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Ziprasidone versus other atypical antipsychotics for schizophrenia

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Abstract

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

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Werner Kissling - protocol development.

Heike Hunger - helped with data extraction and writing.

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DECLARATIONS OF INTEREST

Katja Komossa - none known.

Stefan Leucht - has received speaker/consultancy honoraria from Sanofi-Aventis, BMS, Eli Lilly, Janssen, Lundbeck and Pfizer. He has received research support from Sanofi-Aventis and Eli Lilly.

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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Heike Hunger - none known.

Franziska Schmid - none known.

Sandra Schwarz - none known.

Paranthaman Seth Bhoopathi - none known.

Please refer to Web version for references with author names in Chinese characters

Objectives—To evaluate the effects of ziprasidone compared with other atypical antipsychotics for people with schizophrenia and schizophrenia-like psychoses.

Search methods—We searched the Cochrane Schizophrenia Group Specialised Register (April 2007) and references of all identified studies for further trial citations. We contacted pharmaceutical companies and authors of trials for additional information.

This search was updated July 2012, 254 citations added to awaiting classification section.

Selection criteria—We included all randomised, at least single-blind, controlled trials comparing oral ziprasidone with oral forms of amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone or zotepine in people with schizophrenia or schizophrenia-like psychoses.

Data collection and analysis—We extracted data independently. For continuous data, we calculated weighted mean differences (MD) 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.

Main results—The review currently includes nine randomised controlled trials (RCTs) with 3361 participants. The overall rate of premature study discontinuation was very high (59.1%). Data for the comparisons of ziprasidone with amisulpride, clozapine, olanzapine, quetiapine and risperidone were available. Ziprasidone was a less acceptable treatment than olanzapine (leaving the studies early for any reason: 5 RCTs, n=1937, RR 1.26 CI 1.18 to 1.35, NNH 7 CI 5 to 10) and risperidone (3 RCTs, n=1029, RR 1.11 CI 1.02 to 1.20, NNH 14 CI 8 to 50), but not than the other second generation antipsychotic drugs. Ziprasidone was less efficacious than amisulpride (leaving the study early due to inefficacy: 1 RCT, n=123, RR 4.72 CI 1.06 to 20.98, NNH 8 CI 5 to 50) olanzapine (PANSS total score: 4 RCTs, n=1291, MD 8.32 CI 5.64 to 10.99) and risperidone (PANSS total score: 3 RCTs, n=1016, MD 3.91 CI 0.27 to 7.55). Based on limited data there were no significant differences in tolerability between ziprasidone and amisulpride or clozapine. Ziprasidone produced less weight gain than olanzapine (5 RCTs, n=1659, MD -3.82 CI -4.69 to -2.96), quetiapine (2 RCTs, n=754, RR 0.45 CI 0.28 to 0.74) or risperidone (3 RCTs, n=1063, RR 0.49 CI 0.33 to 0.74). It was associated with less cholesterol increase than olanzapine, quetiapine and risperidone. Conversely ziprasidone produced slightly more extrapyramidal side-effects than olanzapine (4 RCTs, n=1732, RR 1.43 CI 1.03 to 1.99, NNH not estimable) and more prolactin increase than quetiapine (2 RCTs, n=754, MD 4.77 CI 1.37 to 8.16), but less movement disorders (2 RCTs, n=822, RR 0.70 CI 0.51 to 0.97, NNT not estimable) and less prolactin increase (2 RCTs, n=767, MD -21.97 CI -27.34 to -16.60) than risperidone.

Note: the 254 citations in the awaiting classification section of the review may alter the conclusions of the review once assessed.

Authors' conclusions—Ziprasidone may be a slightly less efficacious antipsychotic drug than amisulpride, olanzapine and risperidone. Its main advantage is the low propensity to induce weight gain and associated adverse effects. However, the high overall rate of participants leaving the studies early limits the validity of any findings.

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Benzodiazepines [therapeutic use]; Clozapine [therapeutic use]; Dibenzothiazepines [therapeutic use]; Piperazines [adverse effects];

*therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [therapeutic use]; Schizophrenia [*drug therapy]; Sulpiride [analogs & derivatives; therapeutic use]; Thiazoles [adverse effects; *therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Schizophrenia is usually a chronic and disabling psychiatric disorder which afflicts approximately one per cent of the population world-wide with little gender differences. The annual incidence of schizophrenia averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000 and the risk of developing the illness over one's lifetime averages 0.7%. (Tandon 2008). Its typical manifestations are 'positive' symptoms such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations), '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 antipsychotics for people with schizophrenia (Kane 1993). The re-introduction of clozapine in the United States of America and a finding that clozapine was more efficacious and associated with fewer movement disorders than chlorpromazine (Kane 1988) has boosted the development of so-called 'atypical' or new (second) generation antipsychotics (NGA).

Description of the intervention

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

How the intervention might work

Ziprasidone—(5-[2-[4-(1, 2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-2-indolinone) has a low affinity for dopamine (D2) receptors and a much higher affinity for serotonin (5HT2) receptors; the serotonin/dopamine ratio is one of the highest among the atypicals. It has a low affinity for adrenergic (α_1) and histaminergic (H1) receptors and may block noradrenaline re-uptake (explaining possible antidepressant effects). Its half life is about 4 hours after oral administration and 2.9 hours after intravenous administration and its oral bioavailability is 59% (Bagnall 2000), therefore it must be ingested with food.

Why it is important to do this review

The debate as to how far the NGA improve these outcomes compared to conventional antipsychotics continues (Duggan 2005, El-Sayeh 2006) and the results from recent studies were sobering (Jones 2006, Liebermann 2005). Nevertheless, in some parts of the world, especially in the highly industrialised countries, second generation antipsychotics have become the mainstay of treatment. The second generation antipsychotics also differ in terms of their costs; while amisulpride and risperidone are already generic in many countries, ziprasidone 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 ziprasidone with other second generation antipsychotics.

OBJECTIVES

To evaluate the clinical effects of ziprasidone compared with other atypical antipsychotics 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.

Randomised cross-over studies will be eligible 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. Ziprasidone: any oral form of application, any dose.
2. Other 'atypical' antipsychotic drugs: amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, zotepine: any oral form of application, any dose.

Types of outcome measures—Outcomes were grouped 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 Number of patients hospitalised
- 8. Adverse effects
 - 8.1 Number of participants with at least one adverse effect
 - 8.2 Clinically important specific adverse effects (cardiac effects, death, movement disorders, prolactin increase and associated effects, sedation, seizures, weight gain, effects on white blood cell count)
 - 8.3 Average endpoint in specific adverse effects
 - 8.4 Average change in specific adverse effects

Search methods for identification of studies

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

Electronic searches—1. Cochrane Schizophrenia Group Trials Register

We searched the Cochrane Schizophrenia Group's Specialised Register (April 2007) using the phrase:

[((ziprasidon* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR zotepin*)) in title, abstract or index terms of REFERENCE) or ((ziprasidon* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR zotepin*)) in interventions of STUDY)]

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

2. Cochrane Schizophrenia Group Trials Register

The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register (August 2012)

[(((*ziprasidon* AND (*amisulprid* OR *aripiprazol* OR *clozapin* OR *olanzapin* OR *quetiapin* OR *sertindol* OR *risperidon* OR *zotepin*)) in title, abstract or index terms

of REFERENCE) or ((*ziprasidon* AND (*amisulprid* OR *aripiprazol* OR *clozapin* OR *olanzapin* OR *quetiapin* OR *sertindol* OR *risperidon* OR *zotepin*)) in interventions of STUDY)] The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, handsearches of relevant journals and conference proceedings (see [Group Module](#)). Incoming trials are assigned to existing or new review titles.

Searching other resources—1. Reference searching

We inspected the reference lists of all studies identified in the search for more trials.

2. Personal contact

We contacted the first author of each included study for missing information.

3. Drug companies

We contacted the manufacturers of all atypical antipsychotics included for additional data.

Data collection and analysis

Selection of studies—We independently 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 these trials were added to the list of those awaiting assessment.

Data extraction and management—1. Data extraction

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

2. Management

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

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. In addition, the following minimum standards for instruments were set: the instrument should either be (a) a self-report or (b) completed by an independent rater or relative (not the therapist) and (c) the instrument should be a global assessment of an area of functioning.

Assessment of risk of bias in included studies—Again working independently, authors 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 categorized into:

- A. Low risk of bias: plausible bias unlikely to seriously alter the results (categorized as 'Yes' in Risk of Bias table)
- B. High risk of bias: plausible bias that seriously weakens confidence in the results (categorized as 'No' in Risk of Bias table)
- C. Unclear risk of bias: plausible bias that raises some doubt about the results (categorized as 'Unclear' in Risk of Bias table)

Trials with high risk of bias (defined as at least four out of seven domains were categorized 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

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

2. Dichotomous 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 adverse 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. Conversely, 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 $2SD > (S - S_{min})$, where S is the mean score and S_{min} 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 reason is that when continuous data are presented on a scale which includes a possibility of negative values, it is difficult to tell whether data are non-normally distributed (skewed) or not. This is also the case for change data (endpoint minus baseline). In the absence of individual patient data it is impossible to know if data are skewed, though this is likely. After consulting the ALL-STAT electronic statistics mailing list, we presented change data in RevMan Analyses in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Change data were therefore included and a sensitivity analysis was not applied. For continuous outcomes we estimated a weighted mean difference (MD) between groups. MDs were again

based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. We combined both endpoint data and change data in the analysis, because there is no principal statistical reason why endpoint and change data should measure different effects (Higgins 2008). When standard errors instead of standard deviations (SD) were presented, we converted the former to standard deviations. If both were missing we estimated SDs from p-values or used the average SD of the other studies (Furukawa 2006).

Unit of analysis issues

1. Cluster trials: Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This can cause type 1 errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation coefficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

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

If cluster studies had been appropriately analysed taking into account intraclass correlation coefficients and relevant data documented in the report, 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 drop-out problem in all parts of the review, including the abstract. For this purpose we calculated, presented and commented on frequency statistics (overall rates of leaving the studies early in all studies and comparators pooled).

Assessment of heterogeneity

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

2. Statistical

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

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

Assessment of reporting biases—Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10.1 of the Cochrane Handbook for Systematic Reviews of Interventions (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 were 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 a priori for examining the change in the robustness of the sensitivity to including studies with potentially skewed data. A recent report showed that some of the comparisons of atypical antipsychotics may have been biased by using inappropriate comparator doses (Heres 2006). We therefore also analysed whether the exclusion of studies with inappropriate comparator doses changed the results of the primary outcome and the general mental state.

RESULTS

Description of studies

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

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

Results of the search—The overall search yielded 3620 reports of which 18 were closely inspected. After excluding nine studies, twenty publications on nine studies and five comparisons were included: ziprasidone versus amisulpride (one), ziprasidone versus clozapine (one), ziprasidone versus olanzapine (four), ziprasidone versus quetiapine (two) and ziprasidone versus risperidone (three).

Included studies—Nine studies met the inclusion criteria. All were double-blind and randomised 3361 participants with the diagnosis of schizophrenia or schizoaffective disorder. Four studies were sponsored by the manufacturer of ziprasidone, two studies were sponsored by pharmaceutical companies producing the comparator drugs, three studies had a neutral sponsor.

1. Length of studies: Four of the included studies were short-term trials with a duration of six to twelve weeks. Three studies fell in the medium-term category with a duration of 18 to 26 weeks and two fell in the long-term category with durations of 28 and 78 weeks.

2. Setting: Four studies reported the setting as in- and outpatient, one study outpatient setting, two studies inpatient setting and two studies did not describe their setting.

3. Participants: Eight studies used operationalised criteria to diagnose the participants, mainly based on the Diagnostic and Statistical Manual Version IV (DSM-IV), but one study applied DSM-III-R, another one the International Classification of Disease Version 10 (ICD-10) and one study did not provide further information. Three short-term studies included acutely ill participants with schizophrenia or schizoaffective disorder, three studies

examined people with chronic schizophrenia or with previous non-response to treatment, one study restricted inclusion to participants with predominantly negative symptoms and one study focused on people with schizophrenia or schizoaffective disorder with predominantly depressive symptoms. On average the patients were relatively chronic with mean ages in the late-thirties when reported.

4. Study size: One study included less than fifty people, six studies included between 100 and 500 people and two studies included more than 500 people.

5. Interventions: In five studies ziprasidone was administered in flexible doses with a dose range from 80 to 160 mg per day, in two studies the dose range was 40 to 160 mg per day, one study used fixed doses of 80, 120 or 160 mg per day and one study did not provide information on the ziprasidone dose.

6. Outcomes

6.1 Leaving the study early: We analysed the number of participants leaving the studies early in the following categories: any reason, adverse effects and lack of efficacy.

6.2 Response to treatment: We prespecified at least 50% PANSS/BPRS total score reduction from baseline as a clinically relevant cut-off to define response, but the studies did not report this outcome. Olie 2006 used at least 50% PANSS negative subscore reduction from baseline, Simpson 2004 at least 40% BPRS total score reduction and Breier 2005 at least 30% PANSS total score reduction as response criteria.

