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Sertindole versus other atypical antipsychotics for schizophrenia

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Abstract

Background—In many countries of the industrialised world second generation (atypical) antipsychotics have become the first line drug treatment for people with schizophrenia. The question as to whether and, if so, how much the effects of the various second generation antipsychotics differ is a matter of debate.

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

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CONTRIBUTIONS OF AUTHORS

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

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DECLARATIONS OF INTEREST

Katja Komossa - none known.

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

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

Werner Kissling: received speaker or consultancy honoraria from SanofiAventis, BMS, Lilly, Janssen, Lundbeck, Bayer and Pfizer.

Heike Hunger - none known.

Franziska Schmidt - none known.

Sandra Schwarz - none known.

Ruth Lewis - none known.

Search methods—We searched the Cochrane Schizophrenia Group Trials Register (April 2007) and ClinicalTrials.gov (February 2009).

Selection criteria—We included all randomised trials comparing oral sertindole with oral forms of amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone or zotepine for people with schizophrenia or schizophrenia-like psychosis.

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

Main results—The review currently includes two short-term low-quality randomised trials (total n=508) both comparing sertindole with risperidone. One third of participants left the studies early (2 RCTs, n=504, RR 1.23 CI 0.94 to 1.60). There was no difference in efficacy (2 RCTs, n=493, WMD PANSS total change from baseline 1.98 CI -8.24 to 12.20). Compared with relatively high doses of risperidone (between 4 and 12 mg/day), sertindole produced significantly less akathisia and parkinsonism (1 RCT, n=321, RR 0.24 CI 0.09 to 0.69, NNT 14, CI 8 to 100). Sertindole produced more cardiac effects (2 RCTs, n=508, RR QTc prolongation 4.86 CI 1.94 to 12.18), weight change (2 RCTs, n=328, WMD 0.99 CI 0.12 to 1.86) and male sexual dysfunction (2 RCTs, n=437, RR 2.90 CI 1.32 to 6.35, NNH 13 CI 8 to 33).

Authors' conclusions—Sertindole may induce fewer movement disorders, but more cardiac effects, weight change and male sexual dysfunction than risperidone. However these data are based on only two studies and are too limited to allow firm conclusions. Nothing can be said about the effects of sertindole compared with second generation antipsychotics other than risperidone. There are several relevant trials underway or completed and about to report.

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Imidazoles [adverse effects; *therapeutic use]; Indoles [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Risperidone [adverse effects; *therapeutic use]; Schizophrenia [*drug therapy]

MeSH check words

Humans

BACKGROUND

Description of the condition

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.

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 cheap compounds such as sulpiride or perazine have similar properties (Möller 2000). The second generation antipsychotics raised major hopes of superior effects in a number of areas such as compliance, cognitive functioning, negative symptoms, movement disorders, quality of life and the treatment of people with treatment-resistant schizophrenia.

How the intervention might work

Sertindole is a phenylindole derivative (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl] ethyl-2-imidazolide]) which is manufactured by Lundbeck Ltd and is sold as Serdolect or Serlect (in several European countries) in 4 mg, 12 mg, 16 mg and 20 mg tablets. It is a long acting 5-HT₂ / α ₁ antagonist and a very mild D₂ antagonist (Lewis 2005). Sertindole may cause QT- prolongation and ventricular tachycardia more than some other atypical antipsychotics. Due to this sertindole was taken from the market in 1998. Since 2002 it has been available again for patient treatment in clinical studies, and since December 2005 it became available again in some European countries: Germany, Estonia, Finland, Hungary, Denmark, Czech Republic, Spain, Slovakia and Greece, (Turkey planned 12/06) under special safety conditions; for example: no first choice treatment, not for emergency treatment, ECG observation (Lundbeck 2006).

Why it is important to do this review

The debate as to how far the second generation antipsychotics improve these outcomes compared to conventional antipsychotics continues (Duggan 2005, El-Sayeh 2006) and the results from recent studies were sobering (Lieberman 2005, Jones 2006). Nevertheless, in some parts of the world, especially in the highly industrialised countries, second generation antipsychotics have become the mainstay of schizophrenia treatment. The second generation antipsychotics also differ in terms of their costs: while amisulpride is already generic, risperidone will be generic in many countries in 2008. 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 sertindole with other second generation antipsychotics.

OBJECTIVES

To review the effects of sertindole 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 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.

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. Sertindole: Any oral form of application, any dose

2. Other “atypical” antipsychotic drugs: Amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, zotepine: any oral form of application, any dose.

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

Primary outcomes: 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

Electronic searches—1. We searched the Cochrane Schizophrenia Groups Register (April 2007) using the phrase:

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

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

2. We searched ClinicalTrials.gov (February 2009) using the phrase:

[(schizophrenia OR schizophreniform OR schizoaffective OR schizophrenic OR psychosis OR psychoses OR psychotic OR (tar-dive AND dyskinesia) OR akathisia) and sertindole]

Searching other resources

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

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

3. Drug companies: We contacted the manufacturers of all atypical 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. Rating scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, or are even ad hoc. For outcome instruments some minimum standards have to be set. It has been shown that the use of rating scales which have not been described in a peer-reviewed journal are associated with bias (Marshall 2000), therefore we excluded the results of such scales.

3. General: 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 sertindole.

Assessment of risk of bias in included studies—Again working independently, KK and SL assessed risk of bias using the tool described in the Cochrane Collaboration Handbook (Higgins 2008). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We would not have

included studies where sequence generation was at high risk of bias or where allocation was clearly not concealed.

