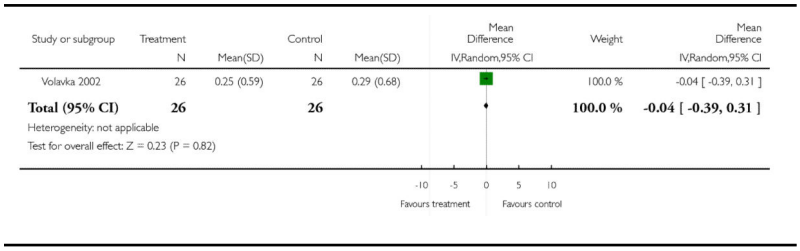
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 14 Cognitive functioning: 1a.General - no clinically important change - medium term (less than SD in Global Neurocognitive Score improved)



Analysis 5.15

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 15 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)

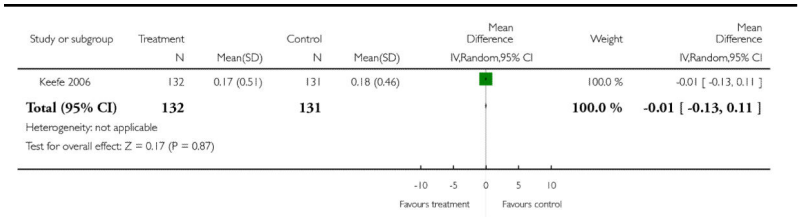
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 15 Cognitive functioning: 1b. General - average endpoint score - medium term (global neurocognitive score, high=poor)



Analysis 5.16

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 16 Cognitive functioning: 1c. General - average endpoint score - long term (neurocognitive composite score, high=poor)

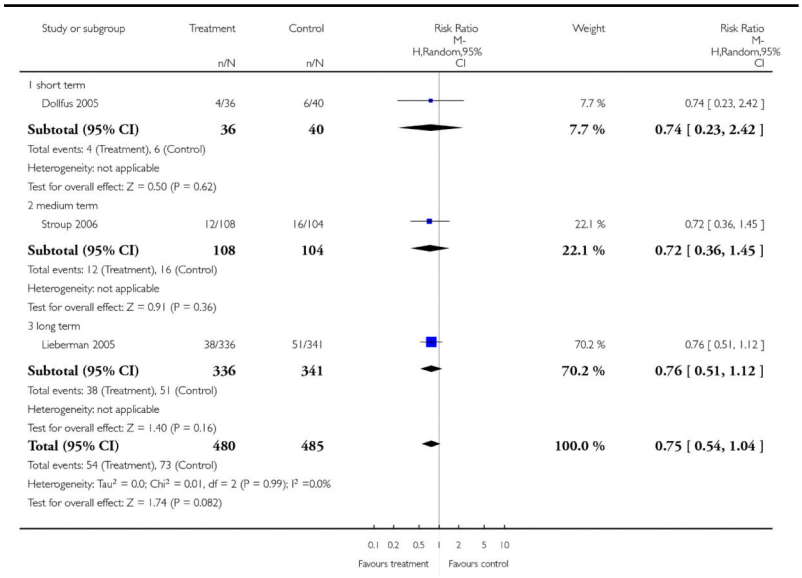
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 16 Cognitive functioning: 1c. General - average endpoint score - long term (neurocognitive composite score, high=poor)



Analysis 5.17

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 17 Service use - number of patients re-hospitalised

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 17 Service use - number of patients re-hospitalised



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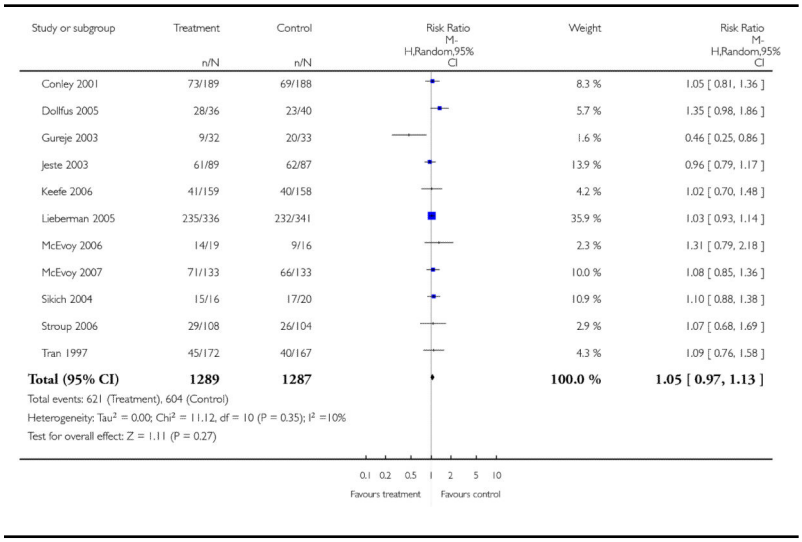
Analysis 5.18

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 18 Adverse effects: 1. General - at least one adverse effect

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 18 Adverse effects: 1. General - at least one adverse effect



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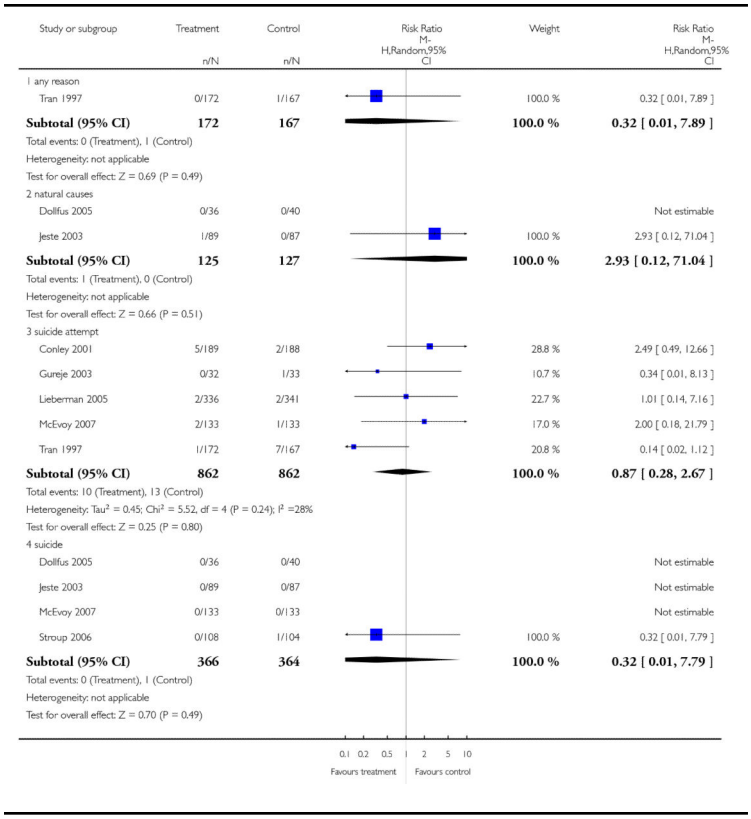
Analysis 5.19
Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 19 Adverse effects: 2. Death

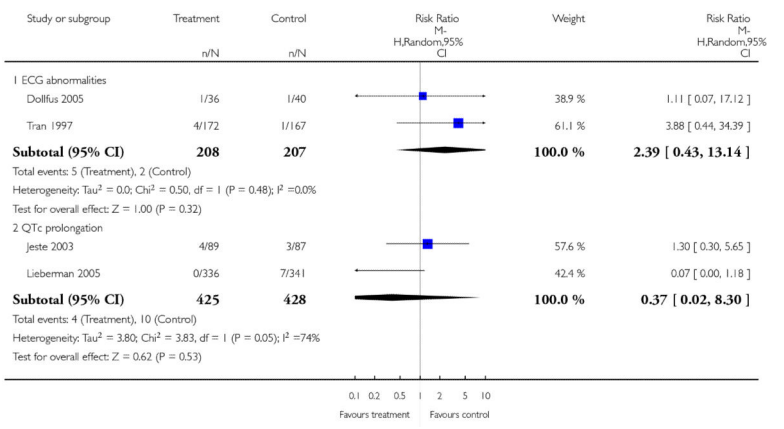
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 19 Adverse effects: 2. Death



Analysis 5.20

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 20 Adverse effects: 3a. Cardiac effects

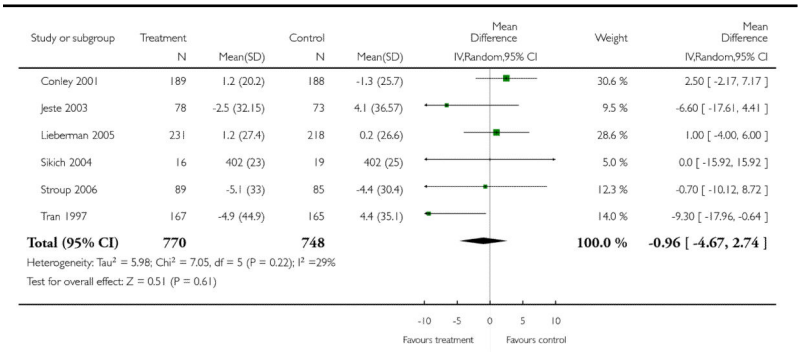
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 20 Adverse effects: 3a. Cardiac effects



Analysis 5.21

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

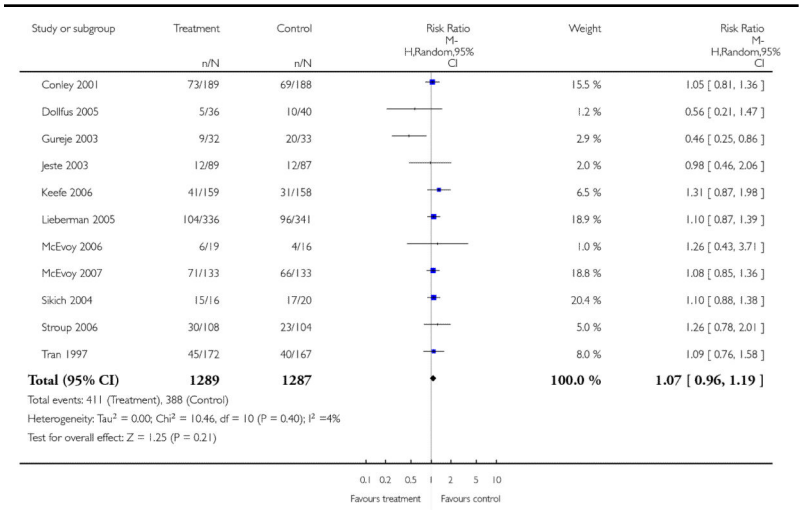
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 21 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms



Analysis 5.22

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 22 Adverse effects: 4a. Central nervous system - sedation

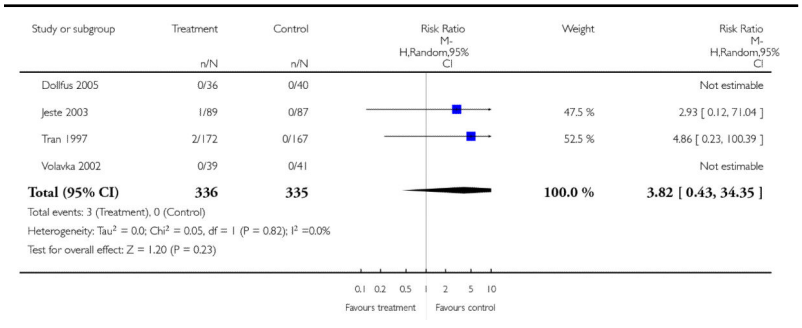
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 22 Adverse effects: 4a. Central nervous system - sedation



Analysis 5.23

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 23 Adverse effects: 4b. Central nervous system - seizures

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 23 Adverse effects: 4b. Central nervous system - seizures



