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Atypical antipsychotics for people with both schizophrenia and depression

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Abstract

Background—Many people (up to 50%) with schizophrenia also have co-morbid depression. It has been suggested that new atypical antipsychotic drugs are beneficial for people with the two diagnoses.

Objectives—To assess the effects of atypical antipsychotic drugs on people who have a diagnosis of both schizophrenia and depression.

Search methods—We searched the Cochrane Schizophrenia's Group Register (to March 2006). We supplemented this by citation searching and personal contact with authors and relevant pharmaceutical companies.

Selection criteria—We included randomised clinical trials of atypical antipsychotic drugs used specifically for the treatment of people with a diagnosis of both schizophrenia and depression.

Data collection and analysis—We extracted data independently. For homogenous dichotomous data we calculated random effects, relative risk (RR), 95% confidence intervals (CI) and, where appropriate, numbers needed to treat (NNT) on an intention-to-treat basis. For continuous data, we calculated weighted mean differences (WMD).

Main results—We found 878 citations but were only able to include three studies (five reports). One trial found no significant difference between quetiapine and haloperidol for the outcome of 'less than 50% reduction in PANSS score' (n=180, RR 0.91 CI 0.8 to 1.0). Those allocated sulpiride had significantly lower depression scores compared with people given chlorpromazine (1

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CONTRIBUTIONS OF AUTHORS

Vivek Furtado - had the original idea for the review, devised the protocol, the initial screening of the studies, reviewed papers, extracted data and contributed to the final version of the review.

Srihari, Vinod - helped with writing the protocol, initial screening of studies, extraction of data and contributed to the final version of the review.

DECLARATIONS OF INTEREST

None identified.

RCT, n=36, WMD CPRS -0.70 CI -1.2 to -0.2). Again, however, in the quetiapine versus haloperidol comparison, the continuous scoring did not highlight differences (1 RCT, n=180, WMD PANSS depression change -0.57 CI -1.4 to 0.30). When clozapine was compared with any other antipsychotic drug plus an antidepressant or placebo, clozapine constantly scored better on Hamilton scores (1 RCT, n=29, WMD vs antipsychotic + mianserin -5.53 CI -8.23 to -2.8 ; 1 RCT, n=32, WMD vs antipsychotic + meclobemide -4.35 CI -6.7 to -2.03 ; 1 RCT, n=33, WMD vs antipsychotic + placebo -6.35 CI -8.6 to -4.1).

Authors' conclusions—There are too few data to guide patients, carers, clinicians or policy makers. Current practice has to be guided by evidence other than that derived from randomised trials and more trials in this important area are indicated.

Medical Subject Headings (MeSH)

Antidepressive Agents [therapeutic use]; Antipsychotic Agents [* therapeutic use];
Chemotherapy, Adjuvant; Comorbidity; Depression [* drug therapy]; Randomized Controlled
Trials as Topic; Schizophrenia [* drug therapy]

MeSH check words

Humans

BACKGROUND

Affective disorders, depression in particular but also mania, can occur in people with schizophrenia and often go untreated (Plasky 1991). The depression or mania is particularly common during the acute phase and the first year of the schizophrenic illness (Addington 1998; Escamilla 2001). Moderate to severe depression, however, is much more common than mania and occurs in 42% to 60% of people with schizophrenia (Martin 1985; Lindenmayer 1991; Markou 1996). This co-morbid depression adversely affects outcomes, resulting in increased episodes of self harm and impaired recovery (Tollefson 1998), increased risk of suicide (Roy 1986), poorer quality of life (Tollefson 1999) and compromised social and vocational functioning (Emsley 1999).

The causes of the depression in people with schizophrenia are unclear and may be due to a variety of factors. Depression may be inherent to the disease process of schizophrenia itself (Tapp 2001) or the drugs used to treat the psychotic illness could promote depression (Perenyi 1998). Neuroleptic-induced akathisia (subjective feeling of restlessness) and akinesia (reduced movements) could cause or be misinterpreted as depression. The negative features of schizophrenia (a set of symptoms characterised by anhedonia, apathy, decreased initiative, blunted affect and social withdrawal) certainly have been misinterpreted as affective illness (Siris 2000). However, studies do suggest that depressive and negative symptoms can be separated in people with chronic schizophrenia.

Treatment of people with schizophrenia who also have co-morbid depression presents a challenge in spite of the array of medicines available today. Some studies suggest that adjunctive antidepressants are not indicated (Kramer 1989) and the findings of a systematic review found no convincing evidence to support or refute the use of antidepressants in

treating depression in people with schizophrenia (Whitehead 2003). Although atypical antipsychotics are said to have some effects on mood, including the induction of hypomania and mania (Rachid 2004), they do appear to cause a significant reduction of depressive symptoms on various scales, not only during the acute episode, but also in people with chronic symptoms (Emsley 2003). These effects seemed to be distinct from improvements in negative and positive symptoms (Myers 2001). Depressive symptoms can also improve with effective antipsychotic treatment (Knights 1981) but the newer atypical antipsychotics may be more effective for this than the older classes of drugs (Levinson 1999).

