Cover sheet

Title

Aripiprazole for schizophrenia (For publication)

Reviewers

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Dates

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External sources of support

None

Contribution of reviewers

Haney George El-Sayeh - protocol and review development and writing.

Carla Morganti - protocol and review development and writing.

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Potential conflict of interest

Hany George El-Sayeh - none known.

Carla Morganti - none known.

What's new

Search run in September 2005.

Five further studies were included since the previous search, and a further one study excluded. Although the new studies did not alter many of the findings significantly, they provided further information on global state and the need for additional antipsychotic and benzodiazepine medication.They altered few adverse events outcomes. It appears that the incidence of akathisia and the need for antiparkinson medication are less in those randomised to aripiprazole versus placebo. It also appears that aripiprazole does not cause more insomnia when compared to typical antipsychotic medications including perphenazine and haloperidol.

Dates

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Synopsis

Plain language summary

Schizophrenia is a serious, chronic and relapsing mental illness with a worldwide lifetime prevalence of about one percent.

First generation 'typical' antipsychotics such as chlorpromazine and haloperidol have been the mainstay of treatment up until the introduction of the second generation 'atypical' antipsychotics such as risperidone and olanzapine. Typical and atypical antipsychotics do provide a treatment response for most people with schizophrenia, whether that is a reduction in psychotic episodes or a lessening in the severity of their illness. However, a proportion of people still do not respond adequately to antipsychotic medication. Additionally, atypical and especially typical antipsychotics are associated with serious adverse effects which can often compromise compliance with medication and therefore increase the incidences of relapse.

Aripiprazole is one of a new generation of antipsychotic drugs with an innovative mechanism of action. We systematically evaluated the effects of this new generation antipsychotic. We were able to include 15 randomised trials. The studies are very poor with enormous loss to follow up in a short space of time. Data reporting is also inadequate. Aripiprazole may be effective for the treatment of schizophrenia but does not differ greatly from typical antipsychotics (haloperidol, perphenazine) or other atypicals (olanzapine, risperidone) in respect of treatment efficacy, response or tolerability.

Abstract

Background
Treatment of people with schizophrenia using older typical antipsychotic drugs such as haloperidol can be problematic. Many fail to respond to these older antipsychotics and more people experience disabling adverse effects. Aripiprazole is said to be one of a new generation of atypical antipsychotics with good antipsychotic properties and minimal adverse effects.

Objectives
To evaluate the effects of aripiprazole for people with schizophrenia and schizophrenia-like psychoses.

Search strategy
We searched the Cochrane Schizophrenia Group's Register (September 2005) which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO. We inspected references of all identified studies for further trials. We contacted relevant pharmaceutical companies, the FDA and authors of trials for additional information.

Selection criteria
All clinical randomised trials comparing aripiprazole with placebo, typical or atypical antipsychotic drugs for schizophrenia and schizophrenia-like psychoses.

Data collection & 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
Despite the fact that 7110 people participated in fifteen randomised aripiprazole studies, we were unable to extract any usable data on death, service outcomes, general functioning, behaviour, engagement with services, satisfaction with treatment; economic outcomes or cognitive functioning. Study attrition was very large and data reporting poor. Compared with placebo, aripiprazole significantly decreased relapse in both the short and medium term (n=300, 1 RCT, RR 0.66 CI 0.5 to 0.8, NNT 5 CI 4 to 8). It also produced better compliance with study protocol (n=2271, 8 RCTs, RR 0.72 CI 0.5 to 0.97, NNT 26 CI 16 to 239). Aripiprazole may decrease prolactin levels below that expected from placebo (n=305, 1 RCT, RR 0.32 CI 0.1 to 0.8, NNT 14 CI 11 to 50). Compared with typical antipsychotics there were no significant benefits for aripiprazole with regards to global state, mental state, quality of life or leaving the study early. Both groups reported similar rates of adverse effects, with the exception of akathisia (n= 955 RR 0.31 CI 0.2 to 0.6, NNT 20 CI 17 to 32) and the need for antiparkinson medication (n=1854, 4 RCTs, RR 0.45 CI 0.3 to 0.6, NNT 4 CI 3 to 5) which were lower in those receiving aripiprazole. When compared with olanzapine and risperidone, aripiprazole was no better or worse on outcomes of global state and leaving the study early. The rates of adverse effects were also similar, with the exception of less elevation of prolactin (n=301, 1 RCT, RR 0.04 CI 0.02 to 0.1, NNT 2 CI 1 to 2.5) and less prolongation of the average QTc (30 mg/day) (n=200, 1 RCT, WMD -10.0, CI -16.99 to -3.0) compared with risperidone. When compared with standard care (mixed group receiving typical and atypical antipsychotics) one aripiprazole study did have significantly less

people not responding to treatment (n=1599, RR 0.70 CI 0.7 to 0.8, NNT 5 CI 4 to 6), not satisfied with care (n=1599, RR 0.62 CI 0.6 to 0.7, NNT 4 CI 4 to 5) and less people leaving the study early (n=1599, 1 RCT, RR 0.81 CI 0.7 to 0.9, NNT 13 CI 8 to 39). Results from the five new papers identified from the updated review search, did not significantly alter the main results or conclusions of the original review.

Reviewers' conclusions

Aripiprazole may be effective for the treatment of schizophrenia, but it does not differ greatly from typical and atypical antipsychotics with respect to treatment response, efficacy or tolerability. In comparison with typical antipsychotics, aripiprazole may have a lower risk of akathisia, and in comparison to atypical antipsychotics, less risk of raised prolactin and prolongation of the QTc interval. Clearly reported pragmatic short, medium and long term randomised controlled trials should be undertaken to determine its position in everyday clinical practice.

Background

'Conventional' antipsychotic drugs such as chlorpromazine and haloperidol have traditionally been used as a first line treatment for people with schizophrenia (Kane 1990, Kane 1993). However, approximately 5 - 25% of people with schizophrenia show poor response to these treatments (Christison 1991, Davis 1977, Meltzer 1992). In addition, adverse effects such as movement disorders and sedation often make compliance with these medications problematic (Kane 1990). Although their efficacy in alleviating positive schizophrenic symptoms (such as delusions and hallucinations) is reasonably clear, their effect on the negative symptoms of schizophrenia (such as apathy and poverty of speech) is limited (Crow 1980, Andreasen 1985).

'Atypical' or 'second generation' antipsychotics include drugs such as clozapine, olanzapine, risperidone, quetiapine, amisulpiride and ziprasidone. Initially, these were said to differ from typical antipsychotics in that they were found not to cause movement disorders (catalepsy) in rats at clinically effective doses. Other more clinically-important distinguishing factors include their reputed effects on both the positive and negative symptoms of schizophrenia (although this is far from certain), their more limited adverse effect profiles, particularly in relation to movement disorders, and the possibility that these drugs may improve cognitive function (Gelder 2001). These atypical drugs however are far from ideal, and problematic adverse effects do occur. With the exception of ziprasidone, most atypicals are associated with marked weight gain and disruption of glucose metabolism that may lead to diabetes. Clozapine, which is used for people whose illness is 'treatment-resistant', may induce life-threatening decreases in white blood cells (agranulocytosis) as well as heart problems (acute myocarditis, cardiomyopathy) and diabetes (Rivas-Vasquez 2003).

Aripiprazole is claimed to be at least as effective as haloperidol for the positive symptoms of schizophrenia such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations). It is also effective for the negative symptoms of schizophrenia, such as apathy and slowing and paucity of movement and thought. It has also been suggested that aripiprazole may be associated with fewer movement disorders (parkinsonism, dystonias, tardive dyskinesia), less weight gain and reduced negative effects on the heart (QTc interval abnormalities) and on glucose metabolism compared with standard antipsychotics (Rivas-Vasquez 2003). In addition, Aripiprazole is said to be useful in both the acute and maintenance phases of schizophrenia, and to have cognitive-enhancing effects.

Technical background

Aripiprazole is a new antipsychotic which is currently being marketed by Otsuka Pharmaceutical and Bristol-Myers Squibb. It is said to be the prototype of a new third generation of antipsychotics; the so-called dopamine-serotonin system stabilisers. It is reported to exert its antipsychotic effects by acting as a partial agonist at D2 dopamine- and 5-HT1a serotonin receptors, and as an antagonist at 5-HT2 serotonin receptors. It has been postulated that, through the above receptor site actions, and hence dopamine and serotonin system stabilisation, a partial D2 agonist would be able to act as an antagonist in pathways where an abundance of dopamine was producing psychosis, yet it would stimulate receptors as an agonist at sites in which low dopaminergic tone would produce side effects (e.g. areas mediating motor movement and prolactin release) (Rivas-Vasquez 2003). Aripiprazole, however, also has an affinity to other receptors including D3, D4, 5-HT2c, 5-HT7, alpha-1 adrenergic and H1 histamine receptors. This may explain adverse effects associated with this compound such as somnolescence, headache, gastrointestinal upset and light-headedness (FDA 2002 a).

The recommended target dose for aripiprazole is 10-15 mg per day (dose range 10-30 mg). Phase

III trials were initially conducted in Japan in 1995, and the drug was granted Approvable Status by the FDA (USA) on the 15th November 2002, for the treatment of schizophrenia (FDA 2002 a). Aripiprazole has since been licensed in most countries worldwide.

Objectives

To review the effects of aripiprazole compared to placebo and conventional antipsychotic drugs for people with schizophrenia.

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 implied that the study was randomised, we included the trial 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 analysed 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 psychoses (schizophreniform and schizoaffective disorders). 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. Aripiprazole: any dose or form of application.
2. Placebo or no treatment.
3. 'Typical' antipsychotic drugs such as haloperidol or chlorpromazine, any dose or form of application.
4. 'Atypical' antipsychotic drugs such as risperidone, olanzapine, amisulpiride, any dose or form of application.
5. 'Standard care' as defined by treating physician.

Types of outcome measures

1. Death - suicide and natural causes

2. Global state
2.1 Relapse*
2.2 No clinically important change in global state (as defined by individual studies)
2.3 Average endpoint global state score
2.4 Average change in global state scores

3. Service outcomes
3.1 Hospitalisation
3.2 Time to hospitalisation

4. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)

4.1 No clinically important change in general mental state
4.2 Average endpoint general mental state score
4.3 Average change in general mental state scores
4.4 No clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia, depression, mania)
4.5 Average endpoint specific symptom score
4.6 Average change in specific symptom scores

5. General functioning.
5.1 No clinically important change in general functioning
5.2 Average endpoint general functioning score
5.3 Average change in general functioning scores
5.4 No clinically important change in specific aspects of functioning, such as social or life skills
5.5 Average endpoint specific aspects of functioning, such as social or life skills
5.6 Average change in specific aspects of functioning, such as social or life skills

6. Behaviour
6.1 No clinically important change in general behaviour
6.2 Average endpoint general behaviour score
6.3 Average change in general behaviour scores
6.4 No clinically important change in specific aspects of behaviour
6.5 Average endpoint specific aspects of behaviour
6.6 Average change in specific aspects of behaviour

7. Adverse effects - general and specific (particularly movement disorders, and those known to occur more commonly with aripiprazole such as anxiety, somnolescence, disturbances of the gastrointestinal tract and headache)
7.1 Clinically important general adverse effects
7.2 Average endpoint general adverse effect score
7.3 Average change in general adverse effect scores
7.4 Clinically important specific adverse effects
7.5 Average endpoint specific adverse effects
7.6 Average change in specific adverse effects

8. Engagement with services

9. Satisfaction with treatment
9.1 Leaving the studies early
9.2 Recipient of care not satisfied with treatment
9.3 Recipient of care average satisfaction score
9.4 Recipient of care average change in satisfaction scores
9.5 Carer not satisfied with treatment
9.6 Carer average satisfaction score
9.7 Carer average change in satisfaction scores

10. Quality of life
10.1 No clinically important change in quality of life
10.2 Average endpoint quality of life score
10.3 Average change in quality of life scores
10.4 No clinically important change in specific aspects of quality of life

10.5 Average endpoint specific aspects of quality of life
10.6 Average change in specific aspects of quality of life

11. Economic outcomes
11.1 Direct costs
11.2 Indirect costs

12. Cognitive functioning
12.1 No clinically important change in cognitive functioning
12.2 Average endpoint cognitive functioning score
12.3 Average change in cognitive functioning scores
12.4 No clinically important change in specific aspects of cognitive functioning
12.5 Average endpoint specific aspects of cognitive functioning
12.6 Average change in specific aspects of cognitive functioning

13. Leaving the study early

* We chose relapse (as defined in the individual studies) as the primary outcome measure.

We grouped outcomes into the short term (up to 12 weeks), medium term (13 to 26 weeks) and long term (over 26 weeks).

Search strategy for identification of studies

1. Electronic searching

We searched the Cochrane Schizophrenia Groups register (September 2005) using the phrase:

[aripiprazole* or abilitat* or abilify* in title or *aripiprazole* or *abilitat* or *abilify* in abstract, index terms of REFERENCE] or [aripiprazole* in interventions of STUDY].

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

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

3. Personal contact
We contacted the first author of each included study for information regarding unpublished trials.

4. Drug companies
We contacted the manufacturers of aripiprazole (Bristol-Myers Squibb) for additional data.

5. The US Food and Drugs Administration website - http://www.fda.gov (August 2003 and September 2005).
We searched this site using the word 'aripiprazole' and also 'abilify'.