Measures of treatment effect

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

2. Dichotomous - yes/no - data: We carried out an intention to treat analysis. Everyone allocated to the intervention was counted, whether they completed the follow up or not. It was assumed that those who dropped out had no change in their outcome. This rule is conservative concerning response to treatment, because it assumes that those discontinuing the studies would not have responded. It is not conservative concerning adverse effects, but we felt that assuming that all those leaving early would have developed side effects would overestimate risk. Where possible, efforts were made to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into “clinically improved” or “not clinically improved”. It was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005a, Leucht 2005b). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

We calculated the relative risk (RR) and its 95% confidence interval (CI) based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant we calculated the number needed to treat (NNT) and the number-needed-to-harm (NNH) as the inverse of the risk difference.

3. Continuous data

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

- a) When a scale started from the finite number zero the standard deviation, when multiplied by two, was more than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, Altman 1996).
- b) If a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if $2SD > (S - S_{min})$, 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 ALLSTAT electronic statistics mailing list, we presented change data in RevMan Analyses in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Change data were therefore included and a sensitivity analysis was not applied. For continuous outcomes we estimated a weighted mean difference (WMD) between groups. WMDs were again based on the random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. We combined both endpoint data and change data in the analysis, because there is no principal statistical reason why endpoint and change data should measure different effects (Higgins 2008). When standard errors instead of standard deviations (SD) were presented, we converted the former to standard deviations. If both were missing we estimated SDs from p-values or used the average SD of the other studies (Furukawa 2006).

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

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

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

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

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

Assessment of heterogeneity—Firstly, we considered all the included studies within any comparison to judge for clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 50% we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003)

Assessment of reporting biases—We entered data from all identified and selected trials into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias. A formal test for funnel-plot asymmetry was not undertaken.

Data synthesis—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.

Subgroup analysis and investigation of heterogeneity—If inconsistency was high and clear reasons explaining the heterogeneity were found, we presented the data separately. If not, we commented on the heterogeneity of the data.

Sensitivity analysis—In sensitivity analyses we excluded studies with potentially skewed data. A recent report showed that some of the comparisons of atypical antipsychotics may have been biased by using inappropriate comparator doses (Heres 2006). We, therefore, also analysed whether the exclusion of studies with inappropriate comparator doses changed the results of the primary outcome and the general mental state.

RESULTS

Description of studies

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

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

Results of the search—The search strategy yielded 3620 reports of which five studies were closely inspected.

Included studies—Two randomised, double-blind studies (508 participants) met the inclusion criteria. One of the studies (Kane 2005) has to date only been published as a poster presenting limited information.

1. Length of trials: Both included studies were short-term studies with a duration of twelve weeks. We identified no medium-term or long-term studies.

2. Participants: All participants were diagnosed according to the Diagnostic and Statistical Manual Version IV (DSM-IV). Azorin 2006 included people with various subtypes of schizophrenia who had to be at least moderately ill. Kane 2005 included only people who were considered to be treatment resistant. There was a clear preponderance of men (71%) and the participants were relatively chronic with mean ages in the end thirties.

3. Setting: Azorin 2006 was conducted in inpatients and outpatients. Kane 2005 did not report on setting.

4. Study size: The studies included 150 (Azorin 2006) and 350 people (Kane 2005).

5. Interventions: In both studies sertindole was given in flexible doses. The dose range was between 12 and 24 mg/day with mean doses of 16.2 mg/day in Azorin 2006 and 18.1 mg/day in Kane 2005.

Risperidone was the comparator drug in both studies. In Azorin 2006 the dose range was 4 to 10 mg/day (mean 6.6 mg/day) and in Kane 2005 it was 6 to 12 mg/day (mean 9.0 mg/day).

6. Outcomes

6.1 Leaving the study early: Both studies reported the number of participants leaving the studies early due to any reason, adverse events and lack of efficacy.

6.2 No clinically significant response to treatment: We prespecified at least 50% PANSS/BPRS reduction from baseline as a clinically meaningful cut-off score to define response which was indeed presented in Azorin 2006. Kane 2005 did not report on the outcome 'no clinically significant response'.

6.3 Adverse effects: Adverse effects were mainly recorded in open interviews. In addition to those listed below continuous data were provided for weight gain, QTc interval and glucose levels.

6.4 Outcome scales: Details of scales that provided usable data are shown below.

6.4.1.1 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 used low scores showing decreased severity and/or overall improvement.

6.4.2.1 Positive and Negative Syndrome Scale - PANSS (Kay 1986): This schizophrenia scale has 30 items, each of which can be defined on a seven-point scoring system varying from 1 - absent to 7 - extreme. It can be divided into three subscales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates less severity.

6.4.3 Global Assessment of Functioning- GAF (APA 2004): A rating scale for a patients overall capacity of psychosocial functioning scoring from 1-100. Higher scores indicate a higher level of functioning.

6.4.4.1 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.

6.4.4.2 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 0 - normal to 3 - severe. In addition, there is an item for rating global severity (from 0 - absent to 5 - severe). A low score indicates low levels of akathisia.

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

6.5 Missing outcomes: Our primary outcome was '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). We identified no useable data on relapse, quality of life/satisfaction with treatment, cognitive functioning, or service use.

Excluded studies—Four studies had to be excluded (Nielsen 2006, Perro 1999; Potkin 1996, Zurich 2008). All but Zurich 2008 were randomised, but Perro 1999 was open label. The other two compared sertindole with treatments not relevant to this review.

Studies awaiting assessment: No studies are awaiting assessment.

Ongoing studies: We identified eight studies that seem to be ongoing or recently completed (Cheung 2005, Lundbeck 2006a, Lundbeck 2006b, Lundbeck 2007a, Lundbeck 2008, Sireling 2003, Spaniel 2008, Weiser 2007). These should report on a variety of clinical outcomes on a total of over 800 people with schizophrenia from right across the world in the next year or so. It is clear that this is an area of considerable research interest and activity.