Technical background

There is extensive evidence to implicate dysregulation of noradrenergic, serotonergic, and dopaminergic neurotransmission in the pathophysiology of mood disorders. The receptor profile of atypical antipsychotics is consistent with possible antidepressant activity. Specifically, some atypical antipsychotics are potent antagonist of central 5-HT_{2A} receptors, addressing symptoms such as insomnia, agitation, and weight loss and may indirectly enhance 5-HT_{1A}-mediated neurotransmission (Myers 2001).

OBJECTIVES

To evaluate the effects of atypical antipsychotics (with or without an adjunct antidepressant) compared with typical antipsychotics (with or without an adjunct antidepressant), placebo or no intervention for treating people with schizophrenia who also have a comorbid diagnosis of depression.

METHODS

Criteria for considering studies for this review

Types of studies—We included all relevant randomised controlled trials. 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, diagnosed by any criteria, irrespective of age, sex, who also had co-morbid depression diagnosed by any standard diagnostic criteria or by a standard rating scale. We excluded trials of people whose depression was clearly stated to be due to dysphoria, akinesia or akathisia due to the effects of neuroleptic medications or due to the negative features of schizophrenia. We excluded studies focusing solely on those with schizoaffective disorders.

Types of interventions

1. Atypical antipsychotics (risperidone/olanzapine/clozapine/amisulpride/quetiapine/loxapine/ziprasidone/clotiapine/sulpiride/arpiprazole/remoxipride/sertindole/zotepine) without co-administration of an antidepressant: any dose, given orally, or by intramuscular injection.
2. Atypical antipsychotics with co-administration of an antidepressant: any dose, given orally, or by intramuscular injection.
3. Typical antipsychotics without co-administration of an antidepressant: any dose, given orally, or by intramuscular injection.
4. Typical antipsychotics with co-administration of an antidepressant: any dose, given orally, or by intramuscular injection.
5. Placebo or no treatment.

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

Primary outcomes

- 1 Mental state
 - 1.1 No clinically important change in depressive symptoms (as defined by each of the studies)
 - 1.2 Not any change in depressive symptoms
 - 1.3 Average endpoint depressive symptoms score
 - 1.4 Average change in depressive symptoms scores
- 2 Adverse effects
 - 2.1 General adverse effects

Secondary outcomes

- 1 Death - suicide or natural causes
- 2 Leaving the study early
- 3 Global state
 - 3.1 Relapse
 - 3.2 Time to relapse
 - 3.3 No clinically important change in global state
 - 3.4 Not any change in global state
 - 3.5 Average endpoint global state score
 - 3.6 Average change in global state score

- 4** Mental state
 - 4.1** No clinically important change in general mental state
 - 4.2** Not any change in general mental state
 - 4.3** Average endpoint general mental state score
 - 4.4** Average change in general mental state scores
 - 4.5** No clinically important change in psychotic symptoms (as defined by each of the studies)
 - 4.6** Not any change in psychotic symptoms
 - 4.7** Average endpoint psychotic symptoms score
 - 4.8** Average change in psychotic symptoms scores
 - 4.9** Emergence of hypomanic or manic symptoms
- 5** General functioning
 - 5.1** No clinically important change in general functioning
 - 5.2** Not any change in general functioning
 - 5.3** Average endpoint general functioning score
 - 5.4** Average change in general functioning scores
 - 5.5** No clinically important change in specific aspects of functioning, such as social or life skills
 - 5.6** Not any change in specific aspects of functioning, such as social or life skills
 - 5.7** Average endpoint specific aspects of functioning, such as social or life skills score
 - 5.8** Average change in specific aspects of functioning, such as social or life skills scores
- 6** Behaviour
 - 6.1** No clinically important change in general behaviour
 - 6.2** Not any change in general behaviour
 - 6.3** Average endpoint general behaviour score
 - 6.4** Average change in general behaviour scores
 - 6.5** No clinically important change in specific aspects of behaviour
 - 6.6** Not any change in specific aspects of behaviour
 - 6.7** Average endpoint specific aspects of behaviour score
 - 6.8** Average change in specific aspects of behaviour scores
- 7** Adverse effects - specific

