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Quetiapine versus other atypical antipsychotics for schizophrenia

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Abstract

Background—In many countries of the industrialised world second generation ('atypical') antipsychotic drugs have become the first line drug treatment for people with schizophrenia. It is not clear how the effects of the various second generation antipsychotic drugs differ.

Objectives—To evaluate the effects of quetiapine compared with other second generation antipsychotic drugs for people with schizophrenia and schizophrenia-like psychosis.

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DECLARATIONS OF INTEREST

Katja Komossa: none known.

Christine Rummel: has received lecture honoraria and travel grants to attend scientific meetings from AstraZeneca, Janssen-Cilag, Eli Lilly and Pfizer.

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Manit Srisurapanont: has received honoraria and support for attending national and international scientific meetings from AstraZeneca (Thailand), Eli Lilly Asia, Inc. (Thailand), GlaxoSmithKline (Thailand), Janssen-Cilag (Thailand), Servier (Thailand) and Solvay Pharmaceuticals (Thailand).

Search methods—We searched the Cochrane Schizophrenia Group Trials Register (April 2007), inspected references of all identified studies, and contacted relevant pharmaceutical companies, drug approval agencies and authors of trials for additional information.

Selection criteria—We included all randomised control trials comparing oral quetiapine with oral forms of amisulpride, aripiprazole, clozapine, olanzapine, 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 21 randomised control trials (RCTs) with 4101 participants. These trials provided data on four comparisons - quetiapine versus clozapine, olanzapine, risperidone or ziprasidone.

A major limitation to all findings is the high number of participants leaving studies prematurely (57.6%) and the substantial risk of biases in studies. Efficacy data favoured olanzapine and risperidone compared with quetiapine (PANSS total score versus olanzapine:10 RCTs, n=1449, WMD 3.66 CI 1.93 to 5.39; versus risperidone: 9 RCTs, n=1953, WMD 3.09 CI 1.01 to 5.16), but clinical meaning is unclear. There were no clear mental state differences when quetiapine was compared with clozapine or ziprasidone.

Compared with olanzapine, quetiapine produced slightly fewer movement disorders (6 RCTs, n=1090, RR use of antiparkinson medication 0.49 CI 0.3 to 0.79, NNH 25 CI 14 to 100) and less weight gain (7 RCTs, n=1173, WMD –2.81 CI –4.38 to –1.24) and glucose elevation, but more QTc prolongation (3 RCTs, n=643, WMD 4.81 CI 0.34 to 9.28). Compared with risperidone, quetiapine induced slightly fewer movement disorders (6 RCTs, n=1715, RR use of antiparkinson medication 0.5 CI 0.3 to 0.86, NNH 20 CI 10 to 100), less prolactin increase (6 RCTs, n=1731, WMD –35.28 CI –44.36 to –26.19) and some related adverse effects, but more cholesterol increase (5 RCTs, n=1433, WMD 8.61 CI 4.66 to 12.56). Compared with ziprasidone, quetiapine induced slightly fewer extrapyramidal adverse effects (1 RCT, n=522, RR use of antiparkinson medication 0.43 CI 0.2 to 0.93, NNH not estimable) and prolactin increase. On the other hand quetiapine was more sedating and led to more weight gain (2 RCTs, n=754, RR 2.22 CI 1.35 to 3.63, NNH 13 CI 8 to 33) and cholesterol increase than ziprasidone.

Authors' conclusions—Best available evidence from trials suggests that most people who start quetiapine stop taking it within a few weeks. Comparisons with amisulpride, aripiprazole, sertindole and zotepine do not exist. Most data that has been reported within existing comparisons are of very limited value because of assumptions and biases within them. There is much scope for further research into the effects of this widely used drug.

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; * therapeutic use]; Benzodiazepines [adverse effects; therapeutic use]; Clozapine [adverse effects; therapeutic use]; Dibenzothiazepines [adverse effects; * therapeutic use]; Medication Adherence [statistics & numerical data]; Piperazines [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse

MeSH check words

Humans

BACKGROUND

Description of the condition

Schizophrenia can be a 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), 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 15-44 years age group, schizophrenia is among the top ten leading causes of disease-related disability in the world (WHO 2001). Conventional antipsychotic drugs, such as chlorpromazine and haloperidol, have traditionally been used as first line antipsychotic drugs for people with schizophrenia (Kane 1993). The reintroduction of clozapine in the USA, and findings to indicate that clozapine seemed more effective than other drugs, as well as being associated with fewer movement disorders than chlorpromazine (Kane 1988), boosted development of new/second/atypical generation antipsychotic drugs (SGA).

Description of the intervention

There is no good definition of what an 'atypical' antipsychotic is, but they were initially said to differ from typical antipsychotic drugs in that they do not cause movement disorders (catalepsy) in rats at clinically effective doses (Arnt 1998). The terms 'new' or 'second generation' antipsychotic drugs are not much better, because clozapine is now a very old drug. According to treatment guidelines (APA 2004, Gaebel 2006) second generation antipsychotic drugs such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine, although it is unclear whether some old and inexpensive compounds such as sulpiride or perazine have similar properties (Möller 2000). The second generation antipsychotic drugs 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 whose illness had formerly been resistant to treatment.

How the intervention might work

Experimental laboratory studies have suggested that quetiapine is a clozapine-like atypical antipsychotic (Migler 1993, Goldstein 1993, Saller 1993). In contrast to olanzapine,

risperidone, sertindole and ziprasidone have high affinities (<50 nM) to both D2 and 5-HT2A receptors, quetiapine is similar to clozapine in having only moderate affinities (<500 nM) to these sites (Goldstein 1995). Quetiapine has a high affinity for histamine receptors (<50 nM) (Srisurapanont 2004).

Why it is important to do this review

The debate as to how far the second generation antipsychotic drugs improve these outcomes compared with conventional antipsychotic drugs 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 antipsychotic drugs have become the mainstay of treatment. They also differ in terms of their costs: while amisulpride and risperidone are already generic in many countries, quetiapine for example is 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 quetiapine with other second generation antipsychotic drugs.

OBJECTIVES

To review the effects of quetiapine compared with other atypical antipsychotic drugs for people with schizophrenia and schizophrenia-like psychosis.

METHODS

Criteria for considering studies for this review

Types of studies—We included relevant 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. Quetiapine: any oral form of application, any dose.

2. Other 'atypical' antipsychotic drugs: amisulpride, aripiprazole, clozapine, olanzapine, 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
- **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 Admitted
- 8 Adverse effects
- 8.1 Number of people 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: [((quetiapin* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR risperidon* OR sertindol* OR ziprasidon* OR zotepin*)) in title, abstract or index terms of REFERENCE) or ((quetiapin* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR risperidon* OR sertindol* OR ziprasidon* 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 references of all identified studies 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 antipsychotic drugs included for additional data.

Data collection and analysis

Selection of studies—KK, CRK and SL independently inspected all reports. We resolved any disagreement by discussion, and where there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained, we independently decided whether the studies met the review criteria. If disagreement could not be resolved by

discussion, we sought further information and added these trials to the list of those awaiting assessment.

Data extraction and management

<u>1. Data extraction:</u> KK, CRK and SL 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.

<u>2. Management:</u> KK, CRK, FS, HH, SS and SL extracted 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 quetiapine.

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)

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

Measures of treatment effect

<u>1. Data types:</u> 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 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 misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number-needed-to-harm (NNH) as the inverse of the risk difference.

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 ALL-STAT electronic statistics mailing list, we presented change data in RevMan Analyses in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Change data were therefore included and a sensitivity analysis was not applied.

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 pvalues or used the average SD of the other studies (Furukawa 2006).

Unit of analysis issues

<u>1. Cluster trials:</u> 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 I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation coefficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of

participants per cluster (m) and the intraclass correlation coefficient (ICC) [Design effect=1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account intraclass correlation coefficients and relevant data documented in the report, we 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 attrition 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

<u>1. Clinical heterogeneity</u>: 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 I²statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I² 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 funnel plot 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—We planned sensitivity analyses for examining the change in robustness of the sensitivity to including studies with potentially skewed data. A recent report showed that some of the comparisons of atypical antipsychotic drugs may have been biased by using inappropriate comparator doses (Heres 2006). We, therefore, also analysed whether the exclusion of studies with inappropriate comparator doses changed the results of the primary outcome and the general mental state.

RESULTS

Description of studies

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

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

Results of the search—The overall search strategy yielded 3620 reports of which 104 were closely inspected.

Included studies—Twenty-one studies with 4101 participants met the inclusion criteria. Six studies were sponsored by pharmaceutical companies producing quetiapine, three were sponsored by the manufacturer of the comparator antipsychotic, and eight had a neutral sponsor. For the remaining four studies the sponsor was unclear.

<u>1. Length of trials</u>: Fifteen studies were short term with a duration of 2-12 weeks. Three studies were medium term and two trials fell into the long term category.

<u>2. Setting:</u> Seven trials were conducted in an in- or outpatient setting, nine studies were conducted exclusively in an inpatient setting and one study was conducted exclusively in an outpatient setting. Four studies did not report the setting.

3. Participants: Seventeen studies included participants with diagnoses according to the Diagnostic and Statistical Manual Fourth revision (DSM-IV). Riedel 2005 additionally used the International Classification of Diseases Version 10 (ICD-10). Li 2002, Li 2005 and Liu 2004 diagnosed participants according to the Chinese Classification of Mental Disorders Version 3 (CCMD-3). Li 2003b used CCMD-2. Two studies included only acutely ill people (Riedel 2007, Svestka 2003b) and one included only people with a first episode of schizophrenia (McEvoy 2007). Two studies included people with chronic schizophrenia or people with more than one schizophrenic episode (Lieberman 2005, Stroup 2006). Only one study focused on treatment resistant participants (Conley 2005).

<u>4. Study size:</u> Lieberman 2005 was the largest study with 1453 participants, while Ozguven 2004 was the smallest, randomising only 22 people. Five studies had less than 50 participants but two randomised more than 400 people.

5. Interventions

5.1 *Quetiapine: all included studies used flexible dosing:* Overall, quetiapine was given in a dose range from 50 mg/day to 800 mg/day. Only Conley 2005 limited the upper dose range to 500 mg/day and Ozguven 2004 had a mean dose which was higher than the upper dose range of 800mg/day (827 mg/day).

5.2 Comparators: the comparator drugs were clozapine, olanzapine, risperidone and *ziprasidone, again given in flexible doses:* Some studies included treatment arms with fluphenazine, perphenazine and perospirone, as well, but as these are not second generation antipsychotic drugs we did not report the results.

6. Outcomes

6.1 Leaving the study early: The number of participants leaving the studies early were reported for the categories 'any reason', 'adverse events' and 'lack of efficacy'.

6.2 No clinically significant response: We pre-specified at least 50% PANSS/BPRS reduction from baseline as a clinical relevant cut-off to define, but only Svestka 2003b reported this outcome. Instead, Liu 2004 indicated at least 50% SANS reduction from baseline, Potkin 2006 and Zhong 2006a at least 30 % PANSS total score reduction from baseline, Ozguven 2004 at least 20% SANS total score reduction from baseline, Conley 2005 a Clinical Global Impression (Guy 1976) of mild or better combined with at least 20% BPRS total reduction from baseline and McEvoy 2007 all PANSS items mild or better plus a Clinical Global Impression of mild or better.

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

6.3.1.1 *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.

6.3.2.1 *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.

6.3.2.2 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.

6.3.2.3 Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1989): This six point scale gives a global rating of the following negative symptoms: alogia, affective blunting, avolition-apathy, anhedonia-associality and attention impairment. Higher scores indicate more symptoms.

6.3.2.4 Scale for the Assessment of Positive Symptoms - SAPS (Andreasen 1984): This four point scale gives a global rating of the following positive symptoms: hallucination, delusion, bizarre attitudes and positive formal thought disorder.

6.3.3 Global Assessment of Functioning - GAF (DSM IV 1994): A rating scale for a patients' overall capacity of psychosocial functioning, scoring from 1-100. Higher scores indicating a higher level of functioning.

6.3.4. 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.

6.3.5.1 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.

6.3.5.2 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.

6.3.5.3 *Extrapyramidal Symptom Rating Scale - ESRS (Chouinard 1980):* This is 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.

6.3.5.4 Simpson Angus Scale - SAS (Simpson 1970): This is a 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.

6.4 Other adverse effects: Other adverse effects were reported as continuous variables for QTc prolongation (ms), cholesterol level (mg/dl), glucose level (mg/dl), prolactin level (ng/ml) and weight (kg). Other adverse events were reported in a dichotomous manner in terms of the number of people with a given effect.

6.5 Service use: Service use was described as the number of patients re-hospitalised during the trial.

Excluded studies—Eighty three studies had to be excluded for the following reasons: eleven were not randomised, 64 were open label, three employed inappropriate intervention, four reported no usable data and one was a pooled analysis rather than a trial.

Awaiting assessment—No studies are waiting assessment.

Ongoing studies—Four randomised trials comparing quetiapine with other antipsychotic drugs seem to be ongoing (Eli Lilly 2004b, Gafoor 2005, Ratna 2003, Reynolds 2001). For further details see 'Characteristics of ongoing studies'.

Risk of bias in included studies

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

Allocation—All of the included studies were described as randomised. Only two studies gave further information about the type of randomisation, Kinon 2006b described computer generated randomisation and Potkin 2006 described using an interactive voice response system for allocation concealment, for all other studies it was unclear whether the allocation strategies were appropriate.

Blinding—Seven of the included studies were 'single-blind' (blind raters), all other included studies were 'double-blind'. Four studies used identical capsules for blinding (Lieberman 2005, McEvoy 2006, Potkin 2006, Riedel 2005). The other trials did not provide any information on the blinding procedure. No study examined whether blinding was effective. We found that the adverse effect profiles of some of the compounds are quite different and think that this may have made blinding difficult. We therefore conclude that the risk of bias for objective outcomes (e.g. death or laboratory values) was less than that for

subjective outcomes, and for the latter there was a considerable risk as a result of poor blinding.

Incomplete outcome data—Fifteen studies indicated the number of participants leaving the studies early for any reason. In these fifteen studies the reasons for premature study discontinuation were usually well described. A major problem, however, was the very high attrition which in nine studies was higher than 30% (57.6% overall) (Conley 2005, Kinon 2006b, Lieberman 2005, McEvoy 2006, McEvoy 2007, Riedel 2005, Riedel 2007, Stroup 2006, Zhong 2006). In most studies the last-observation-carried-forward method was used to account for attrition. This is an imperfect method. It assumes that a participant's outcome would not have changed if he/she had remained in the study which is often wrong. It is, however, questionable whether other methods (e.g. imputation strategies or mixed effect models) could have coped better with such dramatically high rates of attrition. The high loss to follow up is a clear threat to the validity of findings.

Selective reporting—Only two studies were judged to be free of selective reporting (Atmaca 2003, Li 2002). For most of the other trials there was a high risk of bias, mainly for the reason of incomplete reporting of predefined outcomes (Conley 2005, Kinon 2006b, Li 2005, Li 2003, Liu 2004, McEvoy 2006, Mori 2004, Ozguven 2004, Riedel 2005, Riedel 2007, Sacchetti 2004, Sirota 2006, Stroup 2006, Svestka 2003b, Voruganti 2007). In other studies only adverse events that occurred in at least 5% or 10% of participants, or which were moderately severe, have been reported (McEvoy 2007, Potkin 2006, Zhong 2006). The former method is problematic, because rare but important adverse effects may have been missed. In Lieberman 2005 all data from one site were excluded before analysis because of concerns about their integrity.

Other potential sources of bias—No study was clearly free of other potential sources of bias. In six the risk of 'other bias' was, however, unclear. Nine studies were industry sponsored (Kinon 2006b, McEvoy 2007, Potkin 2006, Riedel 2005, Riedel 2007, Sacchetti 2004, Sirota 2006, Voruganti 2007, Zhong 2006). There is evidence that pharmaceutical companies sometimes highlight the benefits of their compounds and tend to suppress their disadvantages (Heres 2006). Other reasons for potential bias were heterogeneity of pre-study treatment (Atmaca 2003, Stroup 2006), lack of or only short wash-out phases (Li 2005, Lieberman 2005, McEvoy 2006, Mori 2004, Voruganti 2007), baseline imbalance in terms of number of previous hospitalisations (Conley 2005), no information on the allowed dose range (Atmaca 2003, Li 2003, Voruganti 2007), or a too fast titration of clozapine which may be associated with more adverse events (Liu 2004).

Effects of interventions

1. Comparison 1. QUETIAPINE versus CLOZAPINE - all data short term—Five studies met the inclusion criteria for the comparison of quetiapine with clozapine.

1.1 Global state:

1.1.1 No clinically significant response - as defined by the original studies: There was no significant difference (1 RCT, n=72, RR 0.94 CI 0.78 to 1.13).

1.1.2 No clinically important change - as defined by the original studies: There was no significant difference (1 RCT, n=72, RR 0.94 CI 0.74 to 1.18).

<u>**1.2 Leaving the study early:**</u> There was no significant difference in the number of participants leaving the studies early due to any reason (2 RCTs, n=95, RR 0.67 CI 0.18 to 2.43), due to adverse events (1 RCT, n=72, RR 0.14 CI 0.01 to 2.6) or due to inefficacy of treatment (1 RCT, n= 72, RR not estimable).

<u>1.3 Mental state:</u>

1.3.1 General mental state: no clinically important change (less than 50% PANSS total score reduction from baseline): There was no clear difference to be found (1 RCT, n=63, RR 1.07 CI 0.53 to 2.14).

1.3.2 General mental state: average score at endpoint - PANSS total: Four short term studies did not indicate a significant difference (4 RCTs, n=232, WMD –0.5 CI –2.85 to 1.86).

1.3.3 General mental state: average score at endpoint - BPRS total There was no significant difference (1 RCT, n=67, WMD –0.89 CI –3.20 to 1.42).

1.3.4 Positive symptoms: average score at endpoint - PANSS positive subscore: There was no significant difference (2 RCTs, n=142, WMD –0.7 CI –2.07 to 0.68).

1.3.5 Negative symptoms: average score at endpoint - PANSS negative subscore: Two small Chinese studies showed a significant superiority of quetiapine (2 RCTs, n=142, WMD -2.23 CI -3.48 to -0.99).

1.3.6 Negative symptoms: no clinically important change (less than 50% SANS total score reduction from baseline): There was no significant difference (1 RCT, n=72, RR 0.94 CI 0.78 to 1.13).

1.3.7 Negative symptoms: average score at endpoint - SANS total There was no significant difference (1 RCT, n=67, WMD –1.64 CI –8.17 to 4.89).

<u>1.4 Adverse effects:</u>

1.4.1 Numbers of participants with at least one adverse effect: There was a significant difference, based on data from Li 2002, favouring the treatment group (1 RCT, n=63, RR 0.42 CI 0.26 to 0.66, NNH 2 CI 1 to 3).

1.4.2 Cardiac effects - ECG abnormalities: There was a significant difference favouring quetiapine (1 RCT, n=72, RR 0.13 CI 0.02 to 0.95, NNH 5 CI 3 to 20).

1.4.3 Central nervous system - sedation: Fewer participants in the quetiapine group reported this outcome (2 RCTs, n=135, RR 0.22 CI 0.11 to 0.47, NNH 3 CI 2 to 8).

1.4.4 Extrapyramidal effects: There was no significant difference in akathisia (2 RCTs, n=135, RR 0.4 CI 0.08 to 1.99), rigor (1 RCT, n=63, RR 1.94 CI 0.18 to 20.3), tremor (2 RCTs, n=135, RR 0.99 CI 0.29 to 3.34) or use of antiparkinsonian medication (1 RCT, n=28, RR not estimable).

1.4.5 Haematological: important decline in white blood cells: There was no significant difference (1 RCT, n=33, RR 0.19 CI 0.01 to 3.88).

1.4.6 Metabolic - weight gain (number of participants with significant weight gain): There was no significant difference (2 RCTs, n=135, RR 0.53 CI 0.25 to 1.11).

1.4.7 Metabolic - weight gain (change from baseline in kg): One small study reported a trend in favour of quetiapine (1 RCT, n=27, WMD -2.11 CI -4.3 to 0.08).

<u>1.5 Publication bias:</u> We did not perform a funnel plot analysis because there were so few studies.

1.6 Investigation for heterogeneity and sensitivity analysis: The exclusion of Li 2002, Li 2003b, Li 2005 from the analysis of the PANSS total score due to possibly skewed data did not change the results to a marked extent.

2. Comparison 2. QUETIAPINE versus OLANZAPINE—Thirteen studies met the inclusion criteria for this comparison.

2.1 Global state:

2.1.1 No clinically significant response - as defined by the original studies: There was no significant difference (3 RCTs, n=339, RR 1.11 CI 0.86 to 1.43).

2.1.2 No clinically important change - as defined by the original studies: There was no significant difference (2 RCTs, n=309, RR 1.18 CI 0.89 to 1.57).

2.2 Leaving the study early: Fewer participants in the olanzapine group (57%) compared with the quetiapine group (70%) left the studies early because of 'any reason' (10 RCTs, n=1651, RR 1.22 CI 1.13 to 1.32, NNH 10 CI 6 to 33) or 'inefficacy' (14% versus 25%, 8 RCTs, n=1563, RR 1.8 CI 1.42 to 2.27, NNH 11 CI 6 to 50), but not due to adverse events (12% versus 11%, 8 RCTs, n=1573, RR 0.90 CI 0.69 to 1.18).

2.3 Mental state:

2.3.1 General mental state: no clinically important change - short term (less than 50% *PANSS total score reduction):* There was no significant difference (1 RCT, n=42, RR 0.91 CI 0.54 to 1.53).

2.3.2 General mental state: average score at endpoint - PANSS total: There was a significant difference favouring olanzapine (10 RCTs, n=1449, WMD 3.66 CI 1.93 to 5.39) in the short term (4 RCTs, n=142, WMD 2.17 CI -1.51 to 5.85), medium term (3 RCTs, n= 483, WMD 5.57 CI 1.97 to 9.17) and long term (3 RCT, n=825, WMD 3.40 CI 0.91 to 5.88)

2.3.3 Positive symptoms: no clinically important change - short term (less than 20% SAPS total score reduction): There was no difference identified with confidence (1 RCT, n=30, RR 15.0 CI 0.93 to 241.2).

2.3.4 *Positive symptoms: average score at endpoint - PANSS positive subscore:* There was a significant difference in favour of olanzapine (7 RCTs, n=679, WMD 1.8 CI 1.02 to 2.59), short term (3 RCTs, n=115, WMD 1.05 CI –0.75 to 2.85), medium term (3 RCTs, n=483, WMD 2.21 CI 0.90 to 3.52), long term (1 RCT, n=81, WMD 1.80 CI 0.39 to 3.21)

2.3.5 *Positive symptoms: average score at endpoint - SAPS total score - short term* (*percentage change from baseline*): There was a significant difference favouring olanzapine (1 RCT, n=30, WMD 40.84 CI 23.97 to 57.71).

2.3.6 Negative symptoms: no clinically important change - short term (less than 20% SANS total score reduction from baseline): There was no significant difference (1 RCT, n=30, RR 1.5 CI 0.53 to 4.26).

2.3.7 Negative symptoms: average score at endpoint - PANSS negative subscore: There was no significant difference (7 RCTs, n=679, WMD 0.41 CI –0.36 to 1.18), short term (3 RCTs, n=115, WMD 0.01 CI –1.72 to 1.73), medium term (3 RCTs, n=483, WMD 0.40 CI –0.67 to 1.47), long term (1 RCT, n=81, WMD 0.70 CI –0.73 to 2.13)

2.3.8 Negative symptoms: average score at endpoint - SANS total score: There was no significant difference (1 RCT, n=335, WMD 3.7 CI -0.48 to 7.88).

2.3.9 Negative symptoms: average score at endpoint - SANS total score (percent change from baseline): There was no significant difference (1 RCT, n=30, WMD 2.46 CI –31.9 to 36.82).

<u>2.4 General functioning: average endpoint total score -medium term GAF:</u> There was a significant difference in favour of olanzapine (1 RCT, n=278, WMD 3.8 CI 0.77 to 6.83).

<u>2.5 Quality of life: average endpoint total score -medium term QLS:</u> There was no significant difference (1 RCT, n=286, WMD 1.8 CI –2.42 to 6.02).

2.6 Service use: number of participants re-hospitalised: There was a significant difference favouring olanzapine (2 RCTs, n=876, RR 1.79 CI 1.30 to 2.47, NNH 11 CI 7 to 25).

2.7 Adverse effects:

2.7.1 Numbers of participants with at least one adverse effect: There was no significant difference (6 RCTs, n=1269, RR 0.97 CI 0.88 to 1.06).

2.7.2 *Death:* There was no significant difference (4 RCTs, n=1410, RR 0.74 CI 0.13 to 4.23).

2.7.3 Cardiac effects:

2.7.3.1 Number of participants with QTc prolongation: There was no significant difference (1 RCT, n=673, RR 12.96 CI 0.73 to 229.17).

2.7.3.2 *Mean change of QTc interval from baseline in ms:* There was a significant difference favouring olanzapine (3 RCTs, n=643, WMD 4.81 CI 0.34 to 9.28).

2.7.4 Central nervous system:

2.7.4.1 Sedation: There was no significant difference (7 RCTs, n=1615, RR 0.97 CI 0.78 to 1.2).

2.7.4.2 *Seizures:* There was no significant difference (1 RCT, n=40, RR 3.3 CI 0.14 to 76.46).

2.7.5 Extrapyramidal effects:

2.7.5.1 Extrapyramidal effects: Fewer participants in the quetiapine group used antiparkinson medication at least once (6 RCTs, n=1090, RR 0.49 CI 0.3 to 0.79, NNH 25 CI 14 to 100). Apart from this, no significant differences in EPS were found for akathisia (6 RCTs, n=1277, RR 0.98 CI 0.68 to 1.4), akinesia (1 RCT, n=267, RR 1.02 CI 0.67 to 1.56), dystonia (1 RCT, n=42, RR 4.57 CI 0.23 to 89.72), any extrapyramidal symptom (2 RCTs, n=245, RR 1.62 CI 0.72 to 3.67), parkinsonism (1 RCT, n=40, RR 0.66 CI 0.18 to 2.41) and tremor (1 RCT, n=44, RR 0.39 CI 0.12 to 1.31).

2.7.5.2 *Scale measured:* Extrapyramidal adverse effects were evaluated with the Barnes Akathisia Scale, the Extrapyramidal Side Effects Rating Scale and the Simpson-Angus Scale. None of these indicated a significant difference between groups.

2.7.6 Prolactin associated side effects: Fewer participants in the quetiapine group suffered from sexual dysfunction (4 RCTs, n=1177, RR 0.8 CI 0.64 to 0.99, NNH 20 CI 10 to 100).

There was no significant difference in abnormally high prolactin (1 RCT, n=42, RR 0.10 CI 0.01 to 1.77), amenorrhoea (3 RCTs, n=252, RR 0.66 CI 0.36 to 1.21), galactorrhoea (4 RCTs, n=1025, RR 0.66 CI 0.25 to 1.73) and gynaecomastia (1 RCT, n=267, RR 0.33 CI 0.09 to 1.20).

2.7.7 Prolactin - change from baseline in ng/ml: Quetiapine was associated with less prolactin increase than olanzapine (5 RCTs, n=1021, RR –5.89 CI –11.62 to –0.16), but the data were heterogeneous. Nevertheless, the single-studies reported a consistent effect in favour of quetiapine (Svestka 2003b: n=35, WMD –40.07 CI –64.10 to –16.04, Lieberman

2005: n=673, WMD -3.20 CI -6.81 to 0.41, McEvoy 2006: n=29, WMD -9.10 CI -19.88 to 1.68, Stroup 2006: n=203, WMD -3.20 CI -11.17 to 4.77, and McEvoy 2007: n=81, WMD -2.80 CI -10.03 to 4.43). Heterogeneity seems more due to differences in degree of prolactin increase rather than direction of effect.

2.7.8 Metabolic:

2.7.8.1 Cholesterol - number of participants with abnormally high cholesterol increase: There was no significant difference (1 RCT, n=267, RR 0.99 CI 0.59 to 1.68).

2.7.8.2 Cholesterol - mean change from baseline in mg/dl: Overall data on cholesterol change from baseline did not show a statistically significant difference between groups (4 RCTs, n=986, WMD -4.69 CI -13.84 to 4.45). There was significant heterogeneity due to one outlier (McEvoy 2007) which was a first-episode study and showed a trend in favour of olanzapine. Excluding this study revealed a significant difference in favour of quetiapine (3 RCTs, n=643, WMD -7.84 CI -14.12 to -1.57).

2.7.8.3 *Glucose - number of participants with abnormally high fasting glucose:* There was no significant difference (1 RCT, n=267, RR 0.71 CI 0.33 to 1.54).

2.7.8.4 Glucose - change from baseline in mg/dl: The mean increase of glucose from baseline was lower in the quetiapine group than in the olanzapine group (4 RCTs, n=986, WMD -9.32 CI -17.82 to -0.82). The data remained heterogeneous even after an outlier study (McEvoy 2007) was excluded, but the superiority of quetiapine remained.

2.7.8.5 Weight gain: Fewer participants in the quetiapine group had a significant weight gain (8 RCTs, n=1667, RR 0.68 CI 0.51 to 0.92, NNH not estimable).

2.7.8.6 Weight gain - change from baseline in kg: Overall participants in the quetiapine group gained less weight than in the olanzapine group (7 RCT, n=1173, WMD –2.68 CI –4.26 to –1.10). Again, there was significant heterogeneity, but the results of the single studies consistently favoured quetiapine (Atmaca 2003: n=27, WMD –4.51 CI –6.57 to –2.45, Lieberman 2005: n=612, WMD –3.8 CI –4.91 to –2.69, Kinon 2006b: n=346, WMD –0.64 CI –1.76 to 0.48), McEvoy 2006: n=34, WMD –2.3 CI –10.18 to 5.58, Sirota 2006: n=40, WMD –3.2 CI –5.51 to –0.89, McEvoy 2007: n=81, WMD –5.18 CI –10.00 to –0.36, Riedel 2007: n=33, WMD –0.48 CI –2.52 to 1.56).

2.8 Publication bias—Funnel plots did not suggest a possible publication bias.

2.9 Investigation for heterogeneity and sensitivity analysis—When Mori 2004 was excluded from the evaluation of the PANSS positive score due to possibly skewed data olanzapine remained more effective.

3. Comparison 3. QUETIAPINE versus RISPERIDONE

Eleven studies met the inclusion criteria for the comparison of quetiapine with risperidone.

3.1 Global state—

3.1.1 No clinically significant response - as defined by the original studies: Overall there was no significant difference. As the results were heterogeneous we present the single studies separately. Potkin 2006 reported a significant difference in favour of risperidone (n=177, RR 1.27 CI 1.05 to 1.55), while Conley 2005 (n=25, RR not estimable), Zhong 2006a (n=495, RR 1.0 CI 0.91 to 1.09) and McEvoy 2007 (n=103, RR 1.18 CI 0.87 to 1.6) found no significant difference between groups. The first three studies reported short term and only McEvoy 2007 reported long term data.