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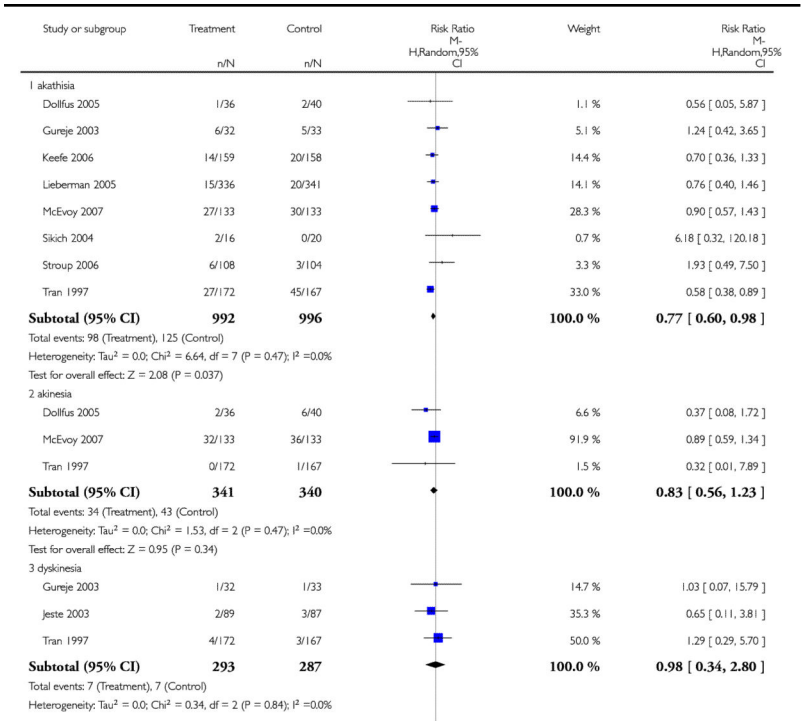
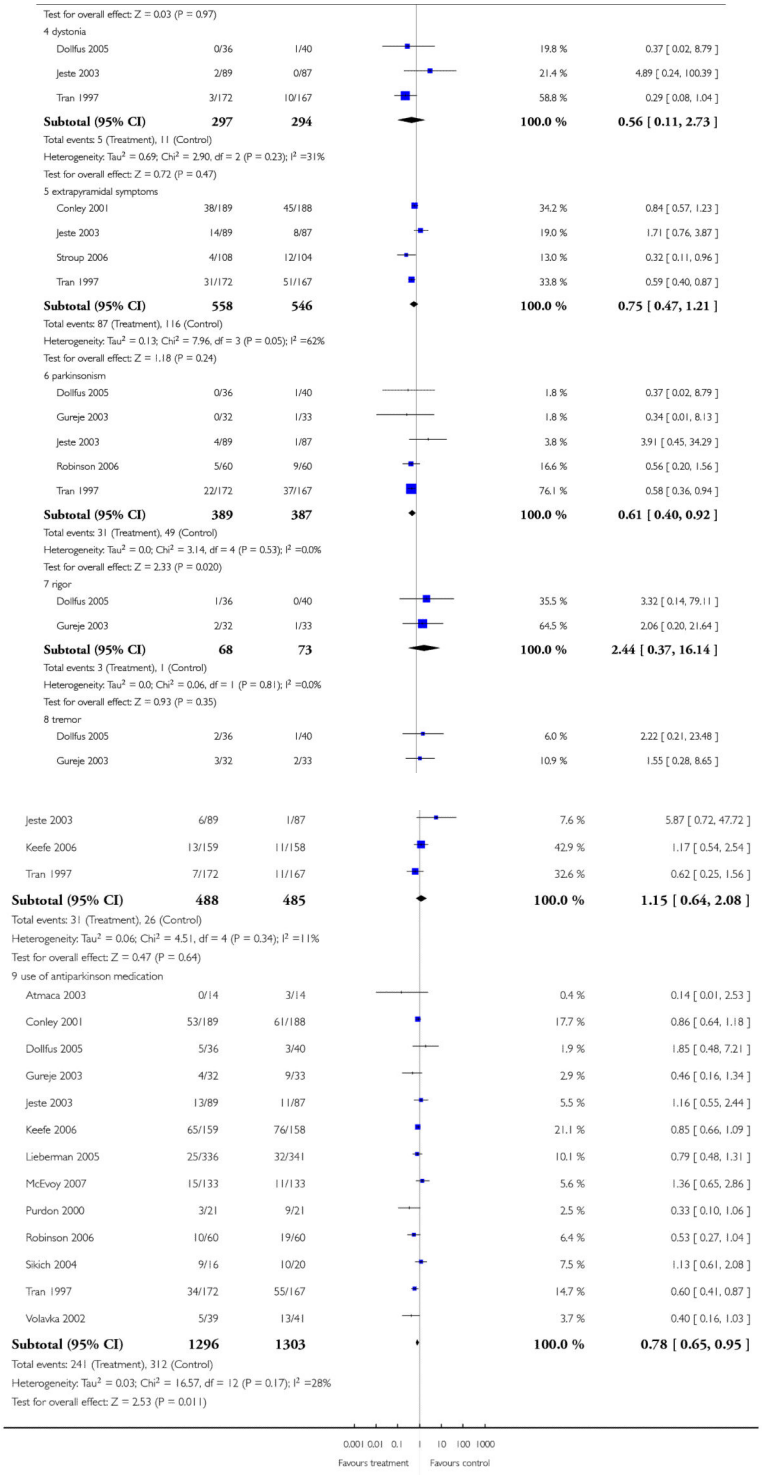
Analysis 5.24
Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 24 Adverse effects: 5a. Extrapyramidal effects

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 24 Adverse effects: 5a. Extrapyramidal effects





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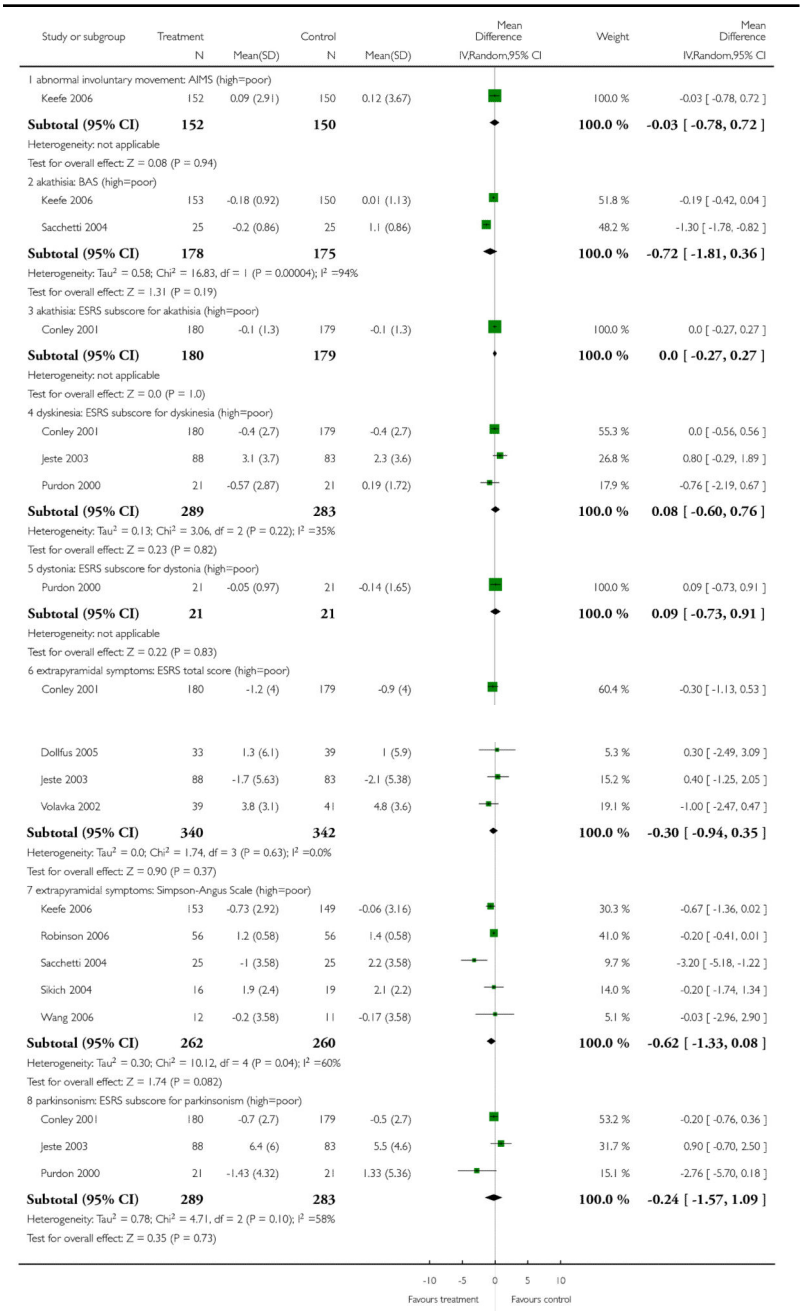
Analysis 5.25

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 25 Adverse effects: 5b. Extrapyramidal effects - scale measured

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 25 Adverse effects: 5b. Extrapyramidal effects - scale measured



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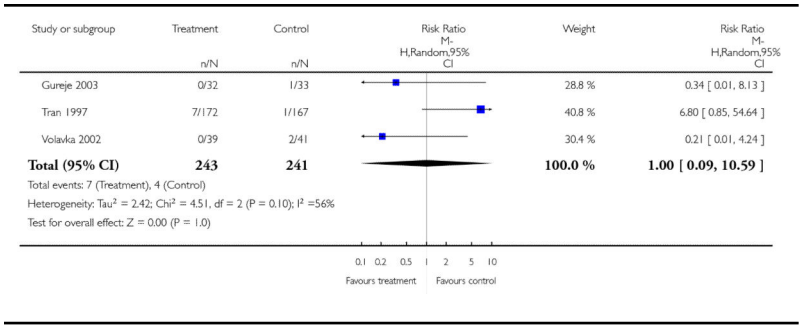
Analysis 5.26

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 26 Adverse effects: 6. Haematological: white blood cells - significant low white blood cell count (as def. by the original studies)

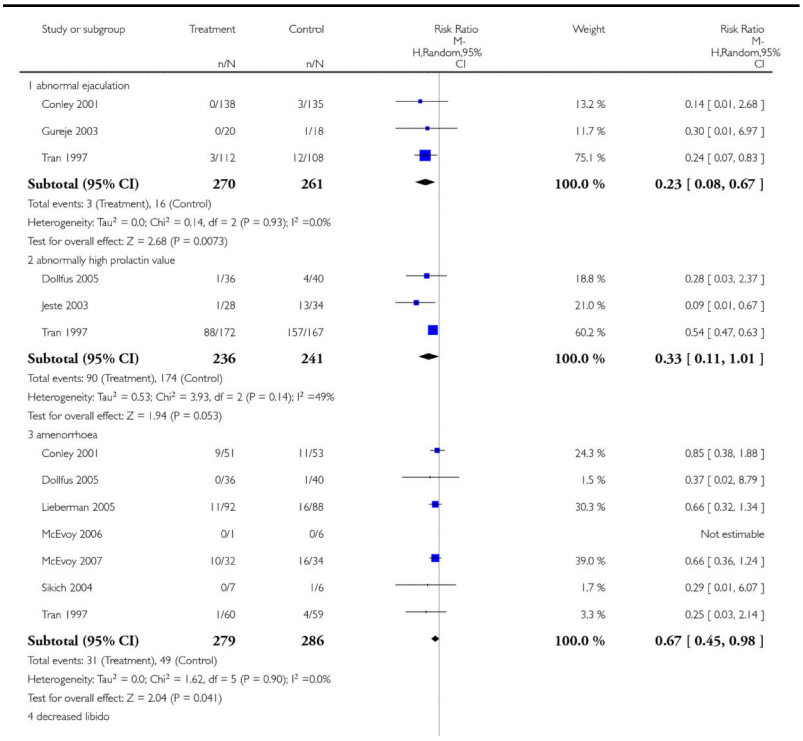
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 26 Adverse effects: 6. Haematological: white blood cells - significant low white blood cell count (as def. by the original studies)