Risk of bias in included studies

For graphical representations of our judgements please refer to risk of bias Figure 1, and Figure 2. Full details of judgements are seen in the Risk of Bias tables.

Allocation—Both included studies were described as randomised, but further details on the randomisation method were not provided. Therefore whether adequate randomisation and allocation methods were used is unclear.

Blinding—Both included studies were double-blind, Azorin 2006 used identical capsules for blinding, while Kane 2005 did not provide any details on the blinding procedure. Whether blinding was effective is unclear. Neither study examined this. The adverse effect profiles of both compounds are quite different 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—Both studies had a considerably high overall attrition rate (33%) which might limit the validity of findings. Both 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.

Selective reporting—Only those adverse events that occurred in at least 5% (Azorin 2006) or 10% (Kane 2005) of the participants were reported. This procedure is problematic, because rare, but potentially serious adverse effects may not have been reported.

Other potential sources of bias—Both studies were sponsored by the pharmaceutical company producing sertindole. In one study (Kane 2005) the lower dose range for risperidone was rather high (6mg). Such a high dose may have led to a relatively high amount of extrapyramidal side-effects in the risperidone group. Both studies were industry sponsored by the manufacturers of sertindole. It has been shown that pharmaceutical companies tend to emphasize the advantages of their drugs and to highlight the problems of the comparator compound (Heres 2006).

Effects of interventions

1.—Two studies comparing sertindole with risperidone met the inclusion criteria, data on other comparisons are not available.

2. Comparison 1: SERTINDOLE versus RISPERIDONE

2.1 Leaving the study early: Data on leaving the study early did not show a significant difference in numbers leaving the study early because of any reason (2 RCTs, n=504, RR 1.23 CI 0.94 to 1.60), adverse effects (2 RCTs, n= 504, RR 1.38 CI 0.74 to 2.57) and inefficacy (2 RCTs, n=504, RR 1.32 CI 0.80 to 2.18).

2.2 Global state

2.2.1 No clinically significant response - as defined by the original studies: There was no significant difference between groups (1 RCT, n= 187, RR 0.88 CI 0.71 to 1.08).

2.2.2 Global state: no clinically important change: There was no significant difference (1 RCT, n=187, RR 0.81 CI 0.59 to 1.10).

2.3 General mental state

2.3.1 No clinically important change (less than 50% PANSS total score reduction): There was no significant difference (1 RCT, n=187, RR 0.88 CI 0.71 to 1.08).

2.3.2 PANSS total score (high=poor): Overall there was no significant difference (2 RCTs, n=493, WMD 1.98 CI -8.24 to 12.20) but results were heterogenous. In one study in treatment-resistant participants risperidone was significantly superior (Kane 2005: n=321, MD 6.94 CI 1.74 to 12.14), while in the other which did not use such a criterion there was a trend in favour of sertindole (Azorin 2006: n=172, MD - 3.50 CI -10.42 to 3.42).

2.3.3 Positive Symptoms: PANSS positive subscore (high=poor): There was no significant difference (1 RCT, n=187, MD -0.80 CI -2.95 to 1.35).

2.3.4 Negative Symptoms: PANSS negative subscore (high=poor): There was no significant difference (1 RCT, n=187, MD -1.30 CI -3.13 to 0.53).

2.4 General functioning: GAF total score: There was no significant difference (1 RCT, n=114, MD -2.90 CI -8.41 to 2.61).

2.5 Adverse effects

2.5.1 At least one adverse effect: There was no significant difference (2 RCTs, n=504, RR 1.03 CI 0.95 to 1.11).

2.5.2 Death: There was no significant difference in terms of suicide (1 RCT, n= 187, RR 0.30 CI 0.01 to 7.34).

2.5.3 Cardiac effects - number of participants with QTc prolongation: Significantly more participants in the sertindole group showed QTc prolongation (2 RCTs, n=508, RR 4.86 CI 1.94 to 12.18, NNH not estimable). The mean increase of the QTc interval was larger in the sertindole group (2 RCTs, n=495, WMD 18.60 CI 14.83 to 22.37).

2.5.4 Central nervous system

2.5.4.1 Sedation: There was no significant difference (2 RCTs, n=508, RR 0.87 CI 0.52 to 1.44).

2.5.4.2 Extrapyramidal adverse effects: Data on extrapyramidal side effects indicated a significant superiority of sertindole in terms of akathisia (1 RCT, n=321, RR 0.45 CI 0.20 to 0.98, NNT not estimable) and parkinsonism (1 RCT, n=321, RR 0.24 CI 0.09 to 0.69, NNT 14 CI 8 to 100), while there were no significant differences in terms of any extrapyramidal symptoms (1 RCT, n=187, RR 0.65 CI 0.38 to 1.11) or tremor (1 RCT, n=187, RR 1.51 CI 0.37 to 6.15). There was no significant difference in the mean values of rating scales in dyskinesia (AIMS: 2 RCTs, n=477, WMD -0.31 CI -0.86 to 0.25) and general EPS (SAS: 2 RCTs, n=500, WMD -0.46 CI -1.24 to 0.32), but there was a significant benefit for sertindole in akathisia (BAS: 2 RCTs, n=500, WMD -0.22 CI -0.41 to -0.03).

2.5.5 Metabolic

2.5.5.1 Cholesterol - change from baseline in mg/dl: There was no significant difference (1 RCT, n=176, MD -4.90 CI -13.53 to 3.73).