Methods of the review

[For definitions of terms used in this, and other sections, please refer to the Glossary]

1. Selection of trials
Material downloaded from electronic sources included details of author, institution or journal of publication.

The principal reviewer (HGE) inspected all reports. These were then re-inspected by CM in order to ensure reliable selection. 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 (HGE and CM) 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.

2. Assessment of methodological quality
We assessed the methodological quality of included trials in this review using the criteria described in the Cochrane Handbook (Higgins 2005) and the Jadad Scale (Jadad 1996). The former is based on the evidence of a strong relationship between allocation concealment and direction of effect (Schulz 1995). 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). For the purpose of the analysis in this review, trials were included if they met the Cochrane Handbook criteria A or B.

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:
1. Was the study described as randomised?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?

Each item receives one point if the answer is positive. In addition, a point can be deducted if either the randomisation or the blinding/masking procedures described are inadequate. For this review we used a cut-off of two points on the Jadad scale to check the assessment made by the Handbook criteria. However, the Jadad Scale was not used to exclude trials.

3. Data collection
HGE independently extracted data from selected trials, while CM separately re-extracted information from two different samples (10%). When disputes arose we attempted to resolve these by discussion. When this was not possible and further information was necessary to resolve the dilemma, data were not entered and we added the trial to the list of those awaiting assessment.

4. Data synthesis
4.1 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 changes' in a person's behaviour) measures. Currently RevMan does not support categorical data so we were unable to analysis this.

4.2 Incomplete data
We did not include trial outcomes if more than 40% of people were not reported in the final analysis.

4.3 Dichotomous - yes/no - data
We carried out an intention to treat analysis. On the condition that more than 60% of people completed the study, everyone allocated to the intervention were counted, whether they completed the follow up or not. It was assumed that those who dropped out had the negative outcome, with the exception of death. 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'. If the authors of a study had used a predefined cut off point for determining clinical effectiveness this was used by the reviewers where appropriate. Otherwise it was generally assumed that if there had been a 50% reduction in a scale-derived score, this could be considered as a clinically significant response. Similarly, a rating of 'at least much improved' according to the Clinical Global Impression Scale (Guy 1976) was considered as a clinically significant response.

The relative risk (RR) and its 95% confidence interval (CI) was calculated 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 which tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. We inspected data to see if an analysis using a fixed effects model made any substantive difference in outcomes that were not statistically significantly heterogeneous. 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.

4.4 Continuous data
4.4.1 Normally distributed data: continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to all 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 the finite number zero, the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996); (c) if a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skew is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied to them. When continuous data are presented on a scale which includes a possibility of negative values (such as change on a scale), it is difficult to tell whether data are non-normally distributed (skewed) or not. Skewed data from studies of less than 200 participants would have been entered in additional tables rather than into an analysis. Skewed data poses less of a problem when looking at means if the sample size is large and would have been entered into a synthesis.

For change data (endpoint minus baseline), the situation is even more problematic. 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, the reviewers presented change data in MetaView in order to summarise available information. In doing this, it was assumed either that data were not skewed or that the analyses could cope with the unknown degree of skew. Without individual patient data it is impossible to test this assumption. Where both change and endpoint data were available for the same outcome category, only endpoint data were presented. The reviewers acknowledge that by doing this much of the published change data were 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. Authors of studies reporting only change data are being contacted for endpoint figures. Non-normally distributed data were reported in the 'other data types' tables.

4.4.2 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 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 (Marshall 2000) are associated with bias, therefore the results of such scales were excluded. Furthermore, we stipulated that the instrument should either be a self report or be completed by an independent rater or relative (not the therapist), and that the instrument could be considered a global assessment of an area of functioning. However, as it was expected that therapists would frequently also be the rater, such data were included but commented on as 'prone to bias'.

Whenever possible we took the opportunity to make direct comparisons between trials that used the same measurement instrument to quantify specific outcomes. Where continuous data were presented from different scales rating the same effect, both sets of data were presented and the general direction of effect inspected.

4.4.3 Summary statistic
For continuous outcomes a weighted mean difference (WMD) between groups was estimated, again based on the random effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity.

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 intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

5. Investigation for heterogeneity
Firstly, we considered all the included studies within any comparison to judge clinical heterogeneity. Then visual inspection of graphs was used 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 75%, we interpreted this as indicating the presence of high levels of heterogeneity (Higgins 2003). If inconsistency was high, we did not summate data, but presented the data separately and investigated the reasons for heterogeneity.

6. Addressing publication bias
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.

7. Sensitivity analyses
Results for high doses (however 'high' was defined in the study or, if such a definition was not presented, greater than 15 mg aripiprazole per day) were compared to those for lower doses with regard to the primary outcome of relapse.

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 aripiprazole.

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

1. Excluded studies
We excluded nine studies from the review. Three were review articles (Carson 2002 a, Petrie 1997, Kujawa 2003). One study was excluded because participants were healthy volunteers (Mallikaarjun 2000). We excluded Auby 2002 because, although randomised, it evaluated one dose of aripiprazole versus another and also reported no data that could be included. We will contact the authors for further information. Stroup 2003 was excluded from the study as participants who received aripiprazole in this trial were not randomised at that stage. We excluded Marcus 2003 since the study described was a review of other short term studies, not an original research article. We excluded Casey 2003 and Saha 2004 from this version of the review as different administration regimens of aripiprazole were randomised rather than the new drug versus others or placebo.

2. Awaiting assessment
Fourteen studies currently await assessment. All reports are minimal and contain no usable data. It is impossible to know if some of these represent further reports of already included or excluded studies. Interestingly, only three of these reports were initially identified by our standard but comprehensive database search (Anonymous 2002, Anonymous 2003, Ramamurthy 2000). The other eleven studies were found after a search of the Federal Drug Administration (FDA) USA web site. These studies have been identified numerically only. Where possible, relevant sources will be contacted for further information. We have already contacted Bristol-Myers Squibb and the Otsuka Pharmaceutical Company for more information on their trials.

3. Ongoing studies
We have identified five ongoing studies. All these reports were identified on the FDA web site and are only identified by a study number. Bristol-Myers Squibb and Otsuka Pharmaceutical Company have been contacted for more information.

4. Included studies

We identified fifteen studies that we could include. All were described as randomised and all but three as being double-blind. Kern 2001, Riera 2004 and Stock 2005 were open-label studies. One of the double-blind studies (Adson 2003) allowed the option of open-label administration of aripiprazole during weeks three to six of the study for people who had not responded to treatment.

4.1 Length of trials

Schizophrenia is a lifelong illness that affects young people. Ten studies reported data on short-term follow-up (up to 12 weeks), three on medium-term follow-up (13 to 26 weeks) and two studies reported data on long-term follow-up (over 26 weeks, Kujawa 2002, Stock 2005). Two studies involved the administration of intramuscular aripiprazole and had extremely short follow-up periods (Daniel 2004, Oren 2005). Some of the ongoing studies may involve medium or long-term follow-up.

4.2 Participants

Eight of the fifteen included studies involved participants without clearly operationalised diagnoses (Carson 2002 b, Daniel 2004, Kern 2001, Kujawa 2002, Marcus 2005, McQuade 2003, Riera 2004, Stock 2005). All but six trials included people with a sole diagnosis of schizophrenia. The remaining six studies included patients with schizophrenia or schizoaffective disorder (Carson 2000 a, Daniel 2004, Kern 2001, Oren 2005, Potkin 2003, Riera 2004). The majority of participants in most studies were male, and had a mean age in their late thirties to early forties. In nine trials we could not elicit definitive exclusion criteria from available reports (Carson 2002 b, Daniel 2004,Kern 2001, Kujawa 2002, Marcus 2005, McQuade 2003, Oren 2005, Riera 2004, Stock 2005). Adson 2003 and Potkin 2003 required people taking part in the trial to have had a history of response to other antipsychotics excluding clozapine, whereas another study excluded participants if they had previously been resistant to clozapine therapy (Kane 2003). In the same vein, Daniel 2000 excluded people with a history of resistance to anti-psychotic medication. One study (Riera 2004) included participants who were due to be prescribed antipsychotics for the first time, or for whom a change of medication was deemed appropriate. Most people in these studies were moderately to severely ill and many were acutely ill.

4.3 Setting

Eight of the fifteen studies were described as occurring in hospital or inpatient settings (Adson 2003, Carson 2000 a, Csernansky 2003, Daniel 2000, Daniel 2004, Marcus 2005, Oren 2005, Potkin 2003). Two trials took place in out-patient or mixed settings (Carson 2002 b, Riera 2004) and we could find no explicit information on the settings of the remaining studies.

4.4 Study size

Riera 2004 with 1599 participants and Kujawa 2002 with 1294 people were by far the largest studies. Csernansky 2003 randomised only 103. All the remaining studies included between 200 and 500 participants.

4.5 Interventions

The trialists administered aripiprazole in a wide range of doses from 1mg per day to 30 mg per day. Comparators were placebo, conventional antipsychotics, (haloperidol (6.5-20 mg/day) and perphenazine (8-64 mg/day)) and the newer generation antipsychotics (olanzapine (10-20 mg/day) and risperidone (6 mg/day)). Most drugs were given orally, however in two studies medication was given intramuscularly (Daniel 2004, Oren 2005). In one open label, naturalistic study, patients were randomised to a safety control group which included antipsychotic medications (both typical and atypical) chosen by the investigator (Riera 2004). The medications used in the safety control group were known to include zisprasidone, olanzapine, risperidone, quetiapine, clozapine at varying

doses.

4.6 Outcomes
Carson 2002 b compared aripiprazole with placebo and reported usable data on global state and mean change in CGI. Riera 2004 also reported data for global state, Clinical Global Impression 'improvement scale' (CGI-I). No other study explicitly reported usable data on this outcome. We have used 'poor compliance with study protocol due to lack of efficacy, deterioration or psychosis' as a global outcome because, surprisingly, there were no more data relevant to global outcomes to be found in any of the reports.

Of all the studies only Kane 2003, comparing aripiprazole with perphenazine, reports usable mental state data. A mental state response was derived from a CGI score of 1-2 or a 30% decrease in PANSS. The validity of this dichotomising from these measures may be widely accepted but is, nevertheless not investigated.

Four studies report usable data on adverse effects but only those spontaneously reported in more than 5-10% of participants. This design precludes reporting of important less frequent effects. Three studies reported usable weight gain data. In Carson 2002 b and Kern 2001 weight gain of at least 7% was documented as being clinically significant. Potkin 2003 reported the mean change in body weight.

All but one included study provides usable data on leaving the study early.

One study reported data on Quality of life (Kane 2003). The Quality of Life Scale data were dichotomised and a clinically significant improvement in this scale was defined as being at least a 20% improvement from baseline.

4.6.1 Outcome scales: details of the only scales that provided usable data are shown below. Reasons for exclusions of data are given under 'Outcomes' in the 'Included studies' table.

4.6.1.1 Global state - Clinical Global Impression Scale - CGI Scale (Guy 1976).
This is used to assess both severity of illness and clinical improvement, by comparing the conditions of the person standardised against other people with the same diagnosis. A seven-point scoring system is usually used with low scores showing decreased severity and/or overall improvement. A CGI-I (CGI-Improvement) score was also validated for used in this review. Carson 2002 b and Riera 2004 reported usable data for this outcome.

4.6.1.2 Mental state - 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. This scale can be divided into 3 sub-scales for measuring the severity of general psychopathology, positive symptoms (PANSS-P), and negative symptoms (PANSS-N). A low score indicates lesser severity. Kane 2003 reported data from this scale.

4.6.1.3 Quality of life - Quality of Life Scale -QLS, (Carpenter 1984)
This is a semi structured interview administered and rated by trained clinicians. It contains 21 items rated on a 7-point scale based on the interviewers judgement of patient functioning. A total QLS and four sub-scale scores are calculated, with higher scores indicating less impairment. Kane 2003 reported data from this scale.

4.6.2 Redundant data
Enormous efforts were invested in studies rating and recording data that are then reported in such a way as to render them useless for reviews such as this. For example, in Carson 2000 a the trialists compare aripiprazole with both haloperidol and placebo. Outcomes such as death, clearly of interest, were reported in an obscure manner so we could not be sure of either the number of deaths or the groups in which they took place. We are only sure that they did take place. At a meeting held with workers from the Outcomes Research department of Bristol Myers Squibb pharmaceuticals (UK) on the 27th October 2004 in Leeds, we requested further clarification on numerous data that appeared on the FDA website. In particular, we were concerned by the high death rates observed in the two studies we identified by FDA study number. It was jointly agreed that this information (as well as other important data) would be provided to us when located by company staff. We did not hear from the company again until we published a short version of this review in a conference (El-Sayeh 2006). Thereafter, in May 2006, one author (H E-S) and editor (CEA) met with representatives of Bristol-Myers Squibb Pharmaceuticals Limited. These representatives were most helpful in clarifying data on the FDA website specifically on death which, on further evaluation, do not suggest an increased risk of mortality as indicated in the conference review (El-Sayeh 2006). They also encouraged the reviewers to ask for more data. We have amended this version and hope to do so again in light of more data provided by industry, especially on those studies that await assessment.