- 7.1** Specific adverse effects
- 7.2** Allergic reactions
- 7.3** Anticholinergic adverse events (blurred vision, dry mouth, constipation, urinary retention)
- 7.4** Extrapyramidal adverse events (general, akathisia, dystonia, dyskinesia, malignant neuroleptic syndrome, muscular stiffness, parkinsonism, tardive dyskinesia, tremor)
- 7.5** Gastrointestinal adverse effects (nausea, vomiting, diarrhoea)
- 7.6** Antihistaminergic adverse effects (hypotension, sedation, weight gain)
- 7.7** Endocrine adverse effects (menstrual disturbances, galactorrhoea, glucose dysregulation, hyperlipidemia)
- 7.8** Sexual dysfunction
- 8** Engagement with services
 - 8.1** No clinically important engagement
 - 8.2** Not any engagement
 - 8.3** Average endpoint engagement score
 - 8.4** Average change in engagement scores
- 9** Satisfaction with treatment
 - 9.1** Recipient of care not satisfied with treatment
 - 9.2** Recipient of care average satisfaction score
 - 9.3** Recipient of care average change in satisfaction scores
 - 9.4** Carer not satisfied with treatment
 - 9.5** Carer average satisfaction score
 - 9.6** Carer average change in satisfaction scores
- 10** Quality of life
 - 10.1** No clinically important change in quality of life
 - 10.2** Not any change in quality of life
 - 10.3** Average endpoint quality of life score
 - 10.4** Average change in quality of life scores
 - 10.5** No clinically important change in specific aspects of quality of life
 - 10.6** Not any change in specific aspects of quality of life
 - 10.7** Average endpoint specific aspects of quality of life
 - 10.8** Average change in specific aspects of quality of life

- 11 Service utilisation
 - 11.1 Hospital admissions
 - 11.2 Duration of stay in hospital
- 12 Economic
 - 12.1 Direct costs
 - 12.2 Indirect costs

Search methods for identification of studies

Electronic searches—We searched the Cochrane Schizophrenia Group Trials Register (March 2005 and March 2006) using the phrase: [(*depress*) in REFERENCE TI/AB/IN fields and (*depress*) in STUDY Health care condition and Intervention fields] This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

Searching other resources

Reference searching: We inspected references of all identified studies, included or excluded for more studies.

Personal contact: We contacted the authors of relevant reviews or studies to enquire about other sources of relevant information.

Pharmaceutical companies: We contacted companies manufacturing atypical antipsychotics for any suitable trials.

Data collection and analysis

1. Selection of trials—We (VAF, SV) independently inspected all titles and abstracts of studies identified by the search. We resolved any disagreement by discussion, and where there was still doubt, we acquired the full article for further inspection. Once the full articles were obtained, we independently decided whether the studies met the review criteria. If disagreement could not be resolved by discussion, we sought further information and added these trials to the list of those awaiting assessment.

2. Assessment of methodological quality—We assessed the methodological quality of included studies using the criteria described in the Cochrane Handbook (Higgins 2005), which is based on the degree of allocation concealment. Poor concealment has been associated with overestimation of treatment effect (Schulz 1995). Category A includes studies in which allocation has been randomised and concealment is explicit. Category B studies are those which have randomised allocation but in which concealment is not explicit. Category C studies are those in which allocation has neither been randomised nor concealed. We were not blinded to the names of authors, institutions or journal of publication as this procedure has been found to have no important impact on the overall assessment of study quality (Berlin 1997). We only included trials that are stated to be randomised (categories A or B of the handbook) in this review. The categories are defined below:

- A. Low risk of bias (adequate allocation concealment)
- B. Moderate risk of bias (some doubt about the results)
- C. High risk of bias (inadequate allocation concealment).

3. Data collection—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.

4. Data synthesis

4.1 Intention to treat analysis: We excluded data from studies where more than 50% of participants in any group were lost to follow up (this did not include the outcome of ‘leaving the study early’). In studies with less than 50% dropout rate, people leaving early were considered to have had the negative outcome, except for the event of death. We analysed the impact of including studies with high attrition rates (25-50%) in a sensitivity analysis. If inclusion of data from this latter group resulted in a substantive change in the estimate of effect, we did not add their data to trials with less attrition, but presented them separately.

4.1.1 Multiple doses: If several doses of an atypical antipsychotic were compared with one dose of the control drug, we pooled the different dose groups of the atypical antipsychotics. For example, for dichotomous data, we considered all patients treated with a particular type of atypical antipsychotic as a single group. For continuous data, we used the mean of all patients on a particular type of atypical antipsychotic in the comparisons.

4.2 Dichotomous- yes/no- data: For binary outcomes we calculated the relative risk (RR) and its 95% confidence interval (CI) based on the fixed effects model. Relative Risk is more intuitive (Boissel 1999) than odds ratios and 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). Where people were lost to follow up at the end of the study, we assumed that they had had a poor outcome and once they were randomised they were included in the analysis (intention-to-treat /ITT analysis).

Where possible, efforts were made to convert outcome measures to binary 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). It was recognised that for many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data were available, the 50% cut-off was used for the definition in the case of non-chronically ill people and 25% for those with chronic illness. If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

4.3 Continuous data

4.3.1 Normal distribution: Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to continuous final value endpoint data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from zero, the standard deviation, when multiplied by two, should be less than the mean (otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution - Altman 1996); In cases with data that are greater than the mean they were entered into 'Other data' table as skewed data. If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skewness is present if $2SD > (S - S_{min})$, where S is the mean score and S_{min} is the minimum score. We reported non-normally distributed data (skewed) in the 'other data types' tables.