2.5.5.2 Glucose - mean change from baseline in mg/dl: There was no significant difference (1 RCT, n=176, WMD -2.00 CI -9.85 to 5.85).

2.5.5.3 Weight: There was no significant difference for weight gain (1 RCT, n=187, RR 1.30 CI 0.70 to 2.41) but there was a significant difference for the change in weight from baseline in kg, favouring risperidone (2 RCTs, n=328, WMD 0.99 CI 0.12 to 1.86).

2.6 Sexual dysfunction: Sertindole produced more sexual side effects in men (2 RCTs, n=437, RR 2.90 CI 1.32 to 6.35, NNH 13 CI 8 to 33).

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

4. Investigation for heterogeneity and sensitivity analysis—The reasons for the preplanned sensitivity analyses did not apply and they were therefore not performed.

DISCUSSION

The current review only includes two short-term, low-quality randomised trials comparing sertindole with risperidone. A considerable number of participants leaving the studies early of 33.7% limits the interpretation of the findings. Currently (early 2009) perhaps one of the most important findings is the considerable research activity in this area. We expect several large relevant trials to begin to be presented and published this year.

Summary of main results

1. General—To date only two studies comparing sertindole with risperidone have been published. There are no available data on the effects of sertindole compared to amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone or zotepine. The overall number

of participants leaving the studies early of 33.7% was considerable and calls the validity of the findings into question, because many data have to be guessed by statistical modelling. Both studies were short term which is far from ideal for judging the relative tolerability and efficacy of antipsychotic drugs in a chronic disease like schizophrenia. Both included trials were sponsored by the manufacturer of sertindole and the study showing sertindole to be less efficacious has, to date, only been presented as a poster and reports few data (Kane 2005).

2. Comparison 1: SERTINDOLE versus RISPERIDONE

2.1 Leaving the studies early: Although the number of participants leaving the studies early due to any reason was considerable (33.7%), there was no significant difference between sertindole and risperidone suggesting similar [rather poor] overall acceptability of treatment. Specific reasons for leaving the studies early (adverse events, inefficacy of treatment) also did not show a difference between both compounds.

2.2 Efficacy: global outcomes, mental state outcomes: There was no clear difference in efficacy based on CGI, PANSS, PANSS positive and negative subscores. Nevertheless, the results on the general mental state as measured by the PANSS total score were heterogeneous. One study suggested that, for people with treatment-resistant schizophrenia, risperidone may be somewhat more effective, while in the other study without this criterion no difference was found. Any interpretation is certainly limited by the small number of included trials and participants. Replication is needed.

2.3 Functioning: Only one short-term study provided data on general functioning and showed no difference between groups. We believe that long-term studies are needed to examine this outcome.

2.4 Adverse effects: There were data on extrapyramidal symptoms, cardiac effects, cholesterol, glucose, sedation, sexual dysfunction, suicide and weight gain.

These limited data suggest that akathisia and parkinsonism may occur less frequently with sertindole than with risperidone. However, relatively high risperidone dose ranges of 4 to 10 mg/day and 4 to 12 mg/day in the included studies must be taken into account. On the other hand cardiac effects (QTc prolongation), male sexual dysfunction and weight change indicated a benefit for risperidone. These differences in tolerability may be considered in drug choice. Due to the known effects of sertindole on the QTc interval the drug can not be recommended for people with schizophrenia and at risk of cardiac problems.

Overall completeness and applicability of evidence

Randomised evidence is available for only one out of eight possible comparisons of sertindole with other second generation antipsychotic drugs. For most comparisons not a single study was identified and the evidence is therefore very incomplete. One of the available studies has, as far as we know, only been presented as a poster. In terms of applicability of the evidence we highlight that both studies were short-term and that long-term effectiveness studies are not available, clearly limiting external validity.

Quality of the evidence

Both studies were randomised and double-blind but some details were presented only for one study (use of identical capsules for blinding). Neither study explored whether blinding was successful. There was also a high risk of bias in terms of incomplete outcome reporting, selective reporting and other biases in both studies. Therefore the overall quality of the evidence is rather low.

Potential biases in the review process

The search for studies is largely based on the Cochrane Schizophrenia Group's register of trials. This is largely made up of searches of already published literature. It is possible that there are unpublished studies we are not aware of. We have not been granted lists of such studies by the relevant company.

This review only includes double-blinded studies. This could influence the review. As this is not a technique used in clinical practice, the interventions used in the studies in this review are also not used in clinical practice. It is not blind administration that happens day to day - it is the open giving of treatments. As open giving has not been evaluated in this review the findings may be biased towards the experimental situation and away from the real world. This could have advantages of the potential for more objective evaluation of outcome. Objective evaluation of outcome is, of course of great value but only when its difference to the less objective assessment of the real world is understood. By understanding the difference between the two, on the assumption that one set of ratings is truly objective and the other approximates the real world, we can get a feel for what proportion of the effects are generated by the 'openness'. Having said this, we have noted that it may have been difficult to blind the trials and several of the so called blind outcomes could well have been open. This issue was untested in these "double-blind" studies. Conversely we are unsure of the proportion of data in the open study we have excluded that we think may not have been effected by blindness - for example outcomes such as death or leaving early. In this version of the review, however, we have omitted the open label studies. It may be, in future versions of this review we include these for at least sensitivity analyses.

We have chosen to use the random-effects model for our analyses. We do so because this model does not assume that the populations from which the different trials are derived are the same. This is, of course, true. However, use of this technique does emphasise the results from smaller trials and it is these studies that are likely to be most prone to bias.