3.1.2 No clinically important change (as defined by the original studies): There was a small superiority of risperidone which did not reach statistical significance (4 RCTs, n=1374, RR 1.16 CI 0.99 to 1.35).

3.2 Leaving the study early—There was no significant difference in the number of participants leaving the studies early due to any reason (quetiapine 57%, risperidone 54%, 10 RCTs, n=2278, RR 1.06 CI 0.98 to 1.15) or due to adverse events (11% versus 9%, 7 RCTs, n=1851, RR 1.19 CI 0.78 to 1.8). Leaving early due to inefficacy showed an almost significant superiority of risperidone (24% versus 19%, 7 RCTs, n=1851, RR 1.26 CI 0.99 to 1.61).

3.3 Mental state—

3.3.1 General mental state: no clinically important change - short term (less than 30% PANSS total score reduction from baseline): There was no significant difference (2 RCTs, n=984, RR 1.11 CI 0.87 to 1.42), but the results were heterogeneous. We therefore present the single studies separately: Potkin 2006 (n=177, RR 1.27 CI 1.05 to 1.55) and Zhong 2006a (n=495, RR 1.0 CI 0.91 to 1.09).

3.3.2 General mental state: no clinically important change - short term (less than 20% BPRS total score reduction) There was no significant difference (1 RCT, n=25, RR 0.98 CI 0.63 to 1.52).

3.3.3 General mental state: average score at endpoint - PANSS total: There was a significant difference in favour of risperidone: overall (9 RCTs, n=1953, WMD 3.09 CI 1.01 to 5.16), short term (5 RCTs, n=1064, WMD 2.44 CI –0.81 to 5.69), medium term (2 RCTs, n=146, WMD 6.27 CI –3.94 to 16.48), long term (2 RCTs, n=743, WMD 3.11 CI 0.40 to 5.82)

3.3.4 General mental state: average score at endpoint - short term - BPRS total: There was no significant difference (1 RCT, n=25, WMD 1.68 CI – 8.33 to 11.69).

3.3.5 Positive symptoms - no clinically important change - short term (less than 40% PANSS positive score reduction from baseline): There was no significant difference (1 RCT, n=673, RR 1.00 CI 0.9 to 1.12).

3.3.6 Positive symptoms: average score at endpoint - PANSS positive subscore: There was a significant difference favouring risperidone overall (7 RCTs, n=1264, WMD 1.82 CI 1.16 to 2.48), short term (4 RCTs, n=1037, WMD 2.10 CI 1.00 to 3.19), medium term (2

RCTs, n=146, WMD 2.15 CI -0.01 to 4.31), long term (1 RCT, n=81, WMD 1.30 CI -0.13 to 2.73)

3.3.7 Positive symptoms: average score at endpoint - short term-BPRS positive subscore: There was a significant difference favouring risperidone (1 RCT, n=25, WMD 1.1 CI 0.18 to 2.02).

3.3.8 Negative symptoms - no clinically important change - short term (less than 40% PANSS negative score reduction from baseline): There was no significant difference (1 RCT, n=673, RR 0.98 CI 0.93 to 1.04).

3.3.9 Negative symptoms: average score at endpoint PANSS negative subscore: There was no significant difference (short term studies, 4 RCTs, n=956, WMD –1.46 CI –4.11 to 1.19; medium term studies, 2 RCTs, n=146, WMD 1.3 CI –0.75 to 3.35; long term stud, 1 RCT, n=81, WMD 0.8 CI –0.64 to 2.24). The short-term results were highly heterogeneous. Excluding a small outlier study (Riedel 2005) in a sensitivity analysis there was a significant superiority of risperidone (6 RCTs, n=1139, WMD 0.79 CI 0.04 to 1.54).

3.3.10 Negative symptoms: average score at endpoint - short term - BPRS negative subscore: There was a significant difference favouring risperidone (1 RCT, n=25, WMD 0.57 CI 0.17 to 0.97).

3.4 Quality of life: average endpoint score - short term - QLS total score— There was no significant difference (1 RCT, n=25, WMD -0.5 CI -13.87 to 12.87).

3.5 Service use: number of participants re-hospitalised—The difference almost reached statistical significance with a slight benefit for the risperidone group (2 RCTs, n=877, RR 1.34 CI 1.0 to 1.79).

3.6 Adverse effects-

<u>3.6.1 General: at least one adverse effect:</u> There was no significant difference (8 RCTs, n=2226, RR 1.04 CI 0.93 to 1.17).

<u>3.6.2 Death</u>: There was no significant difference (7 RCTs, n=3066, RR 0.73 CI 0.17 to 3.09).

3.6.3 Cardiac effects:

3.6.3.1. *Number of participants with QTc prolongation:* There was no significant difference (2 RCTs, n=1351, RR 0.87 CI 0.29 to 2.55).

3.6.3.2 Mean change of QTc interval from baseline in ms: Overall there was no significant difference (3 RCT, n= 940, WMD 2.21 CI –5.05 to 9.48). The data were heterogeneous. In the individual studies Lieberman 2005 found a significant difference in favour of risperidone (n=432, WMD 5.7 CI 0.57 to 10.83), while Stroup 2006 (n=166, WMD 6.3 CI –3.41 to

16.01) and Zhong 2006a (n=342, WMD -3.6 CI -7.55 to 0.35) found no significant difference between groups.

<u>3.6.4 Central nervous system - sedation:</u> There was a significant difference favouring risperidone (8 RCTs, n=2226, RR 1.21 CI 1.06 to 1.38, NNH 20 CI 11 to 50).

3.6.5 Extrapyramidal effects:

3.6.5.1 Extrapyramidal effects: Quetiapine produced fewer movement disorders than risperidone in terms of 'extrapyramidal symptoms' (2 RCTs, n=872, RR 0.59 CI 0.43 to 0.81, NNH 14 CI 8 to 33), dystonia (1 RCT, n= 673, RR 0.06 CI 0.01 to 0.41, NNH 20 CI 13 to 33) and use of antiparkinson medication at least once (6 RCTs, n=1715, RR 0.5 CI 0.3 to 0.86, NNH 20 CI 10 to 100). However, there was no significant difference in akathisia (6 RCTs, n=2170, RR 0.62 CI 0.34 to 1.13), akinesia (1 RCT, n=267, RR 0.91 CI 0.61 to 1.37) or parkinsonism (1 RCT, n=44, RR 0.06 CI 0.0 to 0.96).

3.6.5.2 *As measured by scales:* Quetiapine produced fewer extrapyramidal side effects than risperidone according to the Simpson-Angus Scale (5 RCTs, n= 1077, WMD –0.59 CI –1.16 to –0.02). There was no significant difference in dyskinesia (AIMS, 2 RCTs, n=958, WMD –0.34 CI-0.75 to 0.08) and akathisia (BAS, 2 RCTs, n=700, WMD –0.73 CI –2.0 to 0.54).

<u>3.6.6 Haematological: important decline in white blood cells:</u> There was no significant difference (1 RCT, n=673, RR 2.97 CI 0.12 to 72.73).

3.6.7 Prolactin:

3.6.7.1 *Prolactin associated adverse effects:* Quetiapine produced significantly fewer cases of amenorrhoea (4 RCTs, n=359, RR 0.47 CI 0.28 to 0.79, NNT not estimable), galactorrhoea (5 RCTs, n=478, RR 0.38 CI 0.17 to 0.84, NNT 25 CI 13 to 100) and gynaecomastia (1 RCT, n=78, RR 0.23 CI 0.07 to 0.75, NNT 4 CI 2 to 11), but not dysmenorrhoea (1 RCT, n=163, RR 0.45 CI 0.08 to 2.38). Data on sexual dysfunction showed an almost significant superiority of quetiapine (6 RCTs, n=2157, RR 0.70 CI 0.48 to 1.01).

3.6.7.2 *Change from baseline in ng/ml:* There was a significant and consistent difference favouring quetiapine although the amount of the difference varied leading to statistical heterogeneity (6 RCTs, n=1731, WMD –35.28 CI –44.36 to –26.19; the results of the single studies were: Lieberman 2005, n=678, WMD –24.70 CI –28.72 to –20.68; McEvoy 2006, n=24, WMD –28.6 CI –43.02 to –14.18; Potkin 2006 n=309, WMD –50.4 CI –60.24 to –40.56; Stroup 2006, n=199, WMD –30.3 CI –37.1 to –23.5; Zhong 2006a, n=440, WMD –47.0 CI –52.97 to –41.03), McEvoy 2007, n=81, WMD –30.8 CI –38.1 to –23.5).

3.6.8 Metabolic:

3.6.8.1 Cholesterol - number of participants with a significant cholesterol increase: There was no significant difference (2 RCTs, n=940, RR 1.27 CI 0.72 to 2.24).

3.6.8.2 Cholesterol - mean change from baseline in mg/dl: There was a significant difference favouring risperidone (5 RCTs, n=1433, WMD 8.61 CI 4.66 to 12.56).

3.6.8.3 *Glucose - number of participants with abnormally high fasting glucose:* There was no significant difference (2 RCTs, n=940, RR 1.39 CI 0.56 to 3.45).

3.6.8.4 *Glucose - mean change from baseline in mg/dl:* There was no significant difference (5 RCTs, n=1436, WMD –0.04 CI –2.92 to 2.83).

3.6.8.5 Weight gain - number of participants with 7% or more gain of total body weight: There was no significant difference (7 RCTs, n=1942, RR 0.97 CI 0.82 to 1.14).

3.6.8.6 Weight gain - mean change from baseline in kg: Overall there was no significant difference, but the data were highly heterogeneous presumably due to one small outlier study (Atmaca 2003) that showed a dramatic advantage of risperidone (7 RCTs, n=1446, WMD 0.71 CI –1.04 to 2.47). Nevertheless, excluding this study did not change the overall result.

3.7 Publication bias—A reasonable funnel plot analysis was only possible for the PANSS total score (>10 included studies). It did not suggest a possible publication bias.

3.8 Investigation for heterogeneity and sensitivity analysis—Excluding Mori 2004 from the evaluation of the PANSS positive subscore due to possibly skewed data did not reveal markedly different results. The data on akathisia (Barnes Akathisia Scale) indicated a considerable heterogeneity but clear reasons explaining this could not be found.

4. Comparison 4. QUETIAPINE versus ZIPRASIDONE

Two studies met the inclusion criteria for the comparison quetiapine versus ziprasidone.

4.1 Leaving the study early—There was no significant difference in the number of participants leaving the studies early due to any reason (2 RCTs, n=722, RR 1.05 CI 0.97 to 1.13), due to adverse events (2 RCTs, n=722, RR 1.04 CI 0.72 to 1.49) or due to inefficacy of treatment (2 RCTs, n=722, RR 1.14 CI 0.89 to 1.47).

4.2 Mental state—

4.2.1 General mental State: average score at endpoint - PANSS total: There was no significant difference, but the data of two studies were heterogeneous and are therefore presented separately. Neither Stroup 2006 (medium term data) n=198, WMD 3.7 CI –2.97 to 10.37 nor Lieberman 2005 (long term data) n=512, WMD –2.78 CI –6.81 to 1.25 found a a significant difference between groups.

4.2.2 Positive Symptoms: average score at endpoint - medium term - PANSS positive subscore: There was no significant difference (1 RCT, n=198, WMD 0.0 CI -2.18 to 2.18).

4.2.3 Negative Symptoms: average score at endpoint - medium term - PANSS negative subscore: There was no significant difference (1 RCT, n=198, WMD 1.6 CI -0.34 to 3.54).

<u>4.3 Service use: number of participants re-hospitalised:</u> There was no significant difference neither in the overall analysis (2 RCTs, n=754, RR 1.17 CI 0.85 to 1.59) nor in the analysis of medium term data (1 RCT, n=232, RR 1.25 CI 0.71 to 2.17), or long term data (1 RCT, n=522, RR 1.13 CI 0.78 to 1.65)</u>

4.4 Adverse effects:

4.4.1 General - at least one adverse effect: There was no significant difference (2 RCTs, n=754, RR 1.03 CI 0.91 to 1.17).

4.4.2 Death: There was no significant difference (2 RCTs, n=754, RR 0.41 CI 0.05 to 3.15).

4.4.3 Cardiac effects:

4.4.3.1 Number of participants with QTc prolongation: There was no significant difference (1 RCT, n=522, RR 1.65 CI 0.34 to 8.08).

4.4.3.2 mean change of QTc interval ms: There was no significant difference (2 RCTs, n=549, WMD 3.41 CI –1.37 to 8.18).

4.4.4 Central nervous system -sedation: Significantly fewer participants in the ziprasidone group than in the quetiapine group felt sedated (2 RCTs, n=754, RR 1.36 CI 1.04 to 1.77, NNH 14 CI 7 to 100).

4.4.5 Extrapyramidal effects: Significantly fewer people in the quetiapine group used antiparkinson medication at least once (1 RCT, n=522, RR 0.43 CI 0.2 to 0.93), but there were no clear differences in akathisia (2 RCTs, n=754, RR 0.78 CI 0.42 to 1.45) or 'any extrapyramidal symptoms' (1 RCT, n=232, RR 2.02 CI 0.66 to 6.17).

4.4.6 Prolactin:

4.4.6.1 Prolactin-associated adverse effects: There was no significant difference in amenorrhoea (1 RCT, n=138, RR 0.43 CI 0.15 to 1.24), galactorrhoea (2 RCTs, n=202, RR 0.68 CI 0.23 to 2.01) or sexual dysfunction (2 RCTs, n=754, RR 0.96 CI 0.64 to 1.42).

4.4.6.2 *Mean change from baseline in ng/ml:* There was a significant difference in favour of quetiapine (2 RCTs, n=754, WMD -4.77 CI -8.16 to -1.37).

4.4.7 Metabolic:

4.4.7.1 Cholesterol - mean change from baseline in mg/dl: Ziprasidone was associated with significantly less cholesterol increase than quetiapine (2 RCTs, n=754, WMD 16.01 CI 8.57 to 23.46).

4.4.7.2 *Glucose - mean change from baseline in mg/dl:* There was no significant difference (2 RCTs, n=754, WMD 3.1 CI – 3.99 to 10.19).

4.4.7.3 Weight gain - number of participants with 7% or more gain of total body weight: Significantly more participants in the quetiapine group than in the ziprasidone group gained weight (2 RCTs, n=754, RR 2.22 CI 1.35 to 3.63, NNH 13 CI 8 to 33).

4.4.7.4 Weight gain - change from baseline in kg: There was a superiority of ziprasidone which almost reached statistical significance (1 RCT, n= 466, WMD 1.2 CI –0.05 to 2.45).

<u>4.5 Publication bias:</u> Due to small number of included studies we did not perform a funnel plot analysis.

<u>4.6 Investigation for heterogeneity and sensitivity analysis:</u> The reasons for the preplanned sensitivity analysis did not apply and were therefore not performed.

DISCUSSION

Summary of main results

1. General—This analysis of the effects of quetiapine compared with other second generation antipsychotic drugs in the treatment of schizophrenia currently includes 21 studies reporting data on only four of eight possible comparisons. High discontinuation rates (overall 57.6 %) limit the value of findings. In addition, 15 of the 21 included studies randomised less than 100 people. The duration of the trials was usually short and we identified only two long term studies. Short term trials are not ideal to judge efficacy and tolerability of treatments for a chronic disease. Nine of the 21 studies were sponsored by a pharmaceutical industry with a clear pecuniary interest in the result. This is likely to be a further problem.

2. Comparison 1. QUETIAPINE versus CLOZAPINE—Five studies with a total of 334 participants fell into this comparison.

<u>2.1 Leaving the studies early:</u> The overall rate of participants leaving studies early was remarkably low (8.4%) and showed no clear difference between groups. Nevertheless, this finding was based on only two small (n=135), short term trials limiting any interpretation.

2.2 Efficacy outcomes (global state, overall and specific mental state): There was no significant difference in global state, general mental state or positive symptoms. Quetiapine reduced negative symptoms more than clozapine, but this result must be interpreted with great caution as it was based on two small trials from China (Li 2003b, Li 2005).

<u>2.3 Adverse effects:</u> We found limited data on 'at least one adverse effect', cardiac effects, extrapyramidal symptoms, sedation, weight gain and white blood cell count. Results on 'at

least one adverse effect', cardiac effects and sedation indicated an advantage for quetiapine. As these findings were based on only one or two studies they can not be considered to be robust.

3. Comparison 2. QUETIAPINE versus OLANZAPINE—Most of the studies included in the review contributed data to this comparison (N=13, n=1820).

3.1 Leaving the studies early: Less people in the olanzapine group compared with the quetiapine group left studies early because of 'any reason' or due to 'inefficacy of treatment'. This finding suggests that olanzapine is a more acceptable treatment than quetiapine, at least in the confines of clinical trials. Nevertheless, the overall rate of premature study discontinuations was high (63.2%), limiting the validity of all other results.

3.2 Efficacy outcomes (global state, overall and specific mental state): Quetiapine seems to be slightly less effective than olanzapine for the general mental state and for positive symptoms. There was no significant difference in the reduction of negative symptoms. The interpretation of the latter finding is, however, limited by the fact that most studies included participants with predominant positive symptoms. Such studies are not ideal for evaluating the effects of antipsychotic drugs on negative symptoms.

3.3 General functioning and quality of life: Very limited data on these important outcomes are available. Olanzapine may improve general functioning (GAF total score) more than quetiapine, but this result was based on a single study and needs to be replicated. There are no data indicating a difference in measures of quality of life.

3.4 Service use: number of participants re-hospitalised: The number of participants re-hospitalised was significantly higher in the quetiapine group. Again, this may reflect a certain efficacy advantage of olanzapine, but as this result was based on only two studies more data are needed.

3.5 Adverse effects: Adverse effects were reported as at least one adverse effect, cardiac effects, QTc abnormalities, increase of serum cholesterol, serum glucose, serum prolactin and associated side effects, death, extrapyramidal symptoms, the occurrence of sedation, seizures and weight gain. Among these adverse effects a benefit for quetiapine was found for the use of antiparkinson medication (a proxy measure for extrapyramidal adverse effects), weight gain, glucose elevation, prolactin increase, and some prolactin-associated adverse effects. On the other hand there was a certain superiority of olanzapine in terms of QTc prolongation. Overall, it seems that quetiapine may be more tolerable than olanzapine, but this is weighed against slightly less efficacy.

4. Comparison 3. QUETIAPINE versus RISPERIDONE—Eleven studies with 3770 participants met the inclusion criteria for this comparison.

<u>4.1 Leaving the studies early:</u> There was no clear difference in the number of participants leaving the studies early suggesting a similar overall acceptability of quetiapine and

risperidone. Nevertheless, the overall discontinuation rate was high (56.7%) limiting the interpretation of all other results.

4.2 Efficacy outcomes (global state, overall and specific mental state): The only differences in efficacy were found for the general mental state and positive symptoms. Quetiapine was less effective than risperidone in these aspects of psychopathology. Nevertheless, the differences were small (e.g. only three points on the PANSS total score).

4.3 Adverse effects: Adverse effects were available for at least one adverse effect, cardiac effects, cholesterol increase, changes in serum glucose, increase of prolactin level and associated side effects, death, extrapyramidal adverse effects, sedation, weight gain and white blood cell count. Among these, quetiapine was better than risperidone in various measures of extrapyramidal adverse effects and prolactin associated effects. On the other hand quetiapine was associated with more sedation and cholesterol increase than risperidone. These differences in the adverse effect profile and the slightly lower efficacy of quetiapine may be weighed in drug choice.

5. Comparison 4. QUETIAPINE versus ZIPRASIDONE—Only two studies with 722 participants provided data on this comparison.

5.1 Leaving the studies early: The overall number of participants leaving the studies early very high (80.7%), clearly limiting the interpretation of any findings beyond the outcome of 'leaving the study early'. There was no significant difference between groups, but the acceptability of both compounds seems to be poor.

5.2 Efficacy outcomes (global state, overall and specific mental state): Various efficacy outcomes revealed no difference between quetiapine and ziprasidone. There is currently no randomised data suggesting that either drug should be preferred due to better efficacy.

5.3 Adverse effects: Adverse effects were reported as at least one adverse effect, cardiac effects, death, extrapyramidal side effects, changes in cholesterol, glucose and prolactin, the occurrence of sedation and weight gain. Among those reported there was an advantage of quetiapine in use of antiparkinson medication and prolactin levels, while weight gain and sedation favoured ziprasidone. Treatment decisions should take these differences in the adverse effect profiles into account.

Overall completeness and applicability of evidence

We did not identify a single study for almost half of the possible comparisons of quetiapine with other second generation antipsychotic drugs. Evidence, therefore, is incomplete. Only two studies were long term, limiting applicability of the evidence as, after all, schizophrenia is often a chronic, often life-long, disorder. Furthermore, most of the included studies were efficacy studies, therefore external validity is limited and further effectiveness [pragmatic/ real world] studies are needed.

Quality of the evidence

All studies were randomised and at least single-blind, but details were rarely presented. Therefore it is unclear in almost all studies whether randomisation and blinding were really appropriately done. Furthermore the high numbers of participants leaving the studies early (overall 57.6%) and the small number of long term studies (Lieberman 2005, McEvoy 2007, Voruganti 2007) call the validity of the findings into question. Selective reporting was evident in all but two studies and nine studies were industry sponsored. All these factors limit the quality of the evidence.

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

A previous Cochrane review compared the effects of quetiapine with placebo, first generation antipsychotic drugs and second generation antipsychotic drugs for schizophrenia (Srisurapanont 2004). A single study fell in the last category and compared quetiapine with risperidone. This update and reformatting of the review has identified many new studies, and data are far more comprehensive.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—For people with schizophrenia it may be important to know that most people who start the drug within short trials choose to stop taking it within a few weeks. Quetiapine may also be slightly less effective than risperidone and olanzapine. Quetiapine may have low risk for extrapyramidal adverse effects and prolactin increase and may lead to less weight gain and associated problems than olanzapine, but more so than risperidone and ziprasidone.

2. For clinicians—Clinicians should know that, for only four out of eight possible comparisons of quetiapine with other second generation antipsychotic drugs, relevant studies were identified and that the evidence is limited because very high rates of participants leave the studies early. Our most robust finding is that if a person is started on quetiapine most will be off this drug within a few weeks. Certainly, more studies comparing quetiapine with other second generation antipsychotic drugs are needed.

3. For managers/policy makers—Little information on service use (such as time in hospital) or functioning is available, but the limited data suggest that people on quetiapine may need to be hospitalised more frequently than those receiving risperidone or olanzapine. This may be accompanied by higher overall costs in some settings. Furthermore, a single study suggested better general functioning of participants treated with olanzapine. We do not feel that these findings are sufficiently robust to guide managers.

Implications for research

1. General—We stress how important it is that future studies strictly adhere to the CONSORT statement (Moher 2001). Following these recommendations would clearly improve the conduct and reporting of clinical trials.

2. Specific—Comparisons with amisulpride, aripiprazole, sertindole and zotepine do not exist. Most data that has been reported within existing comparisons are almost without value because of the assumptions and biases within them. There is, therefore, plenty of room for further research into the effects of this widely used drug. We realize that planning for such studies needs meticulous attention to detail but do suggest some pointers that have come from our reading and understanding of the existing trials (see Table 1).

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Internal sources

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External sources

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ür Bildung und Forschung, Nr FKZ: 01 KG 0606, GZ:GF-GFKG01100506, Germany.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Atmaca 2003

Methods	Allocation: Blindness: Duration: 6 Design: pa Location: s	n: random, no further details. :: single, rater-blinded. 6 weeks. arallel. single centre.	
Participants	Diagnosis: N=56. Gender: 24 Age: 19-4¢ mean queti group=32. History: du quetiapine=	osis: (DSM-IV) schizophrenia. pr: 24 M, 29 F. 19-46 years (mean clozapine=31.3 years, mean olanzapine=29.6 years, quetiapine=30.1 years, mean risperidone=27.9 years, mean control =32.1 years). y: duration ill mean clozapine=6.6 years, mean olanzapine=6.3 years, mean pine=5.9 years. mean risperidone=5.6, age at onset: not reported	
Interventions	1	 Clozapine: flexible dose. Allowed dose range: not reported. Mean dose: 207.1 mg/day. N=14. 	
	2	Olanzapine: flexible dose. Allowed dose range: not reported. Mean dose: 15.7 mg/day. N=14.	
	3	Quetiapine: flexible dose. Allowed dose range: not reported. Mean dose: 535.7 mg/day. N=14.	

4	Risperidone: flexible dose. Allowed dose range: not reported. Mean
	dose: 6.7 mg/day. N=14

Outcomes	Leaving the study early: any reason. Mental state: PANSS total score. Adverse effects: EPS (use of antiparkinson medication), weight gain (BMI), laboratory (serum leptin, triglycerid levels)	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	Yes	The overall attrition was low (5.4%). Reason for leaving early 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?	Yes	Probably free of bias. The study focused on serum leptin and triglyceride levels which were adequately described
Free of other bias?	Unclear	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

Conley 2005

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: not reported.		
Participants	 Diagnosis: (DSM-IV) schizophrenia, treatment resistance, persistant positive psychotic symptoms, BPRS total score of 35 or more plus CGI score of 4 or more. N=38. Gender: 30 M, 8 F. Age: 18-65 years (mean fluphenazine=44.2 years, mean quetiapine=43.7 years, mean risperidone=46.3 years). History: duration ill not reported, age at onset not reported. Setting: inpatient. 		
Interventions	 Fluphenazine: flexible dose. Allowed dose range: 10-15 mg/day. Mean dose: 13.2 mg/day. N=13. 		
	2 Quetiapine: flexible dose. Allowed dose range: 300-500 mg/day, Mean dose: 463.6 mg/day. N=12.		
	3 Risperidone: flexible dose. Allowed dose range: 3-5 mg/day. Mean dose: 4.31 mg/day. N=13		
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI.		

Mental State: BPRS total score, BPRS positive subscore, BPRS negative
subscore.
Cognitive functioning: Neuropsychological testing.
Quality of life: QLS.
Adverse effects: open interviews, EPS (use of antiparkinson medication, SAS),
prolactin increase, sexual dysfunction, sedation, weight gain, laboratory
(thyroidal hormones)
Unable to use-
Prolactin increase: no useable data.
Sexual dysfunction: no useable data.
Sexual dysfunction: no useable data.

Notes

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	No	Overall attrition was moderate 36%. The analysis was based on mixed effect models. It is unclear whether this statistical method can account for such a relatively high attrition rate
Free of selective reporting?	No	Not all of the predefined adverse effects were reported.
Free of other bias?	Unclear	There was a slight baseline imbalance in terms of mean age and the mean number of previous hospitalisations (14 in the risperidone and 9.7 in the quetiapine group)

Kinon 2006b

Allocation: random, computer-generated randomisation. Blindness: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre.	
Diagnosis: (DSM-IV) schizophrenia (n=230), schizoaffective disorder (n=116), prominent negative symptoms. N=346. Gender: 228 M, 118 F. Age: mean olanzapine=41.67 years, mean quetiapine=40.45 years. 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.	
 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	
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-	

Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random, computer-generated randomisation.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	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
Blinding? Objective outcomes	Yes	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	No	The overall attrition was very 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
Free of selective reporting?	No	The numbers of participants who received antiparkinson medication or who had leukopenia were not indicated
Free of other bias?	No	The study was sponsored by the manufacturer of olanzapine.

Leukopenia: no useable data. Use of antiparkinson medication: no data.