6.3 Outcome scales: Details of scales that provided usable data are shown below. Reasons for exclusion of data from other instruments are presented under 'outcomes' in the Characteristics of included studies section.

6.3.1.1 Clinical Global Impression Scale - CGI Scale (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 one - absent to seven - 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 zero to six or one to seven. Scores can range from 0-126, with high scores indicating more severe symptoms.

6.3.3 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.

6.3.4.1 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.

6.3.4.2 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 zero - normal to three - severe. In addition, there is an item for rating global severity (from zero - absent to five - severe). A low score indicates low levels of akathisia.

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

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

6.4 Adverse effects: Adverse effects were mainly ascertained in open interviews. In addition continuous adverse effect data were provided for weight, QTc time and glucose levels.

Excluded studies—The search strategy yielded 3620 reports of which 20 studies were closely inspected. Nine of them had to be excluded for the following reasons: three not randomised, four open label, one pooled analysis and one no usable data.

Awaiting assessment: 254 citations of possible studies are awaiting assessment

Ongoing studies: Two studies appear to be ongoing (see 'Characteristics of ongoing studies' table).

Risk of bias in included studies

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

Allocation—All of the included studies were randomised controlled trials. None of the studies gave further details about the randomisation process, therefore it remained unclear whether the randomisation procedure was adequate.

Blinding—All included studies were described as 'double-blind', additionally two authors (Lieberman 2005, Stroup 2006) described using identical capsules for blinding. Whether blinding was effective is unclear because none of the studies examined this. The side-effect profiles of the compounds may differ which may have made blinding difficult. Therefore,

the risk of bias for objective outcomes (e.g. death or laboratory values) may have been low but there was a risk of bias for subjective outcomes.

Incomplete outcome data: Reporting on premature study discontinuation was high, only one study did not report on attrition (Svestka 2005). Overall 59% of randomised people discontinued the studies prematurely for any reason. Most studies applied the last observation carried forward method to account for participants leaving the study early which is an imperfect method. It assumes that a participant who left the study prematurely would not have had a change of his condition if he had stayed in the study. This assumption can obviously be wrong. This may be less of a problem in the studies with low attrition but is clearly problematic in studies with high attrition.

Selective reporting: None of the included studies was free of selective reporting. Two studies (Breier 2005 and Olie 2006) reported only adverse events that occurred in at least 5 or 10% of the participants. This procedure is problematic, because rare but potentially serious adverse effects may be missed. One study (Lieberman 2005) excluded all data from one site from the analysis owing to concern about the integrity of data. Simpson 2004 focused on acutely ill subjects but failed to report on positive symptom reduction. For two studies there was only an abstract (Sacchetti 2006) or no publication available (Svestka 2005). Therefore most of the studies failed to fully report on secondary or even primary outcomes.

Other potential sources of bias—None of the included studies was free from other potential sources of bias. Six studies (Addington 2004, Breier 2005, Kinon 2006, Olie 2006, Sacchetti 2006, Simpson 2004) were industry sponsored by the manufacturers of one of the compounds. There is evidence that pharmaceutical companies sometimes highlight the benefits of their compounds and tend to suppress their disadvantages (Heres 2006). As an example Olie 2006 did not report on positive symptoms. In Simpson 2004 olanzapine doses higher than 15 mg per day were not allowed, although the official olanzapine dose range goes up to 20 mg/day. Further methodological short-comings of included trials were short wash-out phases, selected and usually chronic participants and lack of standardised response criteria (for review see Leucht 2008).

Effects of interventions

Nine studies met the inclusion criteria. These studies provided data on five different comparisons of ziprasidone versus other second generation antipsychotic drugs.

1. Comparison 1. ZIPRASIDONE versus AMISULPRIDE—A single study compared ziprasidone (80-160 mg/day) with amisulpride (100 to 200 mg/day). It included only chronic participants with predominantly negative symptoms.

1.1 No clinically significant response - as defined by the original studies: There was no statistically significant difference between groups (1 RCT, n=123, RR 1.05 CI 0.93 to 1.19).

1.2 Leaving the study early: There was no statistically significant difference in the number of participants discontinuing the study due to any reason (1 RCT, n=123, RR 1.45 CI 0.78 to

2.70) or adverse effects (1 RCT, n= 123, RR 0.79 CI 0.18 to 3.37), but more participants in the ziprasidone group than in the amisulpride group discontinued the study prematurely due to inefficacy (1 RCT, n=123, RR 4.73 CI 1.06 to 20.98, NNH 8 CI 5 to 50).

1.3 Global state

1.3.1 Global state: no clinically important change (as defined by the original studies): No significant difference was reported (1 RCT, n=123, RR 1.11 CI 0.82 to 1.51).

1.4 Mental state

1.4.1 General mental state: PANSS total score: There was no significant difference (1 RCT, n=123, MD 2.70 CI -3.55 to 8.95).

1.4.2 General mental state: BPRS total score: There was no significant difference (1 RCT, n=123, MD 2.10 CI -1.52 to 5.72).

1.4.3 Negative Symptoms: no clinically important change (less than 50% PANSS negative subscore reduction): There was no significant difference (1 RCT, n=123, RR 1.05 CI 0.93 to 1.19).

1.4.4 Negative Symptoms: PANSS negative subscore: There was no significant difference (1 RCT, n=123, MD 0.80 CI -1.40 to 3.00).

1.5 Adverse effects

1.5.1 At least one adverse effect: There was no significant difference (1 RCT, n=123, RR 1.11 CI 0.82 to 1.51).

1.5.2 Cardiac effects - QTc prolongation: There was no occurrence of QTc prolongation in either group.

1.5.3 Extrapyramidal side-effects: There were no significant differences in the occurrence of akathisia (1 RCT, n=123, RR 1.58 CI 0.27 to 9.10), parkinsonism (1 RCT, n=123, RR 6.30 CI 0.78 to 50.80) or use of antiparkinson medication (1 RCT, n=123, RR 1.70 CI 0.94 to 3.07).

1.5.4 Sedation: There was no significant difference (1 RCT, n=123, RR 0.35 CI 0.07 to 1.67). **1.5.5 Weight gain of 7% or more of total body weight** There was no significant difference (1 RCT, n=123, RR 0.48 CI 0.18 to 1.29).

1.6 Publication bias: Due to the small number of included studies we did not apply the funnel plot method.

1.7 Investigation for heterogeneity and sensitivity analysis: The reasons given for the preplanned sensitivity analyses did not occur and they were therefore not performed.

2. Comparison 2. ZIPRASIDONE versus CLOZAPINE—A single study in treatment-resistant participants compared ziprasidone with clozapine.

2.1 Leaving the study early: There was no significant difference in the number of participants leaving the study early due to any reason (1 RCT, n=146, RR 1.00 CI 0.66 to 1.51). The number of participants leaving the study early for specific reasons (adverse events or inefficacy of treatment) has not been reported.

2.2 Mental state

2.2.1 General mental state: PANSS total score: There was no significant difference (1 RCT, n=146, MD -0.50 CI -7.72 to 6.72).

2.3 Adverse effects

2.3.1 Cardiac effects - QTc prolongation: There was no occurrence of QTc prolongation.

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

2.5 Investigation of heterogeneity and sensitivity analysis: The reasons given for the preplanned sensitivity analyses did not occur and they were therefore not performed.

3. Comparison 3. ZIPRASIDONE versus OLANZAPINE

3.1 No clinically significant response - as defined by the original studies: There was no significant difference in the number of participants responding to treatment (2 RCTs, n=817, RR 1.20 CI 0.92 to 1.56), but the data were heterogeneous (I^2 84%). In Breier 2005 olanzapine was significantly superior, while Simpson 2004 (which restricted the upper olanzapine dose range to 15 mg per day) showed no difference between groups.

3.2 Leaving the study early: Olanzapine was statistically significantly superior in terms of leaving the study early for any reason (5 RCTs, n=1937, RR 1.26 CI 1.18 to 1.35, NNH 7 CI 5 to 10) and inefficacy of treatment (5 RCTs, n=1937, RR 1.57 CI 1.27 to 1.94, NNH 17 CI 11–13), but there was no significant difference in leaving early for adverse effects (5 RCTs, n=1937, RR 1.12 CI 0.77 to 1.61).

3.3 Global state: There was no significant difference in global state (1 RCT, n=269, RR 1.18 CI 0.92 to 1.53).

3.4 Mental state

3.4.1 General mental state: no clinically important change (less than 30%): There was a significant difference in terms of less than 30% PANSS reduction favouring olanzapine (1 RCT, n=548, RR 1.36 CI 1.15 to 1.61, NNT 6 CI 4 to 14).

3.4.2 General mental state: PANSS total score: In the overall analysis there was a significant difference in favour of olanzapine (4 RCTs, n=1291, MD 8.32 CI 5.64 to 10.99). Data were reported as short-term data (1 RCT, n=48, MD 8.37 CI -2.00 to 18.74), medium-term data (1 RCT, n=201, MD 6.50 CI -0.07 to 13.07) and long-term data (2 RCTs, n=1042, MD 8.71 CI 5.66 to 11.76).

3.4.3 General mental state: no clinically important change: There was no significant difference (1 RCT, n=269, RR 1.07 CI 0.94 to 1.21).

3.4.4 General mental state: BPRS total score: There was no significant difference (1 RCT, n=251, MD 0.50 CI -2.85 to 3.85).

3.4.5 Positive Symptoms: PANSS positive subscore: There was a significant difference in favour of olanzapine (2 RCTs, n=730, MD 3.11 CI 1.93 to 4.30) in the overall analysis, as well as in the analysis of medium-term data (1 RCT, n=201, MD 3.60 CI 1.45 to 5.75) and long-term data (1 RCT, n=529, MD 2.90 CI 1.47 to 4.33).

3.4.6 Negative Symptoms: PANSS negative subscore: Overall there was no significant difference but the results were heterogeneous and the two available studies are therefore reported separately. Breier 2005 (long-term data) found a significant difference in the PANSS negative subscore favouring olanzapine (1 RCT, n= 529, MD 2.20 CI 0.92 to 3.48), while Stroup 2006 (mediumterm data) reported no difference between groups (1 RCT, n=201, MD -1.00 CI -2.91 to 0.91).

3.5 General Functioning

3.5.1 No clinically important change: There was a significant difference favouring olanzapine (1 RCT, n=394, RR 1.20 CI 1.03 to 1.41, NNT 9 CI 5 to 50).

3.5.2 GAF total score: There was a significant superiority of olanzapine (1 RCT, n=326, MD 3.49 CI 0.64 to 6.34).

3.6 Quality of Life

3.6.1 QLS total score: There was no significant difference (1 RCT, n=393, MD 3.70 CI -1.21 to 8.61).

3.7 Cognitive Functioning

3.7.1 PANSS cognition subscore: There was a significant difference in the PANSS cognition subscore favouring olanzapine (1 RCT, n=528, MD 2.40 CI 1.17 to 3.63).

3.8 Service use

3.8.1 Number of patients re-hospitalised: There was a significant difference favouring olanzapine (2 RCTs, n=766, RR 1.54 CI 1.07 to 2.20, NNH 17 CI 9 to 100), which was also present in long-term data (1 RCT, n=521, RR 1.58 CI 1.03 to 2.44) but not in medium-term data (1 RCT, n=245, RR 1.45 CI 0.75 to 2.79).

3.9 Adverse effects

3.9.1 At least one adverse effect: There was no significant difference (4 RCTs, n=1583, RR 1.05 CI 0.94 to 1.18).

3.9.2 Cardiac effects - number of participants with QTc prolongation: There was no significant difference in the number of participants with QTc prolongation.

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

3.9.4 Cholesterol - number of participants with abnormally high cholesterol: There was no significant difference in the number of participants with high cholesterol levels (1 RCT, n=394, RR 0.70 CI 0.12 to 4.15).

3.9.5 Cholesterol - mean change from baseline in mg/dl: There was a significant difference in favour of ziprasidone (4 RCTs, n=1502, MD -15.83 CI -25.72 to -5.95). The data were heterogeneous, but all of the single studies found a superiority of ziprasidone, as well (1 RCT, n=418, MD -7.39 CI -10.43 to -4.35), (1 RCT, n=521, MD -18.90 CI -29.89 to -7.91), (1 RCT, n=318, MD -9.43 CI -16.82 to -2.04) and (1 RCT, n=245, MD -30.40 CI -39.83 to -20.97). Therefore the studies varied only in the degree of difference, but not in the direction of the effect.

3.10 Death: There was no significant difference (2 RCTs, n=766, RR 1.60 CI 0.24 to 10.45).

3.11 Extrapyramidal side-effects: There was a significant difference in use of antiparkinson medication at least once favouring olanzapine (4 RCTs, n=1732, RR 1.43 CI 1.03 to 1.99, NNT not estimable), but there was no difference in akathisia (2 RCTs, n=766, RR 1.41 CI 0.78 to 2.53), dystonia (1 RCT, n=548, RR 13.29 CI 0.75 to 234.71) and any extrapyramidal symptoms (2 RCTs, n=793, RR 1.90 CI 0.77 to 4.73).