For change data (mean change from baseline on a rating scale) it is impossible to tell whether data are non-normally distributed (skewed) or not, unless individual patient data are available. After consulting the ALLSTAT electronic statistics mailing list, we entered change data in RevMan analyses and reported the finding in the text to summarise available information. In doing this, we assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew.

4.3.2 Final endpoint value versus change data: Where both final endpoint data and change data were available for the same outcome category, we only presented final endpoint data. We acknowledge that by doing this much of the published change data may be excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would be given undeserved equal prominence. We have contacted authors of studies reporting only change data for endpoint figures.

4.3.3 Data synthesis: For continuous outcomes we estimated a weighted mean difference (WMD) between groups based on a fixed effects model.

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

4.5 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 intra class correlation in clustered studies, leading to a unit-of-analysis error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes Type I errors (Bland 1997; Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients 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 co-efficient (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.

5. Investigation for 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. We supplemented this by 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). Where heterogeneity was present, reasons for this were investigated. If it substantially altered the results, data were not summated, but presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias—We entered data from all included studies into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

7. Sensitivity analyses—We analysed the effect of including studies with high attrition rates in a sensitivity analysis. Where a trial was described as ‘double-blind’ but it was implied that the study was randomised, it was also included in a sensitivity analysis.

8. 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 atypical antipsychotics.

RESULTS

Description of studies

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

For substantive descriptions of the studies, please see Included and Excluded Studies tables.

1. Excluded studies—We excluded 23 studies. Six were not randomised. We excluded a further 13 because the participants did not have co-morbid depression in addition to schizophrenia. We excluded four studies because they did not use the correct combination of medications as required by the review criteria.

2. Awaiting assessment—Five studies are awaiting assessment, (Cantillon 1998; Lee 2001; Martin 2002; Yagdiran 2000; Yagdiran 2001). We are currently seeking the full articles of these conference proceeding and brief reports.

3. Ongoing studies—Fleurot 2002 seems to be an ongoing study. This is a randomised trial comparing olanzapine with amisulpride in people with schizophrenia and depression.

4. Included studies—We identified three (Alfredsson 1984; Emsley 2003; Jasovic 1997) studies (five reports) for inclusion. Two studies (Jasovic 1997; Emsley 2003) were described as randomised and double blind, whilst Alfredsson 1984 used double blind methodology but did not report whether participants were randomly allocated to treatments.

4.1 Length of trials: All studies reported data on short-term follow-up (up to 12 weeks). There was no trial reporting data on medium-term (13 to 26 weeks) or long-term follow-up (over 26 weeks).

4.2 Participants: In total 310 people were included in these trials, most in the comparison of atypical versus typical antipsychotics (total n=230). All included trials involved people with a diagnosis of schizophrenia and depression. In the two studies that stipulated the sex of participant, there were more men than women (150 men vs 80 women); Jasovic 1997 did not specify sex of participants. The average age was mid thirties, but again Jasovic 1997 did not make this explicit.

4.3 Setting: Alfredsson 1984 and Emsley 2003 were described as taking place in a hospital setting. Jasovic 1997 did not specify the trial setting.

4.4 Study size: Emsley 2003 is currently the largest relevant study with 180 participants, whilst, Alfredsson 1984 randomised 55 and Jasovic 1997 involved 80 participants.

4.5 Interventions: The trialists administered the antipsychotics in a wide range of doses. Daily doses of atypical antipsychotics used as control in-terventions were also wide ranging (sulpiride 800 mg, quetiapine 6000 mg, clozapine dose not stated) as were those for the typical antipsychotics (chlorpromazine 600 mg, haloperidol 20 mg). Jasovic 1997 did not state the doses of the antidepressants used (amitrytiline, mianserin, meclobemide).

4.6 Outcomes: The included studies did not report any usable data on global state, adverse effects and participants leaving the study early.

4.6.1 Outcome scales: Trials used several scales to measure mental state. For the purposes of analysis we could only report data from the CPRS, PANSS and HRDS, details of these three scales are shown below. We found three studies reporting data related to one or more

of these tools (Alfredsson 1984, Emsley 2003; Jasovic 1997). Data were dichotomous as well as continuous. We have given reasons for exclusion of data from other scales under 'Outcomes' in the 'Included studies' section.

4.6.1.2.1 Comprehensive Psychopathological rating scale - CPRS (Montgomery 1979):

The CPRS consists of 65 scaled items, covering a wide range of psychiatric symptoms. High scores indicate a worse outcome.

4.6.1.2.2 Positive and Negative Syndrome Scale - PANSS (Kay 1986): The Positive and Negative Symptom Scale was developed from the BPRS and the Psychopathology Rating Scale. It is used as a method for evaluating positive, negative and other symptom dimensions in schizophrenia. The scale has 30 items, and each item can be defined on a seven-point scoring system varying from one (absent) to seven (extreme). This scale 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 low levels of symptoms.