Li 2005

Methods	Allocation: random, no further details.
	Blindness: double, no further details.
	Duration: 12 weeks. Design: parallel.
	Location: single centre.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=67.
	Gender: not reported.
	Age: mean=26.18 years. History: duration ill mean clozanine=0.49 years, mean quetianine=0.5 years, age
	at onset not reported.
	Setting: inpatient.
Interventions	 Clozapine: flexible dose. Allowed dose range: 100-550 mg/day. Mean dose: 255.96 mg/day. N=34.
	2 Quetiapine: flexible dose. Allowed dose range: 150-650 mg/day. Mean dose: 362.09 mg/day. N=33
Outcomes	Leaving the study early: any reason. Mental State: PANSS total score, PANSS positive subscore, PANSS pergative
	subscore.
Adverse effects: EPS, sedation.	
	Extrapyramidal symptoms: no data.
	Sedation: no data.
Notes	
Risk of bias	
Item	Authors' judgement Description

Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	No	The overall attrition was 9.1%. Numbers leaving early were only reported due to any reason. Only completer data were assessed
Free of selective reporting?	No	There was no reporting on adverse effects.
Free of other bias?	Unclear	Baseline characteristics have not been presented for both groups separately. Therefore, baseline imbalance can not be excluded. Furthermore, there was no washout period

Li 2002

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre.	
Participants	Diagnosis: (CCMD-3) schizophrenia. N=63. Gender: not reported. Age: mean clozapine=30 years, mean quetiapine=28 years. History: duration ill mean clozapine=0.63 years, mean quetiapine=0.65 years, age at onset not reported. Setting: in- and outpatient.	
Interventions	 Clozapine: flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 270.5 mg/day. N=31. Quetiapine: flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 478.5 mg/day. N=32 	
Outcomes	Leaving the study early: any reason. Global State: CGI. Mental State: PANSS total score. Adverse effects: open interviews, cardiac effects (palpitation), EPS (akathisia, rigor, tremor), sedation, weight gain, laboratory (white blood cell count) Unable to use - Leaving the study early: due to adverse events (not fully reported)	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details
Blinding? Subjective outcomes	Unclear	Double, probably identical capsules. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding

Blinding? Objective outcomes	Yes	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	Unclear	Two participants left the study early due to adverse events in the clozapine group. There is some doubt whether all data on leaving the study early have been presented
Free of selective reporting?	Yes	We did not find evidence for selective reporting.
Free of other bias?	Unclear	There were no data on pre study medication, therefore baseline imbalance can not be excluded
Li 2003		
Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 8 weeks. Design: parallel. Location: single centre	
Participants	Diagnosis: (CCMD-2) schizophrenia. N=76. Gender: not reported. Age: mean clozapine=36.2 years, mean quetiapine=34.7 years. History: duration ill mean clozapine=6.12 years, mean quetiapine=5.71 years, age at onset not reported. Setting: inpatient.	
Interventions	 Clozapine: fixed/flexible dose: not reported. Allowed dose range: start with 25 mg, in two weeks supposed dose, dose: not reported. Mean dose: 325 mg/day. N=38. Quetiapine: fixed/flexible dose: not reported. Allowed dose range: start with 25 mg, in two weeks supposed dose, dose: not reported. Mean dose: 375 mg/day. N=38 	
Outcomes	Leaving the study early. Global State. General Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore. Adverse effects: treatment emergent symptom scale. Unable to use - Leaving the study early: not fully reported.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	Unclear	One participant in the quetiapine group left the study early due to inefficacy. This participant was not included in the analysis. There is some doubt whether all data on leaving the study early have been presented

Free of selective reporting?	No	The study duration was eight weeks, but outcomes only at four weeks were available
Free of other bias?	Unclear	The allowed dose range was not indicated.
Lieberman 2005		
Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre.	
Participants	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years (mean=40.6 years). History: duration ill, age at onset: not reported. Setting: in- and outpatient.	
Interventions	1 Olanzapine dose=20.1	e: flexible dose, allowed dose range: 7.5-30 mg/day, mean mg/day. N=336.
	2 Perphenazi dose=20.8	ine: flexible dose, allowed dose range: 8-32 mg/day, mean mg/day. N=261.
	3 Quetiapine: flexible dose, allowed dose range: 200-800 mg/day, mean dose=543.4 mg/day. N=337.	
	4 Risperidon dose=3.9 n	e: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean ng/day. N=341.
	5 Ziprasidon dose=112.8	e: flexible dose, allowed dose range: 40-160 mg/day, mean 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 patients re-hospitalised. Adverse effects: open interviews, Death (suicide attempt), EPS (use of antiparkinson medication, akathisia), cardiac effects (ECG), prolactin-associated side-effects, sedation, weight gain, laboratory (prolactin, lipids, glucose) Unable to use - Leaving the study early: due to extrapyramidal effects (no usable data)	
Notes	33 participants were excluded from the analysis.	
Risk of bias		-
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Double, identical capsules. Whether blinding was successful has not been examined, but the examined compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	No	The attrition rate was very high (75%). Continuous outcomes were evaluated based on a mixed effects model. It is unclear whether any statistical method can account for such a high attrition rate
Free of selective reporting?	Yes	There was no evidence for selective reporting.
Free of other bias?	Unclear	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
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Liu 2004

Methods	Allocation: random, no Blindness: single, rater Duration: 12 weeks. Design: parallel. Location: single centre	o further details. -blinded.
Participants	Diagnosis: (CCMD-3) schizophrenia. N=72. Gender: not reported. Age: mean clozapine=37.44 years, mean quetiapine=36.86 years. History: duration ill mean clozapine=9.36 years, mean quetiapine=8.64 years, age at onset: not reported. Setting: inpatient.	
Interventions	1 Clozapine: day, after 1	flexible dose. Allowed dose range: initial dose: 50 mg/ 0 days: 400-600 mg/day. Mean dose: not reported N=36.
	2 Quetiapine day, after 1	: flexible dose. Allowed dose range: initial dose: 100 mg/ 10 days: 400-700 mg/day. Mean dose: not reported, N=36
Outcomes	Leaving the study early Global State. Mental State: BPRS to Adverse effects: open i sedation, dry mouth, hy hyperemesis, maldiges Unable to use - Leaving the study early	y: any reason, adverse events, inefficacy. tal, SANS total. interviews, cardiac effects (ECG) EPS (akathisia, tremor), ypersalivation, hypotonia, liver function, dizziness, tion, weight gain y: due to any reason (not fully reported)
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	Unclear	Five participants left the study early, three due to adverse events in the clozapine group and two due to unclear reasons in the quetiapine group. These five participants were not included in the analysis. There is some doubt whether all data on leaving the study early have been presented
Free of selective reporting?	No	The mean doses of the medications used were not

Free of other bias?	No	Clozapine was titrated to 400mg/day within 10 days. Such a fast dose increase can be accompanied by a higher rate of adverse effects
McEvoy 2006		
Methods	Allocation: random, n Blindness: double, ide Duration: 52 weeks (2 Design: parallel. Location: multicentre.	o further details. ntical capsules. 6 weeks observed, because of small group sizes).
Participants	Diagnosis: (DSM-IV) clozapine treatment (n Gender: 80 M, 19 F. Age: 18-65 years (mer History: duration ill, a Setting: in- and outpat	schizophrenia, inadequate efficacy in previous study, =49) was open-label. N=99 (observed N=50). an=39.7 years). ge at onset: not reported. ient.
Interventions	1 Olanzapin dose: 23.4	e: flexible dose. Allowed dose range: 7.5-30 mg/day. Mea mg/day. N=19.
	2 Quetiaping Mean dose	e: flexible dose. Allowed dose range: 200-800 mg/day. e: 642.9 mg/day. N=15.
	3 Risperidor dose: 4.8 r	ne: flexible dose. Allowed dose range: 1.5-6 mg/day. Mea ng/day. N=16
Outcomes	Leaving the study earl Global state: CGI. Mental State: PANSS subscore. Adverse effects: open dysfunction, sedation, level), weight gain Unable to use - Global state: CGI (no	y: any reason, adverse events, inefficacy. total score, PANSS positive subscore, PANSS negative interviews, amenorrhoea, galactorrhoea, sexual laboratory (lipids, glucose, prolactin, haemoglobin A1C data).
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
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Allocation concealment? Unclear No further details. Blinding? Unclear Double, identical capsules. Whether blinding was Subjective outcomes successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding Yes Blinding? Objective outcomes such as laboratory measures or death Objective outcomes are unlikely to have been much affected by problems of blinding Incomplete outcome data No The overall attrition was extremely high (74%). We doubt that the validity of the findings was not affected by this high number addressed? All outcomes Free of selective reporting? No Due to small numbers and the very high attrition only data on 26 weeks treatment (rather than the full duration of 52 weeks) were presented Free of other bias? Unclear The dose ranges were quite different, the upper dose range of olanzapine was 30 mg/day whereas risperidone could only be given in a maximum dose of 6 mg/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 phase

McEvoy 2007

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre.		
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. Gender: 292 M, 108 F. Age: 16-40 years (mean=24.5 years). History: duration ill mean=1.08 years, age at onset 23.5 years. Setting: in- and outpatient.		
Interventions	1 Olanzapine: flexib dose: 11.7 mg/day	ble dose. Allowed dose range: 2.5-20 mg/day. Mean v. N=133.	
	2 Quetiapine: flexib dose: 506 mg/day.	le dose. Allowed dose range: 100-800 mg/day. Mean . N=134.	
	3 Risperidone: flexi dose: 2.4 mg/day.	ble dose. Allowed dose range: 0.5-4 mg/day. Mean 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 (BML waist circumference)		
Notes			
Risk of bias			
Item	Authors' judgement	Description	
Adequate sequence generation?	Unclear	Random, no further details.	
Allocation concealment?	Unclear	No further details.	
Blinding? Subjective outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side effects. This can be a problem for blinding	
Blinding? Objective outcomes	Yes	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	No	The overall attrition was high (70.3.%). The primary analysis was based on a mixed effect model, secondary outcomes used the last-observation-carried forward approach and included only study completers. Nevertheless, it is unclear whether any statistical method can account for such a high attrition	
Free of selective reporting?	No	Adverse events were presented only in case of moderate or worse severity	

Free of other bias?	No	The study was sponsored by the manufacturer of quetiapine.

Mori 2004

Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks (last 4 weeks observed). Design: parallel. Location: single centre.	
Diagnosis: (DSM-IV) schizophrenia disorganised (n=23), paranoid (n=10), undifferentiated (n=34). N=77. Gender: 39 M, 38 F. Age: 28-84 years (mean=59.9 years). History: duration ill mean=34.51 years, age at onset: not reported. Setting: inpatient.	
1 Olanzapine Mean dose	e: flexible dose. Allowed dose range: 2.5-20 mg/day. : 16.5 mg/day. N=20.
2 Perospiron dose: 37.3	e: flexible dose. Allowed dose range: 4-48 mg/day. Mean mg/day. N=18.
3 Quetiapine Mean dose	: flexible dose. Allowed dose range: 50-750 mg/day. : 432.5 mg/day. N=20.
4 Risperidon dose: 7.37	e: flexible dose. Allowed dose range: 1-12 mg/day. Mean mg/day. N=19
Mental State: PANSS t subscore. Cognitive functioning:	otal score, PANSS positive subscore, PANSS negative digit span distractibility test.
Authors' judgement	Description
Unclear	Random, no further details.
Unclear	No further details.
Unclear	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side effects. This can be a problem for blinding
Yes	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
No	Data on leaving the study early have not been presented.
No	Adverse events were not reported. Numbers on use of antiparkinson medication have not been presented
No	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
	Allocation: random, no Blindness: double, no f Duration: 8 weeks (last Design: parallel. Location: single centre Diagnosis: (DSM-IV) : undifferentiated (n=34; Gender: 39 M, 38 F. Age: 28-84 years (marked) Higher and the setting: inpatient. 1 Olanzapine Mean dose 2 Perospiron dose: 37.3 3 Quetiapine Mean dose 4 Risperidon dose: 7.37 Mental State: PANSS t subscore. Cognitive functioning: Authors' judgement Unclear Unclear Yes No No

Ozguven 2004

Methods	Allocation: random, no further details. Blindness: single, no further details. Duration: 6 weeks. Design: parallel. Location: not reported.		
Participants	Diagnosis: (DSM-IV) schizophrenia. N=30. Gender: 8M, 22 F. Age: mean=35.3 years. History: duration ill, age at onset: not reported. Setting: not reported.		
Interventions	1 Olanzapine mg/day. N	e: flexible dose. Allowed dose range: mean dose: 23.0 =15.	
	2 Quetiapine mg/day. N	: flexible dose. Allowed dose range: mean dose: 826.67 =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			
Item	Authors' judgement	Description	
Adequate sequence generation?	Uncloar		
	Ulicieal	Random, no further details.	
Allocation concealment?	Unclear	Random, no further details. No further details.	
Allocation concealment? Blinding? Subjective outcomes	Unclear Unclear	Random, no further details. No further details. 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	
Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes	Unclear Unclear Yes	Random, no further details. No further details. Single, rater blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding	
Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes Incomplete outcome data addressed? All outcomes	Unclear Unclear Yes Yes	Random, no further details. No further details. Single, rater blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding The overall attrition rate was 13%. The method used to address incomplete outcomes has not been presented. Nevertheless, due to the low rate we consider the risk to be low	
Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes Incomplete outcome data addressed? All outcomes Free of selective reporting?	Unclear Unclear Yes Yes No	Random, no further details. No further details. Single, rater blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding The overall attrition rate was 13%. The method used to address incomplete outcomes has not been presented. Nevertheless, due to the low rate we consider the risk to be low The study has only been published as an abstract. Efficacy data have only been presented as percentage change from baseline	

Potkin 2006

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 6 weeks (2 weeks observed). Design: parallel. Location: multicentre.
Participants	Diagnosis: (DSM-IV) schizophrenia (n=341) disorganised, paranoid or undifferentiated or schizoaffective disorder (n=30) plus (n=11), CGI-S of 5 or more, recent exacerbation. N=382. Gender: 251 M, 131 F. Age: 18-65 years (mean=34.8 years). History: duration ill, age at onset: not reported.

	Setting: inpatient.	
Interventions	1 Quetiapine dose: 523.8 N=156.	: flexible dose. Allowed dose range: 50-800 mg/day. Mear 8 mg/day (after 2 weeks), 579.5 mg/day (after 6 weeks).
	2 Risperidom dose: 4.32 n N=153.	e: flexible dose. Allowed dose range: 1-6 mg/day. Mean mg/day (after 2 weeks), 4.7 mg/day (after 6 weeks).
	3 Placebo: N	=73*
Outcomes	Leaving the study early: any reason. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, Depression Hamilton Rating Scale for Depression, Readiness for Discharge Questionnaire. Satisfaction of treatment: Study Medication Satisfaction. Adverse effects: open interviews, death (natural cause), cardiac effects (ECG), EPS (akathisia, rigor, AIMS, BAS, SAS), prolactin associated side effects (amenorrhoea, decreased libido), sedation, headache , insomnia, constipation, laboratory (prolactin) Unable to use - BAS: no data. Cardiac effects-QTc-prolongation: no data.	
Notes	* data not analysed from	m placebo group.
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Yes	The participants were assigned using a centralized interactive voice response system. Probably a correct method
Blinding? Subjective outcomes	Unclear	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
Blinding? Objective outcomes	Yes	Objective outcomes such as laboratory measures or deat are unlikely to have been much affected by problems of blinding
Incomplete outcome data addressed? All outcomes	Yes	The overall attrition was 12%. The last-observation- carried-forward method was used to account for people leaving the study early. It assumes that a participant why 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. Nevertheless, due t the overall low attrition it is unlikely that the results hav been affected
Free of selective reporting?	No	Data on some adverse effects were not available. Side effects had to occur in at least 10% to be reported. Important side effects may have been missed by this procedure
Free of other bias?	No	The study was sponsored by the manufacturer of

Methods	Allocation: random, no further details.
	Blindness: double, identical capsules.
	Duration: 12 weeks.
	Design: parallel.
	Location: not reported.

Participants	Diagnosis: (DSM-IV or ICD-10) schizophrenia, predominant negative symptoms, CGI of 4 or more, PANSS negative subscore of 21 or more. N=44. Gender: 27 M, 17 F. Age: mean quetiapine=30.6 years, mean risperidone=39.3 years. History: duration ill mean quetiapine=5.4 years, mean risperidone=2.5 years, age at onset mean quetiapine=25.3 years, mean risperidone=36.9 years. Setting: partially in- and outpatient.	
Interventions	 Quetiapine: flexible dose. Allowed dose range: 50-800 mg/day, Mean dose: 589.7 mg/day. N=22. 	
	2 Risperidon dose: 4.9 n	e: flexible dose. Allowed dose range: 2-8 mg/day. Mean ng/day. N=22
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, SANS total score. Cognitive functioning: Auditory verbal memory test, Trail Making Test, Wechsler visual memory scale. Adverse effects: open interviews, cardiac effects (ECG), EPS (akathisia, parkinsonism, use of antiparkinson medication, SAS), sedation, headache, nausea, insomnia, dizziness, weight gain, laboratory (prolactin) Unable to use - SANS total score: no data. Prolactin change from baseline in ng/ml: no data. Cardiac effects: no data.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	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
Blinding? Objective outcomes	Yes	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	No	The overall attrition was considerable (45.2%). The data were analysed using a last-observation-carried-forward and a completer analysis. Nevertheless, it is questionable whether any statistical method can account for such a high attrition
Free of selective reporting?	No	Data on negative symptoms (SANS) and some adverse effects were not available

Riedel 2007

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: single centre.
Participants	Diagnosis: (DSM-IV) schizophrenia, acute episode, CGI of more than 4, PANSS total score of more than 60. N=52.

	Gender: 21 M, 12 F (of cognitive assessments a weeks 8)). Age: 18-65 years (mea (of completers). History: duration ill me completers), age at ons years (of completers). Setting: inpatient.	f completers, here defined as those who completed at two or more time points out of three (baseline, week 4, n olanzapine=34.47 years, mean quetiapine=36.69 years) ean olanzapine=4.71 years, mean quetiapine=8.44 years (of et mean olanzapine=29.76 years, mean quetiapine=28.25
Interventions	1 Olanzapine dose: 15.82	e: flexible dose. Allowed dose range: 10-20 mg/day. Mean 2 mg/day. N=26.
	2 Quetiapine Mean dose	: flexible dose. Allowed dose range: 400-800 mg/day. : 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		
Item	Authors' judgement	Description
Item Adequate sequence generation?	Authors' judgement Unclear	Description Random, no further details.
Item Adequate sequence generation? Allocation concealment?	Authors' judgement Unclear Unclear	Description Random, no further details. No further details.
Item Adequate sequence generation? Allocation concealment? Blinding? Subjective outcomes	Authors' judgement Unclear Unclear Unclear	Description Random, no further details. No further details. 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
Item Adequate sequence generation? Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes	Authors' judgement Unclear Unclear Unclear Yes	Description Random, no further details. No further details. Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Item Adequate sequence generation? Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes Incomplete outcome data addressed? All outcomes	Authors' judgement Unclear Unclear Unclear Yes No	Description Random, no further details. No further details. Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding The overall attrition was very 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
Item Adequate sequence generation? Allocation concealment? Blinding? Subjective outcomes Blinding? Objective outcomes Incomplete outcome data addressed? All outcomes Free of selective reporting?	Authors' judgement Unclear Unclear Unclear Yes No No	Description Random, no further details. No further details. Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding The overall attrition was very 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 Data on global state have not been presented.

Sacchetti 2004

Methods	Allocation: random, no further details. Blindness: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre.
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. Gender: not reported. Age: 18-65 years. History: duration ill not reported., age at onset not reported.

	Setting: inpatient.	
Interventions	1 Olanzapine dose: 14.6	e: flexible dose. Allowed dose range: 10-20 mg/day. Mean mg/day. N=25.
	2 Quetiapine Mean dose	: flexible dose. Allowed dose range: 400-800 mg/day. : 602.4 mg/day. N=25.
	3 Risperidon dose: 4.3 m	e: flexible dose. Allowed dose range: 4-8 mg/day. Mean ng/day. N=25
Outcomes	Leaving the study early Mental State: PANSS t subscore, PANSS nega Adverse effects: EPS () Unable to use - Mental State: PANSS t subscore (no usable dat	y: any reason. total score, BPRS hostility cluster score, PANSS positive titve subscore). BAS, SAS), weight gain. total score, PANSS positive subscore, PANSS negative ta)
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	Single, rater-blind. 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	Unclear	The attrition rate was 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
Free of selective reporting?	No	Efficacy data (PANSS) were only presented as percentage change, without indications of standard deviations, standard errors, p-values or ranges. Only interim data after half of the patients had been recruited have been presented
Free of other bias?	No	The study was sponsored by the manufacturer of quetiapine.

Sirota 2006

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 12 weeks. Design: parallel. Location: single centre.
Participants	Diagnosis: (DSM-IV) schizophrenia, PANSS negative subscore of more than 15, SANS total score more than 60. N=40. Gender: 32 M, 8 F. Age: 21-64 years (mean olanzapine=36.2 years, mean quetiapine=38.3 years). History: duration ill mean olanzapine=13.3 years, mean quetiapine=15.9 years, age at onset not reported. Setting: inpatient.

Interventions	1 Olanzapine dose: 16.0	e: flexible dose. Allowed dose range: 5-20 mg/day. Mean mg/day. N=21.
	2 Quetiapine Mean dose	: flexible dose. Allowed dose range: 200-800 mg/day. : 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, negative symptoms SANS (median change). EPS scales: no data. Cardiac effects: no data.	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	Yes	The overall attrition 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. Nevertheless, due to the low attrition we do not think that this led to bias
Free of selective reporting?	No	Efficacy data (PANSS, SANS) have only been presented as median change. There were no data on extrapyramidal side-effects and cardiac effects
Free of other bias?	No	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: not reported.	
Participants	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years (mean olanzapine=40.0 years, mean quetiapine=40.1 years, mean risperidone=41.8 years, mean ziprasidone=41.3 years). 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 dose=565.	e: flexible dose, allowed dose range: 200-800 mg/day, mean 2 mg/day. N=95.
	3 Risperidor dose=4.1 r	ne: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean mg/day. N=104.
	4 Ziprasidor dose=115.	e: flexible dose, allowed dose range: 40-160 mg/day, mean 9 mg/day. N=137
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score. Adverse effects: open interviews, death (suicide), EPS (akathisia), cardiac effects (ECG), prolactin-associated side-effects, weight gain, laboratory (prolactin, glucose, cholesterol)	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re- randomised
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	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
Blinding? Objective outcomes	Yes	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	No	The attrition rate was very high (72.5%). Continuous data were analysed 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?	No	Use of antiparkinson medication was permitted but data on this outcome have not been presented
Free of other bias?	Unclear	Patients had a history of former intolerance to atypical antipsychotic treatment but baseline data on this were not provided

Svestka 2003b

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 6 weeks. Design: parallel. Location: not reported.
Participants	Diagnosis: (ICD-10) acute schizophrenia (n=32), schizoaffective disorder (n=10). N=42. Gender: 42 F. Age: mean=35.78 years. History: duration ill mean=7.05 years, age at onset not reported. Setting: inpatient.
Interventions	 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.
Neter	

Notes

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Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random, no further details.
Allocation concealment?	Unclear	No further details.
Blinding? Subjective outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding
Blinding? Objective outcomes	Yes	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	No	Data on the overall attrition rate were not available.
Free of selective reporting?	No	For some metabolic parameters there were no data available.
Free of other bias?	Unclear	There was a slight baseline imbalance in terms of mean age, which was described being non significant

Voruganti 2007

Methods	Allocation: random, no further details. Blindness: single, rater-blinded. Duration: 52 weeks. Design: parallel. Location: not reported.	
Participants	Diagnosis: schizophrenia. N=86. Gender: not reported. Age: not reported. History: duration ill, age at onset: not reported. Setting: not reported.	
Interventions	 Olanzapine: fixed/flexible dose: not reported Allowed dose range: not reported. Mean dose: 17.2 mg/day. N=42. Quetiapine: fixed/flexible dose, 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 -	

Notes				
Risk of bias				
Item	Authors' judgement	Description		
Adequate sequence generation?	Unclear	Random, no further details.		
Allocation concealment?	Unclear	No further details.		
Blinding? Subjective outcomes	Unclear	Single, rater-blind. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding		
Blinding? Objective outcomes	Yes	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	No	There is a discrepancy between the abstract in the text. While according to the abstract there were fewer participants leaving the study early, this finding was no longer mentioned in the text according to which the overall attrition was only 1.2%		
Free of selective reporting?	No	Use of antiparkinson medication was permitted but numbers have not been presented		
Free of other bias?	No	The study was sponsored by the manufacturer of quetiapine. There was no wash-out period		

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

Zhong 2006

Item	Authors' judgement Description	
Risk of bias		
Notes		
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 (QTc), death (natural causes, suicide), EPS (akathisia, dystonia, parkinsonism, use of antiparkinson medication, AIMS, BAS, SAS), sedation, prolactin associated side effects (dysmenorrhea, galactorrhea, sexual dysfunction) weight gain, laboratory (cholesterol, glucose, prolactin, white blood cell count)	
Interventions	 Quetiapine: flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 525 mg/day. N=338. Risperidone: flexible dose. Allowed dose range: 2-8 mg/day. Mean dose: 5.2 mg/day. N=335 	
Participants	Diagnosis: (DSM-IV) schizophrenia, PANSS of 60 or more, CGI-S of 4 or more. N=673. Gender: 510 M, 163 F. Age: 18-65 years (mean quetiapine=40.2 years, mean risperidone=39.6 years). History: duration ill, age at onset: not reported. Setting: in- and outpatient, initially inpatient.	
Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre.	

Adequate sequence generation? Unclear		Random, no further details.	
Allocation concealment?	Unclear	No further details.	
Blinding? Subjective outcomes	Unclear	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side effects. This can be a problem for blinding	
Blinding? Objective outcomes	Yes	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	No	The overall attrition was high (52.1%). 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. Data on study completers were also available. Nevertheless, it is unclear whether any statistical method can account for such a degree of attrition	
Free of selective reporting?	No	Adverse events were only presented with an incidence of at least 5% among the participants, therefore important side effects may have been missed by this procedure	
Free of other bias?	No	The study was sponsored by the manufacturer of quetiapine.	

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			
An 2003	Allocation: randomised. Blindness: open-label.			
Antonova 2005	Allocation: randomised. Blindness: single-blind (rater-blind). Participants: people with schizophrenia. Interventions: olanzapine, risperidone and quetiapine versus conventional antipsychotics. Outcomes: no usable data.			
Ascher-Svanum 2006	Allocation: not randomised, cohort study.			
Baloescu 2006	Allocation: not randomised, controlled clinical trial.			
Beuzen 2005	Allocation: randomised Blindness: open-label.			
Byerly 1999	Allocation: not reported. Blindness: not reported. Participants: people with schizophrenia. Interventions: clozapine versus quetiapine. Outcomes: no usable data.			
Byerly 2006	Allocation: randomised. Blindness: double-blind. Participants: people with schizophrenia. Interventions: quetiapine versus risperidone. Outcomes: no usable data.			
Canas 2006	Allocation: not randomised, controlled clinical trial.			
Cao 2005	Allocation: randomised. Blindness: open-label.			
Cao 2005a	Allocation: randomised. Blindness: open-label.			
Chaudhry 2006	Allocation: randomised. Blindness: open-label.			
Dai 2004	Allocation: randomised. Blindness: open-label.			
Dai 2005	Allocation: randomised. Blindness: open-label.			
Ding 2004	Allocation: randomised. Blindness: open-label.			
Dossenbach 2005	Allocation: not randomised, cohort study.			
Du 2003	Allocation: randomised. Blindness: open-label.			
Emsley 2005	Allocation: randomised. Blindness: investigator-blind. Participants: people with schizophrenia. Interventions: inappropriate intervention.			
Fan 2005	Allocation: randomised. Blindness: open-label.			
Fleischhacker 2005	Allocation: randomised. Blindness: open-label.			
Fu 2005	Allocation: randomised. Blindness: open-label.			
Gao 2003	Allocation: randomised. Blindness: open-label.			
Garcia 2006	Allocation: not randomised, case series.			

Study	Reason for exclusion
Harrigan 2004	Allocation: randomised. Blindness: open-label.
He 2003	Allocation: randomised. Blindness: open-label.
Huang 2003	Allocation: randomised. Blindness: open-label.
Huber 2004	Allocation: unclear. Blindness: unclear. Intervention: other aims.
Karow 2002	Allocation: not randomised, review.
Keks 2006	Allocation: randomised. Blindness: open-label.
Kelemen 2006	Allocation: not randomised, controlled clinical trial.
Kim 2004	Allocation: not randomised, controlled clinical trial.
Knegtering 2004	Allocation: randomised. Blindness: open-label.
Li 2001	Allocation: randomised. Blindness: open-label.
Li 2002a	Allocation: not randomised.
Li 2003a	Allocation: randomised. Blindness: open-label.
Li 2003b	Allocation: randomised. Blindness: open-label.
Li 2005	Allocation: randomised. Blindness: open-label.
Liu 2004a	Allocation: randomised. Blindness: open-label.
Liu 2005	Allocation: randomised. Blindness: open-label.
Lu 2005	Allocation: randomised. Blindness: open-label.
Luo 2005	Allocation: randomised. Blindness: open-label.
Mintzer 2004	Allocation: randomised. Blindness: open-label.
Mullen 2001	Allocation: randomised. Blindness: open-label
Musil 2006	Allocation: not randomised, cohort study.
Pan 2004	Allocation: randomised. Blindness: open-label.
Pan 2004a	Allocation: randomised. Blindness: open-label.
Pan 2004b	Allocation: randomised. Blindness: open-label.
Pang 2002	Allocation: randomised. Blindness: open-label.
Peng 2004	Allocation: randomised. Blindness: not mentioned. Participants: people with schizophrenia. Interventions: inappropriate intervention.

Study	Reason for exclusion
Oi 2004	Allocation: randomised
QI 2004	Blindness: open-label.
Qian 2004	Allocation: randomised. Blindness: open-label.
Reznik 2004	Allocation: randomised. Blindness: open-label.
Ryu 2006	Allocation: not randomised, controlled clinical trial.
Sajatovic 2002	Allocation: randomised. Blindness: open-label.
Swanson 2006	Allocation: randomised. Blindness: open-label.
Tang 2003	Allocation: randomised. Blindness: open-label.
Tang 2005	Allocation: randomised. Blindness: open-label.
Wang 2000	Allocation: randomised. Blindness: open-label.
Wang 2004	Allocation: randomised. Blindness: open-label.
Wang 2004a	Allocation: not randomised.
Wang 2005	Allocation: randomised. Blindness: open-label.
Wang 2005a	Allocation: randomised. Blindness: open-label.
Wang 2005b	Allocation: randomised. Blindness: open-label.
Wang 2005c	Allocation: randomised. Blindness: open-label.
Wang 2005d	Allocation: randomised. Blindness: open-label.
Weickert 2003	Allocation: randomised. Participants: people with schizophrenia. Interventions: inappropriate intervention.
Xiang 2005	Allocation: randomised. Blindness: open-label.
Xu 2002	Allocation: randomised. Blindness: open-label.
Xu 2003	Allocation: randomised. Blindness: open-label.
Xu 2005	Allocation: randomised. Blindness: open-label.
Yamashita 2005	Allocation: not randomised, case series.
Yang 2004	Allocation: randomised. Blindness: open-label.
Yang 2005	Allocation: randomised. Blindness: open-label.
Yu 2003	Allocation: randomised. Blindness: open-label.
Yuan 2005	Allocation: randomised. Blindness: open-label.

Study	Reason for exclusion
Zhang 2003	Allocation: randomised. Blindness: open-label.
Zhang 2005	Allocation: randomised. Blindness: open-label.
Zhang 2005a	Allocation: randomised. Blindness: open-label.
Zhang 2005b	Allocation: randomised. Blindness: open-label.
Zhang 2005c	Allocation: randomised. Blindness: open-label.
Zhao 2004	Allocation: randomised. Blindness: open-label.
Zhao 2005	Allocation: randomised. Blindness: open-label.
Zhao 2005a	Allocation: randomised. Blindness: open-label.
Zhong 2006a	Allocation: randomised. Blindness: open-label.
Zhou 2003	Allocation: randomised. Blindness: open-label.
Zhou 2003a	Allocation: randomised. Blindness: open-label.

Characteristics of ongoing studies [ordered by study ID]

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.			
Participants	Diagnosis: schizophrenia or schizoaffective disorder. N=not reported. Gender: not reported. Age: 18-75 years. History: duration ill not reported., age at onset not reported. Setting: not reported.			
Interventions	 Olanzapine: flexible dose., allowed dose range: 7.5-20 mg/day., mean dose: not reported., N=not reported. Quetiapine: flexible dose, allowed dose range: 300-800 mg/day, mean dose: not reported N=not reported. 			
	reported, re-nor reported			
Outcomes	Response to treatment. Leaving the study early: any reason, lack of efficacy or worsening of psychiatric syndromes. Global state: CGI, PG-I. Mental State: PANSS, depression MADRS General functioning: DAI-10, GAF. Quality of life: SF-36. Adverse effects: EPS (SAS, BAS, AIMS), vital signs, weight (waist circumference, BMI, appetite, metabolic syndrome), laboratory (fasting glucose, haemoglobin A1c, lipids, insulin)			
Starting date	July 2004.			

Contact information Eli Lilly and company.