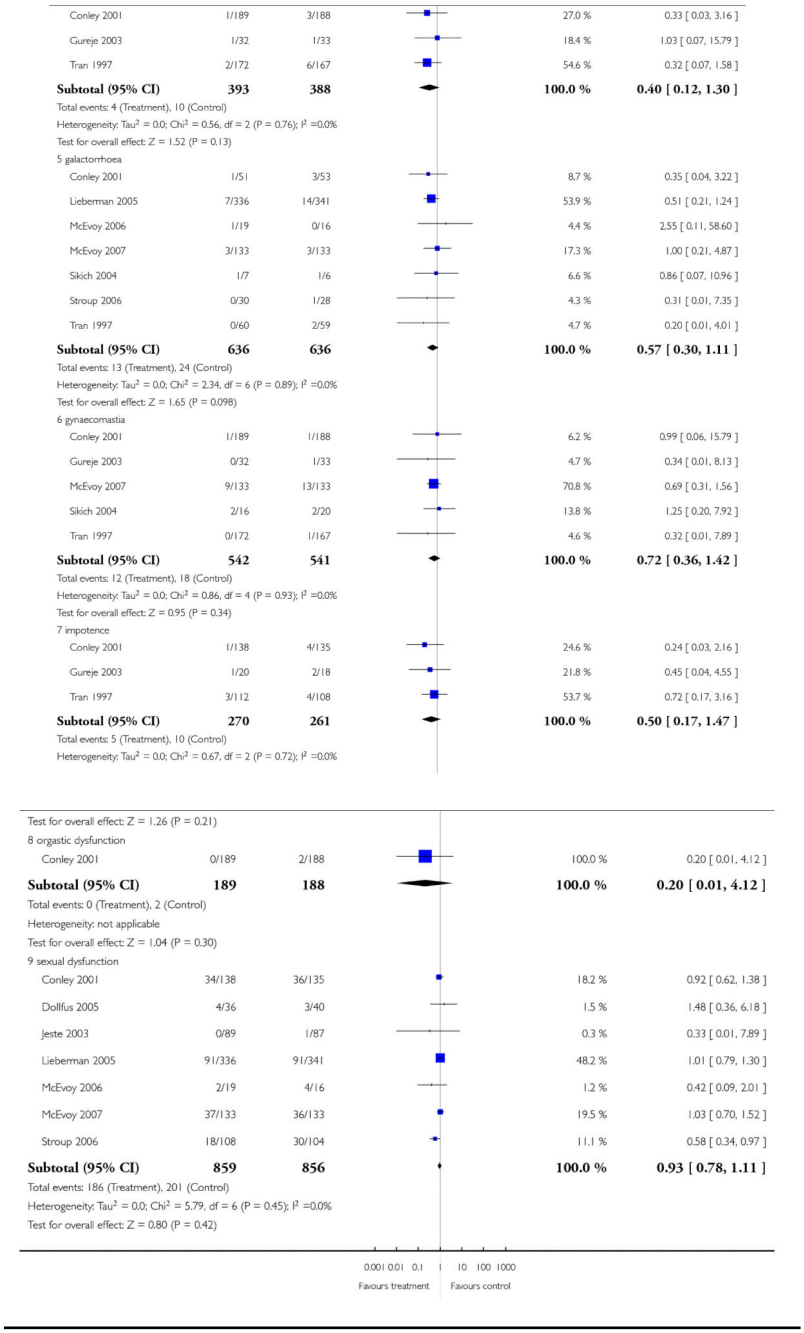


Analysis 5.27

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 27 Adverse effects: 7a. Prolactin associated side effects

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 27 Adverse effects: 7a. Prolactin associated side effects





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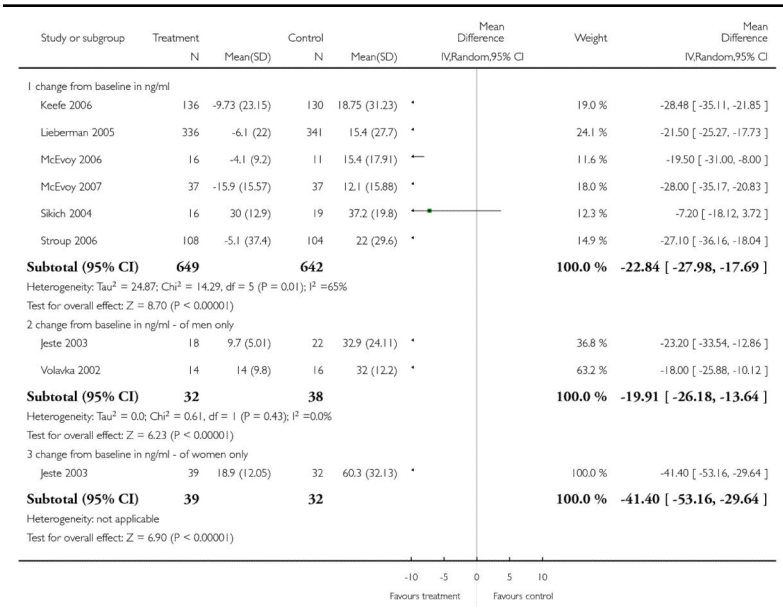
Analysis 5.28

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 28 Adverse effects: 7b. Prolactin - change from baseline in ng/ml

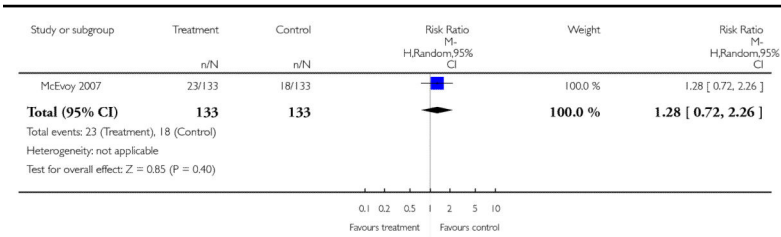
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 28 Adverse effects: 7b. Prolactin - change from baseline in ng/ml



Analysis 5.29

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 29 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase

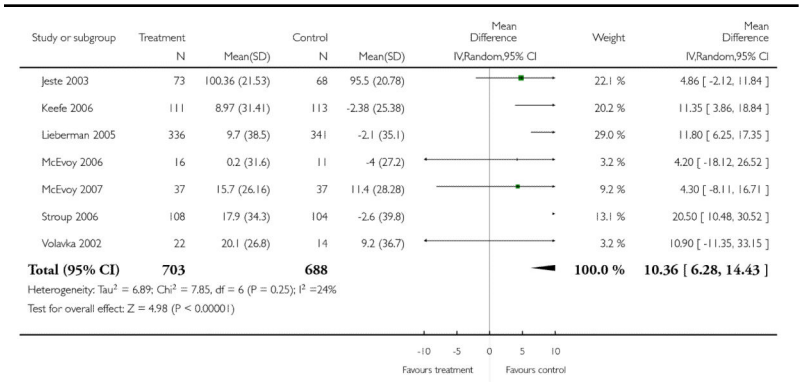
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 29 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase



Analysis 5.30

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 30 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl

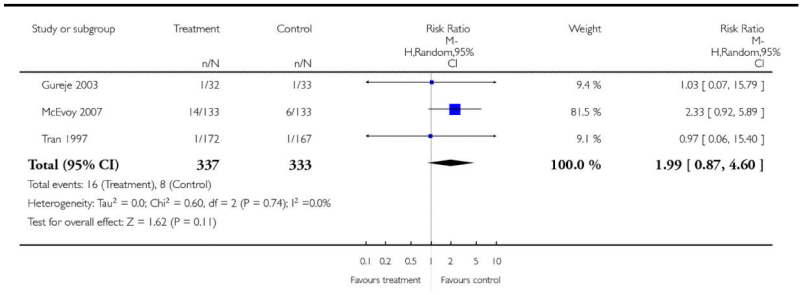
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 30 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 5.31

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 31 Adverse effects: 8c. Metabolic - glucose - abnormally high fasting glucose value

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 31 Adverse effects: 8c. Metabolic - glucose - abnormally high fasting glucose value



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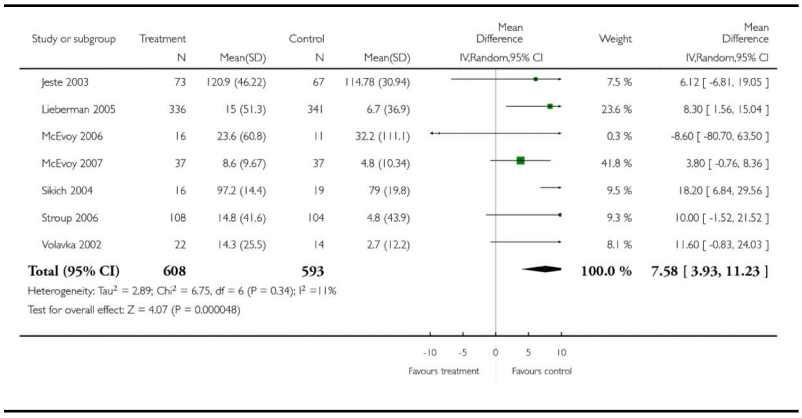
Analysis 5.32

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 32 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 32 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl



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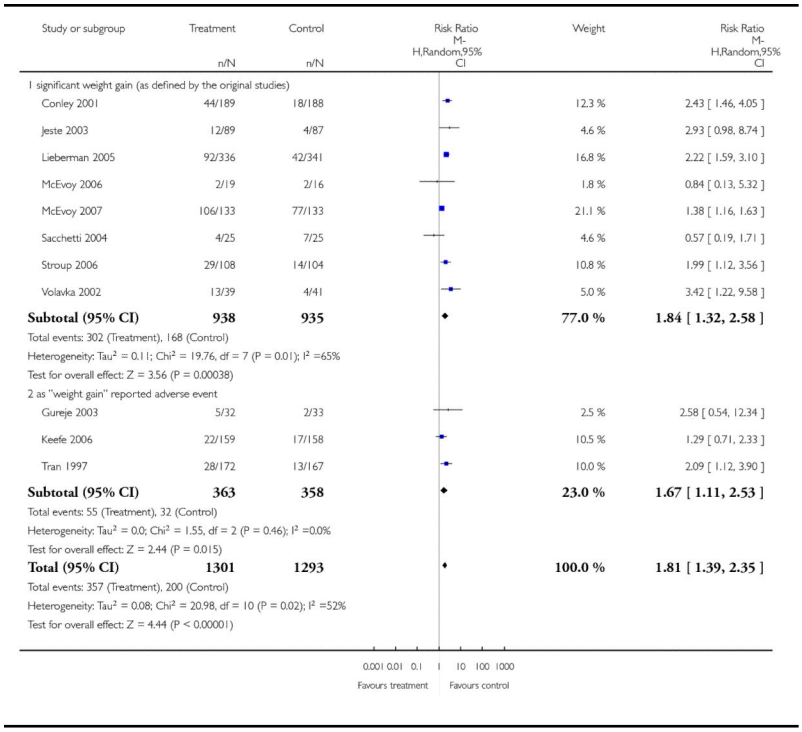
Analysis 5.33
Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 33 Adverse effects: 8e. Metabolic - weight gain

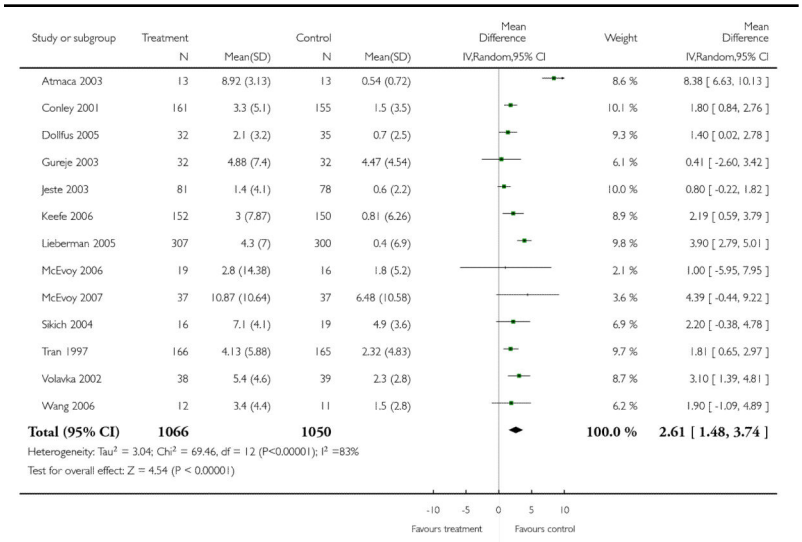
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 33 Adverse effects: 8e. Metabolic - weight gain