Carson 2000 a reported continuous measures of global state (CGI) but no variances are reported. The same applies to their repeated measures of mental state (BPRS, BPRS-PANNS), general functioning (CGI) and adverse effects (Simpson-Angus scale, Barnes Akathisia scale, Abnormal Involuntary Movement scale) and other outcome measures including changes in body weight, serum prolactin, and QTc interval changes. This poor reporting is by no means unique to Carson 2000 a (see Included Studies table, Outcomes). Other problems have included the use of non-externally validated outcome scales such as the POMS (Riera 2004). Participants in trials may be appalled to know how much of their data has been rendered useless. It is possible that there is a systematic bias in which data, such as the simple binary outcome of death, are not reported well.

4.6.3 Missing outcomes
No usable outcomes were found for the following categories: death, service outcomes, general functioning, behaviour, engagement with services, satisfaction with treatment, economic outcomes and cognitive functioning.

4.6.4 Primary outcomes
Our primary outcome of relapse was only reported in Carson 2002 b which compares aripiprazole with placebo. All other outcomes in this review were of secondary importance to the reviewers but we do recognise that they may be of primary interest to others.

Methodological quality of included studies

1. Randomisation
All included studies were said to be randomised. None of the included studies, however, explicitly detailed the method of randomisation. No studies stated that those in charge of allocation were blind to the participant list. This concealment of allocation has repeatedly been shown to be of key importance in excluding selection biases (Jüni 2001). Therefore all trials were category B (moderate risk of bias - some doubt about the results - see Methods). This was confirmed by poor ratings on the Jadad Scale (see Included Studies table). One study (Riera 2004) randomised participants in a 4:1 ratio to aripiprazole and standard care. Participants who were randomised to

standard care received a dose and type of medication which was determined by the investigator and hence were not being randomised to a particular medication.

2. Blindness
Ten studies were described as being double-blind (Carson 2000 a, Carson 2002 b, Csernansky 2003, Daniel 2000, Kujawa 2002, Daniel 2004, Marcus 2005, McQuade 2003, Oren 2005, Potkin 2003). Three trials were described as open-label (Kern 2001, Riera 2004, Stock 2005). Adson 2003 was described as double-blind, but people who showed no improvement or worsening of their symptoms by the third week were offered the option of open-label treatment with aripiprazole during the last three weeks of the study. In Kane 2003 the randomised double-blind treatment phase with aripiprazole was preceded by a 4-6 week open label atypical antipsychotic treatment phase to confirm treatment-resistance, and then by a 2-10 day single-blind placebo-washout phase. One study (Stock 2005) included patients in an open-label study who had previously undergone double-blind treatment. In none of the studies was testing of the blinding reported. If blinding is recognised to be of such importance for minimising observation bias, it could be expected that testing of this blinding would be a priority.

3. Loss to follow up
Several of the included studies reported data in terms of a last observation carried forwards (LOCF) analysis and an OC analysis (observed cases, defined as those completing the trial). Although LOCF analyses are commonly used to account for missing observations, this technique could introduce bias as considerable assumptions are made about people who did not stay in the study. We saw no reporting of attempts to validate assumptions by following up people who did drop out early. In some included studies, dropout rates were more than 40%. Using LOCF, 40% of the data on certain outcomes are assumed and we feel that this amount of fabricated data is too much. We have excluded these data. We tried to undertake an intention-to-treat analysis. Where no data were available for proportions of 40%, we have assumed a negative outcome (see Methods).

The reasons for loss to follow up are reasonably well reported and we have recorded these in the outcomes.

4. Data reporting
Overall much of the data we found could not be used because of poor reporting. Findings which are presented as graphs, in percentiles or just reported as p-values are often of little use to a reviewer. Many studies failed to provide standard deviations when reporting mean changes on a particular outcome measure. We are seeking further data from the first authors of relevant trials.

Results

1. The search
The initial search resulted in over 400 citations. We were only able to include six of these in the review. On contacting the FDA, we were provided with references to a large number of potentially relevant studies both in English and Japanese. From these we were able to obtain enough information to include two more studies. We made direct contact with the relevant drug companies (Otsuka Pharmaceuticals and Bristol Myers-Squibb) in order to obtain information, and were provided with published as well as unpublished data from a limited selection of English language conference posters and papers. This allowed us to include two further studies. Many studies are multiply reported in different media. In the update search (September 2005) we identified a further five studies to include in this review.

2. COMPARISON 1: ARIPIPRAZOLE versus PLACEBO

2.1 Global state
2.1.1 Relapse
Relapse was the primary outcome for this review. Only the aripiprazole versus placebo comparison contained relevant data. Carson 2002 b provided usable data for short term (upto 12 weeks) relapse. There were significantly fewer relapses for people given aripiprazole compared with those in the placebo group (n=310, 1 RCT, RR 0.59 CI 0.6 to 0.8, NNT 5 CI 4 to 8). The same study provided usable data for medium term (13 to 26 weeks) relapse. Again the aripiprazole group had significantly less relapse compared with people given placebo (n=310, 1 RCT, RR 0.66 CI 0.5 to 0.8, NNT 5 CI 4 to 8).

2.1.2 Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
Several reasons for the poor compliance with study protocol were given and several seemed to fall into a natural grouping reporting a poor global outcome. We have grouped these throughout the review. People allocated to aripiprazole encountered this outcome significantly less than those given placebo (n=2275, 8 RCTs, RR 0.72 CI 0.5 to 0.97, NNT 26 CI 16 to 239).

2.1.3 Needing additional antipsychotic medication
There was significantly less need for additional antipsychotic medication in those randomised to aripiprazole compared to those given placebo (N=1062, 4 RCTs, RR 0.70 CI 0.6 to 0.9, NNT 17 CI 12 to 42).

2.1.4 Needing additional benzodiazepines
There was significantly less need for additional benzodiazepine treatment in those randomised to aripiprazole compared to those given placebo in the single study for which data was available (n=263, 1 RCT, RR 0.41 CI 0.2 to 0.8, NNT 6 CI 4 to 18).

2.2 Adverse effects
2.2.1 Clinically important specific adverse effects
People given aripiprazole were no less anxious than those on placebo (n=615, 2 RCTs, RR 0.86 CI 0.5 to 1.4).

There also appeared to be no significant difference between the two comparator groups in terms of reported general extrapyramidal symptoms (n=878, 3 RCTs, RR 0.86 CI 0.3 to 2.7). Neither was there a difference in terms of needing antiparkinson medication (n=623, 3 RCTs, RR 0.78 CI 0.6 to 1.1). Significantly more patients randomised to aripiprazole versus placebo experienced akathisia (N=1175, 4 RCTs, RR 1.64 CI 1.02 to 2.7, NNT 5 CI 2 to 145).

Headaches were commonly reported (~15%) in both those allocated to aripiprazole and those given placebo (n=1175, 4 RCTs, RR 1.11 CI 0.7 to 1.7).

Insomnia was also common (~26%) but not more so for the aripiprazole group (n=878, 3 RCTs, RR 1.04 CI 0.8 to 1.3).

Nausea was experienced by about 6% of people in the studies but not more so for those given aripiprazole (n=1175, 3 RCTs, RR 1.23 CI 0.8 to 2.0). This was not statistically significant. There was also no statistically significant difference between the two groups in terms of vomiting (n=912, 3 RCTs, RR 1.66 CI 0.9 to 2.98)

Weight gain was defined as an increase of weight of equal to or greater than 7% of baseline weight. There appeared to be no significant difference between the two comparator groups in terms of significant weight gain (n=615, 2 RCTs, RR 2.64 CI 0.7 to 9.95) but 9% of people on aripiprazole gained weight to this extent compared with 3% of people given placebo.

2.2.2 Average change in specific adverse effects - QTc interval (ms) from baseline
There appeared to be no significant difference between 20 mg/day aripiprazole and placebo on this continuous outcome measure, although the standard deviations are very large and data could be skewed (n=204, 1 RCT, WMD 3.00 CI -3.2 to 9.2). The same applied for data for the higher dose of aripiprazole (30 mg/day) (n=204, 1 RCT, WMD -1.00 CI -7.2 to 5.2).

2.2.3 Physiological (serum) measures
Total fasting cholesterol (>/=200 mg/dl) was similar between groups (n=310, 1 RCT, RR 1.04 CI 0.8 to 1.3) as were glucose levels (>/=110mg/dl) (n=310, 1 RCT, RR 0.96 CI 0.7 to 1.3). Haemoglobin 1AC (incidence >/=upper limit of normal) levels were also similar in the aripiprazole groups compared with people given placebo, as were levels of low density lipoprotein (>/=130mg/dl). Aripiprazole appeared to produce significantly less rise in serum prolactin than placebo (n=305, 1 RCT, RR prolactin- increase to >/= 23ng/ml
0.32 CI 0.1 to 0.8, NNT 14 CI 11 to 50).

2.3 Leaving the study early
Significantly less people left the aripiprazole group compared with those in the placebo group (n=2585, 9 RCTs, RR leaving for any reason 0.73 CI 0.6 to 0.9, NNT 12 CI 9 to 25). When the reason for leaving was recorded as being due to adverse effects, there was no difference between groups (n=2585, 9 RCTS, RR 0.75 CI 0.4 to 1.4).

3. COMPARISON 2: ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS

3.1 Global state
3.1.1Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
Relapse data were not provided so we can only report one global outcome. There appeared to be no significant difference between aripiprazole and the typical antipsychotic drugs with regards to 'poor compliance with study protocol due to lack of efficacy, deterioration or psychosis' (n=2868, 7 RCTs, RR 1.15 CI 0.9 to 1.4).

3.1.2 Needing additional antipsychotic medication
Only one study provided usable data for this outcome and did not show any significant differences between aripiprazole and typical antipsychotic medications (n=360, 1 RCT, RR 0.92 CI 0.7 to 1.2).

3.1.3 Needing additional benzodiazepines
There was no significant difference in this outcome between the two comparators (n=360, 1 RCT, RR 0.67 CI 0.4 to 1.3) in the single study available.

3.2 Mental state
3.2.1 Response
Only one study reported usable data on mental state (Kane 2003). There appeared to be no significant difference in terms of 'treatment response as defined by PANSS or CGI' between aripiprazole and perphenazine (n=300, 1 RCT, RR 1.23 0.8 to 1.9).

3.3 Adverse effects
3.3.1 Clinically important specific adverse effects

Anxiety occurred in about 10% of both groups (RR 0.85 CI 0.5 to 1.6).

Dyspepsia was a little more common in those allocated to aripiprazole (~11%) but not significantly so (RR 1.79 CI 0.8 to 3.9).

The specific extrapyramidal symptoms of akathisia occurred in approximately 3% of participants randomised to aripiprazole and 7% in those randomised to typical antipsychotic medications. This was a significant difference (n=955 RR 0.31 CI 0.2 to 0.6, NNT 20 CI 17 to 32). In general for the outcome of 'extrapyramidal symptoms no differences between the old and the new drug were apparent (n=660 RR 0.27 CI 0.1 to 1.1). The proxy measure of 'needing additional antiparkinson medication' did suggest that use of aripiprazole did result in less extrapyramidal adverse effects (n=1854, 4 RCTs, RR 0.45 CI 0.3 to 0.6, NNT 4 CI 3 to 5).

Headaches were uncommon and no different between those given aripiprazole compared with those allocated to typical antipsychotics; heterogeneous data (n=955, 3 RCTs, RR 0.94 CI 0.6 to 1.5).

Insomnia was common (23%) but no more common for people allocated the new drug; heterogeneous data (n=660, 2 RCTs, RR 1.02 CI 0.2 to 5.1).

There was no significant difference in the propensity for the new drug to cause significantly more nausea (n=655, 2 RCTs, RR 1.65 CI 0.7 to 3.9).

3.4 Quality of life
There was no conclusive evidence that there was a significant difference in effects on the quality of life measure between aripiprazole and perphenazine (n=300, 1 RCT, RR 0.88 CI 0.8 to 1.0).

3.5 Leaving the study early
About 40% of the people in these studies left before study completion and there was no significant advantage to aripiprazole over typical antipsychotics (n=2868, 7 RCTs, RR leaving for any reason 0.86 CI 0.7 to 1.1). There was also no significant difference between the two groups in terms of those leaving the study early due to adverse effects (n=2868, 7 RCTs RR 0.77 CI 0.4 to 1.5, I-squared 66%).

4. COMPARISON 3: ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS

4.1 Global state
4.1.1Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis is not an ideal global outcome measure, but it is all that we found to work with. Aripiprazole did not seem to hold a clear advantage over olanzapine or risperidone for this outcome (n=618, 2 RCTs, RR 1.76 CI 0.9 to 3.5).

4.2 Adverse effects
4.2.1 Clinically important specific adverse effects
Anxiety was more common for those given aripiprazole (17%) compared with people allocated olanzapine or risperidone (9%), but not significantly so (n=770, 3RCTs, RR 1.65 CI 0.8 to 3.5).

The specific extrapyramidal syndrome of akathisia was equally common for those given aripiprazole compared with people allocated to olanzapine or risperidone (n=770, 3 RCTs, RR 1.43 CI 0.9 to 2.2). This also applied to the more general rating of extrapyramidal syndrome (n=515, 2 RCTs, RR 1.54 CI 0.1 to 25.5).