4.6.1.2.2 Hamilton Rating Scale for Depression - HRSD (Hamilton 1960): This instrument is designed to be used only on patients already diagnosed as suffering from affective disorder of the depressive type. It is used for quantifying the results of an interview, and its value depends entirely on the skill of the interviewer in eliciting the necessary information. The scale contains 17 variables measured on either a five-point or a three-point rating scale, the latter being used where quantification of the variable is either difficult or impossible. Among the variables are: depressed mood, suicide, work and loss of interest, retardation, agitation, gastro-intestinal symptoms, general somatic symptoms, hypochondriasis, loss of insight, and loss of weight. A score of 11 is generally regarded as indicative of a diagnosis of mild depression, 14-17 mild to moderate depression and >17 moderate to severe depression.

4.6.2 Redundant data: Alfredsson 1984 reported the outcome of adverse effects but the data were reported in such a way that we were unable to use them. Emsley 2003 reported the outcome of loss to follow up but did not provide any clear data.

4.6.3 Missing outcomes: We found no usable outcomes for the following categories: service outcomes; engagement with services and satisfaction with treatment. It is possible that there is a systematic bias in which data, such as the simple binary outcome of death, are not reported consistently or well.

4.6.4 Primary outcomes: Our pre-stated primary outcome of relapse was not reported in any of the studies. At the time of writing the protocol, all other outcomes in this review were felt to be of secondary importance but we recognise that they may be of primary interest to others. Where possible, we entered in such a way that the area to the left of the line of no effect indicates a favourable outcome for atypical antipsychotics.

Risk of bias in included studies

- 1. Randomisation**—Two of the three studies included were reported to be randomised, although they did not describe the method of randomisation (Emsley 2003; Jasovic 1997). Whilst Alfredsson 1984 reported that double blind methodology was used, the reports did not state if allocation to treatment was random.
- 2. Blindness**—All three included studies were described as being double-blind but this was not clearly tested.
- 3. Loss to follow up**—Emsley 2003 reported loss to follow up in such a way which rendered it difficult to use data. Alfredsson 1984, Jasovic 1997 did not report this outcome.
- 4. Data reporting**—Due to poor reporting we were unable to use some of the data. Findings presented as graphs, whether as percentiles or as inexact p-values, are often of little use to a reviewer. The studies some-times failed to provide standard deviations when reporting mean changes. We are seeking further data from the first authors of relevant trials.
- 5. Overall**—With the poor reporting of how randomisation sequences were kept concealed it is likely that the studies are prone to at least a moderate degree of bias. For this reason we categorised all studies as 'B' (see Methods 2.).

Effects of interventions

- 1. The search**—We found a total of 878 citations from the electronic search but were only able to include three studies (five reports) for the purposes of this review.
- 2. COMPARISON 1. ATYPICAL versus TYPICAL ANTIPSYCHOTICS**—This comparison included two studies (Alfredsson 1984; Emsley 2003) (total n=226). Neither study reported global state or leaving the study early outcomes.

2.1 Mental state

2.1.1 Not improved (>50% reduction in PANSS score of ≥ 8): We found PANSS scores dichotomised to 'less than 50% reduction' revealed no statistically significant difference between quetiapine and haloperidol (Emsley 2003, n=180, RR 0.91 CI 0.8 to 1.0).

2.1.2 Depression score: Alfredsson 1984 reported data for mental state as average change in CPRS depression score. We found the sulpiride group had significantly lower depression scores compared with those given chlorpromazine (n=36, WMD -0.70 CI -1.2 to -0.2). PANSS depression change scores, however, found no significant differences between quetiapine and haloperidol (Emsley 2003 n=180, WMD -0.57 CI -1.4 to 0.30).

3. COMPARISON 2. ATYPICAL versus ANY ANTIPSYCHOTIC + ANTIDEPRESSANT or PLACEBO

3.1 Mental state

3.1.1 Depression scores - HRSD: We were able to include one study (Jasovic 1997). This four week trial compared the atypical antipsychotic clozapine with other unspecified

antipsychotics combined with antidepressants, or placebo. We found participants given clozapine had significantly lower depression scores ($n=29$, WMD -5.53 CI -8.23 to -2.8) compared with the control group receiving the antipsychotics combined with mianserin. Similarly, participants given clozapine had significantly lower depression scores ($n=32$, WMD -4.35 CI -6.7 to -2.03) compared with people given antipsychotics plus meclobemide antidepressant. Clozapine also showed significantly lower depression scores ($n=33$, WMD -6.35 CI -8.6 to -4.1) compared with the antipsychotic plus placebo group.

DISCUSSION

1. The studies

Atypical antipsychotics are widely reported to be useful in people with both schizophrenia and depression and also in the use of affective symptoms in schizophrenia (Emsley 2003; Levinson 1999). Low frequency of adverse effects and good tolerability of atypical antipsychotics has also been stressed by open clinical studies and materials produced for marketing purposes. In this systematic search for controlled clinical trials we found an extremely small number of poorly reported short studies. It is likely that all three studies are vulnerable to bias and that that bias would favour the newer generation of drugs.