Analysis 5.34

Comparison 5 OLANZAPINE versus RISPERIDONE, Outcome 34 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg

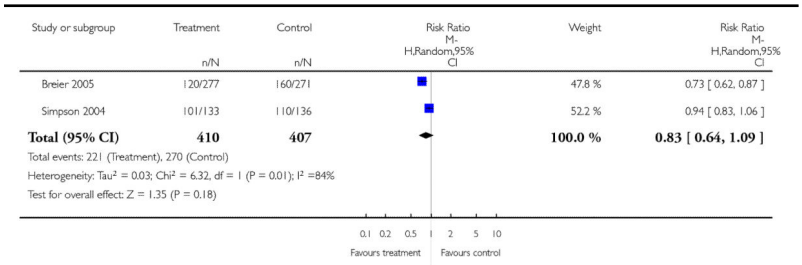
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 5 OLANZAPINE versus RISPERIDONE
Outcome: 34 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg



Analysis 6.1

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 1 Global state: 1a. General - no clinically significant response (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 1 Global state: 1a. General - no clinically significant response (as defined by the original studies)



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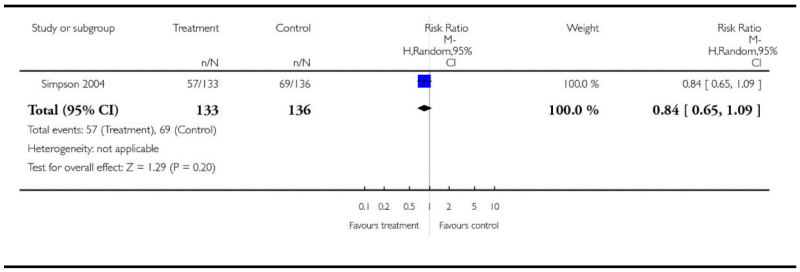
Analysis 6.2

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 2 Global state: 1b. General - no clinically important change (as defined by the original studies)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 2 Global state: 1b. General - no clinically important change (as defined by the original studies)



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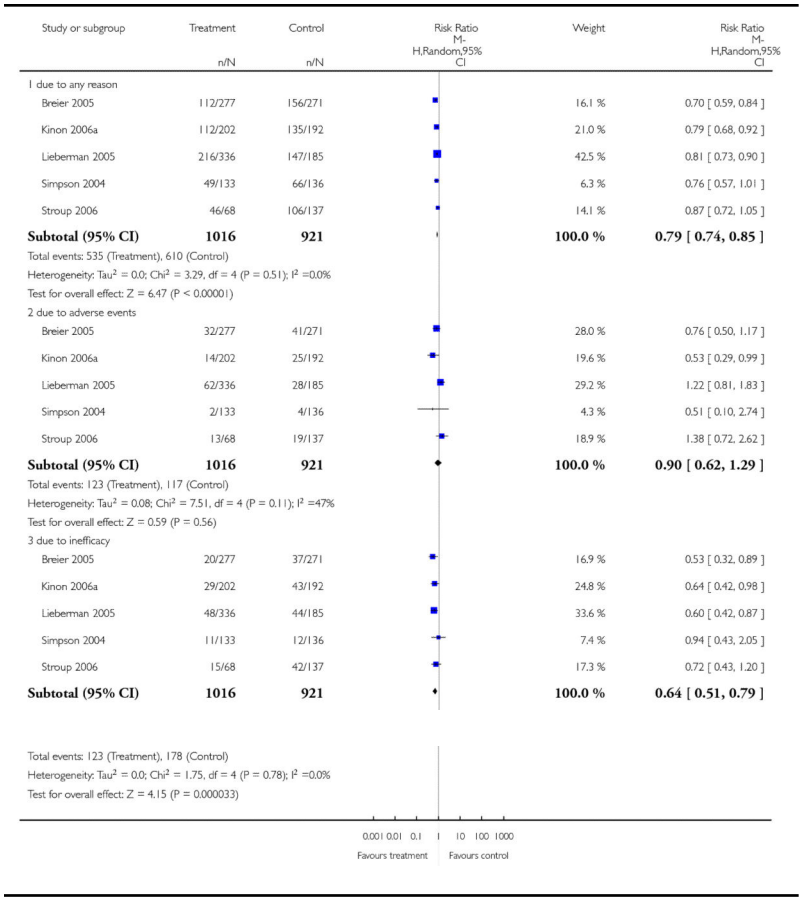
Analysis 6.3
Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 3 Leaving the study early

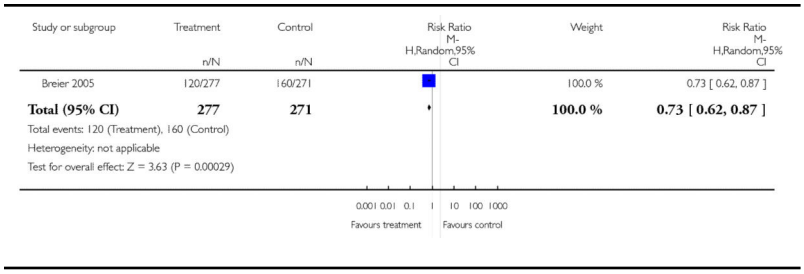
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 3 Leaving the study early



Analysis 6.4

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 4 Mental state: 1a. General - no clinically important change - long term (less than 30% PANSS total score reduction)

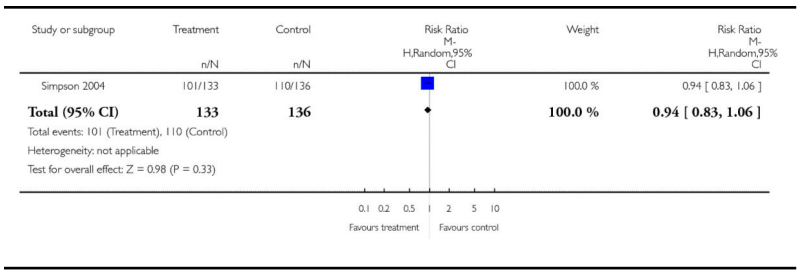
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 4 Mental state: 1a. General - no clinically important change - long term (less than 30% PANSS total score reduction)



Analysis 6.5

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 5 Mental state: 1b. General - no clinically important change - short term (less than 40% BPRS total score reduction)

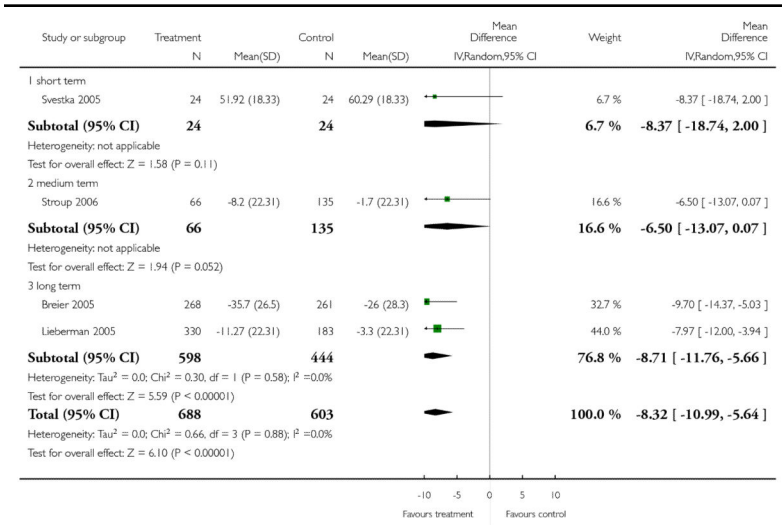
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 5 Mental state: 1b. General - no clinically important change - short term (less than 40% BPRS total score reduction)



Analysis 6.6

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 6 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)

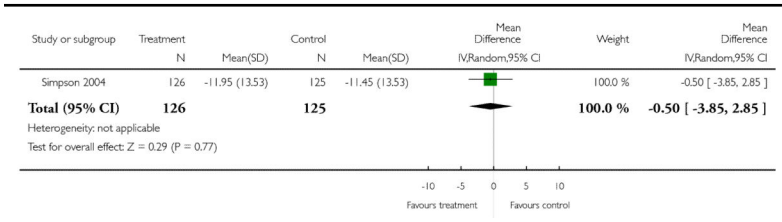
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 6 Mental state: 1c. General - average endpoint score (PANSS total, high=poor)



Analysis 6.7

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 7 Mental state: 1d. General - average endpoint score - short term (BPRS total, high=poor)

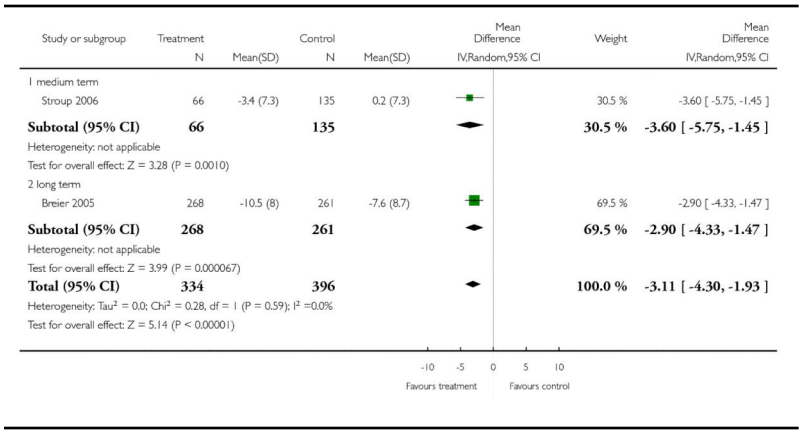
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 7 Mental state: 1d. General - average endpoint score - short term (BPRS total, high=poor)



Analysis 6.8

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 8 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive, high=poor)

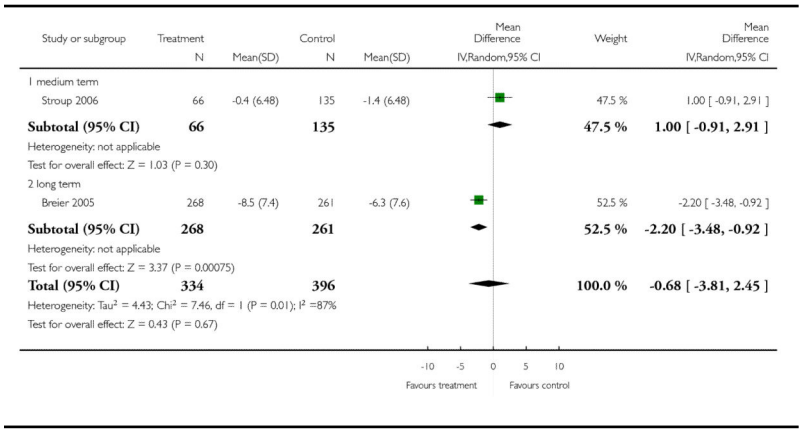
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 8 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive, high=poor)



Analysis 6.9

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 9 Mental state: 3. Negative symptoms - average endpoint score (PANSS negative, high=poor)

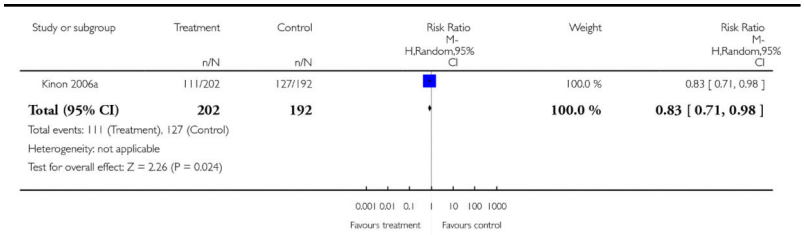
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 9 Mental state: 3. Negative symptoms - average endpoint score (PANSS negative, high=poor)



Analysis 6.10

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 10 General functioning: 1a. General - no clinically important change - medium term (less than 5 points improvement on GAF total score)