Headache was experienced by a quarter of participants in these trials but not more or less so for those allocated to aripiprazole (n=770, 3 RCTs, RR 1.06 CI 0.8 to 1.4).

Insomnia was also surprisingly common, experienced by about 24% of people. There was no difference between aripiprazole and other compounds (n=770, 3 RCTs, RR 1.53 CI 0.8 to 2.8) but data are heterogeneous (I squared 78%).

Nausea was no more or less common for people allocated to aripiprazole (n=556, 2 RCTs, RR 1.43 CI 0.4 to 5.4) although again data were heterogeneous (I squared 85%). When combined, three trials failed to show any difference between aripiprazole and atypical antipsychotics for the outcome of weight gain of >/= 7% over baseline (n=770, 3 RCTs, RR 0.46 CI 0.2 to 1.0) but data are heterogeneous (I squared 75.9%) and, taken alone, the Kern 2001 study, comparing aripiprazole with olanzapine does implicate the latter in considerable weight gain (n=255, RR 0.24 CI 0.1 to 0.5).

4.2.2 Average change in specific adverse effects
Potkin 2003, comparing different doses of aripiprazole with risperidone, measured mean change in QTc interval (ms) from baseline (high change = poor outcome). Aripiprazole at a dose of 20 mg/day, resulted in significantly less change than risperidone (n=200, 1 RCT, WMD -6.0 CI -13.1 to 1.1). This finding held for higher doses of aripiprazole (30 mg/day) (n=200, 1 RCT, WMD -10.00 CI -16.99 to -3.0).

4.2.3 Physiological (serum) measures
Again only Potkin 2003 reported on the outcome of significant increase in prolactin (above 23 ng/ml). When compared with risperidone, aripiprazole produced significantly less increase in prolactin (n=301, RR 0.04 CI 0.02 to 0.1, NNT 2 CI 1 to 2.5). These are not intention to treat data, as baseline prolactin data was only provided on 91/99 of the participants given atypical antipsychotics and on 181/202 of those given aripiprazole.

4.3 Leaving the study early
Overall 49% of people allocated to aripiprazole left the studies before the end of the trial. This compares with 48% in the comparison groups (n=832, 3 RCTs, RR 1.08 CI 0.96 to 1.2). When adverse effects were cited as the reason for attrition no clear difference between aripiprazole and the other atypicals was apparent (n=618, 2 RCTs, RR 0.78 CI 0.4 to 1.4). The most common adverse effect leading to drop-out was reported as 'psychosis' and 'reactive schizophrenia' in McQuade 2003. We also used these data within the outcome of 'Global state'.

5. COMPARISON 4: ARIPIPRAZOLE versus STANDARD CARE

5.1 Global state
5.1.1 Not responded
Riera 2004, compared differences in response rates of aripiprazole with standard care. The proportion of people who did not respond was significantly higher in the standard care group (medication included zisprasidone, olanzapine, risperidone, quetiapine, clozapine at varying doses)

than those receiving aripiprazole (n=1599, RR 0.70 CI 0.7 to 0.8, NNT 5 CI 4 to 6).

5.2 Satisfaction with treatment - Not satisfied with care
Riera 2004 study, reported that the proportion of people not satisfied with care was significantly higher in the standard care group (n=1599, RR 0.62 CI 0.6 to 0.7, NNT 4 CI 4 to 5) compared with those receiving aripiprazole.

5.3 Leaving the study early - due to any reason
Riera 2004 reported that the number of people who left the study early, for any reason, was significantly lower in the aripiprazole group compared with those who received standard care (n=1599, 1 RCT, RR 0.81 CI 0.7 to 0.9, NNT 13 CI 8 to 39).

Discussion

1. Applicability of findings
Five of the fifteen included studies occurred exclusively in North America and a further study took place in a North American and European setting. Although it could not be determined from the limited descriptions of the remaining nine studies, it is likely that the majority took place in a similar environment, or possibly within a Japanese setting. Clinicians should take this into consideration when thinking of using aripiprazole in very different settings of care.

The majority of trials involved inpatient participants with little in the way of physical and psychiatric co-morbidity and with well-defined schizophrenia or schizoaffective disorder. Such people are a minority in everyday care, where people who are not in hospital and suffer from less well defined illness combined with problems such as depression and substance abuse are the norm. The drugs of comparison used in the trials in this review further limit the applicability of its findings. These were of a nature, or used at such a dose, that they distance these trials from everyday practice even more. The reader is subsequently left with the difficult decision as to whether the findings of studies with such over-defined participants, interventions and outcomes and standardised highly developed inpatient settings can still inform practice.

2. Limited data, confusing data
The collection and quality of the data reported was very variable.

With the exception of a two trials, no studies reported outcomes over 26 weeks and most lasted less than 12 weeks. Aripiprazole is a relatively new compound, so it is not surprising that long term studies are rare at this point but it is to be hoped that they are planned. Even if an intervention works in the short term (by 12 weeks) there is no guarantee that this means that the compound has long term benefits.

Data were often not used because of high drop-out rates. The enormous degree of loss to follow up is common in similar studies of other compounds, but rare in everyday practice. This also casts doubt on the applicability of findings to routine care. The design of the studies is clearly encouraging loss to follow up. People leave for many reasons, often not specified, and their last observation is carried forward to the end. These data, sometimes with an assumption on over 50% of people are, nevertheless, acceptable to the regulatory authorities. Until this ends, pharmaceutical companies will see little reason to change their practices, as compounds such as aripiprazole will gain licenses for clinical use even if 40 to 60% of their data is unavailable. Often the trialists do not have an obligation to follow people up for longer than the period during which they took the medication. One possible consequence of this might be that an extreme adverse reaction to

discontinuation of an intervention, such as death, would go unreported if it occurred a week after the treatment stopped. Data beyond the discontinuation of the medications used within the trial are collected but not reported. This data should be reported since it is not the individual compounds in a trial which are randomised but the intention to give those individual compounds.

Trialists tended to report mean figures without giving standard deviations. This renders averages meaningless and of no use to reviewers.

We found it disappointing that, despite considerable investment in clinical trials, no outcome data were available on death, service outcomes, general functioning, behaviour, engagement with services, economic outcomes and cognitive functioning. The primary outcome of this review was relapse and data were only available on this in the aripiprazole-placebo comparison. Other outcomes were of secondary importance to the reviewers, but we have reported what we can in order to present the most complete data set possible for the reader.

Several trials only reported adverse effects which occurred in at least 5 or 10% of participants which could exclude potentially serious less frequent outcomes. Randomised trials are limited in their ability to highlight important rare outcomes, so further restricting what is reported seems odd. We note that the design of the trials did not limit reporting of positive outcomes to only those that occurred at least 5-10% of the time.

Much of the data were obtained from conference proceedings and posters. This made extraction difficult as results were often summarised. Several studies were multiply reported. Without unique study identifiers this gives the impressions that there are more data than actually exist and facilitates erroneous double counting.

A large number of studies which may have been of use in the review, including a number of Japanese phase II and III studies, could not be included due to lack of data. These, along with some others, were only published on the FDA web site. Unfortunately, we cannot include data from these without the further help of Bristol-Myers Squibb and Otsuka Pharmaceuticals who own the material. We intend to make further attempts to obtain this and other vital information (FDA 2002 b).

3. COMPARISON 1: ARIPIPRAZOLE versus PLACEBO

3.1 Global state

3.1.1 Relapse

Relapse, the primary outcome for this review, was only reported by Carson 2002 b and was defined in one of three ways i. a CGI rating of minimally worse or ii. PANSS rating of moderately severe on hostility or uncooperativeness on two successive days or iii. >/= 20% increase in total PANSS score from randomisation. This implies that these measures of severity of illness are indeed markers of a relapse and secondly that the measures agree on the severity of illness needed to constitute a relapse. We are not sure that these scores on these measures really would constitute what clinicians or recipients of care would call relapse. We think that the ratings listed above would be moderate deterioration rather than an event that would be universally recognised as relapse. Nevertheless, it is genuinely heartening that aripiprazole helps avoid these degrees of deterioration and that the number needed to treat is not very large in either the short or medium term (NNT 5 CI 4 to 8).

3.1.2 Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis

This category constituted patients dropping out of the study due to poor efficacy, those with a deterioration in their mental state and those who developed frank psychosis. There was a significant difference in favour of aripiprazole with regard to this outcome, although the number needed to treat is high (NNT 26 CI 16 to 239).

3.1.3 Needing additional antipsychotic medication
Perhaps it is a little odd that so few people needed 'rescue' antipsychotics in the placebo group and that, essentially the risk of needing such a rescue was similar for those in the active treatment group. Nevertheless it has to be seen as encouraging that this new type of drug does seem to have some antipsychotic activity within these studies.

3.1.4 Needing additional benzodiazepines
There did appear to be significantly less need for benzodiazepine medication in the single study that reported usable outcomes for this comparison for the aripiprazole group (NNT 6 CI 4 to 18). The study used intramuscular medication however and the outcomes were only reported over the short term outcomes of up to 24 hours (Oren 2005).

3.2 Adverse effects
3.2.1 Clinically important specific adverse effects
Overall results from the included studies suggest that with the exception of akathisia which was more common in those treated with aripiprazole, there were no significant differences in reported adverse effects in people taking placebo compared to those taking aripiprazole. No objective rating scales appeared to be used in measuring these symptoms, even though for certain symptoms such as anxiety and extrapyramidal side effects these are commonly used in research. Potkin 2003 did repeatedly find more adverse effects than Carson 2002 b and, although there is nothing in the methods of the papers to suggest this, it may be that the former study used more sensitive measures of adverse effects. Potkin 2003 did seem to suggest that aripiprazole may be associated with extrapyramidal symptoms, vomiting and weight gain. Although no different from placebo, about 17% of people given aripiprazole were also medicated with antiparkinson medication. It was unclear from all studies, both those in this comparison and those including an active control group, how the level of significant weight gain (7 percent) was decided upon. There was no mention of this figure in the methodology section of the included study reports and if it was decided on after the data were inspected, any results would be prone to bias.

3.2.2 Average change in QT interval (ms) from baseline (high=poor)
From these data it does not seem that 20 mg/day or 30 mg/day of aripiprazole affects the heart in this way.

3.2.3 Physiological (serum) measures
All data, mostly from Carson 2002 b, suggest little effect on measures of glucose and lipids. The direct clinical significance of these results is, however, unclear. There did appear to be a significant difference in favour of aripiprazole in terms of the numbers of people with a rise in serum prolactin to at least 23 ng/ml (NNT 14 CI 11 to 50). This may have clinical implications in terms of the problems caused by high prolactin, such as galactorrhoea. However data was missing for baseline mean serum prolactin levels in 8/103 people allocated to placebo and 21/202 people given aripiprazole. We have assumed that these people did not have raised prolactin, but if they did and we were incorrect in our assumption, there would be no clear finding in favour of aripiprazole.

3.3 Leaving the study early
Significantly less people left the aripiprazole group compared with placebo (NNT 12 CI 9 to 25)

for any reason. These data are heterogeneous and if the two studies with the most extreme results are removed (Csernansky 2003, Potkin 2003) data becomes more homogeneous and much less favourable for aripiprazole. We do not see obvious reasons for heterogeneity. However, nearly half of all trial participants chose to leave early. This reflects negatively on study design and means that much of the remaining data is uninformative. Adverse effects did not seem to be a reason for study attrition, although again data were heterogeneous. There is no evidence from these studies that aripiprazole is a major cause of unacceptable short term adverse effects. Results from the updated search provided more accurate data for the Carson 2002 b study, however this did not significantly affect the overall results.

4. COMPARISON 2: ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS

4.1 Global state
4.1.1 Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
We could not identify any data on the outcome of relapse. However, participants who were given aripiprazole were no more likely to leave the study early due to a lack of efficacy or development of psychosis than those treated with a typical antipsychotic drug. In six out of seven included studies the typical drug was haloperidol, in the seventh study it was perphenazine (Kane 2003). These data are homogeneous and do suggest that aripiprazole is an effective agent.

4.1.2 Needing additional antipsychotic medication
There was no suggestion in this single, very short term study of intramuscular aripiprazole that more additional antipsychotic medication was required in those randomised to typical antipsychotic drugs (haloperidol). It was unclear why the dose of haloperidol chosen was 6.5 mg for his study, or how it was clinically decided that an additional dose should be offered.

4.1.3 Needing additional benzodiazepines
Patients randomised to aripiprazole did not require more benzodiazepine medication than those receiving intramuscular haloperidol. Up to 4 mg per 24 hours was permitted in this study.

4.2 Mental state
4.2.1 Treatment response (defined by PANSS or CGI)
In keeping with the global measures, there appeared to be no difference for mental state response when aripiprazole was compared with perphenazine.

4.3 Clinically important specific adverse effects
The adverse effects were those spontaneously reported in at least 5% of people, and, as stated earlier, this method of recording may exclude potentially serious, less frequent outcomes, including death. The comparator drugs used were haloperidol in five studies and perphenazine in one (Kane 2003). There were no differences between aripiprazole and typical antipsychotics for all adverse effects with the exception of akathisia. Also, when compared with haloperidol (10-20 mg/day) less people allocated aripiprazole needed additional antiparkinson drugs (NNT 4 CI 3 to 5), although considering haloperidol's propensity to cause movement disorders (Joy 2004), this is unsurprising. Headache (3 RCTs) was an infrequent event and did not affect those receiving aripiprazole more than the typical group. However, only Kane 2003 was of adequate duration for this event to be meaningfully measured (six weeks), whilst Daniel 2004 and Oren 2005 were 24 hour studies.