Notes

Gafoor 2005

Trial name or title	A comparative study of quetiapine and risperidone in patients with first episode psychosis			
Methods	Allocation: random, no further details. Blindness: rater-blinded.			
Participants	Diagnosis: first episode of schizophreniform psychosis (ICD-10 criteria)			
Interventions	 Quetiapine: dose: not reported. Risperidone: dose: not reported 			
	2 Risperdone. dose. not reported.			
Outcomes	Global state: CGI. Mental state: PANSS positive subscale, PANSS negative subscale, Calgary Depression Scale for Schizophrenia, Calgary Anxiety Scale Schizophrenia. General functioning: GAF.			
Starting date	Not known.			
Contact information				
Notes				

Ratna 2003

Trial name or title	Improved response in Schizophrenia -IRIS.		
Methods	Allocation: random, no further details. Blindness: double, no further details.		
Participants	Diagnosis: schizophrenia.		
Interventions	1 Quetiapine: dose: not reported.		
	2 Risperidone: dose: not reported.		
Outcomes	Global state: CGI-S. Mental state: PANSS, GAS, HAM-D scores. Quality of life - SQLS and care giving inventory scores. Health Economics. Adverse effects: EPS (AIMS, SAS, BAS).		
Starting date	1 October 2002.		
Contact information	Dr Lawrence Ratna Barnet Hospital Wellhouse Lane Barnet EN5 3DJ UK		

Reynolds 2001

Trial name or title	A six month, rater blind comparison of quetiapine and risperidone in the treatment of tardive dyskinesia in people with schizophrenia			
Methods	Allocation: random, no further details. Blindness: single, rater-blinded.			
Participants	Diagnosis: schizophrenia. N=30.			
Interventions	1 Quetiapine: dose: not reported.			
	2 Risperidone: dose not reported.			
Outcomes	Not known.			
Starting date	Not known.			
Contact information	Not known.			
Notes				

DATA AND ANALYSES

Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term

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 original studies)	1	72	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
2 Global state: 1b. No clinically important change - short term (as defined by the original studies)	1	76	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.74, 1.18]
3 Leaving the study early	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 any reason	2	95	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.18, 2.43]
3.2 due to adverse events	1	72	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.67]
3.3 due to inefficacy	1	72	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Mental state: 1a. General - no clinically important change - short term (less than 50% PANSS total score reduction)	1	63	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.53, 2.14]
5 Mental state: 1b. General -average endpoint score - short term (PANSS total, high=poor)	4	232	Mean Difference (IV, Random, 95% CI)	-0.50 [-2.85, 1.86]
6 Mental state: 1c. General -average endpoint score - short term (BPRS total, high=poor)	1	67	Mean Difference (IV, Random, 95% CI)	-0.89 [-3.20, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)	2	142	Mean Difference (IV, Random, 95% CI)	-0.70 [-2.07, 0.68]
8 Mental state: 3a. Negative symptoms - no clinically important change - short term (less than 50% SANS total score reduction)	1	72	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
9 Mental state: 3b. Negative symptoms - average endpoint score - short term (PANSS negative subscore, high=poor)	2	142	Mean Difference (IV, Random, 95% CI)	-2.23 [-3.48, -0.99]
10 Mental state: 3c. Negative symptoms - average endpoint score - short term (SANS total, high=poor)	1	67	Mean Difference (IV, Random, 95% CI)	-1.64 [-8.17, 4.89]
11 Adverse effects: 1. General - at least one adverse effect	1	63	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.66]
12 Adverse effects: 2. Cardiac effects: ECG abnormalities	1	72	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.02, 0.95]
13 Adverse effects: 3. Central nervous system - sedation	2	135	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.11, 0.47]
14 Adverse effects: 4. Extrapyramidal effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 akathisia	2	135	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.99]
14.2 rigor	1	63	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.18, 20.30]
14.3 tremor	2	135	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.29, 3.34]
14.4 use of antiparkinson medication	1	28	Risk Ratio (M-H, Random, 95% CI)	Not estimable
15 Adverse effects: 5. Haematological: Important decline in white blood cells	1	63	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.88]
16 Adverse effects: 6a. Metabolic -weight - gain	2	135	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.25, 1.11]
17 Adverse effects: 6b. Metabolic -weight - change from baseline (kg)	1	27	Mean Difference (IV, Random, 95% CI)	-2.11 [-4.30, 0.08]

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)	1.11 [0.86, 1.43]
2 Global state: 1b. No clinically important change (as defined by the original studies)	2	309	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.89, 1.57]
2.1 short term	1	42	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.59, 3.15]
2.2 long term	1	267	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.86, 1.57]
3 Leaving the study early	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 any reason	10	1651	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.13, 1.32]
3.2 due to adverse events	8	1573	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.69, 1.18]
3.3 due to inefficacy	8	1563	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.42, 2.27]
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)	0.91 [0.54, 1.53]
5 Mental state: 1b. General - average endpoint score (PANSS total, high=poor)	10	1449	Mean Difference (IV, Random, 95% CI)	3.66 [1.93, 5.39]
5.1 short term	4	142	Mean Difference (IV, Random, 95% CI)	2.17 [-1.51, 5.85]
5.2 medium term	3	482	Mean Difference (IV, Random, 95% CI)	5.57 [1.97, 9.17]
5.3 long term	3	825	Mean Difference (IV, Random, 95% CI)	3.40 [0.91, 5.88]
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)	15.0 [0.93, 241.20]
7 Mental state: 2b. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)	7	679	Mean Difference (IV, Random, 95% CI)	1.80 [1.02, 2.59]
7.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	1.05 [-0.75, 2.85]
7.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	2.21 [0.90, 3.52]
7.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	1.80 [0.39, 3.21]
8 Mental state: 2c. Positive symptoms - SAPS total score -	1	30	Mean Difference (IV, Random, 95% CI)	40.84 [23.97, 57.71]

Comparison 2 QUETIAPINE versus OLANZAPINE

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)	1.5 [0.53, 4.26]
10 Mental state: 3b. Negative symptoms - average endpoint score (PANSS negative subscore, high=poor)	7	679	Mean Difference (IV, Random, 95% CI)	0.41 [-0.36, 1.18]
10.1 short term	3	115	Mean Difference (IV, Random, 95% CI)	0.01 [-1.72, 1.73]
10.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	0.40 [-0.67, 1.47]
10.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	0.70 [-0.73, 2.13]
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 [-0.48, 7.88]
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 [-31.90, 36.82]
13 General functioning: General - average endpoint score-medium term (GAF total score, high=poor)	1	278	Mean Difference (IV, Random, 95% CI)	3.80 [0.77, 6.83]
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 [-2.42, 6.02]
15 Service use: number of participants re-hospitalised	2	876	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.30, 2.47]
15.1 medium term	1	203	Risk Ratio (M-H, Random, 95% CI)	1.8 [0.92, 3.51]
15.2 long term	1	673	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.24, 2.58]
16 Adverse effects: 1. General - at least one adverse effect	6	1269	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.88, 1.06]
17 Adverse effects: 2. Death	3	1410	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.13, 4.23]
17.1 suicide attempt	2	940	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.05, 2.29]
17.2 suicide	2	470	Risk Ratio (M-H, Random, 95% CI)	4.96 [0.24, 102.41]
18 Adverse effects: 3a. Cardiac effects - QTc prolongation	1	673	Risk Ratio (M-H, Random, 95% CI)	12.96 [0.73, 229.17]
19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	3	643	Mean Difference (IV, Random, 95% CI)	4.81 [0.34, 9.28]
20 Adverse effects: 4a. Central nervous system - sedation	7	1615	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]

Komossa et al.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Adverse effects: 4b. Central nervous system - seizures	1	40	Risk Ratio (M-H, Random, 95% CI)	3.3 [0.14, 76.46]
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)	0.98 [0.68, 1.40]
22.2 akinesia	1	267	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.67, 1.56]
22.3 dystonia	1	42	Risk Ratio (M-H, Random, 95% CI)	4.57 [0.23, 89.72]
22.4 extrapyramidal symptoms	2	245	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.72, 3.67]
22.5 parkinsonism	1	40	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.18, 2.41]
22.6 tremor	1	42	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.31]
22.7 use of antiparkinson medication	6	1090	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.30, 0.79]
23 Adverse effects: 5b. Extrapyramidal effects - scale measured	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
23.1 akathisia: Barnes Akathisia Scale (high=poor)	1	50	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.58, 0.38]
23.2 extrapyramidal symptoms: ESRS total score (high=poor)	1	33	Mean Difference (IV, Random, 95% CI)	Not estimable
23.3 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	1	50	Mean Difference (IV, Random, 95% CI)	0.6 [-1.38, 2.58]
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)	0.10 [0.01, 1.77]
24.2 amenorrhea	3	252	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.36, 1.21]
24.3 galactorrhea	4	1025	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.25, 1.73]
24.4 gynecomastia	1	267	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.09, 1.20]
24.5 sexual dysfunction	4	1177	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 0.99]
25 Adverse effects: 6b. Prolactin -change from baseline in ng/ml	5	1021	Mean Difference (IV, Random, 95% CI)	-5.89 [-11.62, -0.16]
26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase	1	267	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.59, 1.68]
27 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl	4	986	Mean Difference (IV, Random, 95% CI)	-4.69 [-13.84, 4.45]
28 Adverse effects: 7c. Metabolic - glucose - abnormally high fasting glucose value	1	267	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.33, 1.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 Adverse effects: 7d. Metabolic -glucose - change from baseline in mg/dl	4	986	Mean Difference (IV, Random, 95% CI)	-9.32 [-17.82, -0.82]
30 Adverse effects: 7e. Metabolic -weight - gain	8	1667	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.92]
30.1 significant weight gain (as defined by the original studies)	7	1321	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.95]
30.2 as "weight gain" reported adverse events	1	346	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.04, 5.34]
31 Adverse effects: 7f. Metabolic -weight - change from baseline in kg	7	1173	Mean Difference (IV, Random, 95% CI)	-2.68 [-4.26, -1.10]

Comparison 3 QUETIAPINE 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)	4	1274	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.93, 1.35]
2 Global state: 1b. No clinically important change (as defined by the original studies)	4	1274	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.99, 1.35]
2.1 short term	3	1007	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.94, 1.44]
2.2 long term	1	267	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.87, 1.60]
3 Leaving the study early	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 any reason	10	2278	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.15]
3.2 due to adverse events	7	1851	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.78, 1.80]
3.3 due to inefficacy	7	1851	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.99, 1.61]
4 Mental state: 1a General - no clinically important change - short term (less than 30% PANSS total score reduction)	2	982	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.87, 1.42]
5 Mental state: 1b. General - no clinicallly important change - short term (less than 20% BPRS total score reduction)	1	25	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.63, 1.52]
6 Mental state: 1c. General - average endpoint score (PANSS total score, high=poor)	9	1953	Mean Difference (IV, Random, 95% CI)	3.09 [1.01, 5.16]
6.1 short term	5	1064	Mean Difference (IV, Random, 95% CI)	2.44 [-0.81, 5.69]
6.2 medium term	2	146	Mean Difference (IV, Random, 95% CI)	6.27 [-3.94, 16.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 long term	2	743	Mean Difference (IV, Random, 95% CI)	3.11 [0.40, 5.82]
7 Mental state: 1d. General - average endpoint score - short term (BPRS total score, high= poor)	1	25	Mean Difference (IV, Random, 95% CI)	1.68 [-8.33, 11.69]
8 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 40% PANSS positive reduction)	1	673	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.12]
9 Mental state: 2b. Positive symptoms - average endpoint score - (PANSS positive subscore, high=poor)	7	1264	Mean Difference (IV, Random, 95% CI)	1.82 [1.16, 2.48]
9.1 short term	4	1037	Mean Difference (IV, Random, 95% CI)	2.10 [1.00, 3.19]
9.2 medium term	2	146	Mean Difference (IV, Random, 95% CI)	2.15 [-0.01, 4.31]
9.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	1.30 [-0.13, 2.73]
10 Mental state: 2c. Positive symptoms - average endpoint score - short term (BPRS positive subscore, high=poor)	1	25	Mean Difference (IV, Random, 95% CI)	1.1 [0.18, 2.02]
11 Mental state: 3a. Negative symptoms - no clinicallly important change - short term (less than 40% PANSS negative reduction)	1	673	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.93, 1.04]
12 Mental state: 3b. Negative symptoms - average endpoint score - (PANSS negative subscore, high=poor)	7	1183	Mean Difference (IV, Random, 95% CI)	-0.35 [-1.95, 1.26]
12.1 short term	4	956	Mean Difference (IV, Random, 95% CI)	-1.46 [-4.11, 1.19]
12.2 medium term	2	146	Mean Difference (IV, Random, 95% CI)	1.30 [-0.75, 3.35]
12.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	0.80 [-0.64, 2.24]
13 Mental state: 3c. Negative symptoms - average endpoint score - (BPRS negative subscore, high=poor)	1	25	Mean Difference (IV, Random, 95% CI)	0.57 [0.17, 0.97]
14 Quality of life: General- average endpoint score - short term (QLS total score, high=poor)	1	22	Mean Difference (IV, Random, 95% CI)	-0.5 [-13.87, 12.87]
15 Service use: number of participants re-hospitalised	2	877	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.00, 1.79]
15.1 medium term	1	199	Risk Ratio (M-H, Random, 95% CI)	1.3 [0.71, 2.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 long term	1	678	Risk Ratio (M-H	1 35 [0 97 1 88]
15.2 long term	1	078	Random, 95% CI)	1.55 [0.97, 1.86]
16 Adverse effects: 1. General - at least one adverse effect	8	2226	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.17]
17 Adverse effects: 2. Death	5	3066	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.09]
17.1 natural causes	2	982	Risk Ratio (M-H, Random, 95% CI)	Not estimable
17.2 suicide attempt	2	945	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.06, 2.95]
17.3 suicide	3	1139	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.11, 18.32]
18 Adverse effects: 3a. Cardiac effects - QTc prolongation	2	1351	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.29, 2.55]
19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	3	940	Mean Difference (IV, Random, 95% CI)	2.21 [-5.05, 9.48]
20 Adverse effects: 4. Central nervous system - sedation	8	2226	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.06, 1.38]
21 Adverse effects: 5a. Extrapyramidal effects	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 akathisia	6	2170	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.34, 1.13]
21.2 akinesia	1	267	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.61, 1.37]
21.3 dystonia	1	673	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.41]
21.4 extrapyramidal symptoms	2	872	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.81]
21.5 parkinsonism	2	717	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 0.96]
21.6 rigor	1	309	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.16, 1.25]
21.7 use of antiparkinson medication	6	1715	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.30, 0.86]
22 Adverse effects: 5b. Extrapyramidal effects - scale measured	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 abnormal involuntary movement: AIMS (high=poor)	2	958	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.76, 0.08]
22.2 akathisia: Barnes Akathisia Scale (high=poor)	2	700	Mean Difference (IV, Random, 95% CI)	-0.73 [-2.00, 0.54]
22.3 extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	5	1077	Mean Difference (IV, Random, 95% CI)	-0.59 [-1.16, -0.02]
23 Adverse effects: 6. Haematological: important decline in white blood cells	1	673	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.73]
24 Adverse effects: 7a. Prolactin associated side effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 amenorrhea	4	359	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.28, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 dysmenorrhea	1	163	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.08, 2.38]
24.3 galactorrhea	5	1188	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.85]
24.4 gynecomastia	1	267	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.07, 0.79]
24.5 sexual dysfunction	6	2157	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.48, 1.01]
25 Adverse effects: 7b. Prolactin -change from baseline in mg/dl	6	1731	Mean Difference (IV, Random, 95% CI)	-35.28 [-44.36, -26. 19]
26 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase	2	940	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.72, 2.24]
27 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl	5	1433	Mean Difference (IV, Random, 95% CI)	8.61 [4.66, 12.56]
28 Adverse effects: 8c. Metabolic - glucose - abnormally high fasting glucose value	2	940	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.56, 3.45]
29 Adverse effects: 8d. Metabolic -glucose - change from baseline in mg/dl	5	1436	Mean Difference (IV, Random, 95% CI)	-0.04 [-2.92, 2.83]
30 Adverse effects: 8e. Metabolic -weight gain of 7% or more of total body weight	7	1942	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.14]
31 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg	7	1446	Mean Difference (IV, Random, 95% CI)	0.71 [-1.04, 2.47]

Comparison 4 QUETIAPINE versus ZIPRASIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1. 1 any reason	2	722	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.97, 1.13]
1.2 adverse events	2	722	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.72, 1.49]
1.3 inefficacy	2	722	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.89, 1.47]
2 Mental state: 1. General - average endpoint score (PANSS total score, high=poor)	2	710	Mean Difference (IV, Random, 95% CI)	-0.11 [-6.36, 6.14]
2.1 medium term	1	198	Mean Difference (IV, Random, 95% CI)	3.70 [-2.97, 10.37]
2.2 long term	1	512	Mean Difference (IV, Random, 95% CI)	-2.78 [-6.81, 1.25]
3 Mental state: 2. Positive symptoms - average endpoint score - medium term (PANSS positive subscore, high=poor)	1	198	Mean Difference (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Mental state: 3. Negative symptoms - average endpoint score - medium term (PANSS negative subscore, high=poor)	1	198	Mean Difference (IV, Random, 95% CI)	1.60 [-0.34, 3.54]
5 Service use: number of participants re-hospitalised	2	754	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.85, 1.59]
5.1 medium term	1	232	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.71, 2.17]
5.2 long term	1	522	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.78, 1.65]
6 Adverse effects: 1. General - at least one adverse effect	2	754	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.91, 1.17]
7 Adverse effects: 2. Death	2	754	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.05, 3.15]
7.1 suicide attempt	1	522	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.03, 8.73]
7.2 suicide	1	232	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 5.92]
8 Adverse effects: 3a. Cardiac effects - QTc prolongation	1	522	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.34, 8.08]
9 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms	2	549	Mean Difference (IV, Random, 95% CI)	3.41 [-1.37, 8.18]
10 Adverse effects: 4. Central nervous system - sedation	2	754	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.04, 1.77]
11 Adverse effects: 5. Extrapyramidal effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 akathisia	2	754	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.45]
11.2 extrapyramidal symptoms	1	232	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.66, 6.17]
11.3 use of antiparkinson medication	1	522	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.20, 0.93]
12 Adverse effects: 6a. Prolactin associated effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 amenorrhea	1	138	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.24]
12.2 galactorrhea	2	572	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.18, 1.68]
12.3 sexual dysfunction	2	754	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.64, 1.42]
13 Adverse effects: 6b. Prolactin -change from baseline in ng/ml	2	754	Mean Difference (IV, Random, 95% CI)	-4.77 [-8.16,-1.37]
14 Adverse effects: 7a. Metabolic - cholesterol - change from baseline in mg/dl	2	754	Mean Difference (IV, Random, 95% CI)	16.01 [8.57, 23.46]
15 Adverse effects: 7b. Metabolic -glucose- change from baseline in mg/dl	2	754	Mean Difference (IV, Random, 95% CI)	3.10 [-3.99, 10.19]
16 Adverse effects: 7c. Metabolic -weight gain of 7% or more of total body weight	2	754	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.35, 3.63]
17 Adverse effects: 7d. Metabolic - weight gain - change from baseline in kg	1	466	Mean Difference (IV, Random, 95% CI)	1.2 [-0.05, 2.45]

Comparison 5 QUETIAPINE versus CLOZAPINE- 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 - short term (PANSS total, high=poor)	1	27	Mean Difference (IV, Random, 95% CI)	0.18 [-4.11, 4.47]
1.1 short term	1	27	Mean Difference (IV, Random, 95% CI)	0.18 [-4.11, 4.47]

Comparison 6 QUETIAPINE versus OLANZAPINE- 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 subscore, high=poor)	6	639	Mean Difference (IV, Random, 95% CI)	1.82 [0.98, 2.65]
1.1 short term	2	75	Mean Difference (IV, Random, 95% CI)	0.09 [-2.76, 2.93]
1.2 medium term	3	483	Mean Difference (IV, Random, 95% CI)	2.21 [0.90, 3.52]
1.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	1.80 [0.39, 3.21]

Comparison 7 QUETIAPINE versus RISPERIDONE- sensitivity analysis (skewed data excluded)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 6. Positive symptoms - average endpoint score - (PANSS positive subscore, high=poor)	6	1225	Mean Difference (IV, Random, 95% CI)	1.76 [1.04, 2.48]
1.1 short term	3	998	Mean Difference (IV, Random, 95% CI)	2.08 [0.60, 3.56]
1.2 medium term	2	146	Mean Difference (IV, Random, 95% CI)	2.15 [-0.01, 4.31]
1.3 long term	1	81	Mean Difference (IV, Random, 95% CI)	1.30 [-0.13, 2.73]
2 Adverse effects: 1. Extrapyramidal effects - Simpson-Angus Scale (high= poor)	4	1033	Mean Difference (IV, Random, 95% CI)	-0.82 [-1.95, 0.31]

Analysis 1.1 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 1 Global state: 1a. No clinically significant response (as defined by original studies)

Review: Quetiapine versus other atypical antipsychotics: for schizophrenia Comparison: 1QUETIAPINE versus CLOZAPINE - all data short term Outcome: 1 Global state: 1 a. No clinically significant response (as defined by original studies)

Study or subgroup	Quetiapine n/N	Clozapine n/N		Risk M-H,Rando	Ratio m,95% CI	Weight	Risk Ratio M - H, Random, 95% Cl	
Liu 2004	30/36	32/36				100.0	% 0.94 [0.78, 1.13]	
Total (95% CI) Total events: 30 (Quetiap Heterogeneity: not applic Test for overall effect: Z =	36 ine), 32 (Clozapine) able : 0.68 (P = 0.50)	36		•		100.0	% 0.94 [0.78, 1.13]	
		Favours treatment	0.1 0.2	0.5 1	2 Favour	5 10 s control		

Analysis 1.2 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 2 Global state: 1b. No clinically important change - short term (as defined by the original studies)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 2 Global state: lb. No clinically important change - short term (as defined by the original studies)

Study or subgroup	Quetiapine n/N	Clozapine n/N		Ris M - H, Rano	k Ratio 10m,95% CI	Weight	Risk Ratio M-H,Random,95% CI	
Li 2003	29/38	31/38				100.0%	0.94 [0.74, 1.18]	
Total (95% Cl) Total events: 29 (Quetiapi Heterogeneity: not applic: Test for overall effect: Z =	38 ne), 31 (Clozapine) able 0.56 (P = 0.57)	38		•		100.0 %	0.94 [0.74, 1.18]	
		Favours treatment	0.1 0.2	0.5	1 2 Favou	5 10 rs control		

Analysis 1.3 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 3 Leaving the study early

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

Study or subgroup	Quetiapine n/N	Clozapine n/N	Risk Ratio M-H,Random,95% Cl	Risk Ratio M - H, Random, 95% Cl	
1 any reason Atmaca 2003	0/14	1/14	•	0.33 [0.01, 7.55]	
Li 2005	3/33	4/34	— <u> </u>	0.77 [0.19, 3.19]	
Subtotal (95% Cl) Total events: 3 (Quetiapine), Heterogeneity: Tau ² = 0.0; C Test for overall effect: Z = 0.	47 5 (Clozapine) Chi ² = 0.23, df = 1 (P 61 (P = 0.54)	48 = 0.63); l ² =0.0%	•	0.67 [0.18, 2.43]	
2 due to adverse events Liu 2004	0/36	3/36		0.14 [0.01, 2.67]	
Subtotal (95% Cl) Total events: 0 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 1.	36 3 (Clozapine) e 30 (P = 0.19)	36	-	0.14 [0.01, 2.67]	
3 due to inefficacy Liu 2004	0/36	0/36		0.0 [0.0, 0.0]	
Subtotal (95% Cl) Total events: 0 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 0.	36 0 (Clozapine) e 0 (P < 0.00001)	36		0.0 [0.0, 0.0]	
	Fa	0.0 vours treatment	02 0.1 1 10 Favours cont	500 rol	

Analysis 1.4 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 4 Mental state: 1a. General no clinically important change - short term (less than 50% PANSS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 4 Mental state: la. General - no clinically im portant change - short term (less than 50% PANSS total score reduction)

Study or subgroup	Quetiapine n/N	Clozapine n/N		,	Ri 1-H,Ran	sk Ra dom ,	tio 95% Cl		Weight	Risk Ratio M-H,Random,95% Cl	
Li 2002	11/32	10/31			_	•	_		100.0%	1.07 [0.53, 2.14]	
Total (95% Cl) Total events: 11 (Quetiap Heterogeneity: not applic Test for overall effect: Z =	32 ine), 10 (Clozapine) iable = 0.18 (P = 0.86)	31					-		100.0 %	1.07 [0.53, 2.14]	
		Favours treatmen	0.1 t	0.2	0.5	1	2 Favours	5 control	10		

Analysis 1.5 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 5 Mental state: 1b. General average endpoint score - short term (PANSS total, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1QUETIAPINE versus CLOZAPINE - all data short term Outcome: 5 Mental state: lb. General - average endpoint score - short term (PANSS total, high = poor)

Atm aca 2003 14 77.24 (6.08) 13 77.06 (5.28) 30.1 % 0.18 [-4.11, 4.47] Li 2005 33 44.12 (8.91) 34 46.76 (8.23) 32.8 % -2.64 [-6.75, 1.47] Li 2002 32 49.1 (14.3) 31 48.4 (15.2) 10.4 % 0.70 [-6.59, 7.99] Li 2003 37 44.6 (10.3) 38 43.7 (9.8) 26.7 % 0.90 [-3.65, 5.45] Total (95% C) 116 116 100.0 % -0.50 [-2.85, 1.86]	Study or subgroup	Quetiapine N	C Mean(SD)	lozapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Li 2005 33 44.12 (8.91) 34 46.76 (8.23) Li 2002 32 49.1 (14.3) 31 48.4 (15.2) Li 2003 37 44.6 (10.3) 38 43.7 (9.8) Total (95% Cl) 116 116 116 116 116 116 116 116 116 11	Atmaca 2003	14	77.24 (6.08)	13	77.06 (5.28)		30.1 %	0.18 [-4.11, 4.47]
Li 2002 32 49.1 (14.3) 31 48.4 (15.2) 10.4 % 0.70 [-6.59, 7.99] Li 2003 37 44.6 (10.3) 38 43.7 (9.8) 26.7 % 0.90 [-3.65, 5.45] Total (95% Cl) 116 116 116 116 116 116 116 116 116 11	Li 2005	33	44.12 (8.91)	34	46.76 (8.23)		32.8 %	-2.64 [-6.75, 1.47]
Li 2003 37 44.6 (10.3) 38 43.7 (9.8) 26.7 % 0.90 [-3.65, 5.45]	Li 2002	32	49.1 (14.3)	31	48.4 (15.2)		- 10.4 %	0.70 [-6.59, 7.99]
Total (95% CI) 116 116 116 116 116 116 116 116 116 11	Li 2003	37	44.6 (10.3)	38	43.7 (9.8)		26.7 %	0.90 [-3.65, 5.45]
reterogenenty: lau = 0.0; ln = 1.01, dt = 3.0° = 0.66); l = 0.0% Testfor overall effect Z = 0.41 (P = 0.66)	Total (95% Cl) Heterogeneity: Tau ² = (Test for overall effect: Z	116 0.0; Chi ² = 1.61 = 0.41 (P = 0.0	, df = 3 (P = 0.66	116 5); I ² =0.0%		-	100.0 %	-0.50 [-2.85, 1.86]

Analysis 1.6 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 6 Mental state: 1c. General average endpoint score - short term (BPRS total, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 6 Mental state: lc. General - average endpoint score - short term (BPRS total, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
Liu 2004	34	30.53 (4.55)	33	31.42 (5.06)		100.0%	-0.89[-3.20, 1.42]
Total (95% Cl) Heterogeneity: not app Test for overall effect: 7	34 licable Z = 0.76 (P = 0.4)	5)	33		-	100.0 %	-0.89 [-3.20, 1.42]
			F	avours treatment	10 -5 0 5 Favours cor	10 itrol	

Analysis 1.7 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 7 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 7 Mental state: 2. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)

Study or subgroup	Quetiapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
Li 2005	33	14.55 (4.26)	34	15.33 (3.53)		53.6%	-0.78 [-2.66, 1.10]
Li 2003	37	13.5 (4.6)	38	14.1 (4.3)		46.4 %	-0.60 [-2.62, 1.42]
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: ;	70 0.0; Chi ² = 0.02, Z = 0.99 (P = 0.3	df = 1 (P = 0. 2)	72 90); I ² =0.0%	1	•	100.0 %	-0.70 [-2.07, 0.68]
			F	avours treatment	10 -5 0 5 Favours con	10 trol	

Analysis 1.8 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 8 Mental state: 3a. Negative symptoms - no clinically important change - short term (less than 50% SANS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 9 Mental state: 3a. Negative symptoms - no clinically important change - short term (less than 50% SANS total score reduction)

Study or subgroup	Quetiapine n/N	Clozapine n/N		Ris M - H, Rand	k Ratio Iom,95% CI	Weight	Risk Ratio M - H, Random , 95% Cl	
Liu 2004	30/36	32/36		-+		100.0%	0.94 [0.78, 1.13]	
Total (95% Cl) Total events: 30 (Quetiapii Heterogeneity: not applica Test for overall effect: Z =	36 ne), 32 (Clozapine) ble 0.68 (P = 0.50)	36		•	•	100.0 %	0.94 [0.78, 113]	
		Favours treatment	0.1 0.2	0.5	1 2 Favou	5 10 rs control		

Analysis 1.9 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 9 Mental state: 3b. Negative symptoms - average endpoint score - short term (PANSS negative subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 9 Mental state: 3b. Negative symptoms - average endpoint score - short term (PANSS negative subscore, high=poor)

Study or subgroup	Quetiapine N	(Mean(SD)	lozapine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
Li 2005 Li 2003	33 37	9.86 (3.81) 12.9 (4.2)	34 38	12.29 (3.25) 14.9 (3.9)		53.9 % 46.1 %	-2.43 [-4.13, -0.73] -2.00 [-3.84, -0.16]
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: :	70 0.0; Chi ² = 0.11, Z = 3.51 (P = 0.0)	df = 1 (P = 0.74 0045)	72 4); l ² =0.0%		•	100.0 %	-2.23 [-3.48, -0.99]
			F	avours treatment	LO -5 0 5 Favours c	10 ontrol	

Analysis 1.10 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 10 Mental state: 3c. Negative symptoms - average endpoint score - short term (SANS total, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 10 Mental state: 3c. Negative symptoms - average endpoint score - short term (SANS total, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Liu 2004	34	47 (13.99)	33	48.64 (13.29)			100.0 %	-1.64 [-8.17, 4.89]
Total (95% Cl) Heterogeneity: not appli Test for overall effect: Z	34 icable = 0.49 (P = 0.62	2)	33				100.0 %	-1.64 [-8.17, 4.89]
				Favours treatment	-10 -5	0 5 Favours	10 control	

Analysis 1.11 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 11 Adverse effects: 1. General - at least one adverse effect

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 11 Adverse effects: 1. General - at least one adverse effect

Study or subgroup	Quetiapine n/N	Clozapine n/N		Ri M - H, Rar	sk Ratio dom,95	% CI		Weight	Risk Ratio M - H, Random, 95% Cl	
Li 2002	12/32	28/31	-	•				100.0%	0.42[0.26, 0.66]	
Total (95% Cl) Total events: 12 (Quetiap Heterogeneity: not applic Test for overall effect: Z =	32 ine), 28 (Clozapine) able : 3.73 (P = 0.00019)	31						100.0 %	0.42 [0.26, 0.66]	
		Favours treatment	0.1 0.2	0.5	1 2 F	avours (5 control	10		

Analysis 1.12 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 12 Adverse effects: 2. Cardiac effects: ECG abnormalities

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 12 Adverse effects: Z. Cardiac effects: ECG abnormalities

Study or subgroup	Quetiapine n/N	Clozapine n/N		м	Ris -H,Rani	k Ratio dom,95% Cl			Weight	Risk Ratio M - H, Random, 95% Cl	
Liu 2004	1/36	8/36		-	•				100.0%	0.13[0.02,0.95]	
Total (95% Cl) Total events: 1 (Quetiapin Heterogeneity: not applica Test for overall effect: Z =	36 e), 8 (Clozapine) able 2.01 (P = 0.044)	36		-	-				100.0 %	0.13 [0.02, 0.95]	
		Favours treatmen	0.001 t	0.01	0.1	1 10 Fav	1 ours c	00 ontrol	1000		
Analysis 1.13 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 13 Adverse effects: 3. Central nervous system - sedation

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 13 Adverse effects: 3. Central nervous system - sedation