3.12 Extrapyramidal side-effects (scale measured): There was no significant difference between ziprasidone and olanzapine in the results of rating scales for extrapyramidal side-effects (AIMS: 2 RCTs, n=925, MD 0.16, CI -0.15 to 0.46; BAS: 2 RCTs, n=925, MD 0.07 CI -0.04 to 0.17; ESRS: 1 RCT, n=269 MD 0.40 CI -0.73 to 1.53 and SAS: 2 RCTs, n=922, MD 0.34 CI -0.13 to 0.19).

3.13 Glucose - number of participants with abnormally high fasting glucose: There was no significant difference (1 RCT, n=394, RR 1.05 CI 0.15 to 7.39).

3.14 Glucose - mean change from baseline in mg/dl: There was a significant difference in the mean change of glucose levels (4 RCTs, n=1420, MD -8.25 CI -13.72 to -2.77) favouring ziprasidone.

3.15 Prolactin associated side-effects: There was no significant difference in prolactin increase (1 RCT, n=394, RR 0.89, CI 0.59 to 1.35), amenorrhoea (1 RCT, n=148, RR 1.19 CI 0.51 to 2.79) or galactorrhoea (2 RCTs, n=580, RR 1.56 CI 0.53 to 4.56), but sexual dysfunction indicated a slight tendency to the intervention group (2 RCTs, n=766, RR 0.75 CI 0.56 to 1.01).

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

3.17 Sedation: There was no significant difference. The data revealed some heterogeneity, but the direction of the effect was the same in both studies showing a trend in favour of ziprasidone (2 RCTs, n=766, RR 0.64 CI 0.39 to 1.04).

3.18 Weight gain: There was a significant difference favouring ziprasidone (4 RCTs, n=1808, RR 0.20 CI 0.14 to 0.30, NNH 2 CI 5 to 10).

3.19 Weight gain change from baseline in kg: Overall there was a significant difference in favour of ziprasidone (5 RCTs, n=1659, MD -3.82 CI -4.69 to -2.96). The data were heterogeneous but again the direction of the effect was the same in all single studies (n=48, MD -2.12 CI -4.36 to 0.12; n=238, MD -2.62 CI -3.92 to -1.32; n=529, MD -4.18 CI -5.18 to -3.18; n= 468, MD -5.00 CI -6.25 to -3.75 and n=376, MD -4.18 CI -5.10 to -3.26).

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

3.21 Investigation for heterogeneity and sensitivity analysis: Excluding potentially skewed data in Svestka 2005 from the analysis of overall symptoms (PANSS total score) did not reverse the superiority of olanzapine.

4. Comparison 4. ZIPRASIDONE versus QUETIAPINE—We found two RCTs that compared ziprasidone with quetiapine.

4.1 Leaving the study early: There was no significant difference in leaving the studies early due to any reason (2 RCTs, n=722, RR 0.95 CI 0.88 to 1.00), adverse effects (2 RCTs, n=722, RR 0.96 CI 0.67 to 1.39) or inefficacy of treatment (2 RCTs, n=722, RR 0.87 CI 0.68 to 1.12).

4.2 Mental state

4.2.1 General mental state: PANSS total score: There was no significant difference between groups (2 RCTs, n = 710, MD 0.11 CI -6.14 to 6.36). The data were heterogeneous, but reporting them separately showed no significant difference neither medium-term data (n=198, MD -3.70 CI -10.37 to 2.97) nor long-term data (n=511, MD 2.78 CI -1.25 to 6.81).

4.2.2 Positive symptoms: PANSS positive subscore: There was no significant difference (1 RCT, n=198, MD 0.00 CI -2.18 to 2.18).

4.2.3 Negative symptoms: PANSS negative subscore: There was no significant difference (1 RCT, n=198, MD -1.60 CI -3.54 to 0.34).

4.3 Service use

4.3.1 Number of participants re-hospitalised: There was no significant difference (2 RCTs, n=756, RR 0.86 CI 0.63 to 1.17). Data were presented as medium-term data (1 RCT, n=235, RR 0.80 CI 0.46 to 1.40) and long-term data (1 RCT, n= 101, RR 0.88 CI 0.61 to 1.29).

4.4 Adverse effects

4.4.1 At least one adverse effect: There was no significant difference (2 RCTs, n=754, RR 0.97 CI 0.85 to 1.10).

4.4.2 Cardiac effects - number of participants with QTc prolongation: There was no significant difference (1 RCT, n=522, RR 0.61 CI 0.12 to 2.98).

4.4.3 Cardiac effects - mean change of QTc interval from baseline in ms: There was no significant difference (2 RCTs, n=549, MD -3.41 CI -8.18 to 1.37).

4.4.4 Cholesterol - change from baseline in mg/dl: There was a significant difference favouring ziprasidone (2 RCTs, n=754, MD -16.01 CI -23.46 to -8.57).

4.4.5 Death: There was no significant difference (2 RCTs, n=754, RR 2.45 CI 0.32 to 18.83).

4.4.6 Extrapyramidal side-effects: There was a significant difference in the number of participants using at least one dose of antiparkinson medication favouring quetiapine (1 RCT, n=522, RR 2.32 CI 1.07 to 5.00, NNT not estimable), but there was no significant difference in akathisia (2 RCTs, n=754, RR 1.28 CI 0.69 to 2.39) or in any extrapyramidal symptoms (1 RCT, n=232, RR 0.50 CI 0.16 to 1.51).

4.4.7 Glucose - change from baseline in mg/dl: There was no significant difference (2 RCTs, n=754, MD -3.10 CI -10.19 to 3.99).

4.4.8 Prolactin associated side-effects: There was no significant difference in the number of women with amenorrhoea (1 RCT, n=138, RR 2.34 CI 0.81 to 6.79) and galactorrhoea (2 RCTs, n=202, RR 1.46 CI 0.50 to 4.31).

4.4.9 Prolactin - change from baseline in ng/ml: There was a statistically significant difference in favour of quetiapine (2 RCTs, n=754, MD 4.77 CI 1.37 to 8.16).

4.4.10 Sedation: There was a statistically significant difference in favour of ziprasidone (2 RCTs, n=754, RR 0.73 CI 0.55 to 0.97, NNT 13 CI 1 to 100).

4.4.11 Weight gain of 7% or more of total body weight: There was a significant difference favouring ziprasidone (2 RCTs, n=754, RR 0.45 CI 0.28 to 0.74, NNT 13 CI 8 to 33).

4.4.12 Weight gain change from baseline in kg: There was no significant difference (1 RCT, n=466, MD -1.20 CI -2.45 to 0.05).

4.5 Publication bias: Due to the small number of included studies a funnel plot analysis was not meaningful.

4.6 Investigation for heterogeneity and sensitivity analysis: The reasons given for the preplanned sensitivity analyses did not occur and they were therefore not performed.

5. Comparison 5. ZIPRASIDONE versus RISPERIDONE—Three trials contributed data to this comparison.

5.1 No clinically significant response - as defined by the original studies: There was no significant difference (1 RCT, n=296, RR 0.98 CI 0.89 to 1.07).

5.2 Leaving the study early: There was a significant difference in the number of participants leaving the studies early due to any reason favouring risperidone (3 RCTs, n=1019, RR 1.11 CI 1.02 to 1.20, NNH 14 CI 8 to 50). There was however no significant difference in leaving early for adverse effects (3 RCTs, n=1019, RR 1.23 CI 0.76 to 1.98) or for inefficacy of treatment (3 RCTs, n=1019, RR 1.14 CI 0.79 to 1.66).

5.3 Global state

5.3.1 No clinically important change - as defined by the original studies: There was no significant difference (1 RCT, n=296, RR 1.24 CI 0.96 to 1.60).

5.4 Mental state

5.4.1 General mental state: no clinically important change (less than 50% PANSS total reduction): There was no significant difference (1 RCT, n=296, RR 0.98 CI 0.89 to 1.07).

5.4.2 General mental state: PANSS total score: Overall there was a significant superiority favouring risperidone (3 RCTs, n=1016, MD 3.91 CI 0.27 to 7.55). There was some heterogeneity, but the direction of the effect was the same in all three studies: short-term (n=516, MD 6.01 CI 1.99 to 10.03), medium-term (n=204, MD 6.30 CI -0.17 to 12.77) and long-term (n=196, MD 1.50 CI -0.16 to 3.16).

5.4.3 General mental state: BPRS total score: There was no significant difference (1 RCT, n=296, MD 0.70 CI -2.93 to 4.33).

5.4.4 Positive symptoms: PANSS positive subscore: There was a significant difference favouring risperidone (1 RCT, n=204, MD 2.50 CI 0.38 to 4.62).

5.4.5 Positive symptoms: BPRS positive subscore: There was no significant difference (1 RCT, n=296, MD 0.50 CI -0.15 to 1.15). **5.4.6 Negative symptoms: PANSS negative subscore:** There was no significant difference in the overall analysis (2 RCTs, n=500, MD 0.04 CI -1.12 to 1.20) as well as in the analysis of short-term data (1 RCT, n=296, MD 0.00 CI -1.48 to 1.48) or medium-term data (1 RCT, n=204, MD 0.10 CI -1.78 to 1.98).

5.5 Service use

5.5.1 Number of patients re-hospitalised: There was no significant difference in the medium-term data analysis (1 RCT, n=241, RR 1.04 CI 0.58 to 1.89) as well as in the analysis of long-term data (1 RCT, n=526, RR 1.19 CI 0.80 to 1.78) and in the overall analysis (2 RCTs, n=767, RR 1.14 CI 0.82 to 1.59).

5.6 Adverse effects

5.6.1 At least one adverse effect: There was no significant difference (3 RCTs, n=1063, RR 0.93 CI 0.86 to 1.02).

5.6.2 Cardiac effects - number of participants with QTc prolongation: There was no significant difference (2 RCTs, n=822, RR 0.53 CI 0.11 to 2.51).

5.6.3 Cardiac effects - mean change of the QTc interval from baseline in ms: There was no significant difference (3 RCTs, n=798, MD 2.24 CI -1.92 to 6.39).

5.6.4 Cholesterol - change from baseline in mg/dl: There was a significant difference favouring ziprasidone (2 RCTs, n=767, MD -8.58 CI -16.04 to -1.11).

5.6.5 Death: There was no significant difference (2 RCTs, n=767, RR 1.18 CI 0.22 to 6.42).

5.6.6 Extrapyramidal side-effects (dichotomous): There was a significant difference favouring ziprasidone in terms of 'any EPS' (1 RCT, n=241, RR 0.32 CI 0.12 to 0.87, NNT 13 CI 7 to 100) and use of antiparkinson medication (2 RCTs, n=826, RR 0.70 CI 0.51 to 0.97, NNT not estimable), but no significant difference in akathisia (3 RCTs, n=1063, RR 0.98 CI 0.53 to 1.81) or tremor (1 RCT, n=296, RR 1.06 CI 0.53 to 2.11).

5.6.7 Extrapyramidal side-effects (scale measured): Scale measured results on extrapyramidal side-effects showed a statistically significant difference in dyskinesia (AIMS: 1 RCT, n= 296, MD -0.21 CI -0.25 to -0.17), akathisia (BAS: 1 RCT, n= 296, MD -0.56 CI -0.61 to -0.51) and general EPS (SAS: 1 RCT, n=296, MD -0.34 CI -0.60 to -0.14), all in favour of ziprasidone.

5.6.8 Glucose - mean change from baseline in mg/dl: There was no significant difference between groups (2 RCTs, n= 767, MD -4.94 CI -11.80 to 1.91).

5.6.9 Prolactin associated side-effects: There was a significant difference in the frequency of sexual dysfunction (2 RCTs, n=822, RR 0.69 CI 0.50 to 0.97, NNH not estimable) favouring ziprasidone, but not in the frequency of abnormal ejaculation (1 RCT, n=215, RR 0.48 CI 0.15 to 1.54), amenorrhoea (1 RCT, n=81, RR 1.08 CI 0.23 to 5.02), decreased libido (1 RCT, n=298, RR 0.61 CI 0.26 to 1.42), erectile dysfunction (1 RCT, n=215, RR 0.95 CI 0.35 to 2.63) or galactorrhoea (3 RCTs, n=303, RR 0.56 CI 0.25 to 1.28).

5.6.10 Prolactin - change from baseline in ng/ml: There was a significant difference favouring ziprasidone (2 RCTs, n=667, MD -21.97 CI -27.34 to -16.60).

5.6.11 Sedation: There was no significant difference (3 RCTs, n=1063, RR 0.87 CI 0.63 to 1.20).

5.6.12 Weight gain - number of participants with 7% or more increase in total body weight: There was a significant difference (3 RCTs, n=1063, RR 0.49 CI 0.33 to 0.74, NNH 14 CI 10 to 33) favouring ziprasidone.