Insomnia data were also equivocal and heterogeneous for the two pooled studies by Daniel 2004 and Oren 2005. They both used depot aripiprazole and each study, again, lasting for only 24 hours. The only apparent difference was that Oren 2005 used a dose of 10 mg/day of aripiprazole whilst

Daniel 2004 gave different doses of between 1 and 15 mg/day.

It is usually claimed that new drugs are equally clinically effective as older drugs but have a different and more favourable adverse effect profile. Current data do not suggest that this is true for this new drug.

4.4 Quality of life
It is good to see quality of life ratings in the early studies of a new drug and even better that data are reported in a potentially meaningful way. Most people in both groups did not perceive a good change in their quality of life and no difference could be seen between those given aripiprazole and people allocated perphenazine.

4.5 Leaving the study early
Slightly less than half the people entering these short studies left before completion. Homogeneous data suggests that the older drugs are equally unacceptable to the new compound, aripiprazole, or put another way, the new drug confers no advantage in terms of attrition over the older compounds. When leaving early was attributed to adverse effects again no differences are found, although data are heterogeneous and less easy to interpret.

5. COMPARISON 3: ARIPIPRAZOLE versus OTHER ATYPICAL ANTIPSYCHOTICS

5.1 Global state
5.1.1 Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
Again we could find no figures for relapse. Data on the global state outcome of 'poor compliance with study protocol due to lack of efficacy, deterioration or psychosis' suggest that there were no differences between aripiprazole and olanzapine or risperidone. Added together the data even begin to suggest a finding in favour of the 'older atypicals' (n=618, 2 RCTs, RR 1.76 CI 0.9 to 3.5).

5.2 Adverse effects
5.2.1 Clinically important specific adverse effects
Three studies provided usable data on adverse effects (Kern 2001 and Stock 2005 versus olanzapine, Potkin 2003 versus risperidone). No significant differences were found for any of the listed adverse effects. Current data do not show clear differences between aripiprazole and olanzapine or risperidone. With the exception of headaches, they do suggest that more investigation is necessary. Nausea and insomnia outcomes were equivocal with heterogeneous data, but inspection of the studies did not reveal any clear reason as to why such heterogeneity exists. Weight gain may be less frequent with aripiprazole than olanzapine, although data were heterogeneous. More well designed and reported studies would determine whether this was the case.

5.2.2 Average change in QTc interval (ms) from baseline (high=poor)
This appeared to suggest that both 20 mg and 30 mg of aripiprazole produced less change in QTc interval than 6 mg risperidone. There is currently no evidence that aripiprazole causes problems for this aspect of cardiac function.

5.2.3 Physiological (serum) measures
Aripiprazole, at least when compared with risperidone, does not raise levels of prolactin. It is unclear what clinical implications this may have, as problems secondary to elevated prolactin levels are not commonly reported with risperidone as compared to other antipsychotic medications.

5.3 Leaving the study early
Almost 50% of people in these studies did not complete the short trials. The fact that the studies were equally unacceptable to people allocated to aripiprazole and the comparison drugs is little consolation. Data from studies where huge levels of attrition are deemed acceptable are meaningless and clinicians and recipients of care are left with no information upon which to base decisions. The much lower attrition due to adverse effects was also essentially the same for both groups.

6. COMPARISON 4: ARIPIPRAZOLE versus STANDARD CARE

6.1 Global state
6.1.1 Not responded
Only one study (Riera 2004) provided data for the comparison of aripiprazole and standard care. Response rate, dichotomised to those who were considered not to have responded, did significantly favour aripiprazole NNT 5 CI 4 to 6 (54% versus 78% not responded for the standard care group). This result, although encouraging does leave unanswered questions on the accuracy of the result because the standard care group were given either typical or atypical antipsychotics (zisprasidone, olanzapine, risperidone, quetiapine, clozapine at varying doses) and the study was open label.

6.2 Satisfaction with treatment - Not satisfied with care
Riera 2004, also reported on satisfaction which we dichotomised to not satisfied with care. Results were significantly in favour of aripiprazole compared with the standard care group NNT 4 CI 4 to 5. However, again some doubt remains as this was open label with the control group receiving different medication and perhaps if the control group had all received the same drug the size affect may have been different.

6.3 Leaving the study early - due to any reason
Attrition rates from the Riera 2004 study did significantly favour aripiprazole with 35% leaving early compared with 43% in the standard care group NNT 13 CI 8 to 39. Here again doubts remain given the lack of blinding and mixed comparator group which is a pity given these positive results for aripiprazole compared with standard care, especially as this study was by far the largest, randomising an impressive 1599 participants.

Reviewers' conclusions

Implications for practice

1. For people with schizophrenia

Aripiprazole is not clearly different from typical antipsychotics or other atypical antipsychotics in terms of global outcomes or mental state ratings. It does appear to produce a similar degree of adverse effects including movement problems but does not seem to cause the excessive production of prolactin, which can cause unpleasant breast pain and secretion; an adverse effect commonly seen with the older drugs and even some of the new generation atypicals. Aripiprazole may not cause conductance problems in the heart. It may, however, cause less akathisia than typical antipsychotics, and less need for antiparkinson medication. There are far too few data to base any conclusions on, but it would appear that aripiprazole is a new but somewhat unremarkable antipsychotic. The overall findings of this update are unchanged from those found in the original review.

2. For clinicians

Aripiprazole is as effective as typical and atypical antipsychotics for schizophrenia, although data are far too few to allow any confident conclusions to be drawn. Aripiprazole does not offer significant advantages over these two classes of drugs in terms of outcomes with the exception of causing less hyperprolactinaemia and rises in QTc interval than risperidone. More studies are needed to replicate and validate these findings. Aripiprazole may be the first of a new generation of atypical drugs but its clinical effects do not seem to be very different from those of older drugs.

3. For managers/policy makers

Aripiprazole is yet another new antipsychotic drug and it does seem to have an effect on some people with serious mental illnesses. There is currently insufficient clinical evidence to support the claim that aripiprazole is superior to either typical or atypical antipsychotics in respect of treatment response, efficacy or tolerability. Despite the fact that thousands of people have been randomised in trials of aripiprazole, there are no data on service outcomes and few medium or long term data. In the context of finite resources, the lack of good quality data leaves managers and policy makers with difficult decisions to make.

Implications for research

1. General

As with all similar studies, public registration of a study before anyone is randomised would ensure that participants could be confident that people would know that the study had at least taken place. Unique study numbers would help researchers to identify single studies from multiple publications and reduce the risk of duplicating the reporting of data. Compliance with CONSORT (Moher 2001), both on the part of authors and editors, would help to clarify methodology and many outcomes. Failure to comply results in both loss of data and confusion in the results, neither of which help clinicians, patients or managers.

Intention-to-treat analysis should be performed on all outcomes and all trial data should be made easily accessible. A minimal requirement should be that all data should, at least, be presented as numbers. In addition, continuous data should be presented with means, standard deviations (or standard errors) and the number of participants. Data from graphs, 'p' values of differences and statements of significant or non-significant differences are of limited value. Unfortunately, in spite of the large numbers of participants randomised, we were unable to use most of the data in the trials included in this review due to the high drop-out rates observed as well as poor data reporting.

2. Specific
As an antipsychotic agent with a novel mechanism of action, aripiprazole is an interesting compound, but pragmatic, real world, randomised controlled trials should be carried out to determine its value in standard clinical practice. Studies of medium and long-term risks, including mortality, behaviour, satisfaction with treatment and cost-effectiveness-in comparison to typical and atypical antipsychotics, are a priority. Pragmatic entry criteria and non-blinding with hard endpoints may be helpful in decreasing the study attrition (Roland 1998).

Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Adson 2003	Allocation: randomised. Blindness: double (in treatment responders). Duration: 6 weeks, preceded by > 2 day wash-out period. Design: parallel, multicentre. Setting: hospital, North America. Consent: not described. Loss: described.	Diagnosis: schizophrenia (DSM-IV). N=420. Age: over 18, average ~ 41 years. Sex: M 327, F 93. History: acute relapse, response to previous neuroleptics other than clozapine, outpatient >3 months in past year, PANSS total > 60, and > 4 on 2 defined PANSS criteria. Exclusions: pregancy, lactation, schizoaffective disorder, organic, bipolar disorders, hospitalisation for 14 days prior to screening, substance dependence within 3 months, suicide risk, unstable thyroid pathology, history of neuroleptic malignant syndrome, history of unstable medical condition.	1. Aripiprazole: dose 10 mg/day. N=106. 2. Aripiprazole: dose 15 mg/day. N=106. 3. Aripiprazole: dose 20 mg/day. N=100. 4. Placebo. N=108.	Leaving the study early. Unable to use - Death: suicide and natural causes (incomplete data). Mental state: PANSS total , PANSS-derived BPRS core score, PANSS negative score (no SDs).	Greater than 60% discontinuation rate. Patients not responding by week 3 were offered open-label aripiprazole for weeks 4-6. Original protocol amended to provide two secondary outcome criteria. Data reported in both OC and LOCF analyses. Jadad=2.	B
Carson 2000 a	Allocation: randomised, method not described. Blindness: double, no further details. Duration: 4 weeks, preceded by > 5 day washout period.	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N=414. Age: mean~39 years. Sex: M 288, F 126.	1. Aripiprazole: dose 15 mg/day. N=102. 2. Aripiprazole: dose 30 mg/day. N=102. 3. Haloperidol: dose 10 mg/day. N=104.	Leaving the study early Unable to use - Death: suicide and natural causes (incomplete data). Global state: CGI (no SDs).	Overall 40% discontinuation rate. No information given on standard deviations. Data reported in both OC and LOCF analyses.	B

	Design: parallel, multicentre. Setting: hospital, USA. Consent: obtained. Loss: described.	History: acute relapse, mean age at first episode ~22 years, mean number of previous hospitalisations ~10. Exclusions: other psychiatric disorders, history of violence or suicidal ideation/self harm, significant neurological abnormality, psychoactive drug or alcohol abuse/dependence, recent treatment with an investigational drug.	4. Placebo. N=106.	Mental state: BPRS, BPRS-PANSS derived (no SDs). General functioning: CGI (no SDs). Adverse effects: SAS, Barnes Akathisia scale, Abnormal Involuntary Movement scale, other outcome measures including changes in body weight, serum prolactin, and QTc interval changes (no usable/standard deviation data).	Jadad=2.	
Carson 2002 b	Allocation: randomised, method not described. Blindness: double, no further details. Duration: 26 weeks, preceded by 3-14 day washout period. Design: parallel, multicentre. Setting: mixed in and out patients, multi-national. Consent: not described. Loss: not described.	Diagnosis: schizophrenia. N=310. Age: mean ~ 42 years. Sex: M 174, F 136. History: chronic stable, no significant worsening of symptoms in past 3 months, diagnosis for > 2 years, baseline PANSS score mean ~ 82. Exclusions: not described.	1. Aripiprazole: dose 15 mg/day. N=155. 2. Placebo. N=155.	Global state: relapse. Adverse effects: adverse events above 10%, weight gain >7%, fasting plasma glucose >/=110 mg/dl, Hb 1AC >/= upper limit of normal, clinically significant laboratory measurements. Leaving the study early. Unable to use - Global state: CGI (no SDs). Mental state: PANSS, PANSS-derived BPRS (no SDs). Adverse effects: change in weight, change in serum prolactin, SAS, AIMS, Barnes Akathisia rating scale, change in QTc	Limited data given on standard deviations. Different numbers of patients were analysed for efficacy and safety characteristics. Jadad=2.	B

				interval, change in fasting plasma glucose, change in Hb 1AC from baseline (no usable/SDs).		
Csernansky 2003	Allocation: randomised, method not described. Blindness: double. Duration: 4 weeks, preceded by 3-7 day placebo washout period. Design: parallel, multicentre. Setting: inpatient, USA. Consent: not described. Loss: described.	Diagnosis: schizophrenia (DSM-III-R). N=103. Age: 18-65 years, average ~36. Sex: M 91, F 12. History: acute relapse, BPRS score >30 & score of >4 on 2 of 4 positive symptoms, evidence of previous response to antipsychotic medication. Exclusions: >moderate motor symptoms as measured by SAS, AIMS and Barnes Akathisia scale, other primary diagnoses, substance dependence within 2 months, cardiac patients, acute/unstable medical conditions.	1. Aripiprazole (OPC-14597): dose 5 mg/day 1+2, 10 mg/day 3+4, 15 mg/day 5+6, 20 mg/day 7-12, 30 mg/day 13-28. N=34. 2. Haloperidol: dose 5 mg/day 1+2, 10 mg/day 3+4, 15 mg/day 5+6, 20 mg/day 7-12, 20 mg/day 13-28. N=34. 3. Placebo. N=35.	Leaving the study early. Unable to use - Mental state: BPRS (no SDs). Global state: CGI (no usable data).	Overall 48.5% discontinuation rate. Limited information on standard deviations. Considered a 'negative' study by the FDA. Data reported in OC and LOCF analyses. Jadad=2.	B
Daniel 2000	Allocation: randomised, method not described. Blindness: double. Duration: 4 weeks, preceded by 3-7 day washout period. Design: parallel, multicentre. Setting: inpatient. Consent: not described. Loss: described.	Diagnosis: schizophrenia (DSM-IV). N=307. Age: 18-65 years, average ~38. Sex: M 247, F 60. History: acute relapse, BPRS score >36 & score of > 2 on 4 criteria, antipsychotic medication taken for >72	1. Aripiprazole: dose 2 mg/day. N=59. 2. Aripiprazole: dose 10 mg/day. N=60. 3. Aripiprazole: dose 30 mg/day. N=61. 4. Haloperidol: dose 10 mg/day after 5 mg/day 1+2). N=63. 5. Placebo. N=64.	Leaving the study early. Unable to use - Global state: CGI (no SDs). Mental state: BPRS, PANSS (no SDs). Adverse effects: reported adverse effects, extra-pyramidal side effects, mean weight gain, mean	Over 40% overall discontinuation rate. No data given on standard deviations. Marked sex differential in participants. Data reported in both LOCF and OC analyses. Jadad=2.	B