Study or subgroup	Quetiapine n/N	Clozapine n/N	R M-H,Ra	isk Ratio ndom,95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
Li 2002 Liu 2004	3/32 4/36	19/31 13/36		_	45.7 % 54.3 %	0.15 [0.05, 0.47] 0.31 [0.11, 0.85]	
Total (95% Cl) Total events: 7 (Quetiapi Heterogeneity: Tau ² = 0. Test for overall effect: 2 :	68 ne), 32 (Clozapine) 0; Chi ² = 0.83, df = 1 (i = 3.90 (P = 0.000095)	67 P = 0.36); I ² =0.0%	•		100.0 %	0.22 [0.11, 0.47]	
		0 Favours treatment	.001 0.01 0.1	1 10 Favour	100 1000 s control		

Analysis 1.14 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 14 Adverse effects: 4. Extrapyramidal effects

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 14 Adverse effects: 4. Extrapyramidal effects

Study or subgroup	Quetiapine n/N	lozapine n/N	Risk Ratio M-H,Random,95% Cl	Risk Ratio M – H, Random, 95% Cl	
1 akathisia Li 2002	1/32	2/31 +		0.48 [0.05, 5.07]	
Liu 2004	1/36	3/36 🔶		0.33 [0.04, 3.06]	
Subtotal (95% Cl) Total events: 2 (Quetiapine Heterogeneity: Tau ² = 0.0; Test for overall effect: Z =	68), 5 (Clozapine) Chi ² = 0.05, df = 1 (P = 1.12 (P = 0.26)	67 0.82); l ² =0.0%		0.40 [0.08, 1.99]	
2 rigor Li 2002	2/32	1/31	<mark></mark>	→ 1.94 [0.18, 20.30]	
Subtotal (95% Cl) Total events: 2 (Quetiapine Heterogeneity: not applica Test for overall effect: Z =	32), 1 (Clozapine) ble 0.55 (P = 0.58)	31		1.94 [0.18, 20.30]	
3 tremor Li 2002	3/32	2/31		1.45 [0.26, 8.11]	
Liu 2004	2/36	3/36		0.67 [0.12, 3.75]	
Subtotal (95% Cl) Total events: 5 (Quetiapine Heterogeneity: Tau ² = 0.0; Test for overall effect: Z =	68 .), 5 (Clozapine) Chi ² = 0.39, df = 1 (P = 0.02 (P = 0.98)	67 0.53); I ² =0.0%		0.99 [0.29, 3.34]	
4 use of antiparkinson me Atmaca 2003	dication 0/14	0/14		0.0 [0.0, 0.0]	
Subtotal (95% Cl) Total events: 0 (Quetiapine Heterogeneity: not applica Test for overall effect: Z =	14), 0 (Clozapine) ble 0.0 (P < 0.00001)	14		0.0 [0.0, 0.0]	
	E	0.1	0.2 0.5 1 2 5	10	

Analysis 1.15 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 15 Adverse effects: 5. Haematological: Important decline in white blood cells

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 15 Adverse effects: 5. Haematological: Important decline in white blood cells



Analysis 1.16 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 16 Adverse effects: 6a. Metabolic - weight - gain

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 16 Adverse effects: 6a. Metabolic - weight - gain

Study or subgroup	Quetiapine n/N	Clozapine n/N	Ri: M - H, Ran	k Ratio dom,95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
Li 2002	5/32	7/31	<mark></mark> -		51.3 %	0.69 [0.25, 1.95]	
Liu 2004	4/36	10/36	<mark>+</mark>	-	48.7 %	0.40 [0.14, 1.16]	
Total (95% Cl) Total events: 9 (Quetiapii Heterogeneity: Tau ² = 0. Test for overall effect: Z :	68 ne), 17 (Clozapine) 0; Chi ² = 0.53, df = 1 (l = 1.68 (P = 0.093)	67 P = 0.47); l ² =0.0%	•		100.0 %	0.53 [0.25, 1.11]	
		0.1	0.2 0.5	1 2 5 Eavours cr	10		

Analysis 1.17 Comparison 1 QUETIAPINE versus CLOZAPINE - all data short term, Outcome 17 Adverse effects: 6b. Metabolic - weight - change from baseline (kg)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 1 QUETIAPINE versus CLOZAPINE - all data short term Outcome: 11 Adverse effects: 6b. Metabolic - weight - change from baseline (kg)

Study or subgroup	Quetiapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% CI
Atmaca 2003	14	4.41 (2.21)	13	6.52 (3.41)			100.0%	-2.11 [-4.30, 0.08]
Total (95% Cl) Heterogeneity: not app Test for overall effect: 2	14 licable Z = 1.89 (P = 0.05	58)	13		•		100.0 %	-2.11 [-4.30, 0.08]
			F	avours treatment	-10 -5	0 Favo	5 10 urs control	

Analysis 2.1 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M-H,Random,95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
McEvoy 2007	56/134	48/133		70.6%	1.16 [0.86, 1.57]	
Ozguven 2004	6/15	4/15		5.9 %	1.50 [0.53, 4.26]	
Svestka 2003b	12/22	12/20		23.5 %	0.91 [0.54, 1.53]	
Total (95% Cl) Total events: 74 (Quetiapi Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	171 ne), 64 (Olanzapine) ; Chi ² = 0.97, df = 2 (0.81 (P = 0.42)	168 P = 0.61); I ² =0.0%	•	100.0 %	1.11 [0.86, 1.43]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours con	10 trol		

Analysis 2.2 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 2 Global state: 1b. No clinically important change (as defined by the original studies)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 2 Global state: lb. No clinically im portant change (as defined by the original studies)

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random, 95% CI	Weight	Risk Ratio M-H,Random,95% Cl	
1 short term Svestka 2003b	9/22	6/20		11.5 %	1.36 [0.59, 3.15]	
Subtotal (95% Cl) Total events: 9 (Quetiapine Heterogeneity: not applical Test for overall effect: Z = 0	22), 6 (Olanzapine) ble).73 (P = 0.47)	20		11.5 %	1.36 [0.59, 3.15]	
2 long term McEvoy 2007	56/134	48/133		88.5 %	1.16 [0.86, 1.57]	
Subtotal (95% Cl) Total events: 56 (Quetiapin Heterogeneity: not applical Test for overall effect: Z = 1	134 e), 48 (Olanzapine) ble 0.95 (P = 0.34)	133	•	88.5 %	116 [0.86, 157]	
Total (95% Cl) Total events: 65 (Quetiapin Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 3	156 e), 54 (Olanzapine) Chi ² = 0.13, df = 1 .14 (P = 0.25)	153 (P = 0.72); I ² =0.0%	•	100.0 %	1.18 [0.89, 1.57]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours co	10 Introl		

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

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 3 Leaving the study early

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random, 95% Cl	Risk Ratio M - H, Random, 95% Cl	
1 any reason Atmaca 2003	0/14	1/14		0.33 [0.01, 7.55]	
Kinon 2006b	109/175	81/171	-	1.31 [1.08, 1.60]	
Lieberman 2005	277/337	216/336		1.28 [1.16, 1.40]	
McEvoy 2006	13/15	12/19	+	1.37 [0.92, 2.04]	
McEvoy 2007	95/134	91/133	•	1.04 [0.88, 1.21]	
Ozguven 2004	4/15	0/15		9.00 [0.53, 153.79]	
Riedel 2007	17/26	15/26	+	1.13 [0.74, 1.75]	
Sacchetti 2004	4/25	5/25		0.80 [0.24, 2.64]	
Sirota 2006	2/19	3/21		0.74 [0.14, 3.95]	
Stroup 2006	53/63	46/68	-	1.24 [1.02, 1.51]	
Subtotal (95% Cl) Total events: 574 (Quetiapi Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 5	823 ine), 470 (Olanzapine); Chi ² = 9.46, df = 9 5.28 (P < 0.00001)	828 (P = 0.40); I ² =5%		122 [113, 132]	
2 due to adverse events Kinon 2006b	11/175	5/171	-	2 15 [0 76 6 06]	
Lieberman 2005	49/337	62/336		0.79 [0.56, 1.11]	
McEvov 2006	3/15	1/19	— —	3.80 [0.44, 32.94]	
McEvov 2007	13/134	14/133		0.92[0.45, 1.89]	
Ozguven 2004	0/15	0/15		0.010.0.01	
Riedel 2007	1/26	1/26		1.00 [0.07, 15.15]	
Sirota 2006	0/19	1/21		0.37 [0.02, 8.50]	
Stroup 2006	11/63	13/68	-	0.91 [0.44, 1.89]	
Subtotal (95% CI) Total events: 88 (Quetiapin Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 1	784 re), 97 (Olanzapine) Chi ² = 5.35, df = 6 (0.77 (P = 0.44)	789 P = 0.50); l ² = 0.0%	•	0.90 [0.69, 1.18]	
3 due to inefficacy	56/175	22/171	-	2 49 7 1 59 2 00 1	
Lieberman 2005	92/227	49/226	-	1 91 [1 40 2 52]	
McEvov 2006	6/15	6/19		1 27 [0 51 3 14]	
McEvoy 2007	17/134	15/133		1 12 [0.59, 2 16]	
Ozauven 2004	4/15	0/15		9 00 [0 53 153 79]	
Sirota 2006	1/19	1/21		1.11 [0.07, 16.47]	
Stroup 2006	22/63	15/68	-	1.58 [0.90, 2.77]	
Svestka 2003b	0/22	1/20		0.30 [0.01, 7.07]	
Subtotal (95% Cl) Total events: 198 (Quetiapi Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = 4	780 ine), 108 (Olanzapine ; Chi ² = 7.54, df = 7 4.94 (P < 0.00001)	783 (P = 0.38); I ² =7%	•	180 [142, 2.27]	
		0.1 Favours treatment	001 0.01 0.1 1 10 100 Favours con	1000 ttrol	

Analysis 2.4 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 4 Mental state: 1a. General - no clinically important change-short term (less than 50% PANSS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

Study or subgroup	Quetiapine n/N	Olanzapine n/N		Ris M - H, Rano	k Ratio dom,95% CI		Weight	Risk Ratio M-H,Random,95% Cl	
Svestka 2003b	12/22	12/20			-		100.0%	0.91 [0.54, 1.53]	
Total (95% Cl) Total events: 12 (Quetiapi Heterogeneity: not applic Test for overall effect: Z =	22 ine), 12 (Olanzapine) able : 0.36 (P = 0.72)	20					100.0 %	0.91 [0.54, 1.53]	
		0 Favours treatment	.1 0.2	0.5	1 2 Favo	5 urs contro	10 pl		

Analysis 2.5 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 5 Mental state: 1b. General - average endpoint score (PANSS total, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

Quetiapine N	O Mean(SD)	lanzapin N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
14	77.24 (6.08)	13	74.86 (6.41)		13.4 %	2.38 [-2.34, 7.10]
20	72.9 (15.1)	20	69.4 (10.8)		→ 4.5 %	3.50 [-4.64, 11.64]
16	-21.5 (23.39)	17	-17.88 (20.71) +		+ 1.3%	-3.62 [-18.73, 11.49]
22	-43.91 (20.94)	20	-45.65 (11.96) -		→ 2.9 %	1.74 [-8.46, 11.94]
72 ; Chi ² = 0.68 1.16 (P = 0.2	, df = 3 (P = 0.88 25)	70); l ² =0.0	%		22.2 %	2.17 [-1.51, 5.85]
169	-7.2 (21.2)	166	-11.3 (18.3)		- 16.7%	4.10 [-0.14, 8.34]
8	-1.3 (19.23)	10	-7.7 (9.8) -		→ 1.4 %	6.40 [-8.24, 21.04]
63	2 (22.31)	66	-8.2 (22.31)		H 5.1 %	10.20 [2.50, 17.90]
240 ; Chi ² = 1.86 3.03 (P = 0.0	, df = 2 (P = 0.39 J024)	242)); l ² =0.0	%		23.1 %	5.57 [1.97, 9.17]
329	-6.08 (22.31)	330	-11.27 (22.31)		25.8%	5.19 [1.78, 8.60]
44	-15.6 (10.68)	37	-18.4 (9.73)		15.1 %	2.80 [-1.65, 7.25]
44 43	-15.6 (10.68) 49.4 (12)	37 42	-18.4 (9.73) 48.5 (9.9)		15.1 % 13.7 %	2.80 [-1.65, 7.25] 0.90 [-3.77, 5.57]
44 43 416 1; Chi ² = 2.2 2.68 (P = 0.0	-15.6 (10.68) 49.4 (12) 3, df = 2 (P = 0.3)074)	37 42 409 (3); ² =1	-18.4 (9.73) 48.5 (9.9)	-	15.1 % 13.7 % 5 4.7 %	2.80 [-1.65, 7.25] 0.90 [-3.77, 5.57] 3.40 [0.91, 5.88]
	14 20 16 22 72 Chi ² = 0.68 1.16 (P = 0.2 169 8 63 240 Chi ² = 1.86 3.03 (P = 0.1	$\begin{array}{cccc} 14 & 77.24 & (6.08) \\ 20 & 72.9 & (15.1) \\ 16 & -21.5 & (23.39) \\ 22 & -43.91 & (20.94) \\ 72 \\ chi^2 = 0.68, \ df = 3 & (P = 0.88) \\ 1.16 & (P = 0.25) \\ \end{array}$ $\begin{array}{cccc} 169 & -7.2 & (21.2) \\ 8 & -1.3 & (19.23) \\ 63 & 2 & (22.31) \\ 240 \\ chi^2 = 1.66, \ df = 2 & (P = 0.35) \\ 3.03 & (P = 0.0024) \end{array}$	$\begin{array}{ccccccc} 14 & 77.24 & (6.08) & 13 \\ 20 & 72.9 & (15.1) & 20 \\ 16 & -21.5 & (23.39) & 17 \\ 22 & -43.91 & (20.94) & 20 \\ 22 & -43.91 & (20.94) & 20 \\ \end{array}$; ChiP = 0.68, df = 3 (P = 0.88); P = 0.0 \\ 1.16 (P = 0.25) & 166 \\ 8 & -1.3 & (19.23) & 10 \\ 63 & 2 & (22.31) & 66 \\ 242 \\ ChiP = 1.68, df = 2 & (P = 0.39); P = 0.0 \\ 3.03 (P = 0.0024) & 230 \\ \end{array}	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

Analysis 2.6 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 6 Mental state: 2a. Positive symptoms - no clinically important change-short term (less than 20% SAPS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

Study or subgroup	Quetiapine n/N	Olanzapine n/N	м	Ris -H,Ran	sk Ratio dom,95% Cl		Weight	Risk Ratio M-H,Random,95% Cl	
Ozguven 2004	7/15	0/15			,		100.0%	15.00 [0.93, 241.20]	
Total (95% Cl) Total events: 7 (Quetiapin Heterogeneity: not applica Test for overall effect: Z =	15 e), 0 (Olanzapine) uble 1.91 (P = 0.056)	15		1			100.0 %	15.00 [0.93, 241.20]	
		Favours treatment	0.001 0.01	0.1	1 10 Favours	100 s contro	1000 I		

Analysis 2.7 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 7 Mental state: 2b. Positive symptoms average endpoint score (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

	Quetiapine N	0 Mean(SD)	lanzapine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
1 short term Mori 2004	20	13.3 (4.3)	20	11.6 (3.1)		11.5 %	1.70 [-0.62, 4.02]
Riedel 2007	16	-7.78 (7.3)	17	-6.82 (7.3)		2.5 %	-0.96 [-5.94, 4.02]
Svestka 2003b	22	-12.96 (6.28)	20	-13.55 (5.14)		5.2 %	0.59 [-2.87, 4.05]
Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z	58 .0; Chi ² = 0.99, = 1.15 (P = 0.2	df = 2 (P = 0.61 5)	57); l² =0.0%	6	•	19.2 %	1.05 [-0.75, 2.85]
2 medium term Kinon 2006b	169	-0.7 (6.6)	167	-2.3 (5.4)	-	37.3 %	1.60 [0.31, 2.89]
M - C 2000	8	0.6 (5.94)	10	-2.9 (4.11)		2.6 %	3.50 [-1.34, 8.34]
M CEVOY 2006				And the second second second	-		
Stroup 2006	63	0.2 (7.3)	66	-3.4 (7.3)		9.8 %	3.60[1.08, 6.12]
M CEVOY 2006 Stroup 2006 Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z	63 240 .21; Chi ² = 2.26 = 3.31 (P = 0.0	0.2 (7.3) 5, df = 2 (P = 0.3 0093)	66 243 2); I ² =1 25	-3.4 (7.3)	•	9.8% 49.7%	2.21 [0.90, 3.52]
M CEVOY 2006 Stroup 2006 Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term M CEVoy 2007	63 240 .21; Chi ² = 2.26 = 3.31 (P = 0.0	0.2 (7.3) 5, df = 2 (P = 0.3 0093) -5.3 (3.38)	66 243 2); ² =1 25 37	-3.4 (7.3)	◆ +	9.8 % 49.7 % 31.1 %	3.60 [1.08, 6.12] 2.21 [0.90, 3.52] 1.80 [0.39, 3.21]
McEvoy 2006 Stroup 2006 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term McEvoy 2007 Subtotal (95% CI) Heterogeneity: not appli Test for overall effect: Z	63 240 .21; Chi ² = 2.26 = 3.31 (P = 0.0 44 44 cable = 2.50 (P = 0.0	0.2 (7.3) 5, df = 2 (P = 0.3 0093) -5.3 (3.38) 13)	66 243 (2); 1 ² =1 25 37 37 37	-3.4 (7.3)	• + •	9.8% 49.7% 31.1% 31.1%	3.60 [1.08, 6.12] 2.21 [0.90, 3.52] 1.80 [0.39, 3.21] 1.80 [0.39, 3.21]

Analysis 2.8 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 8 Mental state: 2c. Positive symptoms - SAPS total score - percent change-short term (high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 8 Mantal state: 20 Positive symptoms SAPS total score percent ch

Outcome: 8 Mental state: 2c. Positive symptoms - SAPS total score - percent change-short term (high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	Mean IV,Rand	Difference Iom,95% Cl	Weight	Mean Difference IV,Random,95% Cl	
Ozguven 2004	15	-18.03 (27.29)	15	-58.87 (19.13)			► 100.0%	40.84 [23.97, 57.71]	
Total (95% Cl) Heterogeneity: not applic; Test for overall effect: Z =	15 able 4.75 (P < 0.1	00001)	15				100.0 %	40.84 [23.97, 57.71]	
				Favours treatmer	-10 -5 nt	0 5 Favours	10 control		

Analysis 2.9 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 9 Mental state: 3a. Negative symptoms - no clinically important change-short term (less than 20% SANS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia

Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 9 Mental state: 3a. Negative symptoms - no clinically im portant change-short term (less than 2 OS SANS total score reduction)



Analysis 2.10 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 10 Mental state: 3b. Negative symptoms average endpoint score (PANSS negative subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 10 Mental state: 3b. Negative symptoms - average endpoint score (PANSS

negative subscore, high = poor)

j p	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
1 short term Mori 2004	20	23.8 (4.6)	20	22.8 (3.3)		9.5 %	1.00 [-1.48, 3.48]
Riedel 2007	16	-3.98 (6.48)	17	-3.35 (6.48)		3.0 %	-0.63 [-5.05, 3.79]
Svestka 2003b	22	-9.59 (4.91)	20	-8.55 (4.53)		7.2 %	-1.04 [-3.90, 1.82]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z	58 .0; Chi ² = 1.21, = 0.01 (P = 0.9	. df = 2 (P = 0.5 9)	57 55); I ² =0.0%		•	19.7 %	0.01 [-1.72, 1.73]
2 medium term Kinon 2006b	169	-3.6 (6)	167	-4 (5.8)		36.9 %	0.40 [-0.86, 1.66]
McEvov 2006	8	-1.1 (6.22)	10	-0.7 (2.21)		2.9 %	-0.40 [-4.92, 4.12]
,						Contract and Contract	
Stroup 2006	63	0.2 (6.48)	66	-0.4 (6.48)		11.7 %	0.60 [-1.64, 2.84]
Stroup 2006 Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 Jong term	63 240 .0; Chi ² = 0.15, = 0.74 (P = 0.4	0.2 (6.48) . df = 2 (P = 0.9 6)	66 243 93); I ² =0.0%	-0.4 (6.48)	•	11.7 % 51.5 %	0.60 [-1.64, 2.84] 0.40 [-0.67, 1.47]
Stroup 2006 Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term M cEvoy 2007	63 240 .0; Chi ² = 0.15, = 0.74 (P = 0.4 44	0.2 (6.48) df = 2 (P = 0.9 6) -2.8 (3.45)	66 243 93); I ² =0.0% 37	-0.4 (6.48) -3.5 (3.1)	•	11.7 % 51.5 % 28.8 %	0.60 [-1.64, 2.84] 0.40 [-0.67, 1.47] 0.70 [-0.73, 2.13]
Stroup 2006 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term McEvoy 2007 Subtotal (95% CI) Heterogeneity: not appli Test for overall effect: Z	63 240 .0; Chi ² = 0.15, = 0.74 (P = 0.4 44 44 cable = 0.96 (P = 0.3	0.2 (6.48) df = 2 (P = 0.5 -2.8 (3.45) '4)	66 243 93); I ² =0.0% 37 37	-0.4 (6.48) -3.5 (3.1)	*	11.7 % 5 1. 5 % 28.8 % 2 8.8 %	0.60 [-1.64, 2.84] 0.40 [-0.67, 1.47] 0.70 [-0.73, 2.13] 0.70 [-0.73, 2.13]

Analysis 2.11 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 11 Mental state: 3c. Negative symptoms average endpoint score-medium term (SANS total score, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

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

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	M ear IV, Ran	n Difference dom,95% Cl	Weight	Mean Difference IV,Random,95% CI	
Kinon 2006b	169	-8.3 (20.1)	166	-12 (18.9)			100.0%	3.70 [-0.48, 7.88]	
Total (95% Cl) Heterogeneity: not app Test for overall effect: :	169 licable Z = 1.74 (P = 0.01	83)	166			-	100.0 %	3.70 [-0.48, 7.88]	
			F	avours treatment	-10 -5	0 Favo	5 10 urs control		

Analysis 2.12 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 12 Mental state: 3d. Negative symptoms average endpoint score-short term (SANS total scorepercent change, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 12 Montal state: 3d Nagative symptoms, superses endpoint score short

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

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)		Mean IV,Randi	Difference om,95% Cl	Weig	ght	Mean Difference IV,Random,95% CI	
Ozguven 2004	15	-25.68 (53.09)	15	-28.14 (42.33)	•		-	→ 10	0.0%	2.46 [-31.90, 36.82]	
Total (95% Cl) Heterogeneity: not appl Test for overall effect: Z	15 icable = 0.14 (P = 0.	89)	15					100	.0 %	2.46 [-31.90, 36.82]	
			1	Favours treatmer	-10 nt	-5	0 Favo	5 10 urs control			

Analysis 2.13 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 13 General functioning: General - average endpoint score-medium term (GAF total score, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 13 General functioning: General - average endpoint score-medium term (GAF total score, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
Kinon 2006b	140	-2.4 (14)	138	-6.2 (11.7)		100.0 %	3.80 [0.77, 6.83]
Total (95% Cl) Heterogeneity: not appl Test for overall effect: Z	140 icable = 2.46 (P = 0.01	4)	138		-	100.0 %	3.80 [0.77, 6.83]
			F	-10 avours treatment	-5 0 5 Favou	10 rs control	

Analysis 2.14 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 14 Quality of life: General - average endpoint score-medium term (QLS total score, high=poor)

Review: 2 Quetiapine versus OLANZAPINE

Outcome 14 Quality of versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 14 Quality of life: General - average endpoint score-m edium term (QLS total score, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kinon 2006b	143	-2.4 (18.5)	143	-4.2 (17.9)		100.0%	1.80 [-2.42, 6.02]
Total (95% Cl) Heterogeneity: not appl Test for overall effect: Z	143 icable = 0.84 (P = 0.4)	0)	143			100.0 %	1.80 [-2.42, 6.02]
			F	-10 avours treatment	-5 0 5 Favours ci	10 ontrol	

Analysis 2.15 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome eric use nm fatin osale

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 15 Service use: num ber of paiticipants re-hospitalised

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M-H,Random,95% C	Weight	Risk Ratio M - H, Random , 95% Cl	
1 medium term Stroup 2006	19/95	12/108	-	23.2 %	1.80 [0.92, 3.51]	
Subtotal (95% Cl) Total events: 19 (Quetiapin Heterogeneity: not applicab Test for overall effect: Z = 1	95 e), 12 (Olanzapine) Jle 72 (P = 0.085)	108	•	23.2 %	1.80 [0.92, 3.51]	
2 long term Lieberman 2005	68/337	38/336	+-	76.8 %	1.78 [1.24, 2.58]	
Subtotal (95% Cl) Total events: 68 (Quetiapin Heterogeneity: not applicab Test for overall effect: Z = 3	337 e), 38 (Olanzapine) ole 8.09 (P = 0.0020)	336	•	76.8 %	1.78 [1.24, 2.58]	
Total (95% CI) Total events: 87 (Quetiapin Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 3	432 e), 50 (Olanzapine) Chi ² = 0.00, df = 1 (8.54 (P = 0.00040)	444 P = 0.98); I ² = 0.0%	•	100.0 %	1.79 [1.30, 2.47]	
		0.00 Favours treatment	1 0.01 0.1 1 10 Favo	100 1000 ours control		

Analysis 2.16 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 16 Adverse effects: 1. General - at least one adverse effect

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 16 Adverse effects: 1. General - at least one adverse effect

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random , 95% Cl	Weight	Risk Ratio M-H,Random,95% Cl
Lieberman 2005	220/337	235/336		71.6%	0.93 [0.84, 1.04]
McEvoy 2006	10/15	14/19		3.9 %	0.90 [0.58, 1.42]
McEvoy 2007	77/134	71/133	-	16.9%	1.08 [0.87, 1.34]
Riedel 2007	10/26	13/26		2.0 %	0.77 [0.41, 1.43]
Sirota 2006	7/19	7/21		1.1 %	1.11 [0.48, 2.57]
Stroup 2006	32/95	29/108	+	4.5 %	1.25 [0.82, 1.91]
Total (95% Cl) Fotal events: 356 (Quetiapi Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = (626 ne), 369 (Olanzapine Chi ² = 3.69, df = 5 ().77 (P = 0.44)	643) P = 0.59); l ² =0.0%	•	100.0 %	0.97 [0.88, 1.06]
		0.1 Favours treatment	0.2 0.5 1 2 Favours	5 10 control	

Analysis 2.17 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 17 Adverse effects: 2. Death

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

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M-H,Random,95% Cl	Risk Ratio M - H, Random, 95% Cl	
1 suicide attempt Lieberman 2005	1/337	2/336	• •	0.50 [0.05, 5.47]	
McEvoy 2007	0/134	2/133	• <mark>1</mark>	0.20[0.01, 4.10]	
Subtotal (95% Cl) Total events: 1 (Quetiapin Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	471 e), 4 (Olanzapine) ; Chi ² = 0.22, df = 1 (1.10 (P = 0.27)	469 P = 0.64); l ² = 0.09	6	0.35 [0.05, 2.29]	
2 suicide McEvoy 2007	2/134	0/133		4.96 [0.24, 102.41]	
Stroup 2006	0/95	0/108		0.0 [0.0, 0.0]	
Subtotal (95% Cl) Total events: 2 (Quetiapin Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	229 e), 0 (Olanzapine) ; Chi ² = 0.0, df = 0 (P 1.04 (P = 0.30)	241 = 1.00); l ² =0.0%		4.96 [0.24, 102.41]	
Total (95% Cl) Total events: 3 (Quetiapin Heterogeneity: Tau ² = 0.3 Test for overall effect: Z =	700 e), 4 (Olanzapine) 7; Chi ² = 2.36, df = 2 0.34 (P = 0.74)	710 (P = 0.31); ² =15	Ϋ́	0.74 [0.13, 4.23]	
		Envours trantment	0.1 0.2 0.5 1 2 5	10	

Analysis 2.18 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 18 Adverse effects: 3a. Cardiac effects - QTc prolongation

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 18 Adverse effects: 3a. Cardiac effects - QTc prolongation

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Ris M-H,Ran	sk Ratio dom,95% Cl	Weight	Risk Ratio M - H, Random, 95% Cl	
Lieberman 2005	6/337	0/336	_		+ 100.0%	12.96 [0.73, 229.17]	
Total (95% Cl) Total events: 6 (Quetiapine Heterogeneity: not applica Test for overall effect: Z =	337), 0 (Olanzapine) ble 1.75 (P = 0.080)	336	-		100.0 %	12.96 [0.73, 229.17]	
		Favours treatment	0.1 0.2 0.5	1 2 5 Favours contro	10 51		

Analysis 2.19 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 19 Adverse effects: 3b. Cardiac effects - CLTc abnormalities - change from baseline in ms

Study or subgroup	Quetiapine N	O Mean(SD)	lanzapine N	Mean(SD)	Me; IV,Ra	n Difference ndom,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005 Stroup 2006	214	5.9 (27.8)	231	1.2 (27.4)	_	-	75.8%	4.70 [-0.43, 9.83] 7.00 [-2.98, 16.98]
Svestka 2003b	14	0.64 (27.18)	14	4.43 (32.25)	• • •		4.1%	-3.79 [-25.88, 18.30]
Total (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z	309 0.0; Chi ² = 0.77, 2 = 2.11 (P = 0.0	df = 2 (P = 0.68 35)	334); l ² =0.0%				100.0 %	4.81 [0.34, 9.28]
			F	avours treatmen	-10 -5	0 5 Favours c	10 control	

Analysis 2.20 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 20 Adverse effects: 4a. Central nervous system - sedation

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 20 Adverse effects: 4a. Central nervous system - sedation

tudy or subgroup	Quetiapine n/N	Olanzapine n/N	Odds Ratio M - H, Fixed, 95% Cl	Odds Ratio M - H, Fixed, 95% Cl	
Kinon 2006b	40/175	41/171		0.94 [0.57, 1.55]	
Lieberman 2005	103/337	104/336		0.98 [0.71, 1.36]	
McEvoy 2006	5/15	6/19		1.08 [0.26, 4.60]	
McEvoy 2007	77/134	71/133		1.18 [0.73, 1.91]	
Riedel 2007	10/26	13/26		0.63 [0.21, 1.88]	
Sirota 2006	0/19	0/21		0.0 [0.0, 0.0]	
Stroup 2006	22/95	30/108		0.78[0.41, 1.48]	
otal (95% Cl) otal events: 257 (Quetia eterogeneity: Chi ² = 1.7 est for overall effect: Z =	801 pine), 265 (Olanzapine 72, df = 5 (P = 0.89); I ² = 0.28 (P = 0.78)) =0.0%	•	0.97 [0.78, 1.20]	
		0.	1 0.2 0.5 1 2 5	10	

Analysis 2.21 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 21 Adverse effects: 4b. Central nervous system - seizures

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 21 Adverse effects: 4b. Central nervous system - seizures

Study or subgroup	Quetiapine n/N	Olanzapine n/N		Ri M - H, Ran	sk Ratio dom,95% (1	Weight	Risk Ratio M - H, Random , 95% Cl	
Sirota 2006	1/19	0/21				•	► 100.0%	3.30 [0.14, 76.46]	
Total (95% Cl) Total events: 1 (Quetiapini Heterogeneity: not applica Test for overall effect: Z =	19 2), 0 (Olanzapine) ble 0.74 (P = 0.46)	21					■ 100.0 %	3.30 [0.14, 76.46]	
		Favours treatment	0.1 0	.2 0.5	1 2 Fave	5 ours contro	10 I		