5.6.13 Weight gain - mean change from baseline in kg: There was no significant difference (1 RCT, n=461, MD -1.10, CI -2.35 to 0.15).

5.7 Publication bias: Due to the small number of included studies a funnel plot analysis was not meaningful.

5.8 Investigation for heterogeneity and sensitivity analysis: The reasons given for the preplanned sensitivity analyses did not occur and they were therefore not performed.

DISCUSSION

There are several limitations of the evidence. For three comparisons (ziprasidone versus aripiprazole, sertindole and zotepine) not a single study could be included. Thus, nothing can be said about the effects of ziprasidone compared to these second generation antipsychotic drugs. The overall rate of premature study termination was very high (59.1%) limiting the validity of any findings beyond dropout, because more than 50% of the data must be synthesised by statistical modelling. Only one study fell in the long-term category (Liebermann 2005). Therefore, little is known about the long-term effects of ziprasidone. Six of nine included studies were industry-sponsored. We showed in a blinded analysis of abstracts that pharmaceutical companies emphasize the positive aspects of their compounds (Heres 2006). All this is not ideal for judging the comparative effects of antipsychotic drugs in a chronic disorder such as schizophrenia.

Summary of main results

1. General—Currently randomised evidence comparing ziprasidone with amisulpride, clozapine, olanzapine, quetiapine and risperidone is available. A major limitation is the high overall rate of premature study discontinuation (59.1%). Ziprasidone was a less acceptable treatment than olanzapine and risperidone. It was less efficacious than amisulpride, olanzapine and risperidone. Ziprasidone induced less weight gain than olanzapine, quetiapine or risperidone. It was associated with less cholesterol increase than olanzapine, quetiapine and risperidone. Conversely ziprasidone induced slightly more extrapyramidal side-effects than olanzapine and slightly more prolactin increase than quetiapine but less movement disorders and less prolactin increase than risperidone.

Note: the 254 citations in the awaiting classification section of the review may alter the results and conclusions of the review once assessed.

2. Comparison 1. ZIPRASIDONE versus AMISULPRIDE—Only one study with 123 chronic participants and predominantly negative symptoms could be included in this comparison.

2.1 Leaving the study early: The overall number of participants leaving the study early was 25% which is less than in many other current antipsychotic drug trials. As there was no difference in leaving the studies early due to any reason both compounds may be similarly acceptable for people with schizophrenia, at least in the context of a trial. That more

participants in the ziprasidone group left the study early due to inefficacy of treatment reflects an efficacy advantage of amisulpride.

2.2 Efficacy outcomes (global, general, and specific mental state): There was no difference in overall efficacy and in negative symptoms which is important because the study focused on participants with predominantly negative symptoms. Nevertheless, the positive subscore of the PANSS was not reported in this study sponsored by ziprasidone's manufacturer. We interpreted this failure as an example of selective reporting.

2.3 Adverse effects: There were no significant differences in the following adverse events: at least one adverse effect, extrapyramidal side-effects, QTc prolongation, sedation and weight gain. The tolerability of amisulpride and ziprasidone may therefore be similar but such a conclusion would be premature due to the small number of included participants.

3. Comparison 2. ZIPRASIDONE versus CLOZAPINE—Only one study with 146 participants and treatment resistant schizophrenia compared ziprasidone with clozapine.

3.1 Leaving the study early: The overall number of participants leaving the study early was considerable (38.4%) and calls the validity of any other outcomes into question.

3.2 Efficacy related outcomes (global, general, and specific mental state): Efficacy data were poorly reported. Dichotomous data on clinically significant response were not available. Nevertheless overall there was no difference in efficacy according to the PANSS total score which improved similarly in both groups.

3.3 Adverse effects: The only adverse effect reported was the occurrence of QTc prolongation. As there was no case in either group we can not come up with a clear judgement.

4. Comparison 3. ZIPRASIDONE versus OLANZAPINE—This was the largest comparison with five trials and 1985 randomised participants.

4.1 Leaving the study early: The overall number of participants discontinuing the studies prematurely was again high (59.1%), although this may be partly explained by a relatively high number of mid-term and long-term studies. Data on leaving the study early for any reason and for inefficacy of treatment showed a benefit for olanzapine compared to ziprasidone. Therefore, olanzapine may be more acceptable than ziprasidone, largely due to a better efficacy.

4.2 Efficacy outcomes (global state, general and specific mental state): There was a significant superiority of olanzapine in most aspects of efficacy as measured by the PANSS total score, PANSS positive subscore and PANSS negative subscore. The exception were the BPRS data, but these were derived from only one study which limited the olanzapine dose to 15 mg/day which is below the upper limit of 20 mg/day in olanzapine's label (Simpson 2004). As already mentioned above the high rate of patients discontinuing the studies prematurely has to be taken into account.

4.3 General functioning and quality of life: Limited data from one study suggest that olanzapine may improve participants functioning more than ziprasidone but there was no difference in quality of life.

4.4 Cognitive functioning: The PANSS cognition score demonstrated a benefit for olanzapine. More data on this item are needed, because the PANSS cognition score is not ideal for measuring cognitive effects as the scale has never been validated for this purpose. In addition, there is little evidence whether positive effects in cognition translate in better functioning, e.g. in an improved ability to work.

4.5 Service use: Olanzapine was associated with fewer re-hospitalisations, which can be important from a cost-effectiveness point of view.

4.6 Adverse effects: Adverse effects reporting was relatively detailed concerning extrapyramidal side-effects, QTc prolongation, sedation, death, weight gain, cholesterol increase and prolactin increase. Olanzapine was better in terms of use of antiparkinson medication (a proxy measure for extrapyramidal side-effects), while ziprasidone was associated with lower weight gain, cholesterol and glucose increase. The latter side-effects are very important, because in the long run they may lead to vascular problems such as myocardial infarction or stroke.

5. Comparison 4. ZIPRASIDONE versus QUETIAPINE—Two studies with 722 participants fell into this category.

5.1 Leaving the study early: The overall percentage of participants discontinuing the studies early was extremely high (80.7%). This high rate limits any interpretation of outcomes other than premature study discontinuation, although the relatively long study durations of 26 and 51 weeks may have played a role. As there were no significant differences between groups, ziprasidone and quetiapine may be similarly acceptable for people with schizophrenia, at least within the confines of clinical trials.

5.2 Efficacy outcomes (global state, overall and specific mental state): Data on the number of participants with a clinically significant response were not reported. There was no significant difference in the general and specific mental state, but the small number of included trials and randomised people, and the very high dropout rates are certainly important limitations of this evidence.

5.3 Adverse effects: We found limited data on extrapyramidal symptoms, cardiac effects, cholesterol, glucose, prolactin, weight and sedation. Results on cholesterol, weight gain and sedation showed a significant benefit for ziprasidone whereas fewer people in the quetiapine group needed antiparkinson medication (a proxy measure for movement disorders) or developed prolactin increase. This might make ziprasidone somewhat more recommendable than quetiapine for people at risk to develop a metabolic syndrome, but less recommendable for EPS sensitive patients or patients suffering from prolactin associated side-effects. But these conclusions are very tentative because of the limited amount of available data.

6. Comparison 5. ZIPRASIDONE versus RISPERIDONE—Three studies with an overall dropout rate of 63.1% were available for this comparison.

6.1 Leaving the studies early: As more participants in the ziprasidone groups than in the risperidone groups left the studies prematurely, risperidone may be more acceptable for people with schizophrenia. There were no significant differences in specific reasons (adverse events or inefficacy of treatment) for study discontinuation, the reason for this improved acceptability is unclear.

6.2 Efficacy outcomes (global state, general and specific mental state): A significant benefit for risperidone was present in general mental state and in positive symptoms. Although the small number of included trials and the high dropout rates limit the validity of this finding, risperidone maybe somewhat more efficacious for the positive symptoms of schizophrenia than ziprasidone.

6.3 Adverse effects: Ziprasidone was more tolerable than risperidone concerning a number of adverse events: certain extrapyramidal side-effects, glucose, cholesterol, prolactin increase, and weight gain. In treatment decisions this better tolerability profile of ziprasidone needs to be weighted with the somewhat lower efficacy, always keeping in mind the small amount of available data.

Overall completeness and applicability of evidence

For almost half of the possible comparisons of ziprasidone with other second generation antipsychotic drugs not a single study was identified. Therefore the evidence is incomplete. Furthermore, most of the included studies were efficacy studies, therefore external validity is limited and further effectiveness studies are needed.

Quality of the evidence

All studies were randomised and double-blind, but details on these procedures were rarely presented. Therefore it is unclear whether randomisation and blinding were really appropriately done. Additionally two thirds of the studies were industry sponsored and in two of them a potential dose-related bias could not be excluded. Furthermore high rates of participants leaving the studies prematurely (overall 59%) and the scarcity of long-term studies limit the overall quality.

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

A previous Cochrane review compared the effects of ziprasidone with those of any other antipsychotic drugs in schizophrenia (Bagnall 2000). However, at that time not a single randomised controlled trial comparing ziprasidone with another second generation antipsychotic drug was available.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—People with schizophrenia should know that based on this review ziprasidone may be slightly less efficacious than amisulpride, olanzapine and risperidone. The main advantage of ziprasidone is its low propensity to induce weight gain and associated metabolic problems such as cholesterol increase which has been demonstrated compared to olanzapine, quetiapine and risperidone.

2. For clinicians—Clinicians should know that randomised evidence of the effects of ziprasidone compared to other second generation antipsychotic drugs is only available for amisulpride, clozapine, olanzapine, quetiapine and risperidone. Even this evidence is limited, especially by high rates of premature study discontinuation, and more studies are needed to clarify the role of ziprasidone compared to other second generation antipsychotic drugs. Nevertheless, in their decision making process clinicians could weigh the above mentioned possible differences in efficacy and side-effects between ziprasidone and other second generation antipsychotic drugs.

3. For managers/policy makers—For the comparison of ziprasidone with olanzapine only there are very limited data on service use and functioning in society available that are important for managers and policy makers. Even these data are too scarce to make any recommendations.

Implications for research

1. General—High numbers of participants leaving the studies early as in the current review are an enormous threat to the validity of current antipsychotic drug trials. Furthermore, strict adherence to the CONSORT statement (Moher 2001) would make such studies much more informative.

2. Specific—RCTs comparing ziprasidone with second generation antipsychotic drugs other than amisulpride, clozapine, olanzapine, quetiapine and risperidone are urgently needed (see Table 1). New studies could address different disease stages (acute, chronic, first episode, maintenance) and different variants of the illness. Further long-term studies are needed to know more about ziprasidone's relative efficacy and tolerability.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Addington 2004

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: eight weeks. Design: parallel. Location: multicentre.	
Participants	Diagnosis: (DSM-III-R) schizophrenia (n=260) or schizoaffective disorder (n=36), acute exacerbation, PANSS total score of 60. N=296. Age: 18-64 years. Gender: 215 M, 81 F. History: duration of illness not reported, age at onset mean risperidone=24.6 years, mean ziprasidone=25.2 years. Setting: not reported.	
Interventions	1	Risperidone: flexible dose, allowed dose range: 6-10 mg/day, mean dose=7.4 mg/day. N=147.
	2	Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=114.2 mg/day. N=149
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS derived BPRS, BPRS positive subscore, PANSS negative subscore, depression MADRS. General functioning: GAF. Adverse effects: open interviews, EPS (akathisia, tremor, use of antiparkinson medication, AIMS, BAS, SAS), cardiac effects (ECG), prolactin-associated side-effects, sedation, weight gain, laboratory (urine, blood chemistry) Unable to use- GAF total score (no usable data). QTc abnormalities in ms (no usable data).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition rate was 33%. The last observation carried forward method was used to account for people leaving the study early. Data on study completers were also available
Selective reporting (reporting bias)	High risk	Reporting on secondary outcomes was incomplete.
Other bias	High risk	The study was sponsored by the manufacturer of ziprasidone.

Breier 2005

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 28 weeks. Design: parallel. Location: multicentre.
Participants	Diagnosis: (DSM-IV) schizophrenia, BPRS 42, CGI-S 4. N=548. Age: 18-75 years (mean olanzapine=40.1 years, mean ziprasidone=38.2 years). Gender: 352 M, 196 F. History: duration of illness not reported, age at onset mean olanzapine=23.9 years, mean ziprasidone=22.8 years. Setting: in- and outpatient.
Interventions	<ol style="list-style-type: none"> 1 Olanzapine: flexible dose, allowed dose range: 10-20 mg/day, mean dose=15.27 mg/day. N=277. 2 Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=115.96 mg/day. N=271
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, PANSS cognition subscore, depression MADRS, HAM-D. Quality of life: Heinrichs - Carpenter Scale. Adverse effects: open interviews, EPS (use of antiparkinson medication, dystonia, extrapyramidal symptoms, AIMS, BAS, SAS), cardiac effects (ECG), weight gain, laboratory (prolactin, glucose, lipids). Unable to use- Prolactin (no usable data).