		hours prior to randomisation. Exclusions: first episode of schizophrenia, refractory to antipsychotics, moderate to severe EPS, dyskinesia or akathisia, substance abuse, cardiac disease, acute or unstable medical condition, pregnancy, lactation, women not using adequate contraception.		prolactin levels (no usable data).		
Daniel 2004	Allocation: randomised, method not described. Blindness: double. Duration: 24hrs. Design: parallel, multicentre. Setting: inpatient. Consent: not described. Loss: described.	Diagnosis: schizophrenia, schizoaffective disorder, schizophreniform disorder. N=357*. Age: not described. Sex: not described. History: acute agitation. Exclusions: not described.	1. Aripiprazole IM: dose 1 mg/day. N=57 2. Aripiprazole IM: dose 5 mg/day. N=62 3. Aripiprazole IM: dose 10 mg/day. N=56 4. Aripiprazole IM: dose 15 mg/day. N=58 5. Haloperidol IM: dose 7.5 mg/day. N=60 6. Placebo IM. N=62	Global state: poor compliance with study protocol due to lack of efficacy, deterioration, or psychosis. Leaving the study early. Adverse effects: reported in > 5% participants, extrapyramidal symptoms. Unable to use - Behaviour: PEC score- mean change (no SD), CAB score- mean change (no SD), ACES- (no SD), response- >40% reduction in PEC score (unvalidated sub-scale), requiring additional dose of antipsychotic medication, benzodiazepines (incomplete data).	*Two participants not accounted for. Limited data reported on standard deviations. Data reported in LOCF analyses. Jadad=2. Only adverse effects occurring in over 5% participants recorded. Not all outcomes reported at 24hrs.	B
Kane 2003	Allocation: randomised, method not described.	Diagnosis: schizophrenia (DSM-IV).	1. Aripiprazole: dose 15-30 mg/day, average dose 28.8	Leaving the study early. Mental state: response.	Limited data given on standard deviations.	B

	Blindness: double (during treatment phase). Duration: 6 weeks, preceded by 14 day patient screening, 2 day neuroleptic washout, 4-6 weeks confirmation of treatment resistance, 2-10 day neuroleptic washout. Design: multicentre, parallel. Setting: unknown. Consent: not described. Loss: described.	N=300. Age: mean ~42.1 years. Sex: M 208, F 92. History: treatment resistant, mean age at first hospitalisation 23 years, PANSS total score of > 75 & score of > 4 on 2 or more specified PANSS items; CGI severity of illness score > 4. Exclusions: refractory to previous clozapine therapy, prior perphenazine treatment without adequate response.	mg/day. N=154. 2. Perphenazine: dose 8-64 mg/day, average dose 39.1 mg/day. N=146.	Adverse effects. Quality of life: QLS scores. Unable to use - Mental state: PANSS-derived BPRS (no SDs). Adverse affects: AIMS, Barnes Akathisia, SAS, mean prolactin levels, ECG changes, vital signs, body weight (no usable data/SDs).	Data reported in both LOCF and OC analyses. Jadad=2.	
Kern 2001	Allocation: randomised, method not described. Blindness: open-label. Duration: 26 weeks. Design: multicentre, parallel. Setting: outpatient. Consent: not described. Loss: not described.	Diagnosis: schizophrenia or schizoaffective disorder. N=256*. Age: 18-65 years, average ~40 years. Sex: M 164, F 92. History: chronic stable, not hospitalised for > 2 months prior to randomisation, previously on stable dose of antipsychotic for > 2 months. Exclusions: not described.	1. Aripiprazole: dose 30 mg/day. N=128. 2. Olanzapine: dose 15 mg/day, after 10 mg/day 1-7. N=127.	Adverse effects: spontaneously reported adverse effects occurring in >10%, clinically significant weight gain. Unable to use - Adverse effects: mean change in weight, median change in serum cholesterol (no SDs). Cognitive functioning: California Verbal Learning test, Benton visual retention test, Winsconsin card sorting test, Trail making A and B, Continuous performance test, Verbal Fluency, Letter-number sequencing from the WAIS III, Grooved pegboard test (no	*One participant not accounted for. No information given on standard deviations. Only adverse effects occurring in over 10% of participants recorded. Data reported in both LOCF and OC analyses. Jadad=2.	B

				usable/SDs).		
Kujawa 2002	Allocation: randomised, method not described. Blindness: double. Duration: 52 weeks (preceded by variable washout period->5 days). Design: parallel, multicentre. Setting: unknown, USA and Europe. Consent: described. Loss: described.	Diagnosis: schizophrenia (DSM-IV). N=1294. Age: 18-65, average ~37 years. Sex: M 758, F 536. History: acute exacerbation, baseline PANSS of >60, history of prior response to antipsychotic medication, history of outpatient treatment for at least 3 months in the past year. Exclusions: pregnancy and lactation, treatment resistance, suicidal ideation, initial episode of schizophrenia, other psychiatric or neurological disorder, substance dependence, concomitant medication that interferes with metabolism, recent study participants.	1. Aripiprazole: dose 30 mg/day, with possibility of one-off dose decrease to 20 mg for tolerability. N=861. 2. Haloperidol: dose 10 mg/day, with possibility to decrease to 7 mg for tolerability. N=433.	Leaving the study early. Unable to use - Global state: CGI (no usable data). Mental state: PANSS total score, PANSS negative subscale score, MADRS total score, PANSS depression item, PANSS depression/anxiety cluster, PANSS negative subscale score (no SDs). Adverse effects: SAS, Barnes Akathisia rating scale, AIMS, body weight, serum prolactin levels, vital signs, EKG changes (no usable/no SDs).	Greater than 60% discontinuation rate. Limited data on standard deviations given. Different patient numbers analysed for safety and efficacy. Data reported in both LOCF and OC analyses. Jadad=2.	B
Marcus 2005	Allocation: randomised, method not described. Blindness: double. Duration: 6 weeks. Design: parallel, multicentre. Setting: hospital, USA. Consent: not described. Loss: not described.	Diagnosis: schizophrenia. N=367. Age: unknown. Sex: unknown. History: acute relapse. Exclusions: not described.	1. Aripiprazole: dose 2 mg/day. N=93. 2. Aripiprazole: dose 5 mg/day. N=92. 3. Aripiprazole: dose 10 mg/day. N=94. 4. Placebo. N=88.	Leaving the study early. Unable to use - Global state: CGI (no SD). Mental state: PANSS (no SD), time to response (defined by CGI and PANSS) (no usable data). Adverse effects: self-reported	Greater than 40% discontinuation rate. Limited data on standard deviations given. Data reported in LOCF analyses. Jadad=2.	B

				>5% participants (no usable data).		
McQuade 2003	Allocation: randomised, method not described. Blindness: double. Duration: 26 weeks. Design: parallel, multi-centre. Setting: unknown. Consent: not described. Loss: described.	Diagnosis: schizophrenia. N=317. Age: average ~38 years. Sex: M 229, F 88. History: acute relapse, mean age at first episode ~25 years, mean time since current acute episode began ~21 days. Exclusions: not described.	1. Aripiprazole: dose 15-30 mg/day. N=156. 2. Olanzapine: dose 10-20 mg/day. N=161.	Leaving the study early. Unable to use - Global state: CGI (no usable data). Mental state: PANSS total score (no SDs). Adverse effects: mean change in weight (no SDs), clinically significant weight gain, serum prolactin, EPS, plasma lipids outside normal limits (no usable data).	Greater than 60% discontinuation rate. No data on standard deviations reported. Jadad=2.	B
Oren 2005	Allocation: randomised, method not described. Blindness: double. Duration: 24 hours. Design: parallel, multicentre. Setting: hospital. Consent: not described. Loss: described.	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N=448. Age: >/=18 years. Sex: unknown. History: acute agitation, voluntarily hospitalised, able to comply and comprehend protocol, PEC score of >/=15 and </=32, and at least 2 components >/=4(moderate). Exclusions: not described.	1. Aripiprazole IM: dose 10 mg/day. N=175. 2. Placebo IM. N=88. 3. Haloperidol IM: dose 6.5 mg/day. N=185. Allowed concomitant medication of up to 4 mg lorazepam or equivalent.	Global state: poor compliance with study protocol due to lack of efficacy, deterioration, or psychosis, requiring additional dose of antipsychotic medication, benzodiazepines. Leaving the study early. Adverse effects: reported in > 5% participants, extrapyramidal symptoms Unable to use - Global state: CGI (no SD) Behaviour: PEC score- mean change (no SD), CAB score- mean change (no SD), ACES- (no data), response-	Limited information given on standard deviations. Data was analysed in LOCF. Jadad=2. Adverse effects reported occurring in >/=5% participants. Not all outcomes recorded over 24 hrs.	B

				>40% reduction in PEC score (unvalidated sub-scale).		
Potkin 2003	Allocation: randomised, method not described. Blindness: double. Duration: 4 weeks, preceded by 5 day placebo washout period. Design: parallel, multicentre. Setting: hospital, USA. Consent: described. Loss: described.	Diagnosis: schizophrenia or schizoaffective disorder (DSM-IV). N=404. Age: 18-65 years, average ~39. Sex: M 283, F 121. History: acute relapse, responsive to antipsychotic medication other than clozapine, outpatient for > 3 months in past year, PANSS > 60 & score > 2 on psychotic symptom subscale, adequate time interval since receiving previous anti-psychotic. Exclusions: other psychiatric disorders requiring medication, history of violence, suicidal attempts or ideation, significant neurological abnormality, alcohol/psychoactive substance misuse within 1 month of study start, treatment with investigational drug within 4 weeks of washout phase, unstable/acute medical conditions, pregnancy, lactation.	1. Aripiprazole: dose 20 mg/day. N=101. 2. Aripiprazole: dose 30 mg/day. N=101. 3. Risperidone: dose 2 mg day 1, 4 mg day 2, 6 mg/day thereafter. N=99. 4. Placebo. N=103.	Leaving the study early Adverse effects: self-reported >5% participants, mean change in body weight, mean change in serum prolactin, mean change in QTc interval. Unable to use - Global state: CGI- much, or very much improved (no SD). Mental state: PANSS - 30% decrease in baseline score, PANSS-derived BPRS (no SD). Adverse effects: SAS, Barnes Akathisia Rating scale, AIMS, vital signs (no usable data/SD).	Overall 40% discontinuation rate. No information given on standard deviations. Data was analysed in terms of OC and LOCF. Jadad=2.	B

Riera 2004	Allocation: randomised (4:1 ratio), method not described. Blindness: open-label. Duration: 8 weeks. Design: parallel, multicentre. Setting: outpatient. Consent: not described. Loss: not described.	Diagnosis: schizophrenia or schizoaffective disorder. N=1599. Age: mean ~41.9 years. Sex: M 825, F 774. History: initiation of new medication required or if alteration in medication is reasonable. Exclusions: not described.	1. Aripiprazole dose 15-30 mg/day (mean~19.9 mg/day). N=1295. 2. Standard care. N=304.	Global state: response-CGI-I- score of 1 (much improved) or 2 (very much improved). Leaving the study early. Unable to use - Global state: IAQ (physician-rated). Adverse effects: (no usable data). Satisfaction with treatment: POMS (unvalidated scale).	Data analysed in terms of LOCF and OC. Patients randomised to standard care and not to individual treatments in control group- which were physician-selected and prone to bias. Little data on standard deviations provided. Little data provided on outcomes for comparator group.	B
Stock 2005	Allocation: randomised. Blindness: open label. Duration: 52 weeks. Design: parallel, multicentre. Setting: not described. Consent: described. Loss: described.	Diagnosis: schizophrenia. N=214. Age: average ~41.5 yrs. Sex: M 116, F 98. History: extension phase of earlier trial (Carson 2002b); completed (n=112) 26 week trial of aripiprazole in stabilised patients with chronic schizophrenia, or in relapse (n=102) after at least 2 weeks of double-blind treatment. Exclusions: not described.	1. Aripiprazole: dose 15-30 mg/day. N=104. 2. Olanzapine: dose 10-20 mg/day. N=110.	Leaving the study early. Adverse effects: self reported >5% participants, clinically significant weight gain (>7% body weight). Unable to use - Global state: CGI (no usable data). Mental state: PANSS (no SD). Adverse effects: BAS, SAS, AIMS (no usable data), mean change in body weight, total cholesterol, fasting LDL cholesterol (no SD), serum glucose, prolactin (no data).	Data analysed in terms of LOCF and OC. Heterogenous patient group. Adverse effects reported occurring in >5% participants.	B