Agreements and disagreements with other studies or reviews

A previous systematic review compared sertindole with any other treatment (Lewis 2005). It could not draw a conclusion on the effects of sertindole compared to other second generation antipsychotic drugs, because, at that time, no relevant studies were available.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—For people with schizophrenia it is important to know that overall no clear difference in efficacy between sertindole and risperidone has been shown. Sertindole may induce certain movement disorders (inner restlessness and symptoms that mimic Parkinson's disease) less frequently than risperidone, but on the other hand sertindole may lead to more cardiac problems (QTc prolongation - a potentially life threatening heart rate variability), weight change and male sexual dysfunction.

2. For clinicians—Except for risperidone, no randomised evidence compares sertindole with other second generation antipsychotic drugs. Even compared to risperidone only two, insufficiently reported randomised trials are available making clear recommendations impossible and making more studies to clarify sertindole's role compared to other second generation antipsychotic drugs a matter of urgency. Nevertheless, sertindole may be as effective as risperidone. It may induce fewer movement disorders than risperidone - at least when the latter is given in relatively high doses (between 4 and 12 mg/ day). However, sertindole may be associated with more QTc prolongation, weight change, and male sexual dysfunction.

3. For managers/policy makers—Long-term studies reporting on outcomes such as cost effectiveness, service utilisation or functioning in society that are necessary for policy makers are simply not available. Nevertheless, it may be important for them to know that risperidone has lost its patent and is therefore available as a generic in many countries which may be a cheaper alternative than sertindole.

Implications for research

1. General—Outcome reporting remains insufficient in antipsychotic drug trials. Strict adherence to the CONSORT statement would make such studies much more informative (Moher 2001). We look forward to this in the new generation of studies that should be beginning to be reported soon.

2. Specific—Future versions of this review may include a Summary of Findings table. There is also further work to be done investigating the effects of including studies that are open. It may be that we have lost some - although not much - data by exclusion of Perro 1999. In addition, it is important to follow up all ongoing work to see if these studies provide additional data. Should these sources of data not be likely to provide more definitive findings, as currently only two trials compare sertindole with risperidone are available, there is an urgent need for studies comparing sertindole with other second generation antipsychotics. We have outlined a suggested design in Table 1.

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Internal sources

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External sources

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

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Azorin 2006

Methods	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: inpatient and outpatient.	
Participants	Diagnosis: schizophrenia (DSM-IV). N=187. Gender: 113 M, 73 F (intent-to-treat group). Age: 18-65 years (mean ~ 36 years). History: duration ill unclear, age at onset unclear, at least moderately ill on CGI-S	
Interventions	1. Sertindole: flexible dose (permitted range 12-24 mg/day, mean 16.2). N=98 2. Risperidone: flexible dose (permitted range 4-10 mg/day, mean 6.6). N=89	
Outcomes	Leaving study early: any reason, adverse effects, inefficacy. Global state: CGI. Mental state: PANSS (total, positive, negative sub-score). Functioning: GAF. Attitude: Drug attitude inventory. Adverse effect/event: at least one adverse effect, QTc prolongation, death, extrapyramidal side effects (tremor, AIMS, BAS, SAS), prolactin associated effects (amenorrhoea, sexual dysfunction), sedation, weight change	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Subjective outcomes	Unclear risk	Double, identical capsules. Whether blinding was successful was not examined - but adverse effects differ substantially
Blinding? Objective outcomes	Low risk	Outcomes such as laboratory measures or death - unlikely to have been much affected by lack of blinding
Incomplete outcome data addressed? All outcomes	High risk	Data for leaving study early were available but total was high (35.8%). Last-observation-carried-forward method used (assumes that participants who discontinue remain stable)

Free of selective reporting?	High risk	Adverse events - only reported if > 5% occurrence.
Free of other bias?	High risk	Sponsored by manufacturers of sertindole.

Kane 2005

Methods	Allocation: random, no further details. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: not specified.
Participants	Diagnosis: schizophrenia (DMS-IV). N=321. Gender: 250 M, 71 F. Age: 18-55 years (mean ~39). History: duration ill not specified, mean age at onset ~ 22 years, treatment resistance, PANSS total score ≥ 60
Interventions	1. Sertindole: flexible dose (permitted range 12-24 mg/day, mean 18.1). N=216 2. Risperidone: flexible dose (permitted range 6-12 mg/day, mean 9). N=105
Outcomes	Leaving study early: any reason, adverse events, inefficacy. Mental state: PANSS total score. Adverse effects/event: at least one adverse effect, QTc prolongation, cholesterol, extrapyramidal effects (akathisia, parkinsonism, AIMS, BAS, SAS), glucose, sexual dysfunction, sedation, weight
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random, no further details.
Allocation concealment?	Unclear risk	No further details.
Blinding? Subjective outcomes	Unclear risk	Double, no further details. Whether blinding was successful was not examined - but adverse effects differ substantially
Blinding? Objective outcomes	Low risk	Outcome measures such as leaving the study early are unlikely to be influenced by lack of blinding
Incomplete outcome data addressed? All outcomes	High risk	Data for leaving study early were available but total was high (32.4%). Last-observation-carried-forward method used (assumes that participants who discontinue remain stable)
Free of selective reporting?	High risk	Adverse events - only reported if > 10% occurrence.
Free of other bias?	High risk	Sponsored by manufacturers of sertindole. After titration period lower dose limit for risperidone = 6mg/day - rather high and can be associated with extrapyramidal effects

Diagnostic tool

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

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

Rating Scales:

Global rating scales:

CGI - Clinical Global Impressions.
 CGI-S - Clinical Global Impression-Severity.
 CGI-I - Clinical Global Impression-Improvement.
 Mental state:
 BPRS - Brief Psychiatric Rating Scale.
 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.
 SAPS - Scale for the Assessment of Positive Symptoms.
 Side effects:
 AIMS - Abnormal Involuntary Movement Scale.
 BAS - Barnes Akathisia Scale.
 ESRS - Extrapyramidal Syndrome Rating Scale.
 SAS - Simpson-Angus Index - for neurological side effects.
 UKU - Udvælg for kliniske undersøgelser Side Effect Rating Scale -side effect rating scale.
 Quality of Life:
 QLS - Quality of Life Scale.
 SWN -Subjective Well-being List.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Nielsen 2006	Allocation: randomised. Participants: people with schizophrenia - also on clozapine. Interventions: sertindole vs placebo augmentation.
Perro 1999	Allocation: randomised. Blinding: open-label.
Potkin 1996	Allocation: randomised. Participants: hospitalised patients with schizophrenia. Interventions: sertindole 24mg/day vs sertindole 20mg/day vs haloperidol, inappropriate intervention
Zurich 2008	Allocation: not randomised.

Characteristics of ongoing studies [ordered by study ID]

Cheung 2005

Trial name or title	Sertindole versus risperidone safety outcome study.
Methods	Allocation: randomised. Blinding: open label.
Participants	Diagnosis: schizophrenia. N estimate=30. Age: over 18 years. Sex: both.
Interventions	1. Sertindole: dose unknown. 2. Risperidone: dose unknown.
Outcomes	Primary outcome - all causes mortality, cardiac events.

Secondary outcomes - fatal events, hospitalisations, treatment duration	
Starting date	April 2004.
Contact information	Dr Hung Kin Cheung Team B Department of Psychiatry Castle Peak Hospital Hong Kong, China
Notes	Estimated study completion date: December 2006. Sponsor: H. Lundbeck A/S. Key Objectives: To compare the safety of sertindole with that of an active control under normal conditions of use. Status: Publication process ongoing.

Lundbeck 2006a

Trial name or title	A prospective randomised double-blind parallel-group active-referenced trial of sertindole in schizophrenia
Methods	Allocation: random, no further details.
Participants	Diagnosis: schizophrenia.
Interventions	1. Sertindole: no further details. 2. Active control: no further details.
Outcomes	Efficacy safety and tolerability.
Starting date	October 2008.
Contact information	No contact information.
Notes	Status: publication process ongoing.

Lundbeck 2006b

Trial name or title	Exploratory cognition study of sertindole in patients with schizophrenia
Methods	Allocation: random, no further details. Blinding: double. Duration: 12 weeks. Setting: Korea, Taiwan.
Participants	Diagnosis: schizophrenia. N estimate=96. Age: over 18 years-65. Sex: both.
Interventions	1. Sertindole: dose 12 to 20 mg daily. 2. Olanzapine: dose 10 to 20 mg daily.
Outcomes	Primary outcome - global cognitive composite score. Secondary outcomes - cognitive sub-scores.
Starting date	October 2006.
Contact information	Study Director LundbeckClinicalTrials@lundbeck.com
Notes	Estimated study completion date: April 2008. Sponsor: H. Lundbeck A/S.

Lundbeck 2007a

Trial name or title	Study on metabolic parameters of sertindole in patients with schizophrenia
Methods	Allocation: random, no further details. Blinding: double. Duration: 12 weeks. Setting: China.
Participants	Diagnosis: schizophrenia. N estimate=250. Age: over 18 years-65. Sex: both.
Interventions	1. Sertindole: dose 12 to 20 mg daily. 2. Olanzapine: dose 10 to 20 mg daily.
Outcomes	Primary outcome - changes from baseline for each component of metabolic syndrome
Starting date	March 2007.
Contact information	Study Director LundbeckClinicalTrials@lundbeck.com
Notes	Estimated study completion date: April 2008. Sponsor: H. Lundbeck A/S.

Lundbeck 2008

Trial name or title	Efficacy study exploring the effects on cognition of sertindole versus comparator in patients with schizophrenia
Methods	Allocation: random, no further details. Blinding: double. Duration: 12 weeks. Setting: USA.
Participants	Diagnosis: schizophrenia. N estimate=260. Age: over 18 years-55. Sex: both.
Interventions	1. Sertindole: once daily oral dose, day 1-20 4-16 mg/day, day 21-84 12, 16 or 20 mg/day. 2. Quetiapine: twice daily oral dose, day 1-20 50-500 mg/day, day 21-84 400, 500 or 600 mg/day
Outcomes	Primary outcome - neurocognitive effect of treatment based on the overall composite score on the MCCB. Secondary outcomes - domain specific scores on MCCB, PANSS total score, PANSS subscale scores, CGI-S, CDSS, GAF, QLS, UPSA total and subscale scores, ECGs
Starting date	March 2008.
Contact information	Study Director LundbeckClinicalTrials@lundbeck.com
Notes	Estimated study completion date: May 2009.

Sireling 2003

Trial name or title	Sertindole versus risperidone: safety outcome study.
Methods	Allocation: random, no further details. Blinding: partially blinded.
Participants	Diagnosis: not specified.