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The overall attrition was high (48.9%).The last observation carried forward method was used for people leaving the study early. Additionally a mixed models analysis was performed but it is unclear whether any statistical method can account for such high numbers leaving the study early
Selective reporting (reporting bias)	High risk	Only adverse effects with an incidence of at least 10% were reported therefore important side-effects may have been missed by this procedure
Other bias	High risk	The study was sponsored by the manufacturer of olanzapine.

Kinon 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 24 weeks. Design: parallel. Location: multicentre.	
Participants	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder, dominant depressive symptoms, MADRS 16. N=394. Age: 18-60 years. Gender: not reported. History: duration of illness not reported, age at onset not reported. Setting: in- and outpatient.	
Interventions	1	Olanzapine: fixed dose: 10, 15 or 20 mg/day. N=202.
	2	Ziprasidone: fixed dose: 80, 120 or 160 mg/day. N=192.
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, depression MADRS, Calgary depression scale for schizophrenia. General Functioning: GAF Adverse effects: open interviews, EPS (use of antiparkinson medication, AIMS, BAS, SAS), cardiac effects (ECG), weight gain, laboratory (prolactin, glucose, lipids) Unable to use- PANSS (no data).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The overall attrition was very high (62. 7%). The last observation carried forward method was used for people leaving the study early
Selective reporting (reporting bias)	High risk	Secondary outcomes were not fully reported.
Other bias	High risk	The study was sponsored by the manufacturer of olanzapine.

Lieberman 2005

Methods	Allocation: random, no further details. Blindness: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre.
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Participants	Diagnosis: (DSM-IV) schizophrenia, more than one schizophrenic episode, responder. N=1493. Age: 18-65 years (mean=40.6 years). Gender: 1080 M, 380 F. History: duration of illness not reported, age at onset not reported. Setting: in- and outpatient.	
Interventions	1	Olanzapine: flexible dose, allowed dose range: 7.5-30 mg/day, mean dose=20.1 mg/day. N=336.
	2	Perphenazine: flexible dose, allowed dose range: 8-32 mg/day, mean dose=20.8 mg/day. N=261.
	3	Quetiapine: flexible dose, allowed dose range: 200-800 mg/day, mean dose=543.4 mg/day. N=337.
	4	Risperidone: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean dose=3.9 mg/day. N=341.
	5	Ziprasidone: flexible dose, allowed dose range: 40-160 mg/day, mean dose=112.8 mg/day. N=185
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI-S Mental State: PANSS total score Service use: number of patients re-hospitalised. Death: suicide attempt. Adverse effects: open interviews, EPS (use of antiparkinson medication, akathisia), cardiac effects (ECG), prolactin-associated side-effects, sedation, weight gain, laboratory (prolactin, lipids, glucose) Unable to use- Withdrawal due to 'extrapyramidal effects' (no usable data).	
Notes	33 patients were excluded before analysis.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, identical capsules. Whether blind-ing was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition was extremely high (75%) , and it is unclear whether any statistical method can account for such a high dropout rate. Efficacy outcomes were evaluated based on mixed models analysis
Selective reporting (reporting bias)	Low risk	No evidence for selective reporting.
Other bias	Unclear risk	Dose ranges were quite different, the upper dose range of olanzapine was 30 mg whereas risperidone could only be titrated up to 6 mg /day. 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 because ziprasidone was only available at later stages

Olie 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre.	
Participants	Diagnosis: (DSM-III-R) chronic schizophrenia, PANSS negative subscore at least 6 points higher than PANSS positive subscore. N=123. Age: 18-64 years (mean=39 years). Gender: 79 M, 44 F. History: duration of illness not reported, age at onset not reported. Setting: outpatient.	
Interventions	1	Amisulpride: flexible dose, allowed dose range: 100-200 mg/day, mean dose=144.7 mg/day. N=63.
	2	Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=118.0 mg/day. N=60
Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score, BPRS total score, PANSS negative subscore General Functioning: GAF Adverse effects: open interviews, EPS (use of antiparkinson medication, akathisia, parkinsonism, movement disorder burden score), cardiac effects (ECG), sedation, weight gain, laboratory (urine, blood chemistry) Unable to use-GAF (no data) Laboratory (no data).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The rate of leaving the study early was about 25%, the analysis was based on the 'least squares mean change' (last observation carried forward). It is unclear whether the degree of attrition and the method used to account for it led to bias
Selective reporting (reporting bias)	High risk	Predefined laboratory data and data on the Global Assessment of Functioning Scale have not been presented. Treatment emergent adverse events had to occur with an incidence of 5% for reporting. Important side-effects may have been missed by this procedure
Other bias	High risk	The study was sponsored by the manufacturers of ziprasidone. The dose of ziprasidone could be increased to the maximum daily dose, whereas amisulpride could only be increased up to 200 mg which might have led to bias

Sacchetti 2006

Methods	Allocation: random, no further details. Blindness: double, no further details. Duration: 18 weeks. Design: parallel. Location: not reported.	
Participants	Diagnosis: schizophrenia, non-response to or intolerance of three previous antipsychotic treatment trials. N=146. Age: mean clozapine=38.3 years, mean ziprasidone=41.6 years. Gender: 101 M, 45 F. History: duration of illness not reported, age at onset not reported. Setting: not reported.	
Interventions	1	Clozapine: flexible dose, allowed dose range: 250-600 mg/day, mean dose=345.7 mg/day. N=73.
	2	Ziprasidone: flexible dose, allowed dose range: 80-160 mg/day, mean dose=130.4 mg/day. N=73
Outcomes	Leaving the study early: any reason. Global State: CGI. Mental State: PANSS total score, PANSS positive subscore, PANSS negative subscore, depression Calgary depression scale for schizophrenia. Adverse effects: cardiac effects (ECG), laboratory. Unable to use- PANSS positive, negative subscore (no data). CGI (no data). Laboratory parameters (no usable data).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The overall attrition was 38.4%. Data on reasons for dropout were not available. The last observation carried forward method was used to account for people leaving the study early
Selective reporting (reporting bias)	High risk	Data were only presented as an abstract. Primary and secondary outcome data were reported incompletely
Other bias	High risk	The study was sponsored by the manufacturers of ziprasidone.

Simpson 2004

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

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The overall attrition was high (42.8%). The last observation carried forward method was used to account for people leaving the study early
Selective reporting (reporting bias)	High risk	The study focused on acutely ill schizophrenic or schizoaffective patients but data on the positive symptom subscore were not provided
Other bias	High risk	The study was sponsored by the manufacturer of ziprasidone. The upper dose limit of olanzapine was 15 mg/day which is below the maximum dose for this medication

Stroup 2006

Methods	Allocation: two step randomisation before and after the availability of ziprasidone. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: not reported.
Participants	Diagnosis: (DSM-IV) chronic schizophrenia.

N=444.

Age: 18-65 years (mean olanzapine=40.0 years, mean quetiapine=40.1 years, mean risperidone=41.8 years, mean ziprasidone=41.3 years).

Gender: 308 M, 136 F.

History: duration of illness not reported, age at onset not reported.

Setting: in- and outpatient.

Interventions	1	Olanzapine: flexible dose, allowed dose range: 7.5-30 mg/day, mean dose=20.5 mg/day. N=108.
	2	Quetiapine: flexible dose, allowed dose range: 200-800 mg/day, mean dose=565.2 mg/day. N=95.
	3	Risperidone: flexible dose, allowed dose range: 1.5-6.0 mg/day, mean dose=4.1 mg/day. N=104.
	4	Ziprasidone: flexible dose, allowed dose range: 40-160 mg/day, mean dose=115.9 mg/day. N=137

Outcomes	Leaving the study early: any reason, adverse events, inefficacy. Global State: CGI. Mental State: PANSS total score. Death: suicide. Adverse effects: open interviews, EPS (akathisia), cardiac effects (ECG), prolactin-associated side-effects, weight gain, laboratory (prolactin, glucose, cholesterol)
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, 2 step randomisation before and after the availability of ziprasidone, Participants were re-randomised to a different medication than they had received in previous phase 1
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful has not been examined, but both compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition rate was extremely high (72. 5%). Efficacy data analysis was based on mixed models, but it is unclear whether any statistical method can account for such high dropout rates
Selective reporting (reporting bias)	High risk	Use of antiparkinson medication was permitted but data on this was not available
Other bias	Unclear risk	Patients had a history of intolerance to atypical antipsychotic treatment but baseline data on this were not provided

Svestka 2005

Methods	Allocation: random, no further details. Blinding: double, no further details. Duration: six weeks. Design: parallel. Location: not reported.
Participants	Diagnosis: (ICD-10) acute schizophrenia, schizoaffective disorder. N=48. Age: not reported.

Gender: not reported. History: duration of illness not reported, age at onset not reported. Setting: inpatient.		
Interventions	1	Olanzapine: dose: not reported, allowed dose range: not reported, mean dose: not reported. N=24.
	2	Ziprasidone: dose: not reported, allowed dose range: not reported, mean dose: not reported. N=24
Outcomes	Mental State: PANSS total score. Adverse effects: EPS (akathisia, parkinsonoid, dystonia). Unable to use- EPS (no data).	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random, no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful has not been examined, but the compounds differ quite substantially in side-effects. This can be a problem for blinding
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Objective outcomes such as laboratory measures or death are unlikely to have been much affected by problems of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on subjects leaving the study early were not available.
Selective reporting (reporting bias)	High risk	Allowed study medication dose ranges were not indicated. A publication was not available
Other bias	Unclear risk	Insufficient information, although the first author kindly provided us some

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.

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
Ascher-Svanum 2006	Allocation: not randomised, cohort study.
Baloescu 2006	Allocation: not randomised, controlled-trial.
Hagger 1997	Allocation: randomised. Blindness: open-label.
Harrigan 2004	Allocation: randomised. Blindness: open-label.
Harrison 2004	Allocation: randomised, Blindness: double-blind. Participants: people with schizophrenia. Interventions: olanzapine versus ziprasidone. Outcomes: no usable data.
Swanson 2006	Allocation: randomised. Blindness: open-label.
Tang 2005	Allocation: randomised. Blindness: open-label.
Tudor 2006	Allocation: randomisation unclear. Participants: people with schizophrenia. Intervention: inappropriate intervention.
Uzun 2002	Allocation: unclear, pooled analysis.

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

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ACTRN12610000954022

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Addington 2004a

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Addington 2009

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Agid 2010

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Allison 2007

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Anon 2002

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Baldacara 2011

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Beuzen 2005

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Beuzen 2006

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Breier 2005a

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Caroff 2011

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CATIE

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ChiCTR-TRC-10000934

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Dunn 2005

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Eng 2008

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EUFEST

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Fahnestock 2007

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Fleischhacker 2009

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Geng 2008

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Goldstein 2007

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Gong 2008

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Gouzoulis-Mayfrank 2006

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Grootens 2011

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Harrison 2004a

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Harvey 2004

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Houston 2004

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Jiang 2008

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Jiang 2008a

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Keefe 2008

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Kjelby 2011

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Kuwilsky 2010

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Li 2007

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Liang 2007

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Liu 2008a

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Lu 2007

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Lu 2008

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Lublin 2009

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Meyer 2005

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Murray 2003

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Nai 2008

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Newcomer 2009a

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Nie 2007

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Olfson 2011

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Parsons 2008

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Sacchetti 2006a

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Schooler 2011

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Simpson 2005

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Street 2000

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Strom 2007

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Van Veelen 2010

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Woodruff 2003

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Wu 2012

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Yang 2008

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Yue 2010

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Zhang 2011

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Zhao 2008

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Zhu 2010

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Zimbroff 2007

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Zink 2009

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任列, 2009

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何文刚 2011

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兰庆博 2011

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冉昌华 2011

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曹雷明 2010

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冯龙雷 2010

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刘国雄 2007

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刘晓红 2008

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刘曙华 2011

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卢殿军 2011a

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周海晓 2009

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孙付根 2009a

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孙平 2011

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孙爱民 2010

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季林影 2009

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宋新虹 2010

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寇桂華, 2009

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屈建新 2008

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崔开艳 2010

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盧良俊 2010

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张小智 2010

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张峰 2010

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张明松 2009

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张敬龙 2010

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张艳琦 2010

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张香芝 2009

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张鸿燕, 2010

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彭亮 2010

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彭汝春 2009

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律國洪 2010

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律網 2009

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律純, 2010

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律莉萍 2011

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方传荣 2010

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易峰 2010

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朱志高 2010

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李仕军 2010

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李伟峰 2010

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李启斌 2008

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李国胜 2010

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李靖轩 2010

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李春花 2011

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李树敏 2008

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李洪 2009

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李铁群 2009

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杨明华 2011

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杨老虎 2009

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杨胜良 2008

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杨诚, 2010

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杨耀才 2008

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林华毅 2009

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林敏 2011

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段武刚 2010

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熊月珍 2010

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潘占红 2011

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潘天伟 2008

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潘文燕 2008

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熊辉 2011

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王伟宾 2011

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王天龙 2008

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王学军 2009

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王方国 2010

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王永学 2010

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王秀芳 2011

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王金璽 2010

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白劍文 2009

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白曉波 2010

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皮明明 2010

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秦强 2010

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程平 2009

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程燕 2009

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曹薇薇 2009

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薛华斌 2011

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最新 2008

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藤田 2009

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栗松 2009

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許重平 2010

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許志平 2008

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謝錦麟 2009

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谢青南 2010

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赵敬平 2010

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赵明丽 2010

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邓广 2011

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邢睿燕 2011

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郑学宝 2008

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钟小兵 2008

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钟小兵 2009

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阿拜紅 2011

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陆爱静 2009

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陈恩民 2010

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陈慧 2011

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陈春梅 2010

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曹庆华 2008

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Notes To be assessed.