DSM-IV - Diagnostic and Statistical Manual Edition IV
LOCF - Last observation carried forward
OC - Observed cases

IAQ- Investigator's Assessment Questionnaire

Behavioural -
ACES- Agitation-calmness behaviour scale
CAB- Corrigan agitated behaviour scale

Global state -
CGI - Clinical global impression
CGI-I- CGI- improvement scale
CGI-S- CGI severity of illness score

Mental state -
BPRS - Brief psychiatric rating scale
MADRS - Montgomery and Asberg Depression Rating Scale
PANSS - Positive and Negative Symptom Scale
PEC- PANSS excited component scale
POMS- Preference of Medication Questionnaire

Adverse events -
AIMS - Abnormal involuntary movement scale
EKG/ECG - Electrocardiogram
SAS - Simpson Angus scale

Quality of Life -
QLS - Quality of life scale

Characteristics of excluded studies

Study ID	Reason for exclusion
Auby 2002	Allocation: randomised. Participants: people with stable schizophrenia or schizoaffective disorder. Interventions: aripiprazole at multiple doses - no other comparator drug. Outcomes: no usable data.
Carson 2002 a	Allocation: not randomised, review.
Casey 2003	Allocation: randomised. Participants: people with schizophrenia or schizoaffective disorder. Intervention: aripiprazole at different regimens - no other comparator drug.
Kujawa 2003	Allocation: randomised, review article.
Mallikaarjun 2000	Allocation: randomised. Participants: healthy volunteers.
Marcus 2003	Allocation: not randomised, review.
Petrie 1997	Allocation: not randomised, review.
Saha 2004	Allocation: randomised. Participants: first episode of schizophrenia or schizoaffective disorder occurring within 1 year of study. Interventions: aripiprazole at multiple doses- no other comparator drug.
Stroup 2003	Allocation: not randomised.

Characteristics of ongoing studies

Study ID	Trial name	Participants	Interventions	Outcomes	Starting date	Contact info	Notes
Study 138001a	138001 extension	Diagnosis: schizophrenia. N=no information. Age: adults > 18 years. Sex: no information. History: completed acute phase study 138001 & treatment must be indicated for continuation. Exclusions: no information.	1. Aripiprazole: doses unclear	No information.	No information.	No information.	Dosing to continue until December 2002 or whenever aripiprazole is available.
Study 138002a	138002 extension	Diagnosis: schizophrenia. N=no information. Age: adults > 18 years. Sex: no information. History: completed 12 week acute study 138002 & responded to treatment. Exclusions: no information.	1. Aripiprazole: 15mg/day 2. Aripiprazole: 20mg/day. 3. Aripiprazole: 30mg/day. 4. Olanzapine: 10mg/day. 5. Olanzapine: 15mg/day. 6. Olanzapine: 20mg/day.	No information.	No information.	No information.	Dosing to continue until December 2002 or whenever aripiprazole is available.
Study 138003	138003	Diagnosis: acute schizophrenia (DSM-IV). N=704. Age: adults 18-65 years. Sex: no information.	1. Aripiprazole: 15mg/day 2. Aripiprazole: 20mg/day. 3. Aripiprazole: 30mg/day. 4. Olanzapine:	No information.	No information.	No information.	26 weeks.

		History: acute relapse, history of response to neuroleptic treatment other than clozapine. Exclusions: no information.	10mg/day. 5. Olanzapine: 15mg/day. 6. Olanzapine: 20mg/day.				
Study 138032	138032	Diagnosis: treatment-resistant schizophrenia (DSM-IV). N=300. Age: adults > 18 years. Sex: no information. History: no information. Exclusions: no information.	1. Aripiprazole: 15mg/day 2. Aripiprazole: 30mg/day. 3. Perphenazine: 8-64mg/day.	No information.	No information.	No information.	Maximum of 104 weeks.
Study 138047a	138047 extension	Diagnosis: schizophrenia N=no information. Age: adults > 18 years. Sex: no information. History: patients have completed acute study 138047 or who have relapsed after a minimum 2 weeks dosing on study 138047. Exclusions: no information.	1. Aripiprazole: 15-30mg/day. 2. Olanzapine: 10-20 mg/day.	No information.	No information.	No information.	52 weeks.

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{published data only}

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Study 97301

{published data only}

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** indicates the primary reference for the study*

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Table of comparisons

07 insomnia
08 nausea
06 Quality of life: No clinically important improvement in quality of life (defined by QLS score)
07 Leaving the study early
01 due to any reason
02 due to adverse effects
03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
01 Global state: Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis
02 Adverse effects: 1. Clinically important specific adverse effects
01 anxiety
02 extrapyramidal symptoms - akathisia
03 extrapyramidal symptoms - general
04 headache
05 insomnia
06 nausea
07 weight gain >/= 7% over baseline
03 Adverse effects: 2. Average change in QTc interval (ms) from baseline
01 Aripiprazole 20mg/day
02 Aripiprazole 30mg/day
04 Adverse effects: 3. Physiological (serum) measures
01 significant increase in prolactin above 23ng/ml
05 Leaving the study early
01 due to any reason
02 due to adverse effects
04 ARIPIPRAZOLE versus STANDARD CARE
01 Global state: Not responded
02 Satisfaction with treatment: Not satisfied with care
03 Leaving the study early
01 due to any reason

Notes

Unpublished CRG notes

Exported from Review Manager 4.2.7

Published notes

In May 2006 one author (H E-S) and editor (CEA) met with representatives of Bristol-Myers Squibb Pharmaceuticals Limited. These representatives were most helpful in clarifying data on the FDA website specifically on death and encouraging the reviewers to ask for more data. We have amended this version and hope to do so again in light of more data provided by industry, especially on those studies that await assessment.

Amended sections

Cover sheet
Synopsis
Abstract
Background
Objectives
Criteria for considering studies for this review
Search strategy for identification of studies
Methods of the review
Description of studies
Methodological quality of included studies
Results
Discussion
Reviewers' conclusions
Acknowledgements
Potential conflict of interest
References to studies
Other references
Characteristics of included studies
Characteristics of excluded studies
Characteristics of ongoing studies
Comparisons, data or analyses

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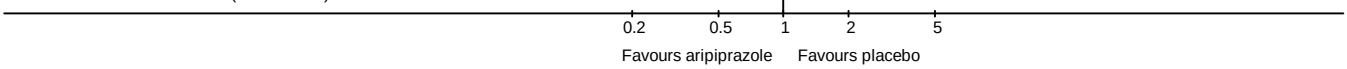
Review: Aripiprazole for schizophrenia (For publication)

Total number of included studies: 15

Comparison or outcome	Studies	Participants	Statistical method	Effect size
01 ARIPIPRAZOLE versus PLACEBO				
01 Global state: 1. Relapse	2	620	RR (random), 95% CI	0.63 [0.53, 0.74]
02 Global state: 2. Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis	8	2275	RR (random), 95% CI	0.72 [0.53, 0.97]
03 Global state: 3. Needing additional antipsychotic medication	4	1062	RR (random), 95% CI	0.70 [0.55, 0.88]
04 Global state: 4. Needing additional benzodiazepines	1	263	RR (random), 95% CI	0.41 [0.21, 0.80]
05 Adverse effects: 1. Clinically important specific adverse effects	28	8046	RR (random), 95% CI	1.08 [0.92, 1.26]
06 Adverse effects: 2. Average change in QTc interval (ms) from baseline	2	408	WMD (random), 95% CI	0.99 [-3.38, 5.37]
07 Adverse effects: 3. Physiological (serum) measures	5	1545	RR (random), 95% CI	0.93 [0.75, 1.14]
08 Leaving the study early	18	5170	RR (random), 95% CI	0.73 [0.61, 0.88]
02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS				
01 Global state: 1. Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis	7	2868	RR (random), 95% CI	1.15 [0.95, 1.38]
02 Global state: 2. Needing additional antipsychotic medication	1	360	RR (random), 95% CI	0.92 [0.72, 1.17]
03 Global state: 3. Needing additional benzodiazepines	1	360	RR (random), 95% CI	0.67 [0.36, 1.27]
04 Mental state: Treatment response (defined by CGI or PANSS)	1	300	RR (random), 95% CI	1.23 [0.81, 1.87]
05 Adverse effects: Clinically important specific adverse effects	18	6339	RR (random), 95% CI	0.65 [0.45, 0.95]
06 Quality of life: No clinically important improvement in quality of life (defined by QLS score)	1	300	RR (random), 95% CI	0.88 [0.78, 1.00]
07 Leaving the study early	14	5736	RR (random), 95% CI	0.81 [0.64, 1.01]
03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS				
01 Global state: Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis	2	618	RR (random), 95% CI	1.76 [0.87, 3.54]
02 Adverse effects: 1. Clinically important specific adverse effects	19	4921	RR (random), 95% CI	1.13 [0.85, 1.49]
03 Adverse effects: 2. Average change in QTc interval (ms) from baseline	2	400	WMD (random), 95% CI	-8.03 [-13.02, -3.05]
04 Adverse effects: 3. Physiological (serum) measures			RR (random), 95% CI	Subtotals only
05 Leaving the study early	5	1450	RR (random), 95% CI	1.06 [0.95, 1.20]
04 ARIPIPRAZOLE versus STANDARD CARE				
01 Global state: Not responded	1	1599	RR (random), 95% CI	0.70 [0.65, 0.75]
02 Satisfaction with treatment: Not satisfied with care	1	1599	RR (random), 95% CI	0.67 [0.62, 0.73]
03 Leaving the study early			RR (random), 95% CI	Subtotals only

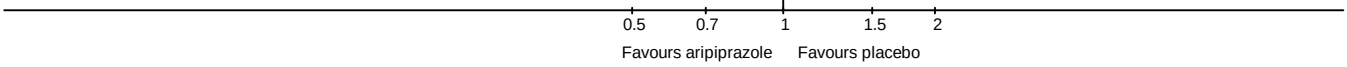
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 01 Global state: 1. Relapse

Study or sub-category	Aripiprazole n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 short term					
Carson 2002 b	50/155	85/155		38.54	0.59 [0.45, 0.77]
Subtotal (95% CI)	155	155		38.54	0.59 [0.45, 0.77]
Total events: 50 (Aripiprazole), 85 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 3.86 (P = 0.0001)					
02 medium term					
Carson 2002 b	67/155	102/155		61.46	0.66 [0.53, 0.81]
Subtotal (95% CI)	155	155		61.46	0.66 [0.53, 0.81]
Total events: 67 (Aripiprazole), 102 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 3.86 (P = 0.0001)					
Total (95% CI)	310	310		100.00	0.63 [0.53, 0.74]
Total events: 117 (Aripiprazole), 187 (Placebo)					
Test for heterogeneity: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%					
Test for overall effect: Z = 5.43 (P < 0.00001)					



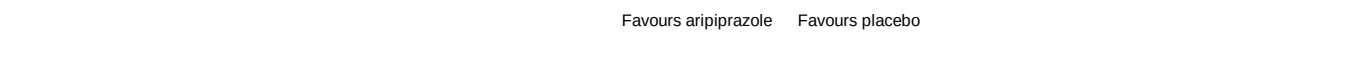
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 02 Global state: 2. Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis

Study or sub-category	Aripiprazole n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Adson 2003	24/312	11/108		13.49	0.76 [0.38, 1.49]
Carson 2000 a	30/204	16/106		17.07	0.97 [0.56, 1.70]
Csernansky 2003	8/34	15/35		12.57	0.55 [0.27, 1.12]
Daniel 2000	24/180	20/64		18.47	0.43 [0.25, 0.72]
Daniel 2004	1/235	1/62		1.22	0.26 [0.02, 4.16]
Marcus 2005	49/279	12/88		16.26	1.29 [0.72, 2.31]
Oren 2005	0/175	1/88		0.92	0.17 [0.01, 4.10]
Potkin 2003	32/202	23/103		20.01	0.71 [0.44, 1.15]
Total (95% CI)	1621	654		100.00	0.72 [0.53, 0.97]
Total events: 168 (Aripiprazole), 99 (Placebo)					
Test for heterogeneity: Chi² = 10.76, df = 7 (P = 0.15), I² = 35.0%					
Test for overall effect: Z = 2.12 (P = 0.03)					



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 03 Global state: 3. Needing additional antipsychotic medication