1.1 Applicability of findings—The studies were conducted in America. The majority of participants in the trials were inpatients with very little physical and psychiatric comorbidity. They had a well-defined diagnosis of schizophrenia but each of the three trials used a different scale to diagnose depression. Such people are a minority in routine clinical practice as it is the norm to find people with co-morbidities such as substance abuse. Even if the trials were large and robust to the effects of biases, applicability of findings is not straightforward.

1.2 Limited data, confusing data—The collection and quality of the data reported was very variable. All included studies reported data only for the short term (less than 12 weeks). For few outcomes like adverse effects and loss to follow up studies did not clearly report the numerical data.

Among the 12 groups of defined outcomes, three were addressed by the studies. We found a lack of information on clinically important outcomes such as death, global state, general functioning, behaviour, engagement with services, satisfaction with treatment and quality of life. We also did not find any data on service utilisation and economic outcomes. For such a widely used drug group, now part of guidelines worldwide, there are surprisingly few data. Outcomes were commonly reported using graphs and p-values instead of tables and confidence intervals.

1.3 Quality of studies—We appreciate that studies in this population group bring unique difficulties. There were, however, important methodological difficulties with the trials and therefore any conclusions must be viewed with caution. There is a danger of inclusion of, at the very least, a moderate risk of bias in these results (Higgins 2003).

2. ATYPICAL ANTIPSYCHOTICS versus TYPICAL ANTIPSYCHOTICS (only short term)

This comparison included two short, small studies (total n=226) but that neither reported global state.

2.1 Mental state—For any one outcome there are very few data. The Emsley 2003 study did report mental state and depression in binary and continuous ways. There is no real suggestion that quetiapine is more or less effective than haloperidol. Even the outcome suggesting benefit for sulpiride over chlorpromazine is a benefit of less than one CPRS point for two groups of less than 20 people. These small studies cannot guide practice. We have found no evidence to support the marketing of atypical antipsychotic drugs as the preferred neuroleptic for depressed people with schizophrenia.

3. ATYPICAL ANTIPSYCHOTIC versus ANY ANTIPSYCHOTIC + ANTIDEPRESSANT or PLACEBO (only short term)

This comparison included one short, small study (total n=80) that did not report global state, adverse effects or leaving the study early.

3.1 Mental state—Though numbers in this study were small, this study repeatedly found that those allocated to clozapine did better than people randomised to the any antipsychotic plus an antidepressant/placebo arms. However, the groups were very small (>20) and differences of about four to six points on the Hamilton Scale were difficult to interpret when most groups fell below the threshold for depression at the end of the trial. All control arms were nearer mild depression scores, but we are not clear about the practical meaning of the differences found in this study.

4. Missing data

There are no data relating to clinically important outcomes such as death, leaving the study early or drop-outs, global state, general functioning, behaviour, adverse effects, engagement with services, satisfaction with treatment, quality of life, service utilisation and economic outcomes. It would be ideal if newer atypical antipsychotics were not widely circulated without such data.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia and depression—There are some suggestions that sulpiride and clozapine may be more beneficial than the older typical antipsychotics for people with both depression and schizophrenia. However the evidence is both poor and open to bias. People with schizophrenia and depression should not feel that they are not being treated correctly if prescribed alternative drugs, but may want to ask for the evidence for the particular treatment that is being offered. People in such a situation may feel that they have a right to be randomised to a relevant trial.

2. For clinicians—The evidence in this area is extremely poor. Guidance is due more to marketing than to robust evidence. Clinicians will still have to make pragmatic decisions

until efforts are made to fully investigate this important area. An alternative for clinicians is to use an adjunctive antidepressant.

3. For managers/policy makers—There are no data on service outcomes and no medium or long term data at all. In the context of finite resources, the lack of good quality data leaves managers and policy makers with difficult decisions to make. At present guidance is forced to rely on studies that are more open to bias than randomised trials.

Implications for research

1. General—Allocation concealment is essential for the result of a trial to be considered valid and gives the assurance that selection bias is kept to the minimum. Well-described and tested blinding could have encouraged confidence in the control of performance and detection bias. It is also important to know how many, and from which groups, people were withdrawn, in order to evaluate exclusion bias. It would have been helpful if authors had presented data in a useful manner which reflects association between intervention and outcome, for example: relative risk, odds-ratio, risk or mean differences, as well as raw numbers. Binary outcomes should be calculated in preference to continuous results, as they are easier to interpret.