Interventions	1. Sertindole: dose unknown. 2. Risperidone: dose unknown.
Outcomes	Not known.
Starting date	November 2002.
Contact information	Dr Lester Sireling Consultant Psychiatrist Primary Care Mental Health Team and Early Intervention Service 6th Floor Premier House 112 Station Road Edgware, Middx HA8 7BJ lester.sireling@beh-mht.nhs.uk
Notes	Dr Sireling contacted and kindly responded: "This study was part of a multi-centre study organised by the drug company. It has been completed. For further information please contact the company"

Spaniel 2008

Trial name or title	ITAREPS Trial
Methods	Allocation: randomised. Blindness: double. Duration: 1 year.
Participants	Diagnosis: schizophrenia. N estimate=150. Age: over 18 years-60. Sex: both. Setting: Czech Republic.
Interventions	1. Information technology-aided program of relapse prevention (may include dose management of sertindole). 2. Treatment as usual.
Outcomes	Primary outcome - hospitalisations for psychotic relapses. Secondary outcomes - EWSQ 10P and 10FM, hospitalisation days, natural course of illness, correlation between baseline CGI and the No. of hospitalisations
Starting date	November 2008.
Contact information	Dr Filip Spaniel Prague Psychiatrc Center Ustavni Czech Republic, 181 03 spaniel@pcp.lf3.cuni.cz
Notes	Sponsor: Ely Lilly. Estimated study completion date: November 2009.

Weiser 2007

Trial name or title	Comparison of cognitive functions of schizophrenic patients treated with sertindole versus risperidone
Methods	Allocation: randomised. Blinding: open label. Duration: 24 weeks.
Participants	Diagnosis: schizophrenia. N estimate=60. Age: over 18 years-65. Sex: both.
Interventions	1. Sertindole: dose unknown.

2. Risperidone: dose unknown.	
Outcomes	Primary outcome: cognitive functioning. Secondary outcome: discontinuation due to all causes, symptomatology and adverse effects
Starting date	Unknown.
Contact information	Dr Mark Weiser Shaba Medical Center Tel-Aviv University Sackler School of Medicine Israel mweiser@netvision.net.il
Notes	

DATA AND ANALYSES

Comparison 1

SERTINDOLE versus RISPERIDONE

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	508	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.60]
1.2 adverse events	2	508	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.74, 2.57]
1.3 inefficacy	2	508	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.80, 2.18]
2 Global state: 1. No important change - as defined by original study - short term	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 no significant response	1	187	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.08]
2.2 no clinically important change	1	187	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.10]
3 Mental state: 1a. General - no clinically important change (<50% PANSS total score reduction)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Short term	1	187	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.71, 1.08]
4 Mental state: 1b. General - average symptom score (PANSS total, high=poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Short term	2	493	Mean Difference (IV, Random, 95% CI)	1.98 [-8.24, 12.20]
5 Mental state: 2. Specific - average positive and negative symptom scores - short term (PANSS subscore, high=poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 positive symptoms	1	172	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.95, 1.35]
5.2 negative symptoms	1	172	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.13, 0.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Functioning: Average score - short term (GAF, high=poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7 Adverse effects: 1a. General - at least one adverse effect	2	508	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.95, 1.11]
8 Adverse effect/event: 1b. General-death	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 suicide	1	187	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.34]
9 Adverse effects: 2. Specific - A. Cardiac - i. QTc prolongation	2	508	Risk Ratio (M-H, Random, 95% CI)	4.86 [1.94, 12.18]
10 Adverse effects: 2. Specific - A. Cardiac - ii. QTc change from baseline (ms, high=poor)	2	495	Mean Difference (IV, Random, 95% CI)	18.60 [14.83, 22.37]
11 Adverse effects: 2. Specific - B. Central nervous system - i. Sedation	2	508	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.44]
12 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - binary outcomes	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 akathisia	1	321	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.20, 0.98]
12.2 extrapyramidal symptoms	1	187	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.38, 1.11]
12.3 parkinsonism	1	321	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.09, 0.69]
12.4 tremor	1	187	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.37, 6.15]
13 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - average scores	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
13.1 abnormal involuntary movements (AIMS, high=poor)	2	477	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.86, 0.25]
13.2 akathisia (Barnes Akathisia Scale, high=poor)	2	500	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.41, -0.03]
13.3 extrapyramidal symptoms (Simpson-Angus Scale, high=poor)	2	500	Mean Difference (IV, Random, 95% CI)	-0.46 [-1.24, 0.32]
14 Adverse effects: 2. Specific - C. Metabolic - i. Cholesterol change from baseline (mg/dl, increase=poor)	1	176	Mean Difference (IV, Random, 95% CI)	-4.90 [-13.53, 3.73]
15 Adverse effects: 2. Specific - C. Metabolic - ii. Glucose change from baseline (mg/dl, increase=poor)	1	176	Mean Difference (IV, Random, 95% CI)	0.00 [-9.85, 5.85]
16 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - significant gain	1	187	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.70, 2.41]
17 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - change from baseline (kg)	2	328	Mean Difference (IV, Random, 95% CI)	0.99 [0.12, 1.86]
18 Adverse effects: 2. Specific - D. Sexual dysfunction	2	437	Risk Ratio (M-H, Random, 95% CI)	2.90 [1.32, 6.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 not-specific - sexual dysfunction	1	187	Risk Ratio (M-H, Random, 95% CI)	4.54 [1.02, 20.16]
18.2 specific - abnormal ejaculation	1	250	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.97, 6.14]

Analysis 1.1. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 1 Leaving the study early

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 1 Leaving the study early

Analysis 1.2. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 2 Global state: 1. No important change - as defined by original study - short term

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 2 Global state: 1. No important change - as defined by original study - short term

Analysis 1.3. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 3 Mental state: 1a. General - no clinically important change (<50% PANSS total score reduction)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 3 Mental state: 1a. General - no clinically important change (<50% PANSS total score reduction)

Analysis 1.4. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 4 Mental state: 1b. General -average symptom score (PANSS total, high=poor)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 4 Mental state: 1b. General - average symptom score (PANSS total, high=poor)