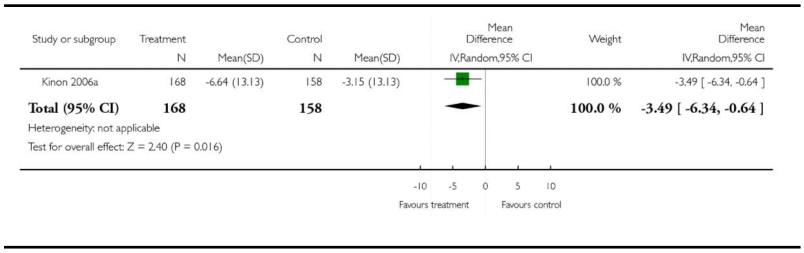
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 10 General functioning: 1a. General - no clinically important change - medium term (less than 5 points improvement on GAF total score)



Analysis 6.11

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 11 General functioning: 1b. General - average endpoint score - medium term (GAF total, high=poor)

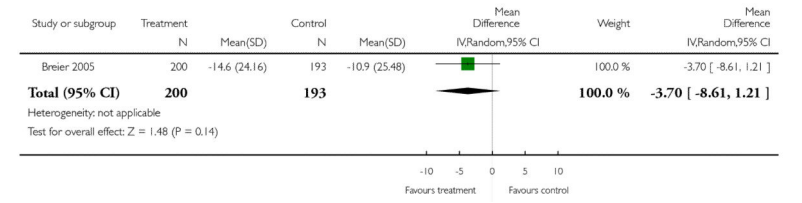
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 11 General functioning: 1b. General - average endpoint score - medium term (GAF total, high=poor)



Analysis 6.12

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 12 Quality of life: General - average endpoint score - long term (QLS total, Heinrichs-Carpenter, high=poor)

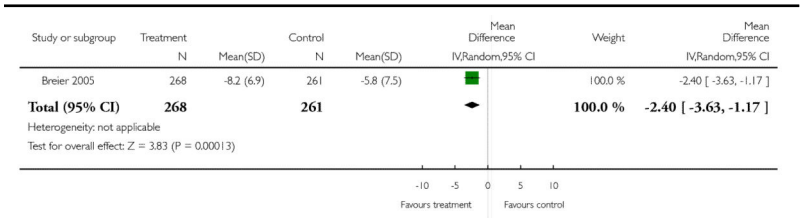
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 12 Quality of life: General - average endpoint score - long term (QLS total, Heinrichs-Carpenter, high=poor)



Analysis 6.13

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 13 Cognitive functioning: General - average endpoint score - long term(PANSS cognitive subscore, high=poor)

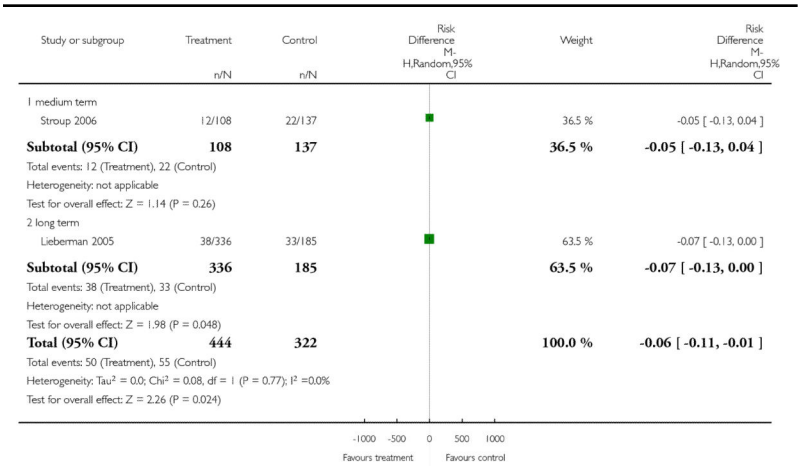
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 13 Cognitive functioning: General - average endpoint score - long term(PANSS cognitive subscore, high=poor)



Analysis 6.14

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 14 Service use - number of patients re-hospitalised

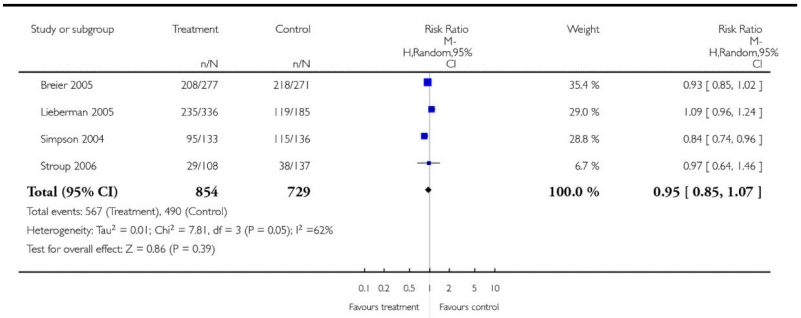
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 14 Service use - number of patients re-hospitalised



Analysis 6.15

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 15 Adverse effects: 1. General - at least one adverse effect

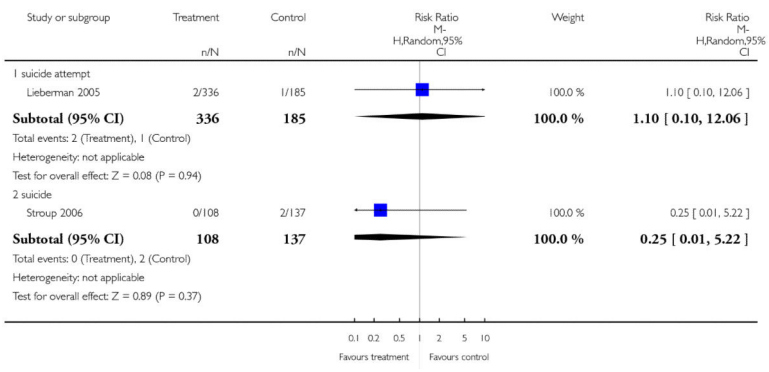
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 15 Adverse effects: 1. General - at least one adverse effect



Analysis 6.16

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 16 Adverse effects: 2. Death

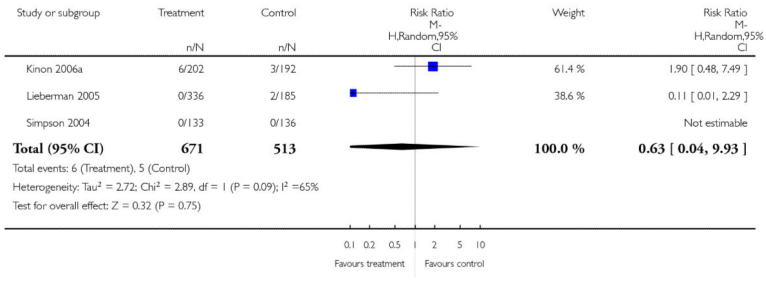
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 16 Adverse effects: 2. Death



Analysis 6.17

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 17 Adverse effects: 3a. Cardiac effects - QTc prolongation

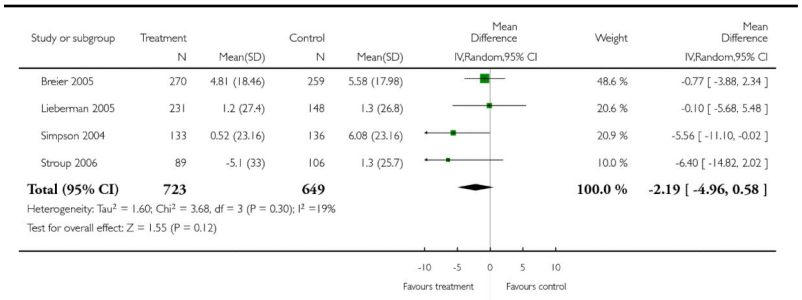
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 17 Adverse effects: 3a. Cardiac effects - QTc prolongation



Analysis 6.18

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 18 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

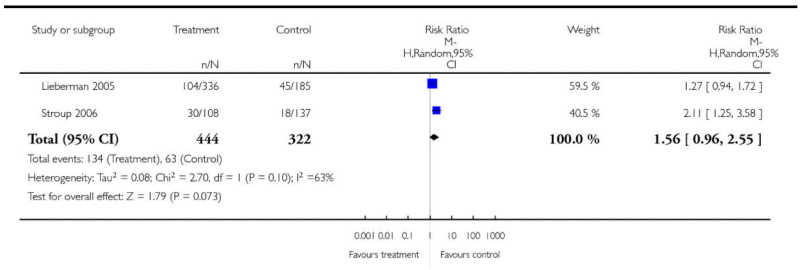
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 18 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms



Analysis 6.19

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 19 Adverse effects: 4. Central nervous system - sedation

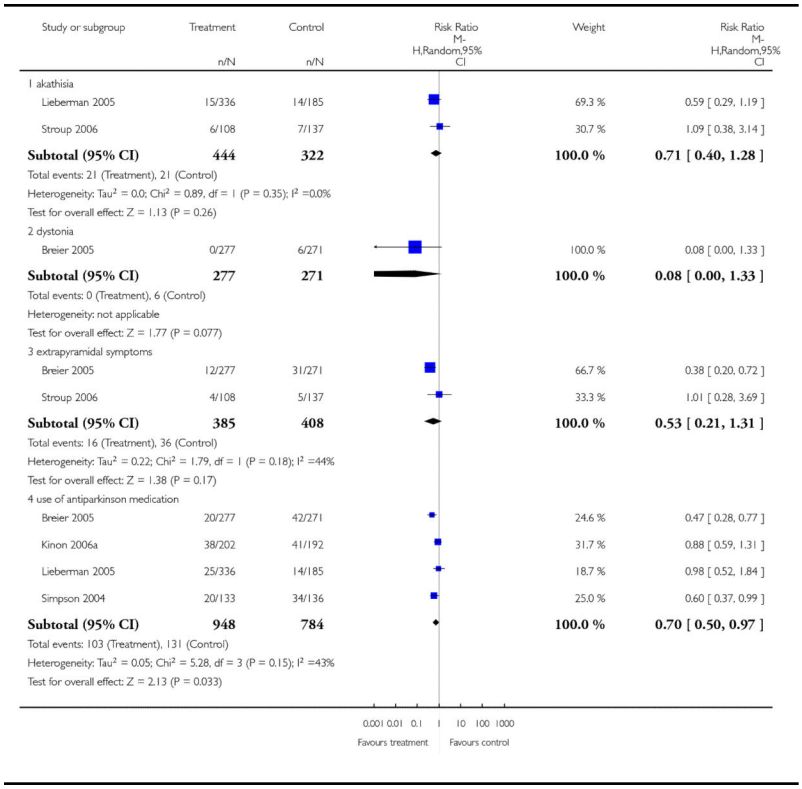
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 19 Adverse effects: 4. Central nervous system - sedation



Analysis 6.20

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 20 Adverse effects: 5a. Extrapyramidal effects

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 20 Adverse effects: 5a. Extrapyramidal effects



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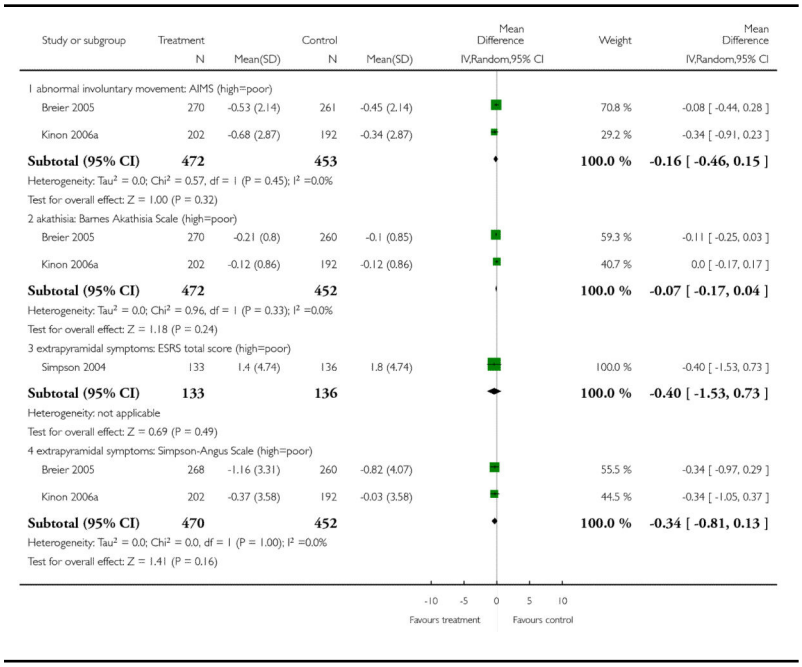
Analysis 6.21