滕建辉 2011

Methods
Participants
Interventions
Outcomes
Notes To be assessed.

马兆峰 2009

Methods
Participants
Interventions
Outcomes
Notes To be assessed.

高星南 2008

Methods
Participants
Interventions
Outcomes
Notes
To be assessed.

黄峰 2010

Methods
Participants
Interventions
Outcomes
Notes
To be assessed.

黄振英 2010

Methods
Participants
Interventions
Outcomes
Notes
To be assessed.

黄智辉 2011

Methods
Participants
Interventions
Outcomes
Notes
To be assessed.

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

Mortimer 2001

Trial name or title	A1281014
Methods	Allocation: random, no further details.

		Blindness: double, double-dummy. Duration: 12 weeks. Design: parallel. Location: multicentre.
Participants		Diagnosis: schizophrenia or schizoaffective disorder. N=unknown. Age: unknown. Gender: unknown. History: duration of illness unknown, age at onset unknown. Setting: unknown.
Interventions	1	Olanzapine:dose: unknown, allowed dose range: unknown, mean dose: unknown. N=unknown.
	2	Ziprasidone: dose: unknown, allowed dose range: unknown, mean dose: unknown. N=unknown
Outcomes		Unknown.
Starting date		6 October 2000.
Contact information		Prof Ann Mortimer Coniston House East Riding Campus Willerby HU10 6NS UK Telephone: 01482 466700 E-mail: A.M.Mortimer@medschool.hull.ac.uk
Notes		

Reveley 2003

Trial name or title		MREC/00/147
Methods		Allocation: random, no further details. Blindness: double, double-dummy. Duration: unknown. Design: parallel. Location: multicentre.
Participants		Diagnosis: schizophrenia or schizoaffective disorder. N=unknown. Age: 18-70 years. Gender: unknown. History: duration of illness unknown, age at onset unknown. Setting: unknown.
Interventions	1	Olanzapine:dose: unknown, allowed dose range: unknown, mean dose: unknown. N=unknown.
	2	Ziprasidone: dose: unknown, allowed dose range: unknown, mean dose: unknown. N=unknown
Outcomes		Global state (CGI). General Mental State (PANSS). Quality of life (QLS). Health of the nation outcome scale (HoNOS). Drug attitude inventory (DAI). Resource utilization questionnaire. Treatment costs.
Starting date		1 May 2001
Contact information		Professor Michael Reveley Department of Psychiatry Section of Neuropsychiatry & Psychopharmacology Leicester General Hospital Leicester

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Notes

DATA AND ANALYSES

Comparison 1 ZIPRASIDONE versus AMISULPRIDE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No clinically significant response (as defined by the original studies)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
2 Leaving the study early	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any reason	1	123	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.78, 2.70]
2.2 Adverse events	1	123	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.18, 3.37]
2.3 Inefficacy	1	123	Risk Ratio (M-H, Random, 95% CI)	4.73 [1.06, 20.98]
3 Global State: No clinically important change (as defined by the original studies)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.51]
3.1 Short term	1	123	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.51]
4 Mental state: 1a. General mental state: PANSS total score (high=poor)	1	122	Mean Difference (IV, Random, 95% CI)	2.70 [-3.55, 8.95]
4.1 Short term	1	122	Mean Difference (IV, Random, 95% CI)	2.70 [-3.55, 8.95]
5 Mental state: 1b. General mental state: BPRS total score (high=poor)	1	122	Mean Difference (IV, Random, 95% CI)	2.10 [-1.52, 5.72]
5.1 Short term	1	122	Mean Difference (IV, Random, 95% CI)	2.10 [-1.52, 5.72]
6 Mental state: 2a. Negative symptoms: no clinically important change (less than 50% PANSS negative subscore reduction)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
6.1 Short term	1	123	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
7 Mental state: 2b. Negative symptoms: PANSS negative subscore (high=poor)	1	122	Mean Difference (IV, Random, 95% CI)	0.80 [-1.40, 3.00]
7.1 Short term	1	122	Mean Difference (IV, Random, 95% CI)	0.80 [-1.40, 3.00]
8 Adverse effects: 1. At least one adverse effect	1	123	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.51]
9 Adverse effects: 2. Cardiac effects - QTc prolongation	1	123	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Adverse effects: 3. Extrapyramidal side-effects	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Akathisia	1	123	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.27, 9.10]
10.2 Parkinsonism	1	123	Risk Ratio (M-H, Random, 95% CI)	6.30 [0.78, 50.80]
10.3 Use of antiparkinson medication	1	123	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.94, 3.07]
11 Adverse effects: 4. Sedation	1	123	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.07, 1.67]
12 Adverse effects: 5. Weight gain of 7% or more of total body weight	1	123	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.18, 1.29]

Comparison 2 ZIPRASIDONE versus CLOZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1	146	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.66, 1.51]
1.1 Any reason	1	146	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.66, 1.51]
2 Mental state: general mental state: PANSS total score (high=poor)	1	146	Mean Difference (IV, Random, 95% CI)	-0.5 [-7.72, 6.72]
2.1 Medium term	1	146	Mean Difference (IV, Random, 95% CI)	-0.5 [-7.72, 6.72]
3 Adverse effects: cardiac effects - QTc prolongation	1	146	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3 ZIPRASIDONE versus OLANZAPINE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No clinically significant response (as defined by the original studies)	2	817	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.92, 1.56]
2 Leaving the study early	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any reason	5	1937	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.18, 1.35]
2.2 Adverse events	5	1937	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.77, 1.61]
2.3 Inefficacy	5	1937	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.27, 1.94]
3 Global State: no clinically important change (as defined by the original studies)	1	269	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.92, 1.53]
3.1 Short term	1	269	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.92, 1.53]
4 Mental state: 1a. General mental state: no clinically important change (less than 30% PANSS total score reduction)	1	548	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.15, 1.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Long term	1	548	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.15, 1.61]
5 Mental state: 1b. General mental state: PANSS total score (high=poor)	4	1291	Mean Difference (IV, Random, 95% CI)	8.32 [5.64, 10.99]
5.1 Short term	1	48	Mean Difference (IV, Random, 95% CI)	8.37 [-2.00, 18.74]
5.2 Medium term	1	201	Mean Difference (IV, Random, 95% CI)	6.50 [-0.07, 13.07]
5.3 Long term	2	1042	Mean Difference (IV, Random, 95% CI)	8.71 [5.66, 11.76]
6 Mental state: 1c. General mental state: no clinically important change (less than 40% BPRS total score reduction)	1	269	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.21]
6.1 Short term	1	269	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.21]
7 Mental state: 1d. General mental state: BPRS total score (high=poor)	1	251	Mean Difference (IV, Random, 95% CI)	0.5 [-2.85, 3.85]
7.1 Short term	1	251	Mean Difference (IV, Random, 95% CI)	0.5 [-2.85, 3.85]
8 Mental state: 2. Positive symptoms: PANSS positive subscore (high=poor)	2	730	Mean Difference (IV, Random, 95% CI)	3.11 [1.93, 4.30]
8.1 Medium term	1	201	Mean Difference (IV, Random, 95% CI)	3.6 [1.45, 5.75]
8.2 Long term	1	529	Mean Difference (IV, Random, 95% CI)	2.90 [1.47, 4.33]
9 Mental state: 3. Negative symptoms: PANSS negative subscore (high=poor)	2	730	Mean Difference (IV, Random, 95% CI)	0.68 [-2.45, 3.81]
9.1 Medium term	1	201	Mean Difference (IV, Random, 95% CI)	1.00 [-2.91, 0.91]
9.2 Long term	1	529	Mean Difference (IV, Random, 95% CI)	2.2 [0.92, 3.48]
10 General Functioning: 1. No clinically important change (less than 5 points improvement on GAF total score)	1	394	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.03, 1.41]
10.1 Medium term	1	394	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.03, 1.41]
11 General Functioning: 2. GAF total score (high=poor)	1	326	Mean Difference (IV, Random, 95% CI)	3.49 [0.64, 6.34]
12 General Functioning: 3. QLS total score (Heinrichs-Carpenter) (high=poor)	1	393	Mean Difference (IV, Random, 95% CI)	3.70 [-1.21, 8.61]
12.1 Long term	1	393	Mean Difference (IV, Random, 95% CI)	3.70 [-1.21, 8.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Cognitive Functioning: PANSS cognition score (high=poor)	1	529	Mean Difference (IV, Random, 95% CI)	2.40 [1.17, 3.63]
13.1 Long term	1	529	Mean Difference (IV, Random, 95% CI)	2.40 [1.17, 3.63]
14 Service use: Number of patients re-hospitalised	2	766	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.07, 2.20]
14.1 Medium term	1	245	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.75, 2.79]
14.2 Long term	1	521	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.03, 2.43]
15 Adverse effects: 1. At least one adverse effect	4	1583	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.94, 1.18]
16 Adverse effects: 2a. Cardiac effects - QTc prolongation	3	1184	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.10, 24.68]
17 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms	4	1372	Mean Difference (IV, Random, 95% CI)	2.19 [-0.58, 4.96]
18 Adverse effects: 3a. Cholesterol - abnormally high cholesterol value	1	394	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.12, 4.15]
19 Adverse effects: 3b. Cholesterol - change from baseline in mg/dl	4	1502	Mean Difference (IV, Random, 95% CI)	-15.83 [-25.72, -5.95]
20 Adverse effects: 4. Death	2	766	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.24, 10.45]
20.1 Suicide attempt	1	521	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.08, 9.95]
20.2 Suicide	1	245	Risk Ratio (M-H, Random, 95% CI)	3.95 [0.19, 81.41]
21 Adverse effects: 5a. Extrapyramidal side-effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Akathisia	2	766	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.78, 2.53]
21.2 Dystonia	1	548	Risk Ratio (M-H, Random, 95% CI)	13.29 [0.75, 234.71]
21.3 Extrapyramidal symptoms	2	793	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.77, 4.73]
21.4 Use of antiparkinson medication	4	1732	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.03, 1.99]
22 Adverse effects: 5b. Extrapyramidal side-effects	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
22.1 Abnormal involuntary movement: AIMS (high=poor)	2	925	Mean Difference (IV, Random, 95% CI)	0.16 [-0.15, 0.46]
22.2 Akathisia: Barnes Akathisia Scale (high=poor)	2	924	Mean Difference (IV, Random, 95% CI)	0.07 [-0.04, 0.17]
22.3 Extrapyramidal symptoms: ESRS total score (high=poor)	1	269	Mean Difference (IV, Random, 95% CI)	0.40 [-0.73, 1.53]
22.4 Extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	2	922	Mean Difference (IV, Random, 95% CI)	0.34 [-0.13, 0.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Adverse effects: 6a. Glucose - abnormally high fasting glucose value	1	394	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.15, 7.39]
24 Adverse effects: 6b. Glucose - change from baseline in mg/dl	4	1420	Mean Difference (IV, Random, 95% CI)	-8.25 [-13.72, -2.77]
25 Adverse effects: 7a. Prolactin-associated side-effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
25.1 Abnormally high prolactin value	1	394	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.59, 1.35]
25.2 Amenorrhoea	1	148	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.51, 2.79]
25.3 Galactorrhoea	2	000	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.53, 4.56]
25.4 Sexual dysfunction	2	766	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.56, 1.01]
26 Adverse effects: 7b. Prolactin - change from baseline in ng/ml	3	1079	Mean Difference (IV, Random, 95% CI)	0.20 [-3.33, 3.72]
27 Adverse effects: 8. Sedation	2	766	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.39, 1.04]
28 Adverse effects: 9a. Weight gain	4	1708	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.14, 0.30]
28.1 Weight gain of 7% or more of total body weight	3	1160	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.14, 0.33]
28.2 Weight gain - as "weight gain" reported adverse event	1	548	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.06, 0.37]
29 Adverse effects: 9b. Weight gain - change from baseline in kg	5	1659	Mean Difference (IV, Random, 95% CI)	-3.82 [-4.69, -2.96]