Analysis 1.5. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 5 Mental state: 2. Specific -average positive and negative symptom scores - short term (PANSS subscore, high=poor)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 5 Mental state: 2. Specific - average positive and negative symptom scores - short term (PANSS subscore, high=poor)

Analysis 1.6. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 6 Functioning: Average score -short term (GAF, high=poor)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 6 Functioning: Average score - short term (GAF, high=poor)

Analysis 1.7. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 7 Adverse effects: 1a. General -at least one adverse effect

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 7 Adverse effects: 1a. General - at least one adverse effect

Analysis 1.8. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 8 Adverse effect/event: 1b. General -death

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 8 Adverse effect/event: 1b. General -death

Analysis 1.9. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 9 Adverse effects: 2. Specific - A. Cardiac - i. QTc prolongation

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 9 Adverse effects: 2. Specific - A. Cardiac - i. QTc prolongation

Analysis 1.10. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 10 Adverse effects: 2. Specific - A. Cardiac - ii. QTc change from baseline (ms, high=poor))

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 10 Adverse effects: 2. Specific - A. Cardiac - ii. QTc change from baseline (ms, high=poor))

Analysis 1.11. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 11 Adverse effects: 2. Specific - B. Central nervous system - i. Sedation

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 11 Adverse effects: 2. Specific - B. Central nervous system - i. Sedation

Analysis 1.12. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 12 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - binary outcomes

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 12 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - binary outcomes

Analysis 1.13. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 13 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - average scores

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 13 Adverse effects: 2. Specific - B. Central nervous system - ii. Specific extrapyramidal movements - average scores

Analysis 1.14. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 14 Adverse effects: 2. Specific - C. Metabolic - i. Cholesterol change from baseline (mg/dl, increase=poor)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 14 Adverse effects: 2. Specific - C. Metabolic - i. Cholesterol change from baseline (mg/dl, increase=poor)

Analysis 1.15. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 15 Adverse effects: 2. Specific - C. Metabolic - ii. Glucose change from baseline (mg/dl, increase=poor)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 15 Adverse effects: 2. Specific - C. Metabolic - ii. Glucose change from baseline (mg/dl, increase=poor)

Analysis 1.16. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 16 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - significant gain

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 16 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - significant gain

Analysis 1.17. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 17 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - change from baseline (kg)

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 17 Adverse effects: 2. Specific - C. Metabolic - iii. Weight - change from baseline (kg)

Analysis 1.18. Comparison 1 SERTINDOLE versus RISPERIDONE, Outcome 18 Adverse effects: 2. Specific - D. Sexual dysfunction

Review: Sertindole versus other atypical antipsychotics for schizophrenia

Comparison: 1 SERTINDOLE versus RISPERIDONE

Outcome: 18 Adverse effects: 2. Specific - D. Sexual dysfunction

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 2, 2009

Date	Event	Description
10 November 2010	Amended	Contact details updated.

Date	Event	Description
11 November 2009	Amended	Contact details updated.
7 August 2009	Amended	Consumer-written plain language summary added.
11 September 2008	Amended	Converted to new review format.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review was slightly adapted to new functions available in Review Manager 5, namely the risk of bias tables.

WHAT'S NEW

Last assessed as up-to-date: 21 August 2007.

Date	Event	Description
17 October 2012	Amended	Contact details updated.

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* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Sertindole versus other atypical antipsychotics for schizophrenia

Schizophrenia is a mental health problem that can be long term and can severely disable some of the people who have it, especially in terms of quality of life and inclusion into wider society. The main treatment is medication (antipsychotics) and while some people find a drug which decreases their symptoms and does not give them a lot of adverse effects, there are others who are 'treatment resistant' i.e. none of the medication available works for them. There are some antipsychotics, such as clozapine and sertindole that can have quite dangerous side-effects in some people. However, if they benefit people for whom nothing else works, the extra monitoring of these side-effects that is needed, can perhaps be justified.

This review aims to compare sertindole to the other newer second generation (atypical) antipsychotics in people who have schizophrenia. Two studies were identified which included 508 people. Both compared sertindole to risperidone, were short (12 weeks) and the participants were either at least moderately ill or treatment resistant. There was no overall significant difference between these two medications in terms of improvement in people's general well-being or their mental state. Also while people on risperidone showed more movement side-effects, those on sertindole were more likely to put on weight, have changes in their heart rhythm and the men were more likely to suffer from sexual dysfunction.

The data from these trials are limited and a considerable number of the participants left the study early. In addition, sertindole has only been compared to one second generation antipsychotic and the trials are relatively short. A larger and longer trial comparing sertindole to other second generation antipsychotics, with the outcomes including mental state, general functioning, adverse effects and quality of life, would enhance our knowledge in this area considerably.

(Plain language summary prepared for this review by Janey Antoniou of RETHINK, UK www.rethink.org).

Figure 1.

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

	Adequate sequence generation?	Allocation concealment?	Blinding? (Subjective outcomes)	Blinding? (Objective outcomes)	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Azorin 2006	?	?	?	+	-	-	-
Kane 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. Blinding: double - described and tested. Duration: 6 months minimum.
Participants	Diagnosis: schizophrenia (operational criteria). N=2700.* Age: any. Sex: both. History: any.
Interventions	1. Sertindole: dose ~ 12-24 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. Ziprasidone: dose ~ 120-160 mg/day. N=300. 9. Zotepine: dose ~ 100-300 mg/day. N=300.
Outcomes	Leaving study early (any reason, adverse events, inefficacy). Service outcomes: hospitalised, time in hospital, attending out patient clinics. Global impression: CGI**, relapse, healthy days. Mental state: PANSS. Adverse events: UKU, ECG. Functioning: employment. Satisfaction: family, patient.

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

** Primary outcome