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 21 Adverse effects: 5b. Extrapyramidal symptoms scales

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 21 Adverse effects: 5b. Extrapyramidal symptoms scales



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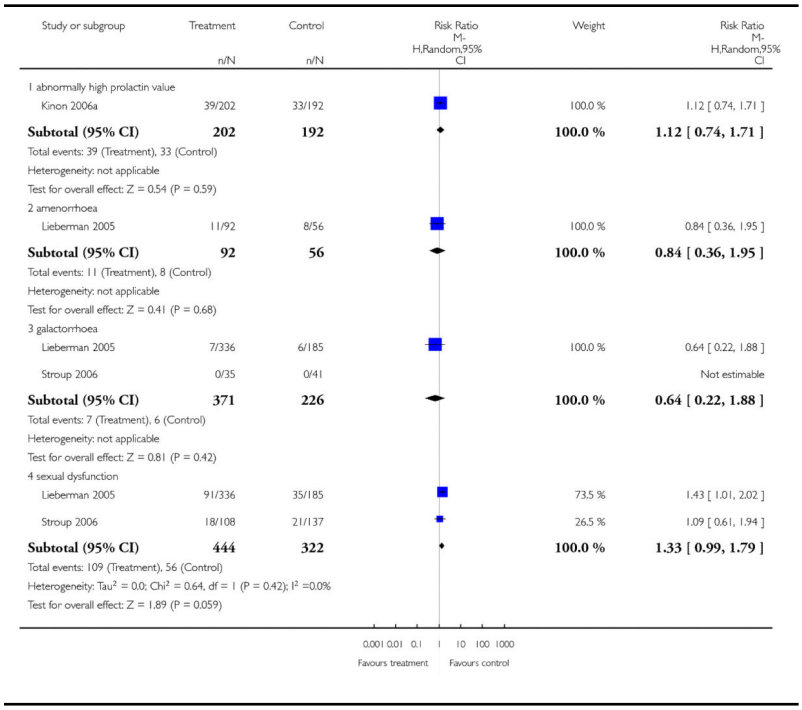
Analysis 6.22

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 22 Adverse effects: 6a Prolactin associated side effects

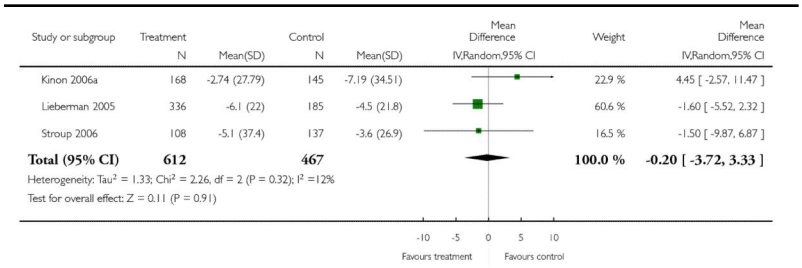
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 22 Adverse effects: 6a Prolactin associated side effects



Analysis 6.23

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 23 Adverse effects: 6b. Prolactin - change from baseline in ng/ml

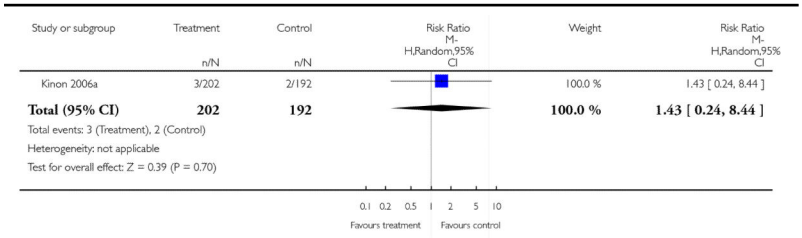
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 23 Adverse effects: 6b. Prolactin - change from baseline in ng/ml



Analysis 6.24

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 24 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase

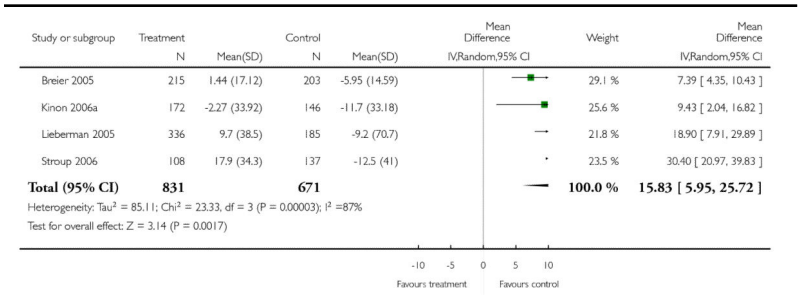
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 24 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase



Analysis 6.25

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 25 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl

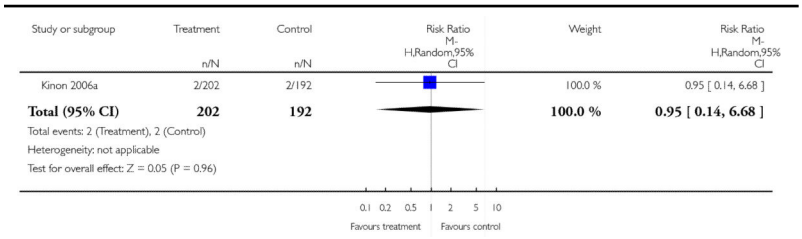
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 25 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl



Analysis 6.26

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 26 Adverse effects: 7c Metabolic - glucose - abnormally high fasting glucose value

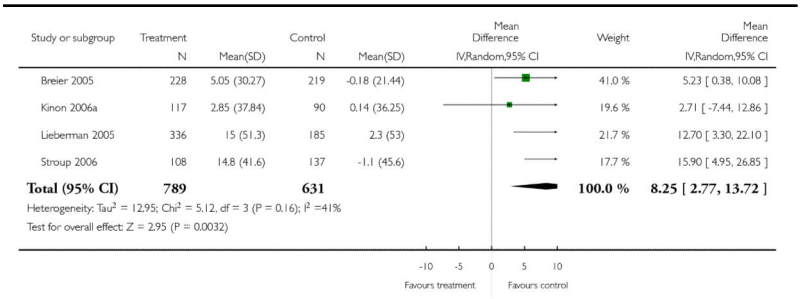
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 26 Adverse effects: 7c Metabolic - glucose - abnormally high fasting glucose value



Analysis 6.27

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 27 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl

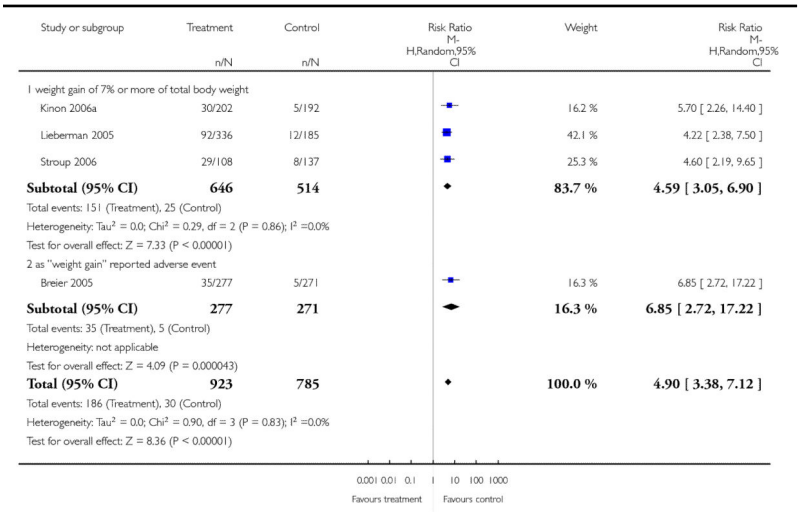
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 27 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl



Analysis 6.28

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 28 Adverse effects: 7e. Metabolic - weight gain

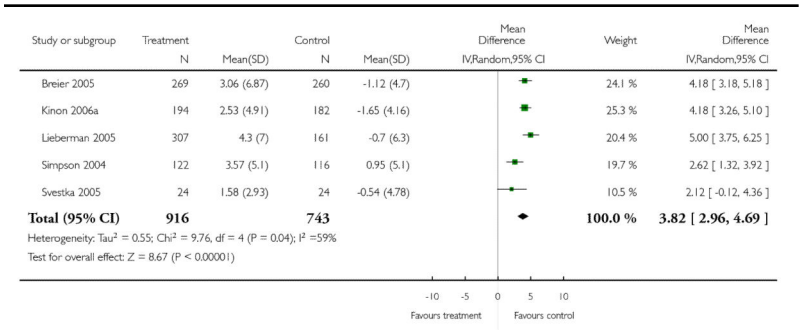
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 28 Adverse effects: 7e. Metabolic - weight gain



Analysis 6.29

Comparison 6 OLANZAPINE versus ZIPRASIDONE, Outcome 29 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg

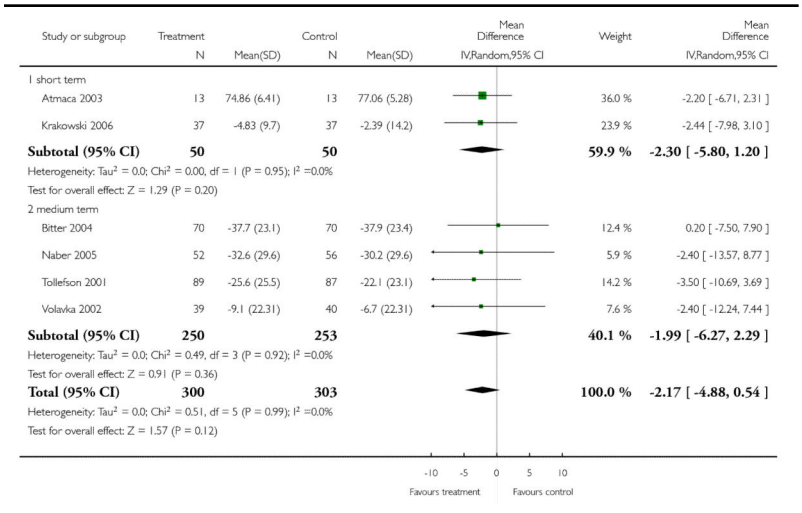
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 6 OLANZAPINE versus ZIPRASIDONE
Outcome: 29 Adverse effects: 7f. Metabolic - weight gain - change from baseline in kg



Analysis 7.1

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 1 Mental state: 1a. General - average endpoint score (PANSS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)
Outcome: 1 Mental state: 1a. General - average endpoint score (PANSS total, high=poor)



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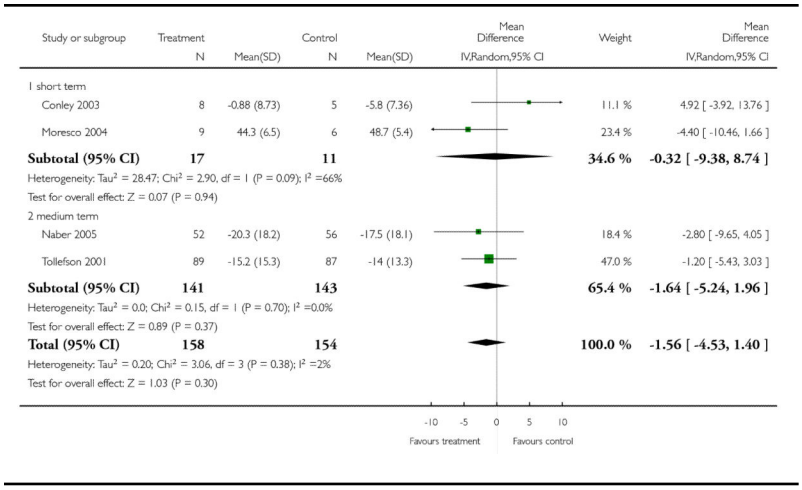
Analysis 7.2

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 2 Mental state: 1b. General - average endpoint score(BPRS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)

Outcome: 2 Mental state: 1b. General - average endpoint score(BPRS total, high=poor)