Comparison 4 ZIPRASIDONE versus QUETIAPINE

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)	0.95 [0.88, 1.03]
1.2 Adverse events	2	722	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.39]
1.3 Inefficacy	2	722	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.68, 1.12]
2 Mental state: 1. General mental state: PANSS total score (high=poor)	2	710	Mean Difference (IV, Random, 95% CI)	0.11 [-6.14, 6.36]
2.1 Medium term	1	198	Mean Difference (IV, Random, 95% CI)	-3.70 [-10.37, 2.97]
2.2 Long term	1	512	Mean Difference (IV, Random, 95% CI)	2.78 [-1.25, 6.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mental state: 2. Positive symptoms: PANSS positive subscore (high=poor)	1	198	Mean Difference (IV, Random, 95% CI)	0.0 [-2.18, 2.18]
3.1 Medium term	1	198	Mean Difference (IV, Random, 95% CI)	0.0 [-2.18, 2.18]
4 Mental state: 3. Negative symptoms: PANSS negative subscore (high=poor)	1	198	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.54, 0.34]
4.1 Medium term	1	198	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.54, 0.34]
5 Service use: Number of patients re-hospitalised	2	754	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.17]
5.1 Medium term	1	232	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.46, 1.40]
5.2 Long term	1	522	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.61, 1.29]
6 Adverse effects: 1. At least one adverse effect	2	754	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.10]
7 Adverse effects: 2a. Cardiac effects - QTc prolongation	1	522	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.12, 2.98]
8 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms	2	549	Mean Difference (IV, Random, 95% CI)	-3.41 [-8.18, 1.37]
9 Adverse effects: 3. Cholesterol - change from baseline in mg/dl	2	754	Mean Difference (IV, Random, 95% CI)	-16.01 [-23.46, -8.57]
10 Adverse effects: 4. Death	2	754	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.32, 18.83]
10.1 Suicide attempt	1	522	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.11, 28.95]
10.2 Suicide	1	232	Risk Ratio (M-H, Random, 95% CI)	3.48 [0.17, 71.64]
11 Adverse effects: 5. Extrapyramidal side effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Akathisia	2	754	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.69, 2.39]
11.2 Extrapyramidal symptoms	1	232	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.16, 1.51]
11.3 Use of antiparkinson medication	1	522	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.07, 5.00]
12 Adverse effects: 6. Glucose - change from baseline in mg/dl	2	754	Mean Difference (IV, Random, 95% CI)	-3.10 [-10.19, 3.99]
13 Adverse effects: 7a. Prolactin-associated side-effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Amenorrhoea	1	138	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.81, 6.79]
13.2 Galactorrhoea	2	572	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.60, 5.57]
13.3 Sexual dysfunction	1	522	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.64, 1.33]
14 Adverse effects: 7b. Prolactin - change from baseline in ng/ml	2	754	Mean Difference (IV, Random, 95% CI)	4.77 [1.37, 8.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15 Adverse effects: 8. Sedation	2	754	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.97]
16 Adverse effects: 9a. Weight gain of 7% or more of total body weight	2	754	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.28, 0.74]
17 Adverse effects: 9b. Weight gain - change from baseline in kg	1	466	Mean Difference (IV, Random, 95% CI)	-1.2 [-2.45, 0.05]

Comparison 5 ZIPRASIDONE versus RISPERIDONE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No clinically significant response (as defined by the original studies)	1	296	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
2 Leaving the study early	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Any reason	3	1029	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.02, 1.20]
2.2 Adverse events	3	1029	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.76, 1.98]
2.3 Inefficacy	3	1029	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.79, 1.66]
3 Global State: No clinically important change (as defined by the original studies)	1	296	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.96, 1.60]
3.1 Short term	1	296	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.96, 1.60]
4 Mental State 1a. General Mental State (less than 50% PANSS total reduction)	1	296	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
4.1 Short term	1	296	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.07]
5 Mental State 1b. General Mental State: PANSS total score (high=poor)	3	1016	Mean Difference (IV, Random, 95% CI)	3.91 [0.27, 7.55]
5.1 Short term	1	296	Mean Difference (IV, Random, 95% CI)	1.5 [-0.16, 3.16]
5.2 Medium term	1	204	Mean Difference (IV, Random, 95% CI)	6.30 [-0.17, 12.77]
5.3 Long term	1	516	Mean Difference (IV, Random, 95% CI)	6.01 [1.99, 10.03]
6 Mental State 1c. General Mental State: BPRS total score (high=poor)	1	296	Mean Difference (IV, Random, 95% CI)	0.70 [-2.93, 4.33]
6.1 Short term	1	296	Mean Difference (IV, Random, 95% CI)	0.70 [-2.93, 4.33]
7 Mental State 2a. Positive Symptoms: PANSS positive subscore (high=poor)	1	204	Mean Difference (IV, Random, 95% CI)	2.5 [0.38, 4.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Medium term	1	204	Mean Difference (IV, Random, 95% CI)	2.5 [0.38, 4.62]
8 Mental State 2b. Positive Symptoms: BPRS positive subscore (high=poor)	1	296	Mean Difference (IV, Random, 95% CI)	0.5 [-0.15, 1.15]
8.1 Short term	1	296	Mean Difference (IV, Random, 95% CI)	0.5 [-0.15, 1.15]
9 Mental State 3. Negative Symptoms: PANSS negative subscore (high=poor)	2	0 0	Mean Difference (IV, Random, 95% CI)	0.04 [-1.12, 1.20]
9.1 Short term	1	296	Mean Difference (IV, Random, 95% CI)	0.0 [-1.48, 1.48]
9.2 Medium term	1	204	Mean Difference (IV, Random, 95% CI)	0.10 [-1.78, 1.98]
10 Service use: Number of patients re-hospitalised	2	767	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.82, 1.59]
10.1 Medium term	1	241	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.58, 1.89]
10.2 Long term	1	526	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.80, 1.78]
11 Adverse effects: 1. At least one adverse effect	3	1063	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.02]
12 Adverse effects: 2a. Cardiac effects - QTc prolongation	2	822	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.11, 2.51]
13 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms	3	793	Mean Difference (IV, Random, 95% CI)	2.24 [-1.92, 6.39]
14 Adverse effects: 3 Cholesterol - change from baseline in mg/dl	2	767	Mean Difference (IV, Random, 95% CI)	-8.58 [-16.04, -1.11]
15 Adverse effects: 4. Death	2	767	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.22, 6.42]
15.1 Suicide attempt	1	526	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.08, 10.10]
15.2 Suicide	1	241	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.14, 16.52]
16 Adverse effects: 5a. Extrapyramidal side effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Akathisia	3	1063	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.53, 1.81]
16.2 Extrapyramidal symptoms	1	241	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.12, 0.87]
16.3 Tremor	1	296	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.53, 2.11]
16.4 Use of antiparkinson medication	2	822	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.97]
17 Adverse effects: 5b. Extrapyramidal side effects	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
17.1 Abnormal involuntary movement: AIMS (high=poor)	1	296	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.25, -0.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.2 Akathisia: Barnes Akathisia Scale (high=poor)	1	296	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.61, -0.51]
17.3 Extrapyramidal symptoms: Simpson-Angus Scale (high=poor)	1	296	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.42, -0.26]
18 Adverse effects: 6. Glucose - change from baseline in mg/dl	2	767	Mean Difference (IV, Random, 95% CI)	-4.94 [-11.80, 1.91]
19 Adverse effects: 7a. Prolactin associated side effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.1 Abnormal ejaculation	1	215	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.15, 1.54]
19.2 Amenorrhoea	2	225	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.68]
19.3 Decreased libido	1	296	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.26, 1.42]
19.4 Erectile dysfunction	1	215	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.35, 2.63]
19.5 Galactorrhoea	3	303	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.28]
19.6 Sexual dysfunction	2	822	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.50, 0.97]
20 Adverse effects: 7b. Prolactin - change from baseline in ng/ml	2	767	Mean Difference (IV, Random, 95% CI)	-21.97 [-27.34, -16.60]
21 Adverse effects: 8. Sedation	3	1063	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.63, 1.20]
22 Adverse effects: 9a. Weight gain of 7% or more of total body weight	3	1063	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.33, 0.74]
23 Adverse effects: 9b. Weight gain - change from baseline in kg	1	461	Mean Difference (IV, Random, 95% CI)	-1.1 [-2.35, 0.15]

Comparison 6
ZIPRASIDONE 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. General Mental State: PANSS total score (high=poor)	3	1243	Mean Difference (IV, Fixed, 95% CI)	8.32 [5.55, 11.08]
1.1 Medium term	1	201	Mean Difference (IV, Fixed, 95% CI)	6.50 [-0.07, 13.07]
1.2 Long term	2	1042	Mean Difference (IV, Fixed, 95% CI)	8.71 [5.66, 11.76]

Analysis 1.1

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 1 No clinically significant response (as defined by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 1 No clinically significant response (as defined by the original studies)

Analysis 1.2

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 2 Leaving the study early.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 2 Leaving the study early

Analysis 1.3
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 3 Global State: No clinically important change
(as defined by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 3 Global State: No clinically important change (as defined by the original studies)

Analysis 1.4
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 4 Mental state: 1a. General mental state:
PANSS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 4 Mental state: 1a. General mental state: PANSS total score (high=poor)

Analysis 1.5
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 5 Mental state: 1b. General mental state:
BPRS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 5 Mental state: 1b. General mental state: BPRS total score (high=poor)

Analysis 1.6
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 6 Mental state: 2a. Negative symptoms: no
clinically important change (less than 50% PANSS
negative subscore reduction).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 6 Mental state: 2a. Negative symptoms: no clinically important change (less than 50% PANSS negative subscore reduction)

Analysis 1.7
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 7 Mental state: 2b. Negative symptoms:
PANSS negative subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 7 Mental state: 2b. Negative symptoms: PANSS negative subscore (high=poor)

Analysis 1.8
Comparison 1 ZIPRASIDONE versus AMISULPRIDE,
Outcome 8 Adverse effects: 1. At least one adverse
effect.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 8 Adverse effects: 1. At least one adverse effect

Analysis 1.9

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 9 Adverse effects: 2. Cardiac effects - QTc prolongation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 9 Adverse effects: 2. Cardiac effects - QTc prolongation

Analysis 1.10

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 10 Adverse effects: 3. Extrapyramidal side-effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 10 Adverse effects: 3. Extrapyramidal side-effects

Analysis 1.11

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 11 Adverse effects: 4. Sedation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 11 Adverse effects: 4. Sedation

Analysis 1.12

Comparison 1 ZIPRASIDONE versus AMISULPRIDE,

Outcome 12 Adverse effects: 5. Weight gain of 7% or more of total body weight.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 1 ZIPRASIDONE versus AMISULPRIDE

Outcome: 12 Adverse effects: 5. Weight gain of 7% or more of total body weight

Analysis 2.1
Comparison 2 ZIPRASIDONE versus CLOZAPINE,
Outcome 1 Leaving the study early.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZIPRASIDONE versus CLOZAPINE

Outcome: 1 Leaving the study early

Analysis 2.2
Comparison 2 ZIPRASIDONE versus CLOZAPINE,
Outcome 2 Mental state: general mental state: PANSS
total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZIPRASIDONE versus CLOZAPINE

Outcome: 2 Mental state: general mental state: PANSS total score (high=poor)

Analysis 2.3
Comparison 2 ZIPRASIDONE versus CLOZAPINE,
Outcome 3 Adverse effects: cardiac effects - QTc
prolongation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 2 ZIPRASIDONE versus CLOZAPINE

Outcome: 3 Adverse effects: cardiac effects - QTc prolongation

Analysis 3.1
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 1 No clinically significant response (as defined
by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 1 No clinically significant response (as defined by the original studies)

Analysis 3.2

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 2 Leaving the study early.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 2 Leaving the study early

Analysis 3.3
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 3 Global State: no clinically important change
(as defined by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 3 Global State: no clinically important change (as defined by the original studies)

Analysis 3.4
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 4 Mental state: 1a. General mental state: no
clinically important change (less than 30% PANSS total
score reduction).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 4 Mental state: 1a. General mental state: no clinically important change (less than 30% PANSS total score reduction)

Analysis 3.5

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 5 Mental state: 1b. General mental state: PANSS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 5 Mental state: 1b. General mental state: PANSS total score (high=poor)

Analysis 3.6

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 6 Mental state: 1c. General mental state: no clinically important change (less than 40% BPRS total score reduction).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 6 Mental state: 1c. General mental state: no clinically important change (less than 40% BPRS total score reduction)

Analysis 3.7
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 7 Mental state: 1d. General mental state:
BPRS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 7 Mental state: 1d. General mental state: BPRS total score (high=poor)

Analysis 3.8
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 8 Mental state: 2. Positive symptoms: PANSS
positive subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 8 Mental state: 2. Positive symptoms: PANSS positive subscore (high=poor)

Analysis 3.9
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 9 Mental state: 3. Negative symptoms: PANSS
negative subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 9 Mental state: 3. Negative symptoms: PANSS negative subscore (high=poor)