2. Specific—We feel that the question as to whether atypical antipsychotic drugs present a better alternative than older neuroleptic medications [plus or minus adjunctive antidepressant therapy] for people with both depression and schizophrenia remains unanswered. We advocate that future trials should be adequately powered for outcomes of depression. We think that it is likely that adjunctive treatment with antidepressants will continue to be the first choice in treatment. However, should an antipsychotic be used as an experimental treatment for schizophrenia in any trial, and should the researchers be interested in the subgroup of people with comorbid depression, then it would seem reasonable that the study is powered, from the outset, to pick up clinically meaningful outcomes in this domain (Table 1). Certainly, methods should be strict and involve good concealment of allocation and follow up. Participants should be people recognisable in everyday life and not those who are so strictly diagnosed as to render them unrecognisable to routine care. They should have a clearly documented diagnosis of schizophrenia with depression. Interventions should involve standard doses of atypical antipsychotics (since only sulpiride and quetiapine have figured in this reviews analyses) and a control drug with or without an anti-depressant that is a real choice in the region of the study. The control drug could be a typical antipsychotic and the anti-depressant could belong to any one of the classes of anti-depressants. Outcomes should be measured over months rather than weeks, as this is the usual period a person would be asked to take the drug. We suggest that if scales are to be used, validated and clinically meaningful outcomes should be predefined. Routine outcomes such as relapse, employment, housing status, satisfaction with care, serious or troubling adverse effects can all be easily recorded without the use of scales and we would suggest that these are included in the study design.

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External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

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

Alfredsson 1984

Methods	Allocation: not reported. Blindness: double. Duration: 8 weeks. Design: parallel groups.	
Participants	Diagnosis: schizophrenia (RDC) and depression. History: acute psychosis of schizophrenia type with co-existing depressive symptoms; informed consent obtained. N=50. Age: mean 30.5 years, range 18-43. Sex: 25 M, 25 F. Setting: hospital.	
Interventions	1	Sulpiride: dose 800 mg/day. N=25.
	2	Chlorpromazine: dose 400 mg/day. N=25.
Outcomes	Mental state: CPRS. Unable to use: Adverse events.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear	B - Unclear

Emsley 2003

Methods	Allocation: randomised. Blindness: double. Duration: 12 weeks. Design: multicentre, international, parallel groups.
Participants	Diagnosis: schizophrenia (DSM-IV) and depression (Kays depressive factor). History: patients with schizophrenia who only had a partial response to conventional antipsychotics. N=180.

Age: mean 37.7 years. Sex: 125 M, 55 F. Setting: hospital.		
Interventions	1 Quetiapine: dose 600 mg/day. N=94. 2 Haloperidol: dose 20 mg/day. N=86. Additional medications: 1. benzodiazepines or anticholinergics permitted to treat cases of acude agitation, severe insomnia, EPS or akathisia 2. continuation of long-term treatment with benzodiazepines was allowed	
Outcomes	Mental state: Kay's depressive factor of the PANSS*. Unable to use: Loss to follow up.	
Notes	*Kays depressive factor of the PANSS includes somatic concern, anxiety, guilt feelings and depression. Data has been included only of those people who had a score of >=8 at baseline	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jasovic 1997

Methods	Allocation: randomised. Blindness: double. Duration: 4 weeks. Design: not stated.	
Participants	Diagnosis: schizophrenia (DSM-IV) and depression (HRSD). History: patients with schizophrenia who also had scores of = 16 on the HRSD. N=80. Age: not stated. Sex : not stated. Setting: not stated.	
Interventions	<div><div>1</div><div>Clozapine: dose not stated. N=18.</div></div> <div><div>2</div><div>Placebo: N=15.</div></div> <div><div>3</div><div>Amitryptilene: dose not stated. N=12.</div></div> <div><div>4</div><div>Mianserin: dose not stated. N=11.</div></div> <div><div>5</div><div>Meclobemide: dose not stated. N=14.</div></div> <div>Additional medication: not stated.</div>	
Outcomes	Mental State: HRSD.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

RDC- Research Diagnostic Criteria

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders - Version IV

Mental State -

MADRS - Montgomery and Asberg Depression Rating Scale

PANSS - Positive and Negative Symptoms Scale

HRSD - Hamilton Rating Scale for Depression

BRMES - Bech-Rafaelsen Melancholia Scale

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Addington 2002	Allocation: randomised. Participants: people with schizophrenia and depression. Interventions: atypical and typical antipsychotic plus sertraline versus atypical and typical antipsychotic plus placebo
Altamura 1999	Allocation: not randomised.
Ames 1996	Allocation: randomised. Participants: people with schizophrenia.
Conley 2001	Allocation: randomised. Participants: people with schizophrenia or schizoaffective disorder
Csernansky 2002	Allocation: randomised. Participants: people with schizophrenia and schizoaffective disorder
Daniel 1999	Allocation: randomised. Participants: people with schizophrenia or schizoaffective disorder
Hou 2002	Allocation: not randomised.
Huang 2003	Allocation: not randomised.
Kascow 2001	Allocation: randomised. Participants: people with schizophrenia and depression. Interventions: typical or atypical antipsychotics and citalopram versus typical or atypical antipsychotics
Kirli 1997	Allocation: randomised. Participants: people with schizophrenia and depression. Interventions: sertraline versus imipramine.
Masciocchi 1974	Allocation: randomised. Participants: people with chronic schizophrenia and ideo-emotional poverty
Moyano 1975	Allocation: randomised. Participants: people with chronic schizophrenia.
Mueller 2002	Allocation: randomised. Participants: people with schizophrenia.
Mulholland 2003	Allocation: randomised. Participants: people with schizophrenia and depression. Interventions: typical and atypical antipsychotics and sertraline versus typical and atypical antipsychotics and placebo
Muller 1998	Allocation: randomised. Participants: people with schizophrenia or schizoaffective disorder
Murasaki 2000	Allocation: randomised. Participants: people with schizophrenia.
Naber 1997	Allocation: not randomised, conference presentation of trials
Nurowska 1980	Allocation: randomised. Participants: people with schizophrenia or endogenous depression or hallucinatory behaviour or hypochondriac
Peuskens 2002	Allocation: randomised, pooled analysis of three studies.
Rein 1997	Allocation: randomised. Participants: people with schizophrenia and negative symptoms
Tollefson 1998	Allocation: randomised. Participants: people with schizophrenia.
Tollefson 1999	Allocation: randomised. Participants: people with schizophrenia.
Zhao 2003	Allocation: not randomised.