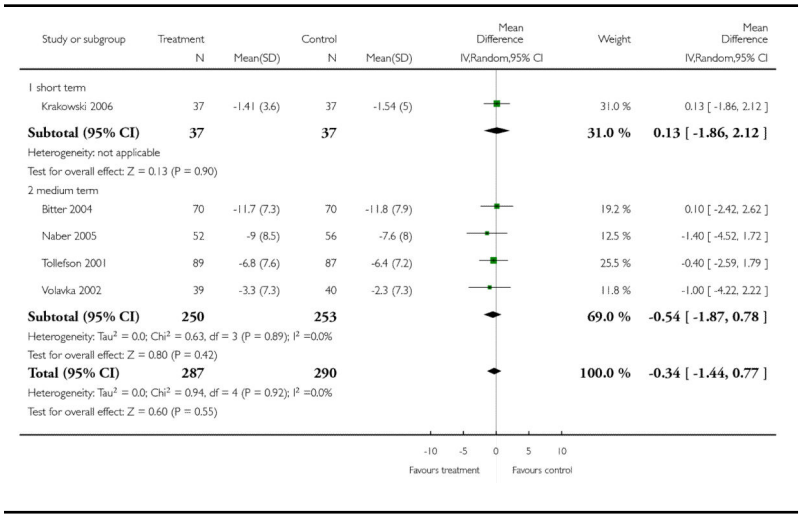
Analysis 7.3

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 3 Mental state: 2a. Positive symptoms - average endpoint score - (PANSS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)

Outcome: 3 Mental state: 2a. Positive symptoms - average endpoint score - (PANSS positive, high=poor)



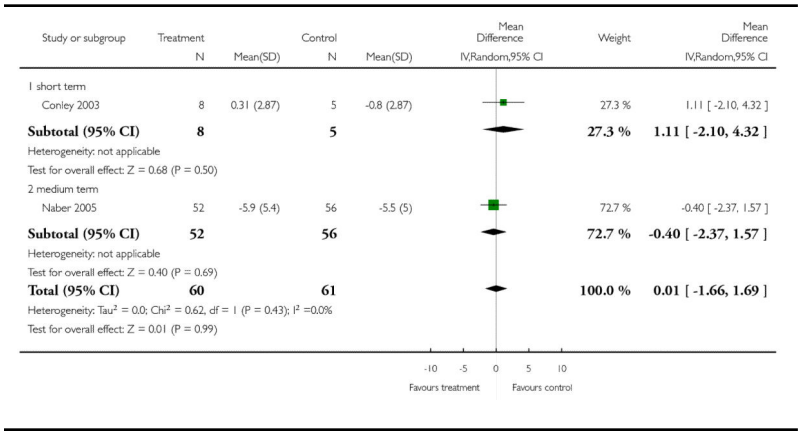
Analysis 7.4

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 4 Mental state: 2b. Positive symptoms - average endpoint score - (BPRS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)

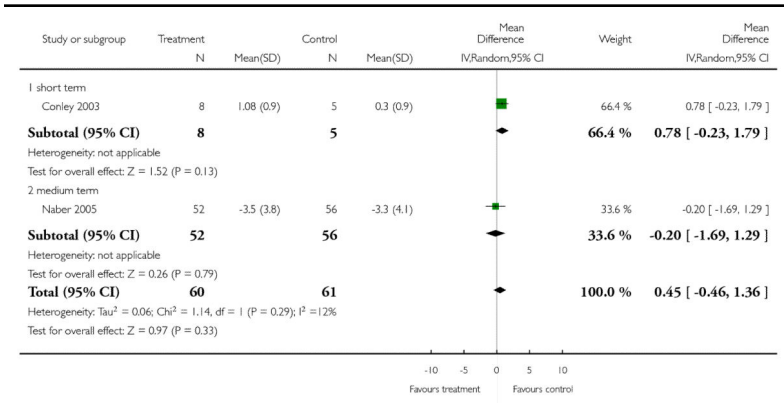
Outcome: 4 Mental state: 2b. Positive symptoms - average endpoint score - (BPRS positive, high=poor)



Analysis 7.5

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 5 Mental state: 3a. Negative symptoms - average endpoint score (BPRS negative, high=poor)

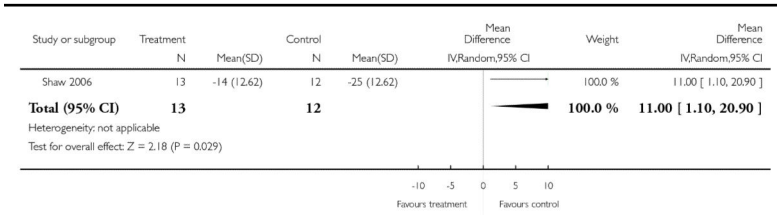
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)
Outcome: 5 Mental state: 3a. Negative symptoms - average endpoint score (BPRS negative, high=poor)



Analysis 7.6

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 6 Mental state: 6. Negative symptoms - average endpoint score - short term (SANS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)
Outcome: 6 Mental state: 6. Negative symptoms - average endpoint score - short term (SANS total, high=poor)



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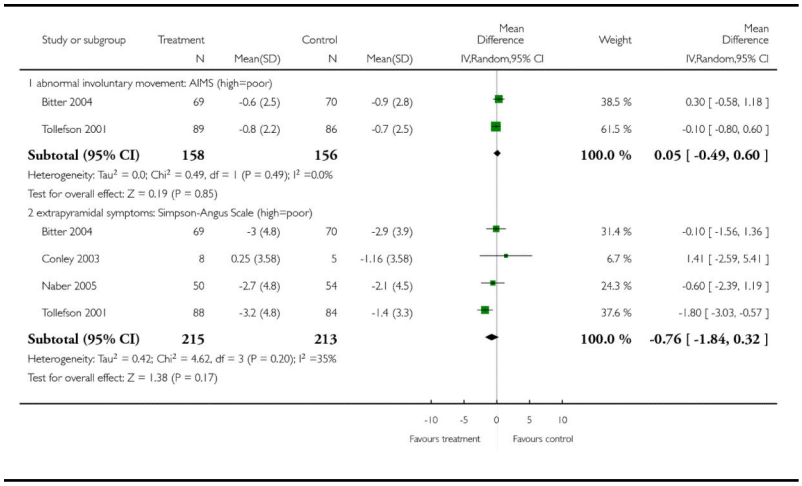
Analysis 7.7

Comparison 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded), Outcome 7 Adverse effects: 1. Extrapyramidal symptoms - scale measured

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 7 OLANZAPINE versus CLOZAPINE - sensitivity analysis (skewed data excluded)

Outcome: 7 Adverse effects: 1. Extrapyramidal symptoms - scale measured



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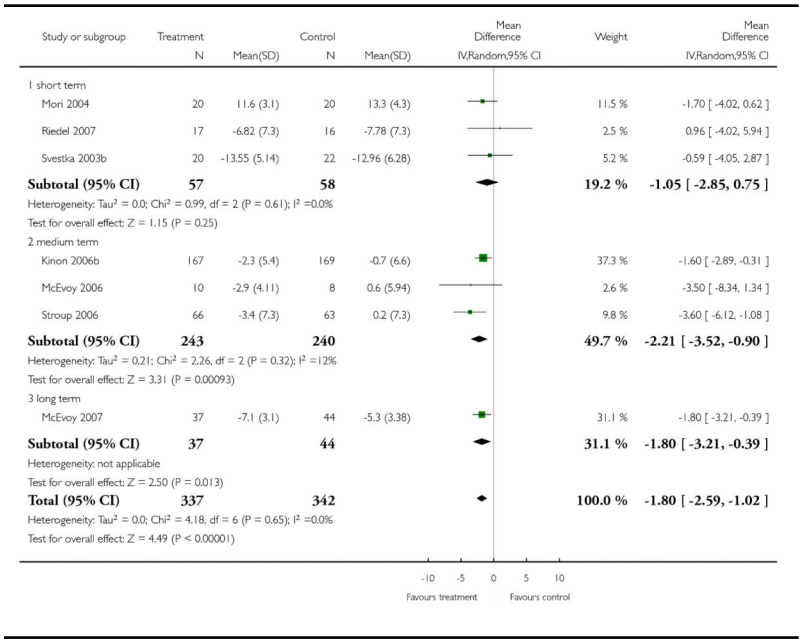
Analysis 8.1

Comparison 8 OLANZAPINE versus QUETIAPINE - sensitivity analysis (skewed data excluded), Outcome 1 Mental state: 1. Positive symptoms - average endpoint score (PANSS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 8 OLANZAPINE versus QUETIAPINE - sensitivity analysis (skewed data excluded)

Outcome: 1 Mental state: 1. Positive symptoms - average endpoint score (PANSS positive, high=poor)



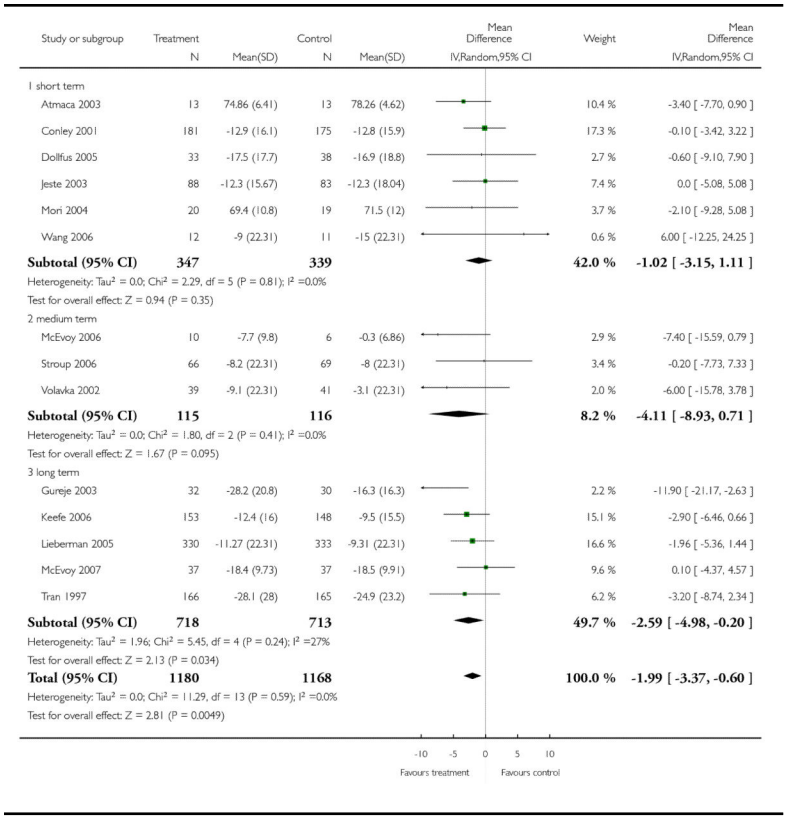
Analysis 9.1

Comparison 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded), Outcome 1 Mental state: 1. General - average endpoint score (PANSS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)

Outcome: 1 Mental state: 1. General - average endpoint score (PANSS total, high=poor)



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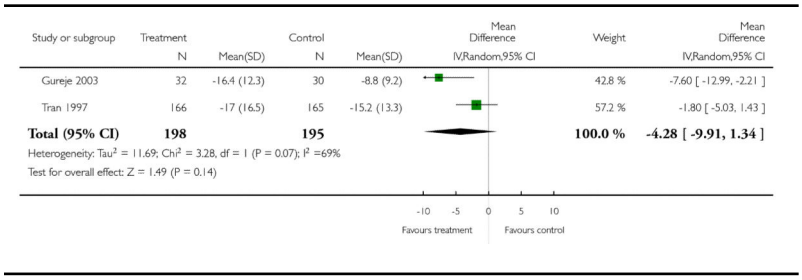
Analysis 9.2

Comparison 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded), Outcome 2 Mental state: 2. General - average endpoint score - long term (BPRS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)

Outcome: 2 Mental state: 2. General - average endpoint score - long term (BPRS total, high=poor)