Analysis 2.22 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 22 Adverse effects: 5a. Extrapyramidal effects

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 22 Adverse effects: 5a. Extrapyramidal effects

study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random, 95% Cl	Risk Ratio M - H, Random , 95% Cl	
1 akathisia Lieberman 2005	16/337	15/336	+	1.06[0.53, 2.12]	
McEvoy 2007	25/134	27/133		0.92 [0.56, 1.50]	
Riedel 2007	0/26	0/26	T	0.0 [0.0, 0.0]	
Sirota 2006	3/19	3/21		1.11 [0.25, 4.83]	
Stroup 2006	6/95	6/108		1.14 [0.38, 3.41]	
Svestka 2003b	0/22	1/20		0.30 [0.01, 7.07]	
Subtotal (95% Cl) Total events: 50 (Quetiapine) Heterogeneity: Tau ² = 0.0; C Test for overall effect: Z = 0.:	633 , 52 (Olanzapine) hi ² = 0.75, df = 4 14 (P = 0.89)	644 (P = 0.95); I ² =0.0%	•	0.98 [0.68, 1.40]	
2 akinesia McEvov 2007	33/134	32/133		1.02 [0.67. 1.56]	
Subtotal (95% Cl) Total events: 33 (Quetiapine) Heterogeneity: not applicabl Test for overall effect: Z = 0.	134 32 (Olanzapine) 11 (P = 0.91)	133	•	102 [0.67, 156]	
3 dystonia Svestka 2003b	2/22	0/20		4 57 [0 23 89 72]	
Subtotal (95% Cl) Total events: 2 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 1.1	22 0 (Olanzapine) 00 (P = 0.32)	20		4.57 [0.23, 89.72]	
4 extrapyramidal symptoms Stroup 2006	7/95	4/108		1.99 [0.60, 6.59]	
Svestka 2003b	6/22	4/20		1.36 [0.45, 4.14]	
Subtotal (95% Cl) Total events: 13 (Quetiapine) Heterogeneity: Tau ² = 0.0; C Test for overall effect: Z = 1.:	117 8 (Olanzapine) hi ² = 0.21, df = 1 17 (P = 0.24)	128 (P = 0.65); ² = 0.0%	•	1.62 [0.72, 3.67]	
5 parkinsonism Sirota 2006	3/19	5/21		0.66 [0.18, 2.41]	
Subtotal (95% Cl) Total events: 3 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 0.1	19 5 (Olanzapine) 52 (P = 0.53)	21	-	0.66 [0.18, 2.41]	
6 tremor Svestka 2003b	3/22	7/20		0.39 [0.12, 1.31]	
Subtotal (95% Cl) Total events: 3 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 1.5	22 7 (Olanzapine) 53 (P = 0.13)	20	-	0.39 [0.12, 1.31]	
7 use of antiparkinson medie Atmaca 2003	ation 0/14	0/14		0.0 [0.0. 0.0]	
Lieberman 2005	11/337	25/336	-	0.44 [0.22, 0.88]	
M cEvey 2007	5/134	15/133		0.33 [0.12, 0.88]	
Ozguven 2004	1/15	2/15		0.50 [0.05, 4.94]	
Riedel 2007	0/26	0/26		0.0.10.0	
Sirota 2006	5/19	6/21		0.92 [0.33, 2.53]	
Subtotal (95% CI)	545	545	•	0.49 [0.30, 0.79]	

Analysis 2.23 Comparison 2 QUETIAPINE versu OLANZAPINE, Outcome 23 Adverse effects: 5b. Extrapyramidal effects - scale measured

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 23 Adverse effects: 5b. Extrapyramidal effects - scale measured

Study or subgroup	Quetiapine N	(Mean(SD))lanzapine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 akathisia: Barnes Akathis Sacchetti 2004	ia Scale (high 25	=poor) -0.3 (0.86)	25	-0.2 (0.86)	+	100.0%	-0.10[-0.58, 0.38]
Subtotal (95% Cl) Heterogeneity: not applical Test for overall effect: Z = 1	25 ble 0.41 (P = 0.6)	B)	25		•	100.0 %	-0.10 [-0.58, 0.38]
2 extrapyramidal symptom Riedel 2007	s: ESRS total s 16	core (high=po 0 (3.92)	or) 17	0 (3.92)		100.0%	0.0 [-2.68, 2.68]
Subtotal (95% CI) Heterogeneity: not applical Test for overall effect: Z = (16 ble 0.0 (P = 1.0)		17			100.0 %	0.0 [-2.68, 2.68]
3 extrapyramidal symptom Sacchetti 2004	s: Simpson-A 25	ngus Scale (hig -0.4 (3.58)	h=poor) 25	-1 (3.58)		100.0%	0.60 [-1.38, 2.58]
Subtotal (95% CI) Heterogeneity: not applical Test for overall effect: Z = 1	25 ble 0.59 (P = 0.5)	5)	25		-	100.0 %	0.60 [-1.38, 2.58]
				-10	-5 0 5	10	
			F	avours treatment	Favours c	ontrol	

Analysis 2.24 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 24 Adverse effects: 6a. Prolactin associated side effects

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 24 Adverse effects: 6a. Prolactin associated side effects

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random , 95% Cl	Risk Ratio M-H,Random,95% Cl	
1 abnormally high prolac Svestka 2003b	tin value 0/22	4/20	— — —	0.10[0.01, 1.77]	
Subtotal (95% Cl) Total events: 0 (Quetiapin Heterogeneity: not applic: Test for overall effect: Z =	22 e), 4 (Olanzapine) able 1.57 (P = 0.12)	20	-	0.10 [0.01, 1.77]	
2 amenorrhea Lieberman 2005	5/82	11/92		0.51 [0.18, 1.41]	
McEvoy 2006	0/3	0/1		0.0 [0.0, 0.0]	
McEvoy 2007	10/42	10/32		0.76 [0.36, 1.61]	
Subtotal (95% Cl) Total events: 15 (Quetiapi Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	127 ne), 21 (Olanzapine) ; Chi ² = 0.40, df = 1 1.35 (P = 0.18)	125 (P = 0.53); I ² =0.0%	•	0.66 [0.36, 1.21]	
3 galactorrhea Lieberman 2005	6/337	7/336	-	0.85 [0.29, 2.52]	
McEvoy 2006	0/15	1/19		0.42 [0.02, 9.55]	
McEvoy 2007	0/134	3/133		0.14 [0.01, 2.72]	
Stroup 2006	0/21	0/30		0.0 [0.0, 0.0]	
Subtotal (95% Cl) Total events: 6 (Quetiapin Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	507 e), 11 (Olanzapine) ; Chi ² = 1.39, df = 2 0.85 (P = 0.40)	518 (P = 0.50); l ² = 0.0%	•	0.66 [0.25, 1.73]	
4 gynecomastia McEvoy 2007	3/134	9/133		0.33 [0.09, 1.20]	
Subtotal (95% Cl) Total events: 3 (Quetiapin Heterogeneity: not applic: Test for overall effect: Z =	134 e), 9 (Olanzapine) able 1.69 (P = 0.091)	133	-	0.33 [0.09, 1.20]	
5 sexual dysfunction Lieberman 2005	69/337	91/336		0.76 [0.57, 0.99]	
McEvoy 2006	2/15	2/19		1.27 [0.20, 7.97]	
McEvoy 2007	35/134	37/133	+	0.94 [0.63, 1.39]	
Stroup 2006	10/95	18/108		0.63 [0.31, 1.30]	
Subtotal (95% Cl) Total events: 116 (Quetiag Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	581 bine), 148 (Olanzapin ; Chi ² = 1.45, df = 3 2.07 (P = 0.039)	596 e) (P = 0.69); I ² =0.0%	•	0.80 [0.64, 0.99]	

Analysis 2.25 **Comparison 2 QUETIAPINE versus OLANZAPINE,** Outcome 25 Adverse effects: 6b. Prolactin - change from baseline in ng/ml

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 25 Adverse effects: 6b. Prolactin - change from baseline in ng/ml

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)		Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	337	-9.3 (25.7)	336	-6.1 (22)			33.1 %	-3.20 [-6.81, 0.41]
McEvoy 2006	13	-13.2 (18.02)	16	-4.1 (9.2)	-		16.2%	-9.10 [-19.88, 1.68]
McEvoy 2007	44	-18.7 (17.64)	37	-15.9 (15.57)	•		23.7 %	-2.80 [-10.03, 4.43]
Stroup 2006	95	-8.3 (18.5)	108	-5.1 (37.4)	•		21.9 %	-3.20 [-11.17, 4.77]
Svestka 2003b	20	-14.74 (26.07)	15	25.33 (41.78)	•		4.9 %	-40.07 [-64.10, -16.04]
Total (95% Cl) Heterogeneity: Tau ² = 1 Test for overall effect: 2	509 22.40; Chi ² = 9 = 2.01 (P = 0.	.84, df = 4 (P = 044)	512 0.04); l ² =59	9%		-	100.0 %	-5.89 [-11.62, -0.16]
			F	avours treatmen	-10 -5 nt	0 5 Favours	10 control	

Analysis 2.26 **Comparison 2 QUETIAPINE versus OLANZAPINE,** Outcome 26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 26 Adverse effects: 7a. Metabolic - cholesterol - significant cholesterol increase

Study or subgro	up Quetiapine n/N	Olanzapine n/N		м	Ri: I-H,Ran	sk Rat dom,s	tio 95% Cl		Weight	Risk Ratio M - H, Random, 95% Cl	
McEvoy 2007	23/134	23/133			-		-		100.0%	0.99 [0.59, 1.68]	
Total (95% Cl Total events: 23 Heterogeneity: n Test for overall e) 134 (Quetiapine), 23 (Olanzapine) ot applicable (ffect: Z = 0.03 (P = 0.98)	133							100.0 %	0.99 [0.59, 1.68]	
		Favours treatmen	0.1 nt	0.2	0.5	1	2 Favours	5 contro	10 I		

Analysis 2.27 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 27 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 7.1 Adverse effects: 7b. Metabolic - cholesterol - change from baseline in mg/dl

idy or subgroup	Quetiapine N	Mean(SD)	Dlanzapine N	Mean(SD)	Mear IV,Ran	dom,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Lieberman 2005	337	5.3 (38.6)	336	9.7 (38.5)	← –		35.1 %	-4.40 [-10.22, 1.42]
McEvoy 2006	13	-13 (24.5)	16	0.2 (31.6)	•		13.5 %	-13.20 [-33.62, 7.22]
McEvoy 2007	44	25.2 (29.58)	37	15.7 (26.16)			23.8 %	9.50 [-2.64, 21.64]
Stroup 2006	95	4.8 (37)	108	17.9 (34.3)	·		27.7 %	-13.10[-22.96, -3.24]
stal (95% Cl) terogeneity: Tau ² = 1 st for overall effect: 2	489 53.21; Chi ² = 8. 1 = 1.01 (P = 0.3	72, df = 3 (P = 0 31)	497 0.03); l ² =66	%			100.0 %	-4.69 [-13.84, 4.45]
					-10 -5	0 5	10	

Analysis 2.28 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 28 Adverse effects: 7c. Metabolic - glucose abnormally high fasting glucose value

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE

Outcome: 2B Adverse effects: 7c. Metabolic - glucose - abnorm ally high fasting glucose value

Study or subgroup	Quetiapine n/N	Olanzapine n/N			Ri M-H,Ran	sk Rat dom, S	io 95% CI		Weight	Risk Ratio M - H, Random , 95% Cl	
McEvoy 2007	10/134	14/133		-		-			100.0%	0.71 [0.33, 1.54]	
Total (95% Cl) Total events: 10 (Quetiapi Heterogeneity: not applic: Test for overall effect: Z =	134 ine), 14 (Olanzapine) able : 0.87 (P = 0.38)	133		-	-				100.0 %	0.71 [0.33, 1.54]	
		Favours treatmen	0.1 t	0.2	0.5	1	2 Favour:	5 s contro	10		

Analysis 2.29 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 29 Adverse effects: 7d. Metabolic - glucose change from baseline in mg/dl

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 29 Adverse effects: 7d. Metabolic - glucose - change from baseline in mg/dl

Study or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)		Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Lieberman 2005	337	6.8 (45.9)	336	15 (51.3)	•			32.7 %	-8.20 [-15.56, -0.84]
McEvoy 2006	13	-23.3 (44)	16	23.6 (60.8)	←			4.4 %	-46.90 [-85.10, -8.70]
McEvoy 2007	44	6.2 (11.08)	37	8.6 (9.67)			<u> </u>	38.6 %	-2.40 [-6.92, 2.12]
Stroup 2006	95	-0.2 (41.9)	108	14.8 (41.6)	•			24.2 %	-15.00[-26.51,-3.49]
Total (95% Cl) Heterogeneity: Tau ² = 4 Test for overall effect: Z	489 3.37; Chi ² = 9.4 = 2.15 (P = 0.0	45, df = 3 (P = 32)	497 0.02); l ² =68	%				100.0 %	-9.32 [-17.82, -0.82]
			F	avours treatmen	-10 nt	-5	0 5 Favours cont	10 rol	

Analysis 2.30 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 30 Adverse effects: 7e. Metabolic - weight gain

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 30 Adverse effects: 7e. Metabolic - weight - gain

Study or subgroup	Quetiapine n/N	Olanzapine n/N	Risk Ratio M - H, Random , 95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
1 significant weight gain (Lieberman 2005	as defined by the orig 49/337	inal studies) 92/336	-	28.2 %	0.53 [0.39, 0.73]	
McEvoy 2006	2/15	2/19		2.5 %	1.27 [0.20, 7.97]	
McEvoy 2007	67/134	106/133	+	35.1 %	0.63 [0.52, 0.76]	
Riedel 2007	8/26	8/26	+	10.0 %	1.00 [0.44, 2.26]	
Sacchetti 2004	9/25	4/25		6.8 %	2.25 [0.80, 6.36]	
Stroup 2006	12/95	29/108		14.9 %	0.47 [0.25, 0.87]	
Svestka 2003b	3/22	0/20		1.0 %	6.39 [0.35, 116.57]	
Subtotal (95% Cl) Total events: 150 (Quetiap Heterogeneity: Tau ² = 0.07 Test for overall effect: Z =	654 ine), 241 (Olanzapine) 7; Chi ² = 12.02, df = 1 2.27 (P = 0.023)	667 5 (P = 0.06); I ² =50%	•	98.5 %	0.69 [0.51, 0.95]	
2 as "weight gain" reported Kinon 2006b	d adverse events 1/175	2/171		1.5 %	0.49[0.04, 5.34]	
Subtotal (95% Cl) Total events: 1 (Quetiapine Heterogeneity: not applica Test for overall effect: Z =	175 e), 2 (Olanzapine) uble 0.59 (P = 0.56)	171		1.5 %	0.49 [0.04, 5.34]	
Total (95% Cl) Total events: 151 (Quetiap Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	829 Sine), 243 (Olanzapine) 6; Chi ² = 12.06, df = 3 2.54 (P = 0.011)	838 7 (P = 0.10); I ² =42%	•	100.0 %	0.68 [0.51, 0.92]	
	2	0.0 Favours treatment	01 0.01 0.1 1 10 10 Favours co	0 1000 ntrol		

Analysis 2.31 Comparison 2 QUETIAPINE versus OLANZAPINE, Outcome 31 Adverse effects: 7f. Metabolic - weight change from baseline in kg

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 2 QUETIAPINE versus OLANZAPINE Outcome: 31 Adverse effects: 7f. Metabolic - weight - change from baseline in kg

ıdy or subgroup	Quetiapine N	Mean(SD)	Olanzapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Atmaca 2003	14	4.41 (2.21)	13	8.92 (3.13)		16.4 %	-4.51 [-6.57, -2.45]
Kinon 2006b	175	0.39 (4.74)	171	1.03 (5.78)		20.5 %	-0.64 [-1.76, 0.48]
Lieberman 2005	305	0.5 (7)	307	4.3 (7)		20.5 %	-3.80 [-4.91, -2.69]
McEvoy 2006	15	0.5 (8.91)	19	2.8 (14.38)	• • • •	3.4 %	-2.30 [-10.18, 5.58]
McEvoy 2007	44	5.69 (11.47)	37	10.87 (10.64)		7.3 %	-5.18 [-10.00, -0.36]
Riedel 2007	16	3.28 (3.17)	17	3.76 (2.77)	—•	16.5 %	-0.48 [-2.52, 1.56]
Sirota 2006	19	-0.9 (3.73)	21	2.3 (3.73)		15.3 %	-3.20 [-5.51, -0.89]
t al (95% Cl) terogeneity: Tau ² = 1	588 2.86; Chi ² = 24.	88, df = 6 (P =	585 0.00036); I²	=76%	•	100.0 %	-2.68 [-4.26, -1.10]
stior overall ellect. 2	- 5.52 (r = 0.0	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					
					-10 -5 0 5	10	

Analysis 3.1 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 1 Global state: 1a. No clinically significant response (as defined by the original studies)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

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

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M-H,Random,95% Cl	Risk Ratio M-H,Random,95% Cl	
Conley 2005	12/12	13/13		0.0 [0.0, 0.0]	
McEvoy 2007	56/134	47/133		1.18 [0.87, 1.60]	
Potkin 2006	100/156	77/153	-	1.27 [1.05, 1.55]	
Zhong 2006	248/338	247/335	+	1.00 [0.91, 1.09]	
Total (95% CI) Total events: 416 (Quetia Heterogeneity: Tau ² = 0. Test for overall effect: Z =	640 pine), 384 (Risperidon 02; Chi ² = 6.09, df = 2 = 1.19 (P = 0.23)	634 e) (P = 0.05); I ² =67%	•	1.12 [0.93, 1.35]	
		0.1 Favours treatment	0.2 0.5 1 2 Favours o	5 10 control	

Analysis 3.2 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 2 Global state: 1b. No clinically important change (as defined by the original studies)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 2 Global state: lb. No clinically im portant change (as defined by the original studies)

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random , 95% CI	Risk Ratio M - H, Random , 95% Cl	
1 short term Conley 2005	12/12	13/13		0.0 [0.0, 0.0]	
Potkin 2006	113/156	85/153	-	1.30 [1.10, 1.55]	
Zhong 2006	206/338	195/335	•	1.05 [0.92, 1.19]	
Subtotal (95% Cl) Total events: 331 (Quetiap Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	506 pine), 293 (Risperidon 2; Chi ² = 4.12, df = 1 1.35 (P = 0.18)	e) (P = 0.04); I ² =76%		1.16 [0.94, 1.44]	
2 long term McEvoy 2007	56/134	47/133	-	1.18 [0.87, 1.60]	
Subtotal (95% Cl) Total events: 56 (Quetiapi Heterogeneity: not applic: Test for overall effect: Z =	134 ne), 47 (Risperidone) able 1.08 (P = 0.28)	133	•	1.18 [0.87, 1.60]	
Total (95% Cl) Total events: 387 (Quetia Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	640 bine), 340 (Risperidon 11; Chi ² = 4.19, df = 2 1.87 (P = 0.061)	634 e) (P = 0.12); I ² =52%	•	1.16 [0.99, 1.35]	
		0.001 Favours treatment	0.01 0.1 1 10 100 Favours con	1000 trol	

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Analysis 3.3 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 3 Leaving the study early

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 3 Leaving the study early

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random , 95% Cl	Weight	Risk Ratio M-H, Random, 95% Cl	
1 any reason Atmaca 2003	0/14	1/14		0.1 %	0.33 [0.01, 7.55]	
Conley 2005	5/12	4/13		0.6 %	1.35 [0.47, 3.89]	
Lieberman 2005	277/377	253/341		37.4 %	0.99 [0.91, 1.08]	
McEvoy 2006	13/15	12/16	+	5.0 %	1.16 [0.82, 1.63]	
McEvoy 2007	95/134	95/133	-	19.7 %	0.99 [0.85, 1.16]	
Potkin 2006	24/156	14/153	-+-	1.7 %	1.68 [0.90, 3.13]	
Riedel 2005	9/22	10/22	-	1.4 %	0.90 [0.46, 1.78]	
Sacchetti 2004	4/25	5/25		0.5 %	0.80 [0.24, 2.64]	
Stroup 2006	53/63	45/70	-	12.6 %	1.31 [1.07, 1.61]	
Zhong 2006	184/338	167/335		21.1 %	1.09 [0.94, 1.26]	
Subtotal (95% Cl) Total events: 664 (Quetiapin Heterogeneity: Tau ² = 0.00, Test for overall effect: Z = 1	1156 ne), 606 (Risperidon ; Chi ² = 10.73, df = 50 (P = 0.13)	1122 e) 9 (P = 0.29); ² =16%	1	100.0 %	106 [0.98, 115]	
2 due to adverse events Conley 2005	2/12	0/13		1.9%	5.38 [0.28, 101.96]	
Lieberman 2005	49/337	34/341	-	33.6 %	1.46 [0.97, 2.20]	
McEvoy 2006	3/15	0/16		2.0 %	7.44 [0.42, 132.95]	
McEvoy 2007	13/134	13/133	-	19.7 %	0.99 [0.48, 2.06]	
Riedel 2005	0/22	3/22		2.0 %	0.14 [0.01, 2.61]	
Stroup 2006	11/63	7/70		15.3 %	1.75 [0.72, 4.23]	
Zhong 2006	19/338	25/335	-	25.5 %	0.75 [0.42, 1.34]	
Subtotal (95% Cl) Total events: 97 (Quetiapini Heterogeneity: Tau ² = 0.09 Test for overall effect: Z = 0	921 e), 82 (Risperidone) ; Chi ² = 8.92, df = 6 1.82 (P = 0.42)	930 (P = 0.18); ² = 33%	•	100.0 %	119 [0.78, 1.80]	
3 due to inefficacy Conley 2005	3/12	3/13	_	2.8 %	1.08 [0.27, 4.37]	
Lieberman 2005	92/337	91/341		34.8 %	1.02 [0.80, 1.31]	
McEvey 2006	6/15	6/16		6.6 %	1.07 [0.44, 2.59]	
McEvoy 2007	17/134	12/133	-	9.8 %	1.41 [0.70, 2.83]	
Riedel 2005	3/22	5/22		3.2 %	0.60 [0.16, 2.21]	
Stroup 2006	22/63	18/70	-	15.4 %	1.36 [0.81, 2.29]	
Zhong 2006	82/338	46/335	-	27.3 %	1.77 [1.27, 2.45]	
Subtotal (95% Cl) Total events: 225 (Quetiapin Heterogeneity: Tau ² = 0.03, Test for overall effect: Z = 1	921 ne), 181 (Risperidon ; Chi ² = 8.41, df = 6 90 (P = 0.058)	930 (P = 0.21); I ² =29%	•	100.0 %	1.26 [0.99, 1.61]	
		0.0 Favours treatment	01 0.01 0.1 1 10 10 Favours co	0 1000 ntrol		

Analysis 3.4 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 4 Mental state: 1a General - no clinically important change - short term (less than 30% PANSS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 4 Mental state: 1a General - no clinically im poitant change - shoit term (less than 30% PANSS total score reduction)

Study or subgroup	Quetiapine n/N	Risperidone n/N		Ri M - H, Ran	sk Ratio dom,95%	cı	Weight	Risk Ratio M - H, Random, 95% Cl	
Potkin 2006 Zhong 2006	100/156 248/338	77/153 247/335			 -		43.8 % 56.2 %	1.27 [1.05, 1.55] 1.00 [0.91, 1.09]	
Total (95% Cl) Total events: 348 (Quetia Heterogeneity: Tau ² = 0. Test for overall effect: Z =	494 pine), 324 (Risperidon 03; Chi ² = 5.26, df = 1 = 0.82 (P = 0.41)	488 e) (P = 0.02); I ² =81%			•		100.0 %	111 [0.87, 1.42]	
		0.1 Favours treatment	0.2	0.5	1 2 Fax	5 ours contr	10 ol		

Analysis 3.5 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 5 Mental state: 1b. General - no clinically important change - short term (less than 20% BPRS total score reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 5 Mental state: lb. General - no clinically im portant change - short term (less than 2 OS BPRS total score reduction)

Study or subgroup	Quetiapine n/N	Risperidone n/N		м	Ri: -H,Ran	sk Rat dom,9	io 95% CI		Weight	Risk Ratio M - H, Random, 95% Cl	
Conley 2005	9/12	10/13			-	-			100.0%	0.98 [0.63, 1.52]	
Total (95% Cl) Total events: 9 (Quetiapine Heterogeneity: not applica Test for overall effect: Z =	12 2), 10 (Risperidone) ble 0.11 (P = 0.91)	13			-				100.0 %	0.98 [0.63, 1.52]	
2		Favours treatmen	0.1 t	0.2	0.5	1	2 Favours	5 control	10		

Analysis 3.6 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 6 Mental state: 1c. General - average endpoint score (PANSS total score, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 6 Mental state: lc. General - average endpoint score (PANSS total score, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 short term Atmaca 2003	14	77.24 (6.08)	13	78.26 (4.62)		17.1 %	-1.02 [-5.08, 3.04]
Mori 2004	20	72.9 (15.1)	19	71.5 (12)		5.3 %	1.40 [-7.14, 9.94]
Potkin 2006	156	-20.5 (22.31)	152	-27.7 (22.31)		12.8 %	7.20 [2.22, 12.18]
Riedel 2005	22	-30.4 (22.31)	22	-29.7 (22.31)	• •	2.4 %	-0.70[-13.88, 12.48]
Zhong 2006	328	-15.1 (25.36)	318	-18.1 (25)		18.0%	3.00 [-0.88, 6.88]
Subtotal (95% Cl) Heterogeneity: Tau ² = 5 Test for overall effect: 2	540 5.16; Chi² = 6.6 = 1.47 (P = 0.1	5, df = 4 (P = 0 4)	524 .16); l ² =409	6		55.5 %	2.44 [-0.81, 5.69]
2 medium term McEvoy 2006	8	-1.3 (19.23)	6	-0.3 (6.86)	• • • •	2.0 %	-1.00 [-15.41, 13.41]
Stroup 2006	63	2 (22.31)	69	-8 (22.31)		6.4 %	10.00 [2.38, 17.62]
Subtotal (95% Cl) Heterogeneity: Tau ² = 2 Test for overall effect: 2	71 25.91; Chi ² = 1.2 = 1.20 (P = 0.2	75, df = 1 (P = 3)	75 0.19); l ² =43	3%		8.4 %	6.27 [-3.94, 16.48]
3 long term Lieberman 2005	329	-6.08 (22.31)	333	-9.31 (22.31)		21.2 %	3.23 [-0.17, 6.63]
McEvoy 2007	44	-15.6 (10.68)	37	-18.5 (9.91)		14.9 %	2.90 [-1.59, 7.39]
Subtotal (95% Cl) Heterogeneity: Tau ² = 1 Test for overall effect: 2	373 0.0; Chi ² = 0.01, = 2.25 (P = 0.0	df = 1 (P = 0.9 25)	370 91); I ² =0.0%			36.1 %	3.11 [0.40, 5.82]
Total (95% Cl) Heterogeneity: Tau ² = 2 Test for overall effect: 2	984 2.27; Chi² = 10.! 2 = 2.92 (P = 0.0	50, df = 8 (P = 035)	969 0.23); I ² =24	8%	•	100.0 %	3.09 [1.01, 5.16]
			F	avours treatmer	-10 -5 0 5 t Favours control	10	

Analysis 3.7 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 7 Mental state: 1d. General - average endpoint score - short term (BPRS total score, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 7 Mental state: 1d. General - average endpoint score - short term (BPRS total score, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)		Mean IV,Rando	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% CI
Conley 2005	12	53.83 (13.14)	13	52.15 (12.34)	-			100.0%	1.68 [-8.33, 11.69]
Total (95% CI) Heterogeneity: not appli Test for overall effect: Z	12 cable = 0.33 (P = 0.3	74)	13					100.0 %	1.68 [-8.33, 11.69]
				wours treatment	-10	-5	0 5	i 10	
			F	avours treatment	C .		Favou	irs control	

Analysis 3.8 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 8 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 40% PANSS positive reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 8 Mental state: 2a. Positive symptoms - no clinically important change - short term (less than 40% PANSS positive reduction)

Study or subgroup	Quetiapine n/N	Risperidone n/N			Ri M - H, Rar	isk R ndorr	tatio 1,95% CI		Weight	Risk Ratio M - H, Random, 95% Cl	
Zhong 2006	222/338	220/335				+			100.0%	1.00 [0.90, 1.12]	
Total (95% CI) Total events: 222 (Quetiap Heterogeneity: not applica Test for overall effect: Z =	338 ine), 220 (Risperidon ble 0.00 (P = 1.0)	335 e)		1		•			100.0 %	1.00 [0.90, 1.12]	
	1	Favours treatmen	0.1 t	0.2	0.5	1	2 Favour	5 s contro	10		

Analysis 3.9 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 9 Mental state: 2b. Positive symptoms average endpoint score - (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

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

study of subgroup	Quetiapine N	R Mean(SD)	isperidone N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI
1 short term Mori 2004	20	13.3 (4.3)	19	10.8 (2.2)		9.5 %	2.50 [0.37, 4.63]
Potkin 2006	156	-5.9 (6.24)	152	-8.7 (6.16)	-	22.5 %	2.80 [1.42, 4.18]
Riedel 2005	22	-3.8 (7.3)	22	-7.6 (7.3)		2.3 %	3.80 [-0.51, 8.11]
Zhong 2006	328	-4.5 (7.24)	318	-5.6 (7.13)		35.2 %	1.10 [-0.01, 2.21]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z	526 .44; Chi ² = 4.67 = 3.76 (P = 0.0	7, df = 3 (P = 0.2 0017)	5 11 20); l² =36%	⁶	•	69.5 %	2.10 [1.00, 3.19]
2 medium term	8	0.6 (5.94)	6	-0.5 (1.71)	,	2.3 %	1.10 [-3.24, 5.44]
MCEVUY 2006							
Stroup 2006	63	0.2 (7.3)	69	-2.3 (7.3)		6.9 %	2.50 [0.01, 4.99]
Stroup 2006 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z	63 71 .0; Chi ² = 0.30, = 1.95 (P = 0.0	0.2 (7.3) df = 1 (P = 0.58 51)	69 75 3); I ² =0.0%	-2.3 (7.3)	•	6.9 % 9.2 %	2.50 [0.01, 4.99] 2.15 [-0.01, 4.31]
Stroup 2006 Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term McEvoy 2007	63 71 .0; Chi ² = 0.30, = 1.95 (P = 0.0	0.2 (7.3) df = 1 (P = 0.58 51) -5.3 (3.38)	69 75 37); I ² =0.0%	-2.3 (7.3) -6.6 (3.16)	•	6.9 % 9.2 %	2.50 [0.01, 4.99] 2.15 [-0.01, 4.31] 1.30 [-0.13, 2.73]
Stroup 2006 Subtotal (95% CI) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term M EEvoy 2007 Subtotal (95% CI) Heterogeneity: not appli Test for overall effect: Z	63 71 .0; Chi ² = 0.30, = 1.95 (P = 0.0 44 44 cable = 1.79 (P = 0.0	0.2 (7.3) df = 1 (P = 0.58 51) -5.3 (3.38) 74)	69 75 37 37 37	-2.3 (7.3) -6.6 (3.16)	• •	6.9 % 9.2 % 21.2 % 21.2 %	2:50 [0.01, 4:39] 2:15 [-0.01, 4:31] 1:30 [-0.13, 2:73] 1:30 [-0.13, 2:73]