Characteristics of ongoing studies [ordered by study ID]

Fleurot 2002

Trial name or title	Amisulpiride versus olanzapine in schizophrenia	
Methods		
Participants	People with schizophrenia or schizophreniform disorder	
Interventions	1	Amisulpiride dose 400-800 mg/day
	2	Olanzapine dose 10-20 mg/day
Outcomes	Mental State: PANSS, BPRS Adverse effects	
Starting date	not stated	
Contact information	Fleurot O	
Notes		

Mental State -

PANSS - Positive and Negative Symptoms Scale

BPRS - Brief Psychopathological Rating Scale

DATA AND ANALYSES

Comparison 1 ATYPICAL vs TYPICAL ANTIPSYCHOTICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: 1. Not important change (>50% reduction in Kay's score of >=8)	1	180	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.03]
2 Mental state: 2a. Average change in depression score (CPRS, high = poor)	1	36	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.20, -0.20]
3 Mental state: 2b. Average change in depression score (PANSS, high = poor)	1	180	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.44, 0.30]

Comparison 2 ATYPICAL vs ANY ANTIPSYCHOTIC + ANTIDEPRESSANT or PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental state: Average end point score (HRSD, high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 amitryptiline	1	30	Mean Difference (IV, Fixed, 95% CI)	-3.61 [-6.58, -0.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 mectloberide	1	32	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-6.67, -2.03]
1.3 mianserin	1	29	Mean Difference (IV, Fixed, 95% CI)	-5.53 [-8.23, -2.83]
1.4 placebo	1	33	Mean Difference (IV, Fixed, 95% CI)	-6.35 [-8.58, -4.12]

WHAT'S NEW

Last assessed as up-to-date: 11 November 2007.

Date	Event	Description
7 December 2011	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2008

Date	Event	Description
17 March 2010	Amended	Contact details updated.
5 August 2009	Amended	Contact details updated.
23 April 2008	Amended	Converted to new review format.
11 November 2007	New citation required and conclusions have changed	Substantive amendment

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* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Atypical antipsychotics for people with both schizophrenia and depression

It is well known that depression occurs in people with schizophrenia. Atypical antipsychotics are used to treat the symptoms of schizophrenia but their specific effects on those with schizophrenia and depression are unclear, although they are marketed for this purpose.

In this review we evaluated the effects of atypical antipsychotics for people with both schizophrenia and depression and unfortunately found a distinct lack of information. We wanted to assess the available evidence to ascertain whether atypical antipsychotic drugs represent a better alternative than older neuroleptic medications [plus or minus adjunctive antidepressant therapy] for people with both depression and schizophrenia. However, due to the paucity of trials of antipsychotic drugs that are sold as also having antidepressant effects, we were unable to draw any firm conclusions. More well-conducted randomised controlled trials are needed.

Table 1
Suggested design of study

Methods	Participants	Interventions	Outcomes	Notes
Allocation: centralised sequence generation with table of random numbers or computer generated code, stratified by severity of illness, sequence concealed till interventions assigned. In the context of limited provision, randomisation may be the only equitable way of distributing care. Blindness: double - tested. Duration: 1 year. Design: parallel groups.	Diagnosis: it may be preferred not to use diagnostic categories such as DSM IV and just to include those whose mental health problem is designated as schizophrenia or psychosis and depression. N=300. Age-any. Sex: either. Setting: anywhere (preferably hospital setting). History: non-acute.	1 Antipsychotic drug X: dose and choice at clinician's and patient's discretion. N=150. 2 Antipsychotic drug Y: dose - clinician's and patient's discretion. N= 150	Quality of life: healthy days. Service outcomes: days in hospital, time attending psychiatric outpatient clinic. Satisfaction with care: patients/carers. Global state: CGI.*** Mental state: CGI, relapse.** Functioning: engagement with services, leaving the study early, living independently. Adverse effects: including mortality. Economic outcomes: cost-effectiveness and cost-benefit.	* size of study to detect a 10% difference in improvement with 80% certainty. *** Primary outcome. If scales are used to measure outcome then there should be binary cut off points, defined before study start, of clinically important improvement