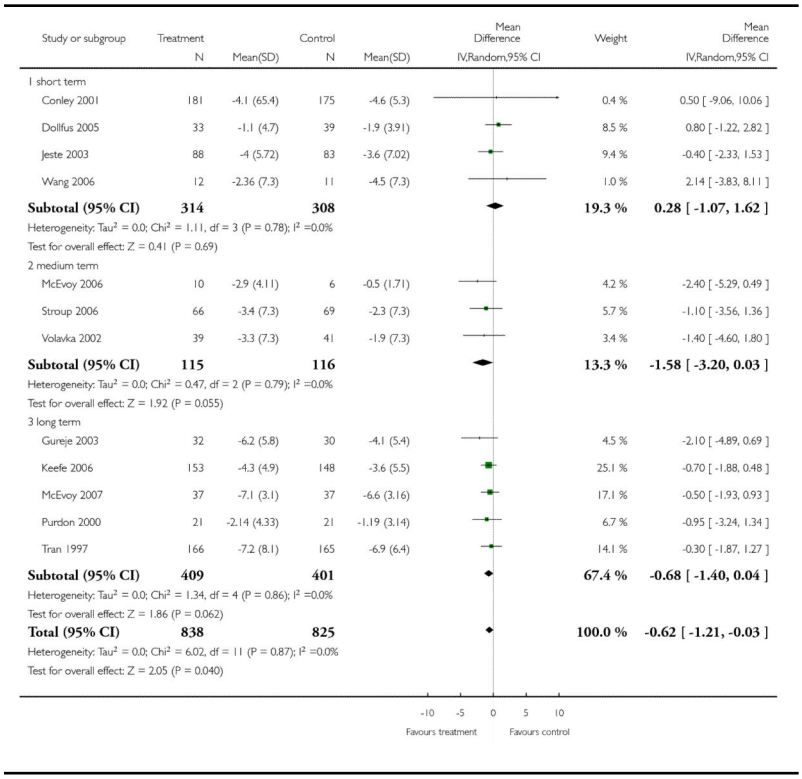
Analysis 9.3

Comparison 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded), Outcome 3 Mental state: 3. Positive symptoms - average endpoint score (PANSS positive, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)

Outcome: 3 Mental state: 3. Positive symptoms - average endpoint score (PANSS positive, high=poor)



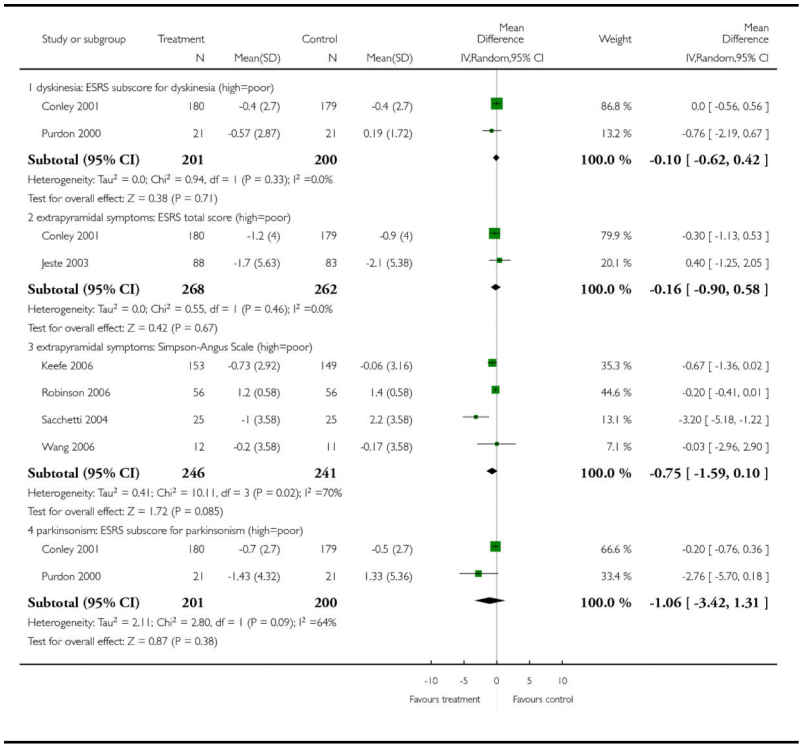
Analysis 9.4

Comparison 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded), Outcome 4 Adverse effects: 1. Extrapyramidal symptoms - scale measured

Review: Olanzapine versus other atypical antipsychotics for schizophrenia

Comparison: 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)

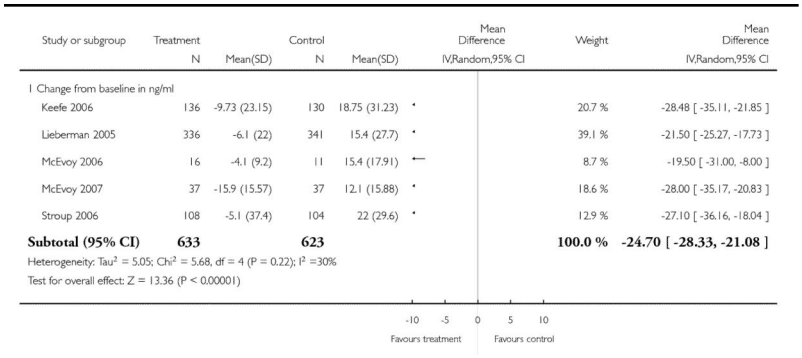
Outcome: 4 Adverse effects: 1. Extrapyramidal symptoms - scale measured



Analysis 9.5

Comparison 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded), Outcome 5 Adverse effects: 2. Prolactin - change from baseline in ng/ml

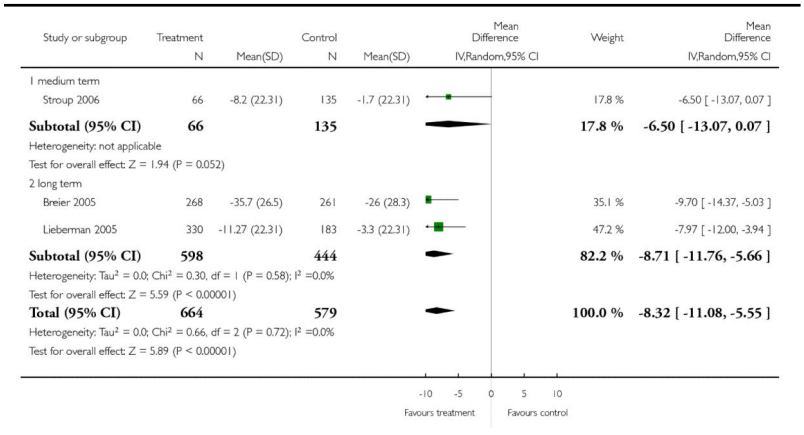
Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 9 OLANZAPINE versus RISPERIDONE - sensitivity analysis (skewed data excluded)
Outcome: 5 Adverse effects: 2. Prolactin - change from baseline in ng/ml



Analysis 10.1

Comparison 10 OLANZAPINE versus ZIPRASIDONE - sensitivity analysis (skewed data excluded), Outcome 1 Mental State: 1. General - average endpoint score (PANSS total, high=poor)

Review: Olanzapine versus other atypical antipsychotics for schizophrenia
Comparison: 10 OLANZAPINE versus ZIPRASIDONE - sensitivity analysis (skewed data excluded)
Outcome: 1 Mental State: 1. General - average endpoint score (PANSS total, high=poor)



WHAT'S NEW

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

Date	Event	Description
1 May 2013	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 3, 2010

Date	Event	Description
10 November 2010	Amended	Contact details updated.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was slightly adapted to new functions available in Review Manager 5, namely the risk of bias table.

References to studies included in this review

Atmaca 2003 {published data only} . *Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. Journal of Clinical Psychiatry. 2003; 64(5):598–604. [PubMed: 12755665]

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Olanzapine versus other atypical antipsychotics for schizophrenia

This review examined the effects of olanzapine compared to other second generation antipsychotic drugs for schizophrenia. We identified 50 relevant studies with 9476 participants, comparing olanzapine with amisulpride, aripiprazole, clozapine, quetiapine, risperidone and ziprasidone. Comparisons of olanzapine with the second generation antipsychotic drugs sertindole or zotepine are currently not available. Olanzapine was somewhat more efficacious than aripiprazole, quetiapine, risperidone and ziprasidone, whereas there was no efficacy difference compared to amisulpride and clozapine. The main disadvantage of olanzapine was its higher weight gain and associated metabolic problems compared to all other second generation antipsychotic drugs, except for clozapine.

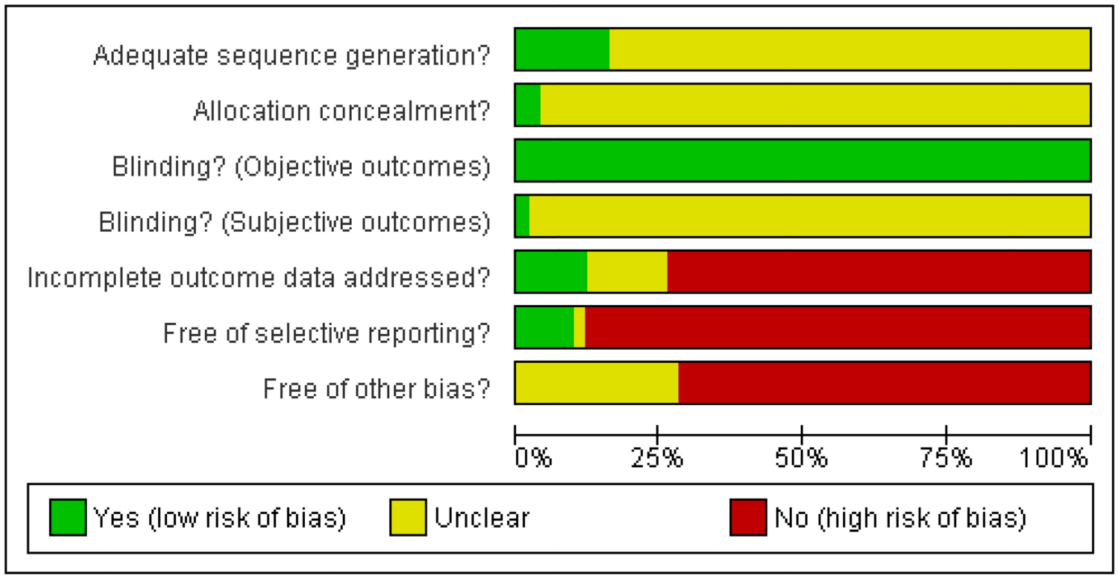

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

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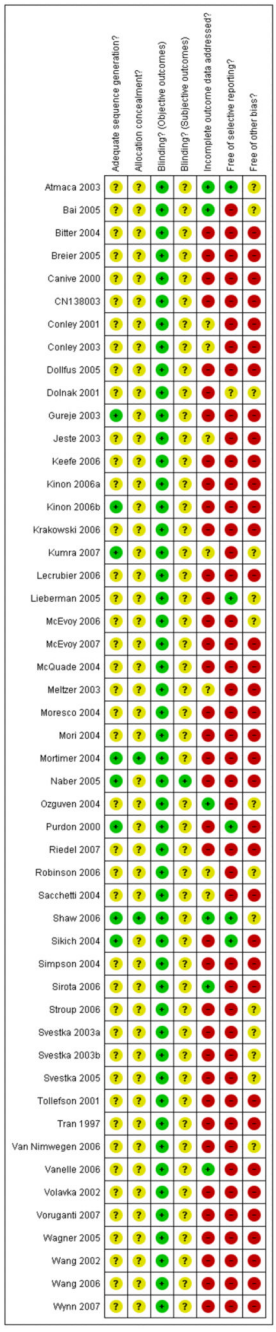

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

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Table 1

Suggested design of future study

Methods	Allocation: randomised - clearly described generation of sequence and concealment of allocation. Blindness: double - described and tested. Duration: 6 months minimum.	
Participants	Diagnosis: schizophrenia (operational criteria). N=2700.* Age: any. Sex: both. History: any.	
Interventions	**1**	Olanzapine: dose ~ 10-20 mg/day. N=300.
	2	Amisulpride: dose ~ 400-800 mg/day. N=300.
	3	Aripiprazole: dose ~ 10-30 mg/day. N=300.
	4	Clozapine: dose ~ 300-800 mg/day. N=300.
	5	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