Analysis 3.10 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 10 Mental state: 2c. Positive symptoms average endpoint score - short term (BPRS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: IB Mental state: 2c. Positive symptoms - average endpoint score - short term (BPRS positive subscore, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)	Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Conley 2005	12	-0.67 (1.02)	13	-1.77 (1.31)			100.0 %	1.10 [0.18, 2.02]
Total (95% CI) Heterogeneity: not appli Test for overall effect: Z	12 cable = 2.35 (P = 0.0)	19)	13			•	100.0 %	1.10 [0.18, 2.02]
			Fi	-] avours treatment	10 -5	0 Favor	5 10 Irs control	

Analysis 3.11 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 11 Mental state: 3a. Negative symptoms - no clinically important change - short term (less than 40% PANSS negative reduction)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 11 Mental state: 3a. Negative symptoms - no clinically im portant change - short term (less than 40% PANSS negative reduction)

Study or subgroup	Quetiapine n/N	Risperidone n/N		Ri M - H, Ran	sk Ratio dom,95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
Zhong 2006	293/338	295/335			+	100.0%	0.98 [0.93, 1.04]	
Total (95% Cl) Total events: 293 (Quetiap Heterogeneity: not applic: Test for overall effect: Z =	338 bine), 295 (Risperidon able 0.54 (P = 0.59)	335 e)				100.0 %	0.98 [0.93, 1.04]	
		Favours treatmen	0.1 0 t	.2 0.5	1 2 Favou	5 10 rs control		

Analysis 3.12 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 12 Mental state: 3b. Negative symptoms average endpoint score - (PANSS negative subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 12 Mental state: 3b. Negative symptoms - average endpoint score - (PANSS negative subscore, high = poor)

stady of subgroup	Quetiapine N	R Mean(SD)	isperidone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
1 short term Mori 2004	20	23.8 (4.6)	19	25.6 (4.8)		12.3 %	-1.80 [-4.75, 1.15]
Potkin 2006	156	-2.5 (5)	152	-4 (4.93)		19.3 %	1.50 [0.39, 2.61]
Riedel 2005	22	-12.8 (6.48)	22	-4.2 (6.48)		9.6 %	-8.60 [-12.43, -4.77]
Zhong 2006	281	-3.7 (6.71)	284	-4.1 (6.74)		19.3 %	0.40 [-0.71, 1.51]
Subtotal (95% Cl) Heterogeneity: Tau ² = 5 Test for overall effect: Z	479 5.88; Chi ² = 27.1 = 1.08 (P = 0.2	13, df = 3 (P<0.0 28)	477 0001); l ² =	=89%	•	60.6 %	-1.46 [-4.11, 1.19]
2 medium term McEvoy 2006	8	-1.1 (6.22)	6	0 (4.16)		6.1 %	-1.10 [-6.55, 4.35]
Stroup 2006	63	0.2 (6.48)	69	-1.5 (6.48)		15.1 %	1.70 [-0.51, 3.91]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z	71 0.0; Chi ² = 0.87, = 1.25 (P = 0.2	, df = 1 (P = 0.35 21)	75 i); l² =0.0%			21.3 %	1.30 [-0.75, 3.35]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term McEvoy 2007	71 0.0; Chi ² = 0.87, = 1.25 (P = 0.2 44	. df = 1 (P = 0.35 1) -2.8 (3.45)	75 i); l ² =0.0% 37	-3.6 (3.16)	-	2 1.3 %	1.30 [-0.75, 3.35] 0.80 [-0.64, 2.24]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0 Test for overall effect: Z 3 long term McEvoy 2007 Subtotal (95% Cl)	71 0.0; Chi ² = 0.87, = 1.25 (P = 0.2 44 44	. df = 1 (P = 0.35 1) -2.8 (3.45)	75 i); I ² =0.0% 37 37	-3.6 (3.16)	+ +	21.3 % 18.2 % 18.2 %	1.30 [-0.75, 3.35] 0.80 [-0.64, 2.24] 0.80 [-0.64, 2.24]
Subtotal (95% CI) Heterogeneity: Tau ² = C Test for overall effect: Z 3 long term McEvoy 2007 Subtotal (95% CI) Heterogeneity: not appl Test for overall effect: Z	71 0.0; Chi ² = 0.87, = 1.25 (P = 0.2 44 44 icable = 1.09 (P = 0.2	, df = 1 (P = 0.35 21) -2.8 (3.45) 28)	75); 1 ² =0.0% 37 37	-3.6 (3.16)	÷	21.3 % 18.2 % 18.2 %	1.30 [-0.75, 3.35] 0.80 [-0.64, 2.24] 0.80 [-0.64, 2.24]

Analysis 3.13 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 13 Mental state: 3c. Negative symptoms average endpoint score - (BPRS negative subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 13 Mental state: 3c. Negative symptoms - average endpoint score - (BPRS negative subscore, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)		Mean IV,Randi	Difference om,95% C	e I	Weight	Mean Difference IV,Random,95% CI
Conley 2005	12	0.42 (0.51)	13	-0.15 (0.51)			+		100.0%	0.57 [0.17, 0.97]
Total (95% Cl) Heterogeneity: not appli Test for overall effect: Z	12 cable = 2.79 (P = 0.00	052)	13				•		100.0 %	0.57 [0.17, 0.97]
			F	avours treatment	-10	-5	0 Fav	5 5 vours control	.0	

Analysis 3.14 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 14 Quality of life: General- average endpoint score - short term (QLS total score, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 14 Quality of life: General- average endpoint score - short term (QLS total score,

high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)		Mean I IV,Rando	Difference om,95% Cl		Weight	Mean Difference IV,Random,95% Cl
Conley 2005	10	27.9 (15.93)	12	28.4 (15.93)	•				100.0%	-0.50 [-13.87, 12.87]
Total (95% Cl) Heterogeneity: not app Test for overall effect: 2	10 licable 2 = 0.07 (P = 0.9	4)	12						100.0 %	-0.50 [-13.87, 12.87]
			F	avours treatmen	-10 t	-5	0 Favo	5 urs control	10	

Analysis 3.15 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 15 Service use: number of participants rehospitalised

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 15 Service use: num ber of participants re-hospitalised

1 m edium term Stroup 2006 19/95 16/104 23.0 % 1.30 [0.71, 2.38] Subtotal (95% CI) 95 104 23.0 % 1.30 [0.71, 2.38] Total events: 19 (Quetiapine), 15 (Risperidone) 4 23.0 % 1.30 [0.71, 2.38] Vertor geneity: not applicable 77.0 % 1.35 [0.97, 1.88] Subtotal (95% CI) 337 341 77.0 % 1.35 [0.97, 1.88] Subtotal (95% CI) 337 341 77.0 % 1.35 [0.97, 1.88] Total events: 68 (Quetiapine), 51 (Risperidone) 422 445 445 Total events: 67 (Quetiapine), 57 (Risperidone) 432 445 445 Total events: 67 (Quetiapine), 57 (Risperidone) 1.34 [1.00, 1.79] 1.34 [1.00, 1.79] Test for overall effect 2.7 (P = 0.045) * 100.0 % 1.34 [1.00, 1.79]	itudy or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random, 95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
Subtoral (95% CI) 95 104 23.0 % 1.30 [0.71, 2.38] Total events: 19 (Justiapine), 15 (Risperidone) 4 1.30 [0.71, 2.38] Hetrogeneily: not applicable 77.0 % 1.35 [0.97, 1.88] Subtoral (95% CI) 337 341 77.0 % 1.35 [0.97, 1.88] Subtoral (95% CI) 337 341 77.0 % 1.35 [0.97, 1.88] Total events: 68 (Quetiapine), 51 (Risperidone) Hetrogeneity: not applicable 77.0 % 1.35 [0.97, 1.88] Total events: 67 (Quetiapine), 67 (Risperidone) 445 100.0 % 1.34 [1.00, 1.79] Total events: 67 (Quetiapine), 57 (Risperidone) Hetrogeneity: Tau ² = 0.0; Ch ² = 0.0; CH ² = 0.02; P = 0.0% Test for overal leffect 2 = 1.78 (P = 0.045)	l medium term Stroup 2006	19/95	16/104	-	23.0 %	1.30 [0.71, 2.38]	
2 long term 1 77.0 % 1.35 [0.97, 1.88] Lieberman 2005 68/337 51/341 77.0 % 1.35 [0.97, 1.88] Jotal events: 68 (Quetiapine), 51 (Risperidone) 837 341 77.0 % 1.35 [0.97, 1.88] Total events: 68 (Quetiapine), 51 (Risperidone) 1.88 [0.97, 1.88] 1.35 [0.97, 1.88] 1.35 [0.97, 1.88] Test for overall effect: 2 = 1.78 (P = 0.076) 1.35 [0.97, 1.87, 1.37] 1.35 [0.97, 1.88] Total events: 87 (Quetiapine), 57 (Risperidone) 432 445 100.0 % 1.34 [1.00, 1.79] Test for overall effect: 2 = 0.01, df = 1 (P = 0.92); P = 0.0% Test for overall effect: 2 = 1.79 (P = 0.49) 1.34 [1.00, 1.79]	S ubtotal (95% Cl) Fotal events: 19 (Quetiapine Heterogeneity: not applicab Fest for overall effect: Z = 0	95 e), 16 (Risperidone) le .85 (P = 0.39)	104	•	23.0 %	1.30 [0.71, 2.38]	
Subtotal (05% CI) 337 341 ↑ 77.0 % 1.35 [0.97, 1.88] Total synts: St (Quatiapine), 51 (Risperidone) Haterogeneticy: not applicable 1 <td>2 long term Lieberman 2005</td> <td>68/337</td> <td>51/341</td> <td></td> <td>77.0%</td> <td>1.35 [0.97, 1.88]</td> <td></td>	2 long term Lieberman 2005	68/337	51/341		77.0%	1.35 [0.97, 1.88]	
Total (95% Cl) 432 445 ♦ 100.0 % 1.34 [1.00, 1.79] Total events: 87 (Quetiapine), 67 (Risparidone) teterogeneity: Tau ² = 0.0; Ch ² = 0.04), df = 1 (P = 0.92); l ² = 0.0% restfor overall effect. Z = 1.97 (P = 0.049) restfor overall effect. Z = 1.97 (P = 0.049)	S ubtotal (95% Cl) Fotal events: 68 (Quetiapine Heterogeneity: not applicab Fest for overall effect: Z = 1	337 e), 51 (Risperidone) le .78 (P = 0.076)	341	•	77.0 %	135 [0.97, 1.88]	
	Total (95% Cl) Fotal events: 87 (Quetiapine Heterogeneity: Tau ² = 0.0; 1 Fest for overall effect: Z = 1	432 (), 67 (Risperidone) Chi ² = 0.01, df = 1 (.97 (P = 0.049)	445 P = 0.92); I ² =0.0%	•	100.0 %	134 [100, 179]	

Analysis 3.16 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 16 Adverse effects: 1. General - at least one adverse effect

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 16 Adverse effects: 1. General - at least one adverse effect

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M-H,Random,95% Cl	Weight	Risk Ratio M - H, Random, 95% Cl	
Conley 2005	5/12	7/13		1.8 %	0.77 [0.33, 1.79]	
Lieberman 2005	220/337	232/341	-	30.4 %	0.96 [0.86, 1.07]	
McEvoy 2006	10/15	9/16		3.9 %	1.19[0.68, 2.08]	
McEvoy 2007	77/134	66/133	-	16.1 %	1.16 [0.92, 1.45]	
Potkin 2006	22/156	29/153		4.6 %	0.74 [0.45, 1.24]	
Riedel 2005	17/22	8/22		3.4 %	2.13 [1.17, 3.86]	
Stroup 2006	32/95	26/104		6.0 %	1.35 [0.87, 2.08]	
Zhong 2006	258/338	256/335	•	33.7 %	1.00 [0.92, 1.09]	
Total (95% Cl) Total events: 641 (Quetia Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	1109 pine), 633 (Risperidon 01; Chi ² = 12.21, df = = 0.72 (P = 0.47)	e) 7 (P = 0.09); I ² =43%	•	100.0 %	1.04 [0.93, 1.17]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours co	10 ntrol		

Analysis 3.17 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 17 Adverse effects: 2. Death

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 17 Adverse effects: 2. Death

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random, 95% Cl	Risk Ratio M - H, Random, 95% Cl	
1 natural causes Potkin 2006	0/156	0/153		0.0 [0.0, 0.0]	
Zhong 2006	0/338	0/335		0.0 [0.0, 0.0]	
Subtotal (95% CI) Total events: 0 (Quetiapini Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	494 e), 0 (Risperidone) ; Chi ² = 0.0, df = 0 (P 0.0 (P < 0.00001)	488 <0.00001); ² = 0.0%		0.0 [0.0, 0.0]	
2 suicide attempt Lieberman 2005	1/337	2/341 🕶		- 0.51 [0.05, 5.55]	
McEvoy 2007	0/134	1/133 🕶		0.33 [0.01, 8.05]	
Subtotal (95% Cl) Total events: 1 (Quetiapin) Heterogeneity: Tau ² = 0.0, Test for overall effect: Z =	471 e), 3 (Risperidone) ; Chi ² = 0.04, df = 1 (0.85 (P = 0.39)	474 -		0.43 [0.06, 2.95]	
3 suicide McEvoy 2007	2/134	0/133		4.96 [0.24, 102.41]	
Stroup 2006	0/95	1/104 +		0.36 [0.02, 8.84]	
Zhong 2006	0/338	0/335		0.0 [0.0, 0.0]	
Subtotal (95% CI) Total events: 2 (Quetiaping Heterogeneity: Tau ² = 0.9 Test for overall effect: Z =	5 67 e), 1 (Risperidone) 1; Chi ² = 1.36, df = 1 0.27 (P = 0.79)	572 (P = 0.24); l ² =26%		1.41 [0.11, 18.32]	
Total (95% Cl) Total events: 3 (Quetiaping Heterogeneity: Tau ² = 0.0, Test for overall effect: Z =	1532 e), 4 (Risperidone) ; Chi² = 2.08, df = 3 (0.43 (P = 0.67)	1534 P = 0.56); l ² =0.0%		0.73 [0.17, 3.09]	
		0.1 Favours treatment	0.2 0.5 1 2 Favours	5 10 control	

Analysis 3.18 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 18 Adverse effects: 3a. Cardiac effects - QTc prolongation

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

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk M-H,Rand	: Ratio om,95% CI	Risk Ratio M - H, Random , 95% Cl	
Lieberman 2005 Zhong 2006	6/337 0/338	7/341 0/335			0.87 [0.29, 2.55] 0.0 [0.0, 0.0]	
Total (95% Cl) Total events: 6 (Quetiapin Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	675 e), 7 (Risperidone) ; Chi² = 0.0, df = 0 (P 0.26 (P = 0.80)	676 = 1.00); I ² =0.0%			0.87 [0.29, 2.55]	
		0. Favours treatment	1 0.2 0.5 1	2 5 Favours cont	10 irol	

Analysis 3.19 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 19 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

Study or subgroup	Quetiapine N	R Mean(SD)	isperidone N	Mean(SD)	Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	214	5.9 (27.8)	218	0.2 (26.6)			→ 36.2%	5.70 [0.57, 10.83]
Stroup 2006	81	1.9 (33.3)	85	-4.4 (30.4)		-	→ 24.7 %	6.30 [-3.41, 16.01]
Zhong 2006	174	-2.3 (19)	168	1.3 (18.3)	-	+	39.1 %	-3.60 [-7.55, 0.35]
Total (95% Cl) Heterogeneity: Tau² = 3 Test for overall effect: Z	469 1.07; Chi² = 9.4 = 0.60 (P = 0.5)	4, df = 2 (P = 0. 5)	471 .01); I ² =79	%			100.0 %	2.21 [-5.05, 9.48]
			Fa	-10 avours treatment) -5	0 5 Favours c	10 ontrol	

Analysis 3.20 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 20 Adverse effects: 4. Central nervous system - sedation.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 20 Adverse effects: 4. Central nervous system - sedation

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Fixed, 95% CI	Weight	Risk Ratio M-H,Fixed,95% Cl	
Conley 2005	3/12	5/13		1.8 %	0.65 [0.20, 2.15]	
Lieberman 2005	103/337	96/341		34.9 %	1.09 [0.86, 1.37]	
McEvoy 2006	5/15	4/16		1.4 %	1.33 [0.44, 4.05]	
McEvoy 2007	77/134	66/133		24.2 %	1.16 [0.92, 1.45]	
Potkin 2006	15/156	10/153		3.7 %	1.47 [0.68, 3.17]	
Riedel 2005	17/22	5/22		1.8 %	3.40 [1.52, 7.59]	
Stroup 2006	22/95	23/104	+	8.0 %	1.05 [0.63, 1.75]	
Zhong 2006	89/338	66/335	-	24.2 %	1.34 [1.01, 1.77]	
Total (95% CI) Total events: 331 (Quetiaj Heterogeneity: Chi ² = 9.4 Test for overall effect: Z =	1109 pine), 275 (Risperidon 4, df = 7 (P = 0.22); ² 2.87 (P = 0.0041)	e) =26%	•	100.0 %	1.21 [1.06, 1.38]	
		0.00	1 0.01 0.1 1 10 10	00 1000		

Analysis 3.21 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 21 Adverse effects: 5a. Extrapyramidal effects.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 21 Adverse effects: 5a. Extrapyramidal effects

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random , 95% CI	Risk Ratio M - H, Random, 95% Cl	
1 akathisia Lieberman 2005	16/337	20/341	+	0.81 [0.43, 1.54]	
McEvov 2007	25/134	30/133	-	0.83 [0.52, 1.33]	
Potkin 2006	1/156	11/153		0.09[0.01, 0.68]	
Riedel 2005	0/22	8/22 +		0.06[0.00, 0.96]	
Stroup 2006	6/95	3/104		2.19 [0.56, 8.51]	
Zhong 2006	13/338	28/335	-	0.46[0.24, 0.87]	
Subtotal (95% CI)	1082	1088	•	0.62 [0.34, 1.13]	
Total events: 61 (Quetiapin Heterogeneity: Tau² = 0.28 Test for overall effect: Z = 1	e), 100 (Risperidone) ; Chi ² = 12.56, df = .57 (P = 0.12)	$5 (P = 0.03); I^2 = 60\%$			
2 akinesia McEvov 2007	33/134	36/133		0 91 [0 61 1 37]	
Subtotal (95% CI)	134	133	•	0.91 [0.61, 1.37]	
Total events: 33 (Quetiapin Heterogeneity: not applicat Test for overall effect: Z = (e), 36 (Risperidone) ble 0.46 (P = 0.65)		1		
dystonia Zhong 2006	1/338	18/335		0.06[0.01, 0.41]	
Subtotal (95% CI)	338	335	-	0.06 [0.01, 0.41]	
Fotal events: 1 (Quetiapine) Heterogeneity: not applicat Fest for overall effect: Z = 2), 18 (Risperidone) ole 2.83 (P = 0.0047)				
extrapyramidal symptom: Stroup 2006	7/95	12/104	-	0.64 [0.26 1.55]	
7hong 2006	43/338	73/335		0.58[0.4] 0.82]	
Subtotal (95% Cl) Total events: 50 (Quetiapin Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 3	433 e), 85 (Risperidone) Chi ² = 0.03, df = 1 (8.21 (P = 0.0013)	439 P = 0.85); l ² = 0.0%	•	0.59 [0.43, 0.81]	
5 parkinsonism					
Riedel 2005	0/22	8/22		0.06[0.00, 0.96]	
Zhong 2006	0/338	0/335			
Fotal events: 0 (Quetiapine) Heterogeneity: Tau ² = 0.0; Fest for overall effect: Z = 1	, 8 (Risperidone) Chi ² = 0.0, df = 0 (P 	= 1.00); P =0.0%		0.00 [0.00, 0.90]	
5 rigor Potkin 2006	5/156	11/153	-	0.45 [0.16, 1.25]	
Subtotal (95% Cl) Total events: 5 (Quetiapine) Heterogeneity: not applicab Test for overall effect: Z = 1	156 (, 11 (Risperidone) ole 53 (P = 0.13)	153	•	0.45 [0.16, 1.25]	
use of antiparkinson med	lication	2014			
Annaca 2003	0/14	3/14		0.14 [0.01, 2.53]	
Linkerran 2005	3/12	2/13	-	1.03 [0.33, 0.11]	
McEvov 2007	5/134	11/122		0.55[0.16, 0.66]	
Riadal 2005	2/22	9/22		0.22 [0.05 0.91]	
Zhong 2005	19/228	22/225		0.22 [0.03, 0.31]	
Subtotal (95% CI)	857	858	•	0.50 [0.30 0.86]	
fotal events: 40 (Quetiapin Heterogeneity: Tau ² = 0.15 Fest for overall effect: Z = 2	e), 80 (Risperidone) ; Chi² = 7.90, df = 5 2.50 (P = 0.012)	(P = 0.16); l ² = 37%	•	0.30 [0.30, 0.80]	
		0.001	0.01 0.1 1 10 100	1000	
		Favours treatment	Favours cont	ol	

Analysis 3.22 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 22 Adverse effects: 5b. Extrapyramidal effects - scale measured.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 22 Adverse effects: 5b. Extrapyramidal effects - scale measured

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 abnormal involuntary m Potkin 2006	ovement: AIM: 156	5 (high=poor) -0.1 (2.5)	153	0.3 (2.47)	-	56.9 %	-0.40 [-0.95, 0.15]
Zhong 2006	329	-0.51 (4.17)	320	-0.25 (4.11)		43.1 %	-0.26 [-0.90, 0.38]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	485 ; Chi ² = 0.11, 1.59 (P = 0.1	df = 1 (P = 0. 1)	473 75); I ² =0.0%		•	100.0 %	-0.34 [-0.76, 0.08]
2 akathisia: Barnes Akathi Sacchetti 2004	sia Scale (high 25	=poor) -0.3 (0.86)	25	1.1 (0.86)		48.3 %	-1.40 [-1.88, -0.92]
Zhong 2006	329	-0.09 (0.73)	321	0.01 (0.72)		51.7 %	-0.10 [-0.21, 0.01]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.8 Test for overall effect: Z =	354 1; Chi ² = 27.0 1.12 (P = 0.2	08, df = 1 (P<0 6)	346 .00001); l ² =	96%	•	100.0 %	-0.73 [-2.00, 0.54]
3 extrapyramidal sympton Conley 2005	ns: Simpson-A 12	ngus Scale (hi -1.64 (3.15)	gh=poor) 13	-1.3 (3.15)		5.0 %	-0.34 [-2.81, 2.13]
Potkin 2006	156	-0.1 (2.5)	153	0.8 (15.65)		4.9%	-0.90[-3.41, 1.61]
Riedel 2005	22	0.17 (1.04)	22	0.8 (1.04)		39.5 %	-0.63 [-1.24, -0.02]
Sacchetti 2004	25	-0.4 (3.58)	25	2.2 (3.58)		7.5 %	-2.60 [-4.58, -0.62]
Zhong 2006	328	-0.41 (3.62)	321	-0.21 (3.58)		43.1 %	-0.20 [-0.75, 0.35]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	543 2; Chi² = 5.71 2.02 (P = 0.04	., df = 4 (P = 0 44)	534 .22); l² =30%		•	100.0 %	-0.59 [-1.16, -0.02]

Analysis 3.23 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 23 Adverse effects: 6. Haematological: important decline in white blood cells.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 23 Adverse effects: S. Haematological: important decline in white blood cells

Study or subgroup	Quetiapine n/N	Risperidone n/N			Ri M - H, Ran	sk Ratio dom,95% (:	W	Veight	Risk Ratio M - H, Random , 95% Cl	
Zhong 2006	1/338	0/335					•	·	100.0%	2.97 [0.12, 72.73]	
Total (95% Cl) Total events: 1 (Quetiapin Heterogeneity: not applica Test for overall effect: Z =	338 e), 0 (Risperidone) able 0.67 (P = 0.50)	335						- 1	00.0 %	2.97 [0.12, 72.73]	
		Favours treatmen	0.1 t	0.2	0.5	1 2 Fav	5 ours con	10 trol			

Analysis 3.24 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 24 Adverse effects: 7a. Prolactin associated side effects.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 24 Adverse effects: 1a. Prolactin associated side effects

Study or subgroup	Quetiapine n/N	Risperidone n/N	Risk Ratio M - H, Random, 95% Cl	Risk Ratio M - H, Random, 95% Cl	
1 amenorrhea Lieberman 2005	5/82	16/88		0.34 [0.13, 0.87]	
McEvoy 2006	0/3	0/6		0.0 [0.0, 0.0]	
McEvoy 2007	10/42	16/34		0.51 [0.26, 0.97]	
Potkin 2006	1/56	0/48		2.58 [0.11, 61.88]	
Subtotal (95% Cl) Total events: 16 (Quetiapine) Heterogeneity: Tau ² = 0.0; C Test for overall effect: Z = 2.	183 , 32 (Risperidone) hi ² = 1.63, df = 2 (P 82 (P = 0.0048)	176 = 0.44); l ² =0.0%	•	0.47 [0.28, 0.79]	
2 dysmenorrhea Zhong 2006	2/86	4/77	_ <mark></mark>	0.45 [0.08, 2.38]	
Subtotal (95% Cl) Total events: 2 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 0.	86 4 (Risperidone) e 94 (P = 0.35)	77	-	0.45 [0.08, 2.38]	
3 galactorrhea Lieberman 2005	6/337	14/341		0.43 [0.17, 1.12]	
McEvoy 2006	0/15	0/16		0.0 [0.0, 0.0]	
McEvoy 2007	0/134	3/133		0.14 [0.01, 2.72]	
Stroup 2006	0/21	1/28	.	0.44 [0.02, 10.28]	
Zhong 2006	0/86	2/77		0.18 [0.01, 3.68]	
Subtotal (95% Cl) Total events: 6 (Quetiapine), Heterogeneity: Tau ² = 0.0; C Test for overall effect: Z = 2.	593 20 (Risperidone) hi ² = 0.76, df = 3 (P 33 (P = 0.020)	595 = 0.86); l ² =0.0%	•	0.37 [0.16, 0.85]	
4 gynecomastia McEvov 2007	3/134	13/133		0.23 [0.07, 0.79]	
Subtotal (95% Cl) Total events: 3 (Quetiapine), Heterogeneity: not applicabl Test for overall effect: Z = 2.	134 13 (Risperidone) e 34 (P = 0.019)	133	•	0.23 [0.07, 0.79]	
5 sexual dysfunction Lieberman 2005	69/337	91/341	-	0.77 [0.58, 1.01]	
McEvoy 2006	2/15	4/16		0.53 [0.11, 2.50]	
McEvoy 2007	35/134	36/133	-	0.96 [0.65, 1.44]	
Potkin 2006	1/156	0/153		2.94 [0.12, 71.68]	
Stroup 2006	10/95	30/104	-	0.36 [0.19, 0.71]	
Zhong 2006	0/338	3/335		0.14 [0.01, 2.73]	
Subtotal (95% CI) Total events: 117 (Quetiapin	1075 e), 164 (Risperidone)	1082 = 0.14): ² =40%	•	0.70 [0.48, 1.01]	

Analysis 3.25 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 25 Adverse effects: 7b. Prolactin - change from baseline in mg/dl.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 25 Adverse effects: ?b. Prolactin - change from baseline in mg/dl

udy or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)		Mean Di IV,Random	fference 1,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	337	-9.3 (25.7)	341	15.4 (27.7)	•			18.7%	-24.70 [-28.72, -20.68]
McEvoy 2006	13	-13.2 (18.02)	11	15.4 (17.91)	•			13.0 %	-28.60 [-43.02, -14.18]
McEvoy 2007	44	-18.7 (17.64)	37	12.1 (15.88)	•			17.2 %	-30.80 [-38.10, -23.50]
Potkin 2006	156	-10.1 (44.96)	153	40.3 (43.29)	•			15.8 %	-50.40 [-60.24, -40.56]
Stroup 2006	95	-8.3 (18.5)	104	22 (29.6)	•			17.5 %	-30.30 [-37.10, -23.50]
Zhong 2006	209	-11.5 (33.25)	231	35.5 (30.4)	•			17.9 %	-47.00 [-52.97, -41.03]
'otal (95% Cl) eterogeneity: Tau ² = 1 est for overall effect: Z	854 10.99; Chi ² = = 7.61 (P < 0.	50.68, df = 5 (F 00001)	877 '<0.00001); F	² =90%				100.0 %-3	5.28 [-44.36, -26.19]
					-10	-5 0	5	10	
					-10	- 5 0			

Analysis 3.26 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 26 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 26 Adverse effects: 8a. Metabolic - cholesterol - significant cholesterol increase

Study or subgroup	Quetiapine n/N	Risperidone n/N			Ri M - H, Ran	sk R dom	atio ,95% CI			Risk Ratio M - H, Random, 95% Cl	
McEvoy 2007 Zhong 2006	23/134 0/338	18/133 0/335			_	•	-			1.27 [0.72, 2.24] 0.0 [0.0, 0.0]	
Total (95% Cl) Total events: 23 (Quetiap) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	472 ine), 18 (Risperidone)); Chi ² = 0.0, df = 0 (P : 0.82 (P = 0.41)	468 = 1.00); l ² =0.0%				-				1.27 [0.72, 2.24]	
		Favours treatment	0.1	0.2	0.5	1	2 Favour	5 s contro	10 		
Analysis 3.27 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 27 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 21 Adverse effects: 8b. Metabolic - cholesterol - change from baseline in mg/dl

udy or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)		Mean IV,Rando	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Lieberman 2005	337	5.3 (38.6)	341	-2.1 (35.1)				43.9%	7.40 [1.84, 12.96]
McEvoy 2006	13	-13 (24.5)	11	-4 (27.2)	•			3.5 %	-9.00[-29.87,11.87]
McEvoy 2007	44	25.2 (29.58)	37	11.4 (28.28)				9.5 %	13.80 [1.17, 26.43]
Stroup 2006	95	4.8 (37)	104	-2.6 (39.8)				13.1 %	7.40 [-3.27, 18.07]
Zhong 2006	218	4.9 (38.3)	233	-6.45 (36.2)				29.9%	11.35 [4.46, 18.24]
otal (95% Cl) leterogeneity: Tau ² = est for overall effect: 2	707 1.21; Chi² = 4.2 2 = 4.27 (P = 0.0	2, df = 4 (P = 0 00019)	726 .38); l ² =5%					100.0 %	8.61 [4.66, 12.56]
			F	avours treatmer	-10	-5	0 5 Favours contro	10	

Analysis 3.28 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 28 Adverse effects: 8c. Metabolic - glucose abnormally high fasting glucose value

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 2B Adverse effects: 8c. Metabolic - glucose - abnorm ally high fasting glucose value