Analysis 3.10
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 10 General Functioning: 1. No clinically
important change (less than 5 points improvement on
GAF total score).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 10 General Functioning: 1. No clinically important change (less than 5 points improvement on GAF total score)

Analysis 3.11
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 11 General Functioning: 2. GAF total score
(high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 11 General Functioning: 2. GAF total score (high=poor)

Analysis 3.12
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 12 General Functioning: 3. QLS total score
(Heinrichs-Carpenter) (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 12 General Functioning: 3. QLS total score (Heinrichs-Carpenter) (high=poor)

Analysis 3.13

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 13 Cognitive Functioning: PANSS cognition score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 13 Cognitive Functioning: PANSS cognition score (high=poor)

Analysis 3.14

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 14 Service use: Number of patients re-hospitalised.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 14 Service use: Number of patients re-hospitalised

Analysis 3.15

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 15 Adverse effects: 1. At least one adverse effect.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 15 Adverse effects: 1. At least one adverse effect

Analysis 3.16

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 16 Adverse effects: 2a. Cardiac effects - QTc prolongation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 16 Adverse effects: 2a. Cardiac effects - QTc prolongation

Analysis 3.17
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 17 Adverse effects: 2b. Cardiac effects - QTc
abnormalities - change from baseline in ms.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 17 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms

Analysis 3.18
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 18 Adverse effects: 3a. Cholesterol -
abnormally high cholesterol value.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 18 Adverse effects: 3a. Cholesterol - abnormally high cholesterol value

Analysis 3.19
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 19 Adverse effects: 3b. Cholesterol - change
from baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 19 Adverse effects: 3b. Cholesterol - change from baseline in mg/dl

Analysis 3.20
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 20 Adverse effects: 4. Death.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 20 Adverse effects: 4. Death

Analysis 3.21
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 21 Adverse effects: 5a. Extrapyramidal side-effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 21 Adverse effects: 5a. Extrapyramidal side-effects

Analysis 3.22

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 22 Adverse effects: 5b. Extrapyramidal side-effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 22 Adverse effects: 5b. Extrapyramidal side-effects

Analysis 3.23

Comparison 3 ZIPRASIDONE versus OLANZAPINE,

Outcome 23 Adverse effects: 6a. Glucose - abnormally high fasting glucose value.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 23 Adverse effects: 6a. Glucose - abnormally high fasting glucose value

Analysis 3.24
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 24 Adverse effects: 6b. Glucose - change from
baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 24 Adverse effects: 6b. Glucose - change from baseline in mg/dl

Analysis 3.25
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 25 Adverse effects: 7a. Prolactin-associated
side-effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 25 Adverse effects: 7a. Prolactin-associated side-effects

Analysis 3.26
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 26 Adverse effects: 7b. Prolactin - change
from baseline in ng/ml.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 26 Adverse effects: 7b. Prolactin - change from baseline in ng/ml

Analysis 3.27
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 27 Adverse effects: 8. Sedation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 27 Adverse effects: 8. Sedation

Analysis 3.28
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 28 Adverse effects: 9a. Weight gain.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 28 Adverse effects: 9a. Weight gain

Analysis 3.29
Comparison 3 ZIPRASIDONE versus OLANZAPINE,
Outcome 29 Adverse effects: 9b. Weight gain - change
from baseline in kg.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 3 ZIPRASIDONE versus OLANZAPINE

Outcome: 29 Adverse effects: 9b. Weight gain - change from baseline in kg

Analysis 4.1

Comparison 4 ZIPRASIDONE versus QUETIAPINE,

Outcome 1 Leaving the study early.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 1 Leaving the study early

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

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 2 Mental state: 1. General mental state: PANSS total score (high=poor)

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

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 3 Mental state: 2. Positive symptoms: PANSS positive subscore (high=poor)

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

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 4 Mental state: 3. Negative symptoms: PANSS negative subscore (high=poor)

Analysis 4.5
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 5 Service use: Number of patients re-
hospitalised.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 5 Service use: Number of patients re-hospitalised

Analysis 4.6

Comparison 4 ZIPRASIDONE versus QUETIAPINE,

Outcome 6 Adverse effects: 1. At least one adverse effect.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 6 Adverse effects: 1. At least one adverse effect

Analysis 4.7

Comparison 4 ZIPRASIDONE versus QUETIAPINE,

Outcome 7 Adverse effects: 2a. Cardiac effects - QTc prolongation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 7 Adverse effects: 2a. Cardiac effects - QTc prolongation

Analysis 4.8
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 8 Adverse effects: 2b. Cardiac effects - QTc
abnormalities - change from baseline in ms.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 8 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms

Analysis 4.9
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 9 Adverse effects: 3. Cholesterol - change
from baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 9 Adverse effects: 3. Cholesterol - change from baseline in mg/dl

Analysis 4.10
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 10 Adverse effects: 4. Death.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 10 Adverse effects: 4. Death

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

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 11 Adverse effects: 5. Extrapyramidal side effects

Analysis 4.12
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 12 Adverse effects: 6. Glucose - change from baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 12 Adverse effects: 6. Glucose - change from baseline in mg/dl

Analysis 4.13
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 13 Adverse effects: 7a. Prolactin-associated
side-effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 13 Adverse effects: 7a. Prolactin-associated side-effects

Analysis 4.14
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 14 Adverse effects: 7b. Prolactin - change
from baseline in ng/ml.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 14 Adverse effects: 7b. Prolactin - change from baseline in ng/ml

Analysis 4.15
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 15 Adverse effects: 8. Sedation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 15 Adverse effects: 8. Sedation

Analysis 4.16
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 16 Adverse effects: 9a. Weight gain of 7% or
more of total body weight.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 16 Adverse effects: 9a. Weight gain of 7% or more of total body weight

Analysis 4.17
Comparison 4 ZIPRASIDONE versus QUETIAPINE,
Outcome 17 Adverse effects: 9b. Weight gain - change
from baseline in kg.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 4 ZIPRASIDONE versus QUETIAPINE

Outcome: 17 Adverse effects: 9b. Weight gain - change from baseline in kg

Analysis 5.1
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 1 No clinically significant response (as defined
by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 1 No clinically significant response (as defined by the original studies)

Analysis 5.2

Comparison 5 ZIPRASIDONE versus RISPERIDONE,

Outcome 2 Leaving the study early.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 2 Leaving the study early

Analysis 5.3

Comparison 5 ZIPRASIDONE versus RISPERIDONE,

Outcome 3 Global State: No clinically important change (as defined by the original studies).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 3 Global State: No clinically important change (as defined by the original studies)

Analysis 5.4
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 4 Mental State 1a. General Mental State (less
than 50% PANSS total reduction).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 4 Mental State 1a. General Mental State (less than 50% PANSS total reduction)

Analysis 5.5
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 5 Mental State 1b. General Mental State:
PANSS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 5 Mental State 1b. General Mental State: PANSS total score (high=poor)

Analysis 5.6
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 6 Mental State 1c. General Mental State:
BPRS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 6 Mental State 1c. General Mental State: BPRS total score (high=poor)

Analysis 5.7
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 7 Mental State 2a. Positive Symptoms: PANSS
positive subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 7 Mental State 2a. Positive Symptoms: PANSS positive subscore (high=poor)

Analysis 5.8
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 8 Mental State 2b. Positive Symptoms: BPRS
positive subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 8 Mental State 2b. Positive Symptoms: BPRS positive subscore (high=poor)

Analysis 5.9
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 9 Mental State 3. Negative Symptoms: PANSS
negative subscore (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 9 Mental State 3. Negative Symptoms: PANSS negative subscore (high=poor)

Analysis 5.10

Comparison 5 ZIPRASIDONE versus RISPERIDONE,

Outcome 10 Service use: Number of patients re-hospitalised.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 10 Service use: Number of patients re-hospitalised

Analysis 5.11

Comparison 5 ZIPRASIDONE versus RISPERIDONE,

Outcome 11 Adverse effects: 1. At least one adverse effect.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 11 Adverse effects: 1. At least one adverse effect

Analysis 5.12
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 12 Adverse effects: 2a. Cardiac effects - QTc
prolongation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 12 Adverse effects: 2a. Cardiac effects - QTc prolongation

Analysis 5.13
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 13 Adverse effects: 2b. Cardiac effects - QTc
abnormalities - change from baseline in ms.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 13 Adverse effects: 2b. Cardiac effects - QTc abnormalities - change from baseline in ms

Analysis 5.14
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 14 Adverse effects: 3 Cholesterol - change
from baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia
 Comparison: 5 ZIPRASIDONE versus RISPERIDONE
 Outcome: 14 Adverse effects: 3 Cholesterol - change from baseline in mg/dl

Analysis 5.15
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 15 Adverse effects: 4. Death.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia
 Comparison: 5 ZIPRASIDONE versus RISPERIDONE
 Outcome: 15 Adverse effects: 4. Death

Analysis 5.16
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 16 Adverse effects: 5a. Extrapyramidal side
effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 16 Adverse effects: 5a. Extrapyramidal side effects

Analysis 5.17
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 17 Adverse effects: 5b. Extrapyramidal side
effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 17 Adverse effects: 5b. Extrapyramidal side effects

Analysis 5.18
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 18 Adverse effects: 6. Glucose - change from
baseline in mg/dl.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 18 Adverse effects: 6. Glucose - change from baseline in mg/dl

Analysis 5.19
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 19 Adverse effects: 7a. Prolactin associated
side effects.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 19 Adverse effects: 7a. Prolactin associated side effects

Analysis 5.20
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 20 Adverse effects: 7b. Prolactin - change
from baseline in ng/ml.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 20 Adverse effects: 7b. Prolactin - change from baseline in ng/ml

Analysis 5.21
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 21 Adverse effects: 8. Sedation.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 21 Adverse effects: 8. Sedation

Analysis 5.22
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 22 Adverse effects: 9a. Weight gain of 7% or
more of total body weight.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 22 Adverse effects: 9a. Weight gain of 7% or more of total body weight

Analysis 5.23
Comparison 5 ZIPRASIDONE versus RISPERIDONE,
Outcome 23 Adverse effects: 9b. Weight gain - change
from baseline in kg.

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 5 ZIPRASIDONE versus RISPERIDONE

Outcome: 23 Adverse effects: 9b. Weight gain - change from baseline in kg

Analysis 6.1

Comparison 6 ZIPRASIDONE versus OLANZAPINE - sensitivity analysis (skewed data excluded), Outcome 1 Mental State: 1. General Mental State: PANSS total score (high=poor).

Review: Ziprasidone versus other atypical antipsychotics for schizophrenia

Comparison: 6 ZIPRASIDONE versus OLANZAPINE - sensitivity analysis (skewed data excluded)

Outcome: 1 Mental State: 1. General Mental State: PANSS total score (high=poor)

WHAT'S NEW

Last assessed as up-to-date: 30 April 2007.

Date	Event	Description
22 August 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies), 254 citations added to Studies awaiting classification.
11 November 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 4, 2009

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 risk of bias tables.

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Ziprasidone versus other atypical antipsychotics for schizophrenia

Ziprasidone is one of a group of new 'atypical' antipsychotics used for treating schizophrenia. This review wanted to find out if there was evidence to support that there is any difference between ziprasidone and the other atypical medications. Because of the large number of people that dropped out of the studies it is difficult to draw any firm conclusions, however, people taking ziprasidone did not do as well regarding their symptoms, as those taking olanzapine and risperidone and perhaps amisulpride, but they were less likely to gain weight.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): Subjective outcomes	Blinding (performance bias and detection bias): Objective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Addington 2004	?	?	?	+	-	-	-
Breier 2005	?	?	?	+	-	-	-
Kinon 2006	?	?	?	+	-	-	-
Lieberman 2005	?	?	?	+	-	+	?
Olie 2006	?	?	?	+	?	-	-
Sacchetti 2006	?	?	?	+	-	-	-
Simpson 2004	?	?	?	+	-	-	-
Stroup 2006	?	?	?	+	-	-	?
Svestka 2005	?	?	?	+	-	-	?

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Table 1
Suggested design of future study

Methods	Allocation: randomised - clearly described generation of sequence and concealment of allocation. Blindness: double - described and tested. Duration: 6 months minimum.
Participants	Diagnosis: schizophrenia (operational criteria). N=2700.* Age: any. Sex: both. History: any.
Interventions	<ol style="list-style-type: none"> 1 Ziprasidone: dose ~ 120-160 mg/day. N=300. 2 Amisulpride: dose ~ 400-800 mg/day. N=300. 3 Aripiprazole: dose ~ 10-30 mg/day. N=300. 4 Clozapine: dose ~ 300-800 mg/day. N=300. 5 Olanzapine: dose ~ 10-20 mg/day. N=300. 6 Quetiapine: dose ~ 300-800 mg/day. N=300. 7 Risperidone: dose ~ 4-8 mg/day. N=300. 8 Sertindole: dose ~ 12-24 mg/day. N=300. 9 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