Analysis 3.29 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 29 Adverse effects: 8d. Metabolic - glucose change from baseline in mg/dl.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 29 Adverse effects: 8d. Metabolic - glucose - change from baseline in mg/dl

tudy or subgroup	Quetiapine N	F Mean(SD)	lisperidone N	Mean(SD)	Mea IV, Ran	n Difference dom,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	337	6.8 (45.9)	341	6.7 (36.9)		•	21.0 %	0.10[-6.17, 6.37]
McEvoy 2006	13	-23.3 (44)	11	32.2 (111.1)	•		• 0.2 %	-55.50 [-125.38, 14.38]
McEvoy 2007	44	6.2 (11.08)	37	4.8 (10.34)		-	37.9 %	1.40 [-3.27, 6.07]
Stroup 2006	95	-0.2 (41.9)	104	4.8 (43.9)	• • •		- 5.8%	-5.00 [-16.92, 6.92]
Zhong 2006	220	3.9 (26.7)	234	4.5 (26)			35.1 %	-0.60 [-5.45, 4.25]
F otal (95% Cl) leterogeneity: Tau ² = ('est for overall effect: Z	709).0; Chi ² = 3.50, = 0.03 (P = 0.9	df = 4 (P = 0.41 8)	727 3); I ² =0.0%			-	100.0 %	-0.04 [-2.92, 2.83]
			Fi	avours treatmen	-10 -5 nt	0 5 Favours	10 control	

Analysis 3.30 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 30 Adverse effects: 8e. Metabolic - weight gain of 7% or more of total body weight.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE

Outcome: 30 Adverse effects: 8e. Metabolic - weight gain of 7% or m ore of total body weight



Analysis 3.31 Comparison 3 QUETIAPINE versus RISPERIDONE, Outcome 31 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 3 QUETIAPINE versus RISPERIDONE Outcome: 31 Adverse effects: 8f. Metabolic - weight gain - change from baseline in kg

	N	Mean(SD)	N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Atmaca 2003	14	4.41 (2.21)	13	0.54 (0.72)		20.4 %	3.87 [2.65, 5.09]
Conley 2005	12	-1.2 (11.22)	13	-0.65 (2.43)		5.5 %	-0.55 [-7.03, 5.93]
Lieberman 2005	305	0.5 (7)	300	0.4 (6.9)	-	20.7 %	0.10[-1.01, 1.21]
McEvoy 2006	15	0.5 (8.91)	16	1.8 (5.2)		7.6 %	-1.30 [-6.48, 3.88]
McEvoy 2007	44	5.69 (11.47)	37	6.48 (10.58)		8.4 %	-0.79[-5.60, 4.02]
Riedel 2005	22	2.93 (4.02)	22	1.72 (3.57)		16.5 %	1.21 [-1.04, 3.46]
Zhong 2006	324	1.64 (6.66)	309	2.12 (6.68)		20.9 %	-0.48 [-1.52, 0.56]
"otal (95% Cl) leterogeneity: Tau ² = 3.5 est for overall effect: Z =	736 5; Chi ² = 32.1 0.79 (P = 0.4	89, df = 6 (P = 3)	710 0.00001); ²	=82%	•	100.0 %	0.71 [-1.04, 2.47]

Analysis 4.1 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 1 Leaving the study early.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 1 Leaving the study early

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk Ratio M - H, Random , 95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
1 any reason Lieberman 2005	277/337	147/185	+	71.5 %	1.03 [0.95, 1.13]	
Stroup 2006	53/63	106/137		28.5 %	1.09 [0.94, 1.25]	
Subtotal (95% Cl) Total events: 330 (Quetiap Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	400 bine), 253 (Ziprasidon ; Chi ² = 0.35, df = 1 (1.26 (P = 0.21)	322 e) P = 0.56); l ² =0.0%		100.0 %	105 [0.97, 113]	
2 adverse events Lieberman 2005	49/337	28/185		71.6 %	0.96 [0.63, 1.47]	
Stroup 2006	11/63	19/137		28.4 %	1.26 [0.64, 2.49]	
Subtotal (95% Cl) Total events: 60 (Quetiapi Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	400 ne), 47 (Ziprasidone) ; Chi ² = 0.44, df = 1 (0.20 (P = 0.84)	322 P = 0.51); l ² =0.0%	•	100.0 %	104 [0.72, 1.49]	
3 inefficacy Lieberman 2005	92/337	44/185		64.6 %	1.15 [0.84, 1.57]	
Stroup 2006	22/63	42/137		35.4 %	1.14 [0.75, 1.73]	
Subtotal (95% Cl) Total events: 114 (Quetiap Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	400 bine), 86 (Ziprasidone) ; Chi² = 0.00, df = 1 (1.06 (P = 0.29)	322 P = 0.98); l ² =0.0%	•	100.0 %	114 [0.89, 1.47]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours c	i 10 ontrol		

Analysis 4.2 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 2 Mental state: 1. General - average endpoint score (PANSS total score, high=poor).

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 2 Mental state: 1. General - average endpoint score (PANSS total score, high = pnor)

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% CI	
1 medium term Stroup 2006	63	2 (22.31)	135	-1.7 (22.31)		+ 41.2 %	3.70 [-2.97, 10.37]	
Subtotal (95% CI)	63 bla		135			- 41.2 %	3.70 [-2.97, 10.37]	
Test for overall effect: Z =	1.09 (P = 0.2	8)						
2 long term Lieberman 2005	329	-6.08 (22.31)	183	-3.3 (22.31)		58.8 %	-2.78 [-6.81, 1.25]	
Subtotal (95% CI)	329		183		-	58.8 %	-2.78 [-6.81, 1.25]	
Test for overall effect: Z =	1.35 (P = 0.1	8)						
Total (95% Cl) Heterogeneity: Tau ² = 13. Test for overall effect: Z =	392 09; Chi ² = 2.6 0.03 (P = 0.9	5, df = 1 (P = 7)	318 0.10); l ² =62	%		100.0 %	-0.11 [-6.36, 6.14]	
					-10 -5 0 5	10		
			F	avours treatment	Favours contr	ol		

Analysis 4.3 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 3 Mental state: 2. Positive symptoms - average endpoint score - medium term (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 3 Mental state: 2. Positive symptoms - average endpoint score - medium term (PANSS positive subscore, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% Cl
Stroup 2006	63	0.2 (7.3)	135	0.2 (7.3)		100.0 %	0.0 [-2.18, 2.18]
Total (95% Cl) Heterogeneity: not app Test for overall effect:	63 licable Z = 0.0 (P = 1.0)		135		-	100.0 %	0.0 [-2.18, 2.18]
			F	-10 avours treatment	-5 0 5 Favours c	10 ontrol	

Analysis 4.4 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 4 Mental state: 3. Negative symptoms average endpoint score - medium term (PANSS negative subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 4 Mental state: 3. Negative symptoms - average endpoint score - medium term (PANSS negative subscore, high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)	Mean IV, Rando	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Stroup 2006	63	0.2 (6.48)	135	-1.4 (6.48)	-		100.0%	1.60 [-0.34, 3.54]
Total (95% CI) Heterogeneity: not appli	63		135			٠	100.0 %	1.60 [-0.34, 3.54]
Test for overall effect: Z	= 1.62 (P = 0.11)						
			F	avours treatment	-10 -5 t	0 Favo	5 10 urs control	

Analysis 4.5 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 5 Service use: number of participants rehospitalised.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 5 Service use: number of participants re-hospitalised

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk Ratio M - H, Random, 95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
1 medium term Stroup 2006	19/95	22/137		31.3 %	1.25 [0.71, 2.17]	
Subtotal (95% Cl) Total events: 19 (Quetiapin Heterogeneity: not applical Test for overall effect: Z = (95 e), 22 (Ziprasidone) ble 0.77 (P = 0.44)	137		31.3 %	1.25 [0.71, 2.17]	
2 long term Lieberman 2005	68/337	33/185		68.7 %	1.13 [0.78, 1.65]	
Subtotal (95% Cl) Total events: 68 (Quetiapin Heterogeneity: not applical Test for overall effect: Z = (337 e), 33 (Ziprasidone) ble 0.64 (P = 0.52)	185	•	68.7 %	113 [0.78, 1.65]	
Total (95% Cl) Total events: 87 (Quetiapin Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = (432 e), 55 (Ziprasidone) Chi ² = 0.08, df = 1 (0.97 (P = 0.33)	322 P = 0.78); l ² =0.0%	•	100.0 %	1.17 [0.85, 1.59]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours cor	10 ntrol		

Analysis 4.6 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 6 Adverse effects: 1. General - at least one adverse effect.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 6 Adverse effects: 1. General - at least one adverse effect

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk Ratio M-H,Random,95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
Lieberman 2005 Stroup 2006	220/337 32/95	119/185 38/137		89.7 % 10.3 %	1.01 [0.89, 1.16] 1.21 [0.82, 1.79]	
Total (95% Cl) Total events: 252 (Quetiap Heterogeneity: Tau ² = 0.0, Test for overall effect: Z =	432 ine), 157 (Ziprasidon ; Chi ² = 0.77, df = 1 (0.52 (P = 0.60)	322 e) P = 0.38); I ² = 0.0%	•	100.0 %	1.03 [0.91, 1.17]	
		0.1 Favours treatment	0.2 0.5 1 2 Favour	5 10 rs control		

Analysis 4.7 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 7 Adverse effects: 2. Death.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 7 Adverse effects: 2. Death

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk M-H,Rando	Ratio m,95% Cl	Weight	Risk Ratio M - H, Random, 95% Cl	
1 suicide attempt Lieberman 2005	1/337	1/185	• •		54.5 %	0.55 [0.03, 8.73]	
Subtotal (95% Cl) Total events: 1 (Quetiapine) Heterogeneity: not applicat Test for overall effect: Z = 0	337), 1 (Ziprasidone) ole).42 (P = 0.67)	185			54.5 %	0.55 [0.03, 8.73]	
2 suicide Stroup 2006	0/95	2/137	• •		45.5 %	0.29 [0.01, 5.92]	
Subtotal (95% Cl) Total events: 0 (Quetiapine) Heterogeneity: not applicab Test for overall effect: Z = 0	95), 2 (Ziprasidone) ble).81 (P = 0.42)	137			45.5 %	0.29 [0.01, 5.92]	
Total (95% Cl) Total events: 1 (Quetiapine) Heterogeneity: Tau ² = 0.0; Test for overall effect: Z = 0	432), 3 (Ziprasidone) Chi ² = 0.10, df = 1 ().86 (P = 0.39)	322 P = 0.75); l ² =0.0	%		100.0 %	0.41 [0.05, 3.15]	
		Favours treatmen	0.1 0.2 0.5 1 t	2 5 Favours contro	10		

Analysis 4.8 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 8 Adverse effects: 3a. Cardiac effects - QTc prolongation

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 8 Adverse effects: 3a. Cardiac effects - QTc prolongation

Study or subgroup	Quetiapine n/N	Ziprasidone n/N		Ris M - H, Ran	k Ratio dom,95% Cl	Weight	Risk Ratio M - H, Random , 95% Cl	
Lieberman 2005	6/337	2/185			•	100.0%	1.65 [0.34, 8.08]	
Total (95% Cl) Total events: 6 (Quetiapin Heterogeneity: not applicz Test for overall effect: Z =	337 e), 2 (Ziprasidone) ble 0.61 (P = 0.54)	185		_		100.0 %	1.65 [0.34, 8.08]	
		Favours treatment	0.1 0.2 t	0.5	1 2 Favours o	5 10 ontrol		

Analysis 4.9 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 9 Adverse effects: 3b. Cardiac effects - QTc abnormalities - change from baseline in ms

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 9 Adverse effects: 3b. Cardiac effects - Q.Tc abnormalities - change from baseline in ms

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)		Mean D IV,Rando)ifference m,95% Cl	Weight	Mean Difference IV,Random,95% CI	
Lieberman 2005 Stroup 2006	214 81	5.9 (27.8) 1.9 (33.3)	148 106	1.3 (26.8) 1.3 (25.7)			•	70.2 %	4.60 [-1.10, 10.30] 0.60 [-8.15, 9.35]	
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 2	295 0.0; Chi ² = 0.56, 2 = 1.40 (P = 0.1)	df = 1 (P = 0.4 5)	254 5); 1² =0.0%				-	100.0 %	3.41 [-1.37, 8.18]	
			F	avours treatmen	-10 t	-5 () 5 Favour:	10 control		

Analysis 4.10 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 10 Adverse effects: 4. Central nervous system - sedation

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 10 Adverse effects: 4. Central nervous system - sedation

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Ris M-H,Fix	k Ratio ed,95% Cl	Weight	Risk Ratio M - H, Fixed, 95% Cl	
Lieberman 2005 Stroup 2006	103/337 22/95	45/185 18/137		+- -∎	79.8 % 20.2 %	1.26 [0.93, 1.70] 1.76 [1.00, 3.10]	
Total (95% Cl) Total events: 125 (Quetia Heterogeneity: Chi ² = 1.0 Test for overall effect: Z =	432 pine), 63 (Ziprasidone) 17, df = 1 (P = 0.30); I ² = 2.27 (P = 0.023)	322 =7%		•	100.0 %	136 [104, 177]	
		Favours treatment	0.001 0.01 0.1	1 10 Favours	100 1000 control		

Analysis 4.11 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 11 Adverse effects: 5. Extrapyramidal effects.

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 11 Adverse effects: 5. Extrapyramidal effects

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk Ratio M - H, Random , 95% Cl	Weight	Risk Ratio M-H,Random,95% Cl	
1 akathisia Lieberman 2005	16/337	14/185		68.1 %	0.63[0.31, 1.26]	
Stroup 2006	6/95	7/137		31.9 %	1.24 [0.43, 3.56]	
Subtotal (95% Cl) Total events: 22 (Quetiapine Heterogeneity: Tau ² = 0.02; Test for overall effect: Z = 0	432), 21 (Ziprasidone) Chi ² = 1.10, df = 1 .79 (P = 0.43)	322 (P = 0.29); I ² =9%	•	100.0 %	0.78 [0.42, 1.45]	
2 extrapyramidal symptoms Stroup 2006	7/95	5/137	- <mark></mark> -	100.0%	2.02 [0.66, 6.17]	
Subtotal (95% Cl) Total events: 7 (Quetiapine), Heterogeneity: not applicab Test for overall effect: Z = 1	95 5 (Ziprasidone) le .23 (P = 0.22)	137	-	100.0 %	2.02 [0.66, 6.17]	
3 use of antiparkinson medi Lieberman 2005	cation 11/337	14/185		100.0%	0.43 [0.20, 0.93]	
Subtotal (95% Cl) Total events: 11 (Quetiapine Heterogeneity: not applicab Test for overall effect: Z = 2	337), 14 (Ziprasidone) le 14 (P = 0.032)	185	•	100.0 %	0.43 [0.20, 0.93]	
		0. Favours treatment	001 0.01 0.1 1 10 100 Favours cor	0 1000 ntrol		

Analysis 4.12 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 12 Adverse effects: 6a. Prolactin associated effects

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 12 Adverse effects: Sa. Prolactin associated effects

Study or subgroup	Quetiapine n/N	Ziprasidone n/N	Risk Ratio M-H,Random,95% Cl	Risk Ratio M-H, Random, 95% Cl	
1 amenorrhea Lieberman 2005	5/82	8/56		0.43 [0.15, 1.24]	
Subtotal (95% Cl) Total events: 5 (Quetiapino Heterogeneity: not applica Test for overall effect: Z =	82 a), 8 (Ziprasidone) ble 1.57 (P = 0.12)	56		0.43 [0.15, 1.24]	
2 galactorrhea Lieberman 2005	6/337	6/185		0.55 [0.18, 1.68]	
Stroup 2006	0/21	0/29	_	0.0[0.0,0.0]	
Total events: 6 (Quetiaping Heterogeneity: Tau ² = 0.0, Test for overall effect: Z = 3 sexual dysfunction	208 e), 6 (Ziprasidone) ; Chi² = 0.0, df = 0 (P 1.05 (P = 0.29)	2 14 = 1.00); ² =0.0%		0.33 [0.10, 1.00]	
Lieberman 2005	69/337	35/185		1.08 [0.75, 1.56]	
Stroup 2006	10/95	21/137		0.69 [0.34, 1.39]	
Subtotal (95% Cl) Total events: 79 (Quetiapin Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	432 ne), 56 (Ziprasidone) 2; Chi ² = 1.26, df = 1 0.22 (P = 0.83)	322 (P = 0.26); I ² =21%	•	0.96 [0.64, 1.42]	
		0.1 Favours treatment	0.2 0.5 1 2 5 Favours contr	10 rol	

Analysis 4.13 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 13 Adverse effects: 6b. Prolactin - change from baseline in ng/ml

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 13 Adverse effects: 6b. Prolactin - change from baseline in ng/m I

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)		Mean Dif IV,Random,	ference ,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Lieberman 2005	337	-9.3 (25.7)	185	-4.5 (21.8)				66.2 %	-4.80 [-8.97, -0.63]
Stroup 2006	95	-8.3 (18.5)	137	-3.6 (26.9)	← ∎			33.8 %	-4.70 [-10.54, 1.14]
Total (95% Cl) Heterogeneity: Tau² = 0 Test for overall effect: Z	432 .0; Chi ² = 0.00, = 2.75 (P = 0.0	df = 1 (P = 0.9 059)	322 8); I ² =0.0%		-	-		100.0 %	-4.77 [-8.16, -1.37]

Analysis 4.14 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 14 Adverse effects: 7a. Metabolic - cholesterol - change from baseline in mg/dl

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 14 Adverse effects: 7a. Metabolic - cholesterol - change from baseline in mg/dl

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)		Mean IV,Rando	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	337	5.3 (38.6)	185	-9.2 (70.7)				45.9%	14.50 [3.51, 25.49]
Stroup 2006	95	4.8 (37)	137	-12.5 (41)				→ 54.1 %	17.30 [7.18, 27.42]
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: :	432 0.0; Chi ² = 0.13, Z = 4.22 (P = 0.0	df = 1 (P = 0.7 00025)	322 1); I ² =0.0%					- 100.0 %	16.01 [8.57, 23.46]
			F	avours treatmer	-10 it	-5	0 5 Favour:	10 s control	

Analysis 4.15 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 15 Adverse effects: 7b. Metabolic - glucosechange from baseline in mg/dl

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE Outcome: 15 Adverse effects: 7b. Metabolic - glucose- change from baseline in mg/dl

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)	M IV,I	lean Difference Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Lieberman 2005	337	6.8 (45.9)	185	2.3 (53)			61.1%	4.50 [-4.57, 13.57]
Stroup 2006	95	-0.2 (41.9)	137	-1.1 (45.6)	•		38.9%	0.90 [-10.47, 12.27]
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: 2	432 0.0; Chi² = 0.24, = 0.86 (P = 0.3	df = 1 (P = 0.6 9)	322 (3); I ² =0.0%				100.0 %	3.10 [-3.99, 10.19]
					-10 -5	0 5	10	

Analysis 4.16 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 16 Adverse effects: 7c. Metabolic - weight gain of 7% or more of total body weight

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 1 6 Adverse effects: 7c. M etabolic - weight gain of 7% or m ore of total body weight

Study or subgroup	Quetiapine n/N	Ziprasidone n/N		Ri M - H, Ran	sk Ratio dom,95	% CI		Weight	Risk Ratio M - H, Random, 95% Cl	
Lieberman 2005 Stroup 2006	49/337 12/95	12/185 8/137			-			66.6 % 33.4 %	2.24 [1.22, 4.11] 2.16 [0.92, 5.09]	
Total (95% Cl) Total events: 61 (Quetiapi Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	432 ne), 20 (Ziprasidone) ; Chi ² = 0.00, df = 1 (3.15 (P = 0.0016)	322 P = 0.95); l ² =0.0	%		•			100.0 %	2.22 [1.35, 3.63]	
		Favours treatmen	0.001 0.0: t	0.1	1 F	10 avours	100 contro	1000 		

Analysis 4.17 Comparison 4 QUETIAPINE versus ZIPRASIDONE, Outcome 17 Adverse effects: 7d. Metabolic - weight gain - change from baseline in kg

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 4 QUETIAPINE versus ZIPRASIDONE

Outcome: 17 Adverse effects: 7d. Metabolic - weight gain - change from baseline in kg

Study or subgroup	Quetiapine N	Mean(SD)	Ziprasidone N	Mean(SD)	Mean IV,Rand	Difference om,95% Cl	Weight	Mean Difference IV,Random,95% CI
Lieberman 2005	305	0.5 (7)	161	-0.7 (6.3)			100.0%	1.20 [-0.05, 2.45]
Total (95% Cl) Heterogeneity: not appl Test for overall effect: Z	305 licable = 1.88 (P = 0.06	50)	161			•	100.0 %	1.20 [-0.05, 2.45]
			F	-10 avours treatment	-5	0 Favor	5 10 Irs control	

Analysis 5.1 Comparison 5 QUETIAPINE versus CLOZAPINEsensitivity analysis (skewed data excluded), Outcome 1 Mental state: 1. General - average endpoint score -short term (PANSS total, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 5 QUETIAPINE vers us CLOZAPINE- sensitivity analysis (skewed data excluded)

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

Study or subgroup	Quetiapine N	Mean(SD)	Clozapine N	Mean(SD)	Mean Difference IV, Random, 95% Cl	Weight	Mean Difference IV,Random,95% CI
1 short term Atmaca 2003	14	77.24 (6.08)	13	77.06 (5.28)	-	100.0%	0.18 [-4.11, 4.47]
Total (95% Cl) Heterogeneity: not app Test for overall effect: :	14 licable Z = 0.08 (P = 0.9	3)	13		-	100.0 %	0.18 [-4.11, 4.47]
			1	-10 Favours treatment	-5 0 5 Favours	10 control	

Analysis 6.1 Comparison 6 QUETIAPINE versus OLANZAPINEsensitivity analysis (skewed data excluded), Outcome 1 Mental state: 1. Positive symptoms - average endpoint score (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 6 QUETIAPINE versus OLANZAPINE- sensitivity analysis (skewed data excluded)

Outcome: 1 Mental state: 1. Positive symptoms - average endpoint score (PANSS positive subscore, high = poor)

Study or subgroup	Quetiapine N	O Mean(SD)	lanzapine N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
1 short term Riedel 2007	16	-7.78 (7.3)	17	-6.82 (7.3)		2.8 %	-0.96 [-5.94, 4.02]
Svestka 2003b	22	-12.96 (6.28)	20	-13.55 (5.14)		5.9 %	0.59[-2.87, 4.05]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	38); Chi² = 0.25, : 0.06 (P = 0.9	df = 1 (P = 0.62 5)	37 2); I ² =0.0%	1		8.7 %	0.09 [-2.76, 2.93]
2 medium term Kinon 2006b	169	-0.7 (6.6)	167	-2.3 (5.4)		42.2 %	1.60 [0.31, 2.89]
McEvoy 2006	8	0.6 (5.94)	10	-2.9 (4.11)		- 3.0 %	3.50 [-1.34, 8.34]
Stroup 2006	63	0.2 (7.3)	66	-3.4 (7.3)		11.0 %	3.60 [1.08, 6.12]
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.2 Test for overall effect: Z =	240 21; Chi ² = 2.26 3.31 (P = 0.0	5, df = 2 (P = 0.3 0093)	243 22); l ² =1 29	C.	•	56.2 %	2.21 [0.90, 3.52]
3 long term McEvoy 2007	44	-5.3 (3.38)	37	-7.1 (3.1)		35.1 %	1.80 [0.39, 3.21]
Subtotal (95% CI)	44		37		•	35.1 %	1.80 [0.39, 3.21]
Heterogeneity: not applic Test for overall effect: Z =	able 2.50 (P = 0.0	13)					
Total (95% Cl) Heterogeneity: Tau ² = 0.(Test for overall effect: Z =	322); Chi ² = 4.17, : 4.25 (P = 0.0	df = 5 (P = 0.52 00021)	317 2); I ² =0.0%	i.	•	100.0 %	1.82 [0.98, 2.65]
lest for overall effect: Z =	: 4.25 (P = 0.0	00021)	F	-10 avours treatment	-5 0 5 Favours co	10 Introl	

Analysis 7.1 Comparison 7 QUETIAPINE versus RISPERIDONEsensitivity analysis (skewed data excluded), Outcome 1 Mental state: 6. Positive symptoms - average endpoint score - (PANSS positive subscore, high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 7 QUETIAPINE versus RISPERIDONE- sensitivity analysis (skewed data excluded)

Outcome: 1 Mental state: 6. Positive symptoms - average endpoint score - (PANSS positive subscore, high = poor)

uetiapine N	Mean(SD)	Risperidone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
156	-5.9 (6.24)	152	-8.7 (6.16)		25.0 %	2.80 [1.42, 4.18]
22	-3.8 (7.3)	22	-7.6 (7.3)	+ + +	2.7 %	3.80 [-0.51, 8.11]
328	-4.5 (7.24)	318	-5.6 (7.13)		37.7 %	1.10 [-0.01, 2.21]
506 Chi ² = 4.35 .76 (P = 0.0	i, df = 2 (P = 0 058)	492 .11); l² =54%	i	•	65.5 %	2.08 [0.60, 3.56]
8	0.6 (5.94)	6	-0.5 (1.71)		2.7 %	1.10 [-3.24, 5.44]
63	0.2 (7.3)	69	-2.3 (7.3)		8.1 %	2.50 [0.01, 4.99]
71 Chi ² = 0.30, .95 (P = 0.0)	df = 1 (P = 0.5 51)	75 58); l ² =0.0%		•	10.8 %	2.15 [-0.01, 4.31]
44	-5.3 (3.38)	37	-6.6 (3.16)		23.7 %	1.30 [-0.13, 2.73]
44 44	-5.3 (3.38)	37 37	-6.6 (3.16)	÷	23.7 % 23.7 %	1.30 [-0.13, 2.73] 1.30 [-0.13, 2.73]
44 44 .79 (P = 0.0)	-5.3 (3.38) 74)	37 37	-6.6 (3.16)	<u>+</u> ◆	23.7 % 23.7 %	1.30 [-0.13, 2.73] 1.30 [-0.13, 2.73]
-	156 22 328 506 Chi ² = 4.35 76 (P = 0.0) 8 63 63 63 71 hi ² = 0.30, 95 (P = 0.0)	$\begin{array}{cccc} 156 & -5.9 \ (6.24) \\ 22 & -3.8 \ (7.3) \\ 328 & -4.5 \ (7.24) \\ \hline \textbf{506} \\ \text{Chi}^2 = \textbf{4}.35, \ df = 2 \ (P = 0 \\ 76 \ (P = 0.0058) \\ \hline \textbf{8} & 0.6 \ (5.94) \\ 63 & 0.2 \ (7.3) \\ \hline \textbf{71} \\ \textbf{50} \\ \textbf{63} \\ \textbf{71} \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	156 -5.9 (6.24) 152 -8.7 (6.16) 22 -3.8 (7.3) 22 -7.6 (7.3) 328 -4.5 (7.24) 318 -5.6 (7.13) 506 492 Chi ² = 4.35, df = 2 (P = 0.11); P = 54% 8 0.6 (5.94) 6 -0.5 (1.71) 63 0.2 (7.3) 69 -2.3 (7.3) 71 75 75 0.9 (f = 1 (P = 0.58); P = 0.0% 55 (P = 0.051)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

Analysis 7.2 Comparison 7 QUETIAPINE versus RISPERIDONEsensitivity analysis (skewed data excluded), Outcome 2 Adverse effects: 1. Extrapyramidal effects -Simpson-Angus Scale (high=poor)

Review: Quetiapine versus other atypical antipsychotics for schizophrenia Comparison: 7 QUETIAPINE vers us RISPERIDONE- sensitivity analysis (skewed data excluded)

Outcome: 2 Adverse effects: 1. Extrapyramidal effects - Simpson-Angus Scale (high = poor)

Study or subgroup	Quetiapine N	Mean(SD)	Risperidone N	Mean(SD)	Mean Difference IV,Random,95% Cl	Weight	Mean Difference IV,Random,95% Cl
Conley 2005	12	-1.64 (3.15)	13	-1.3 (3.15)		15.3 %	-0.34 [-2.81, 2.13]
Potkin 2006	156	-0.1 (2.5)	153	0.8 (15.65)		14.9 %	-0.90[-3.41, 1.61]
Sacchetti 2004	25	-0.4 (3.58)	25	2.2 (3.58)		20.6 %	-2.60 [-4.58, -0.62]
Zhong 2006	328	-0.41 (3.62)	321	-0.21 (3.58)	=	49.3 %	-0.20 [-0.75, 0.35]
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: i	521 0.60; Chi ² = 5.3 2 = 1.42 (P = 0.1	8, df = 3 (P = 0 6)	512 .15); l² =445	6	•	100.0 %	-0.82 [-1.95, 0.31]
			F	-10 avours treatment	-5 0 5 Favours co	10 ontrol	

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 1, 2010

Date	Event	Description				
15 October 2008	Amended	Converted to new review format.				

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

References to studies included in this review

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- * Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Quetiapine versus other atypical antipsychotic drugs for schizophrenia

This review compares the effects of quetiapine compared with other second generation antipsychotic drugs. There was a high number of participants leaving the studies early and we identified random controlled trials for only half of the possible drug comparisons. This limits the interpretation of the relative effects of quetiapine compared with other second generation antipsychotic drugs. Nevertheless, quetiapine may be slightly less effective than olanzapine and risperidone. It produced comparably few extrapyramidal symptoms, and prolactin increase. It produced less weight gain than olanzapine but more so than risperidone and ziprasidone.

	Adequate sequence generation?	Allocation concealment?	Blinding? (Subjective outcomes)	Blinding? (Objective outcomes)	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	
Atmaca 2003	?	?	?	•	•	•	?	
Conley 2005	?	?	?	•		•	?	
Kinon 2006b	•	?	?	•	•	•	•	
Li 2005	?	?	?	•	•	•	?	
Li 2002	?	?	?	•	?	•	?	
Li 2003	?	?	?	•	?	•	?	
Lieberman 2005	?	?	?	•	•	•	?	
Liu 2004	?	?	?	•	?	•	•	
McEvoy 2006	?	?	?	٠	•	•	?	
McEvoy 2007	?	?	?	•	•	•	•	
Mori 2004	?	?	?	•	•	•	•	
Ozguven 2004	?	?	?	•	•	•	?	
Potkin 2006	?	•	?	•	•	•	•	
Riedel 2005	?	?	?	•	•	•	•	
Riedel 2007	?	?	?	•	•	•	•	
Sacchetti 2004	?	?	?	•	?	•	•	
Sirota 2006	?	?	?	•	•	•	•	
Stroup 2006	?	?	?	•		•	?	

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

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Svestka 2003b Voruganti 2007

Zhong 2006



Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

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. Gender: both. History: any.					
Interventions	1	Quetiapine: dose -300-800 mg/day. N=300.				
	2	Amisulpride: dose - 400-800 mg/day. N=300.				
	3	Aripiprazole: dose - 10-30 mg/day. N=300.				
	4	Clozapine: dose - 300-800 mg/day. N=300.				
	5	Olanzapine: dose - 10-20 mg/day. N=300.				
	6	Ziprasidone: dose - 120-160 mg/day. N=300.				
	7	Risperidone: dose - 4-8 mg/day. N=300.				
	8	Sertindole: dose - 12-24 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