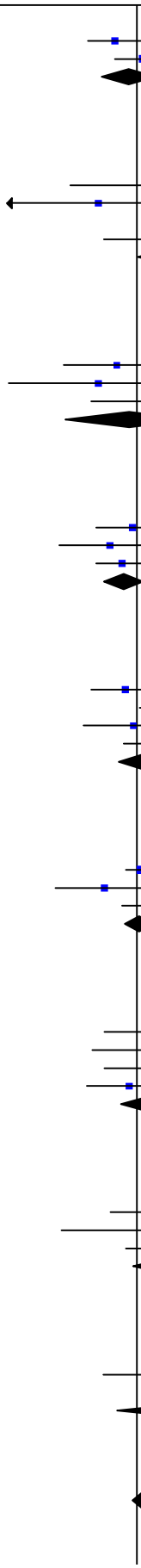
Study or sub-category	Aripiprazole n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Adson 2003	12/312	6/108		6.01	0.69 [0.27, 1.80]
Carson 2000 a	9/204	9/106		6.87	0.52 [0.21, 1.27]
Csernansky 2003	4/35	1/34		1.20	3.89 [0.46, 33.02]
Oren 2005	71/175	51/88		85.93	0.70 [0.54, 0.90]
Total (95% CI)	726	336		100.00	0.70 [0.55, 0.88]
Total events: 96 (Aripiprazole), 67 (Placebo)					
Test for heterogeneity: Chi² = 2.91, df = 3 (P = 0.41), I² = 0%					
Test for overall effect: Z = 2.99 (P = 0.003)					



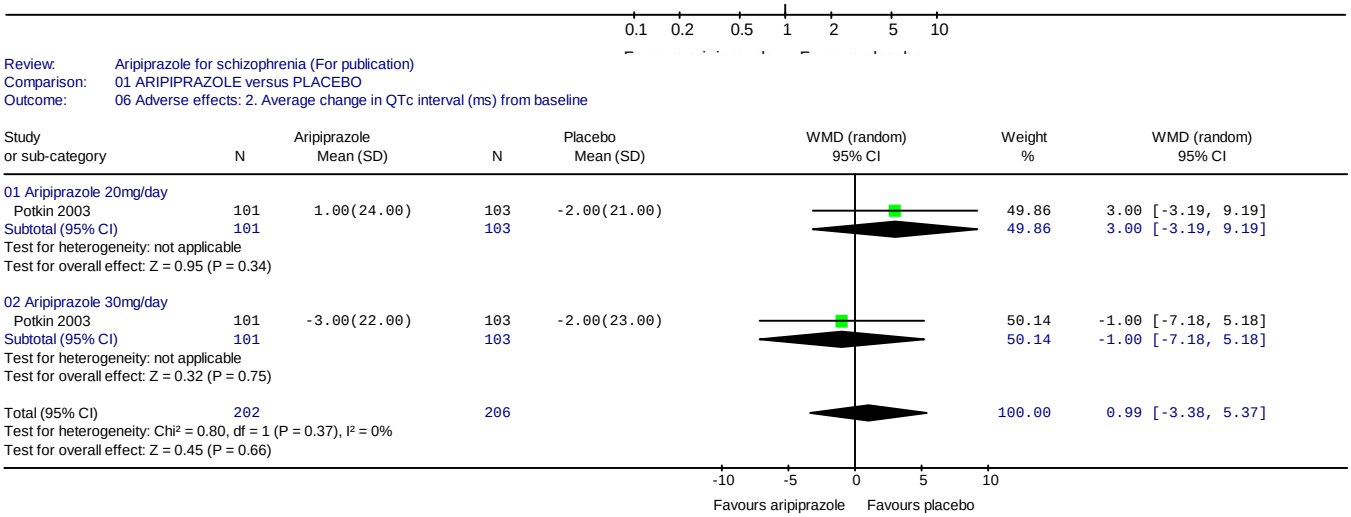
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 04 Global state: 4. Needing additional benzodiazepines

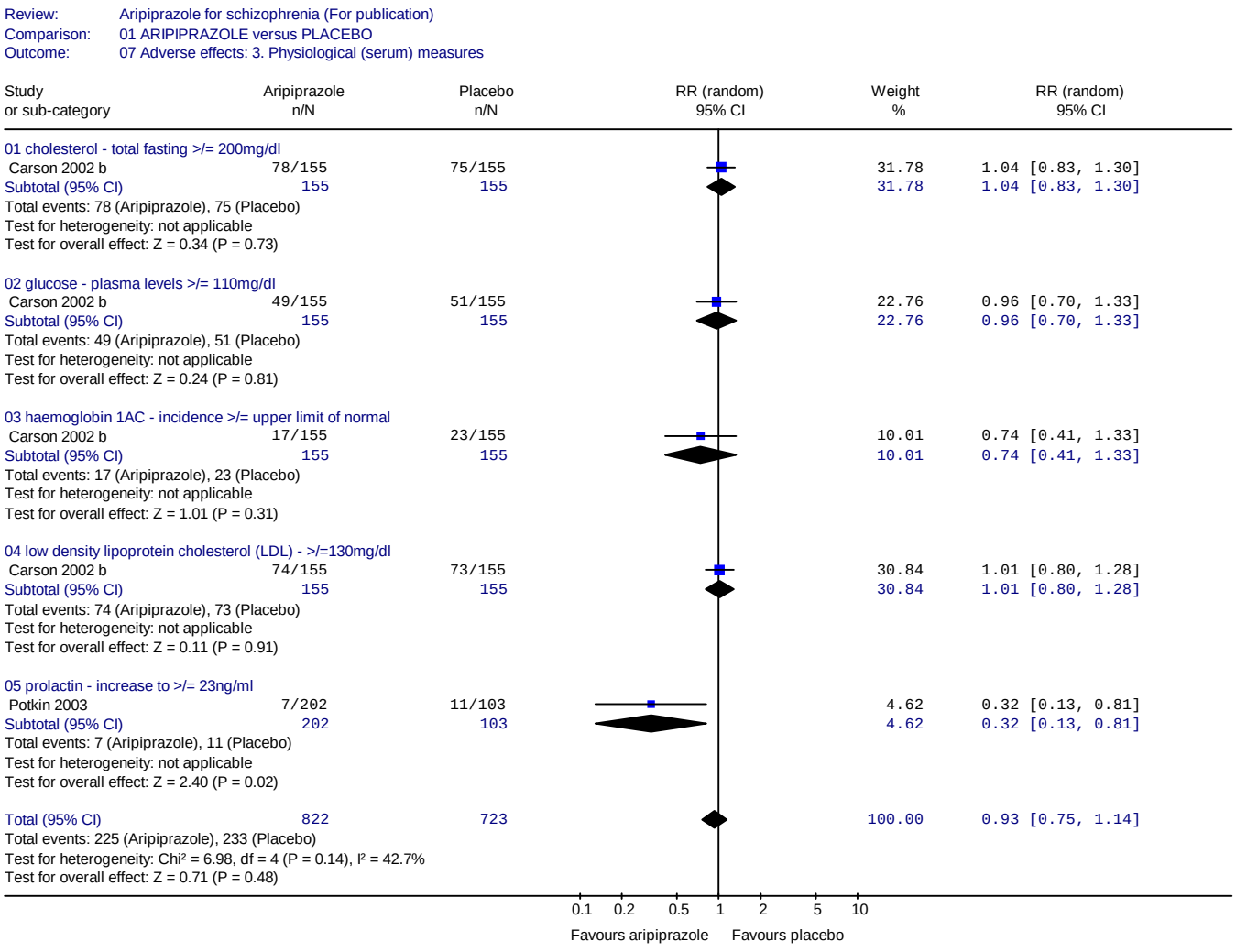
Study or sub-category	Aripiprazole n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Oren 2005	14/175	17/88		100.00	0.41 [0.21, 0.80]
Total (95% CI)	175	88		100.00	0.41 [0.21, 0.80]
Total events: 14 (Aripiprazole), 17 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.62 (P = 0.009)					

Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 05 Adverse effects: 1. Clinically important specific adverse effects

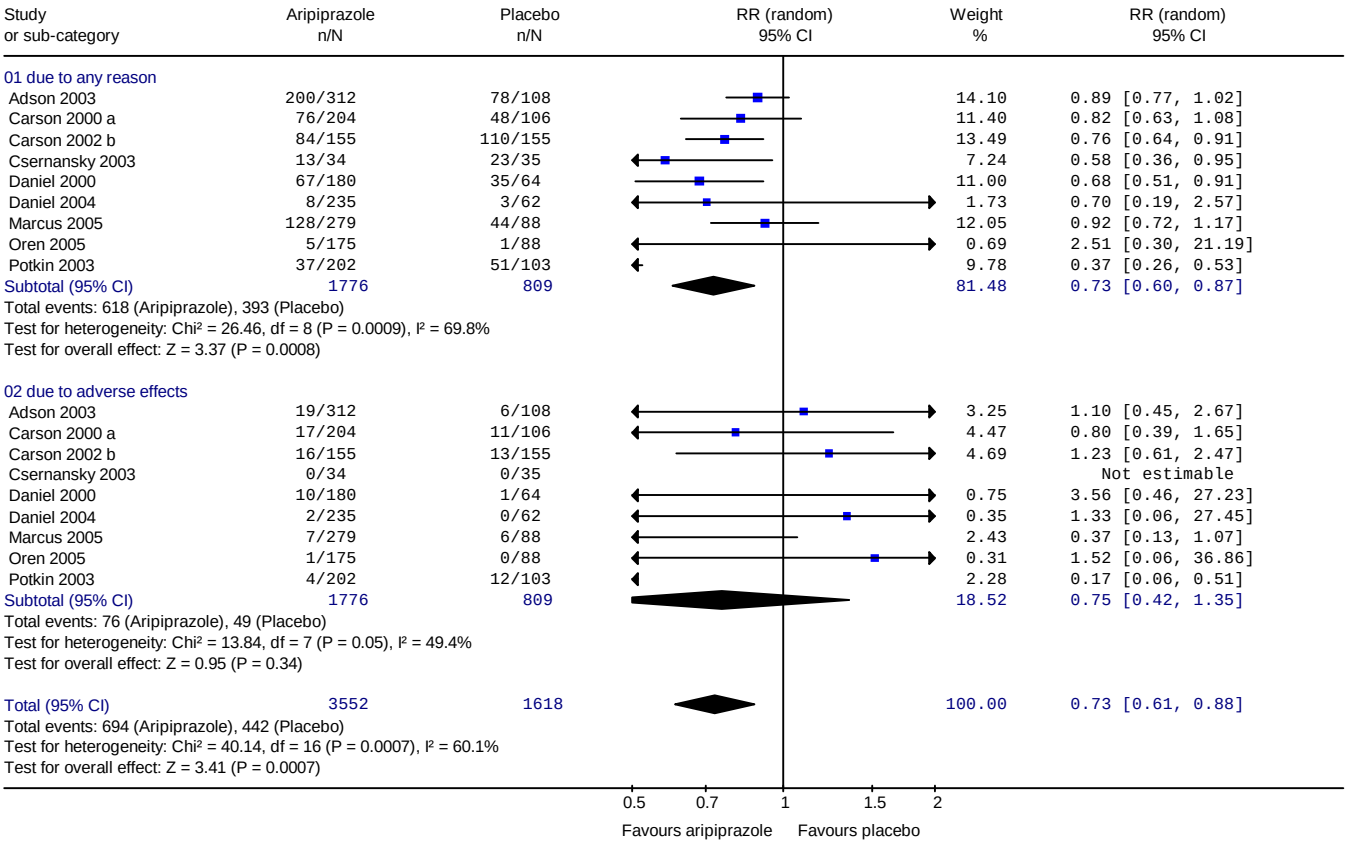


Study or sub-category	Aripiprazole n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 anxiety					
Carson 2002 b	23/155	34/155		6.87	0.68 [0.42, 1.09]
Potkin 2003	41/202	19/103		6.70	1.10 [0.67, 1.80]
Subtotal (95% CI)	357	258		13.57	0.86 [0.53, 1.39]
Total events: 64 (Aripiprazole), 53 (Placebo)					
Test for heterogeneity: Chi² = 1.93, df = 1 (P = 0.16), I² = 48.3%					
Test for overall effect: Z = 0.62 (P = 0.54)					
02 extrapyramidal symptoms - akathisia					
Daniel 2004	9/235	1/62		0.57	2.37 [0.31, 18.39]
Oren 2005	1/175	1/88		0.32	0.50 [0.03, 7.94]
Potkin 2003	40/202	9/103		4.14	2.27 [1.14, 4.49]
Carson 2002 b	14/155	12/155		3.66	1.17 [0.56, 2.44]
Subtotal (95% CI)	767	408		8.69	1.64 [1.02, 2.65]
Total events: 64 (Aripiprazole), 23 (Placebo)					
Test for heterogeneity: Chi² = 2.53, df = 3 (P = 0.47), I² = 0%					
Test for overall effect: Z = 2.02 (P = 0.04)					
03 extrapyramidal symptoms - general					
Carson 2002 b	7/155	10/155		2.43	0.70 [0.27, 1.79]
Oren 2005	3/175	3/88		0.94	0.50 [0.10, 2.44]
Potkin 2003	7/202	0/103		0.30	7.68 [0.44, 133.24]
Subtotal (95% CI)	532	346		3.67	0.86 [0.28, 2.67]
Total events: 17 (Aripiprazole), 13 (Placebo)					
Test for heterogeneity: Chi² = 3.12, df = 2 (P = 0.21), I² = 36.0%					
Test for overall effect: Z = 0.25 (P = 0.80)					
04 extrapyramidal symptoms - needing antiparkinson medication at least once					
Carson 2000 a	23/204	13/106		4.60	0.92 [0.49, 1.74]
Csernansky 2003	6/34	10/35		2.65	0.62 [0.25, 1.51]
Daniel 2000	41/180	19/64		7.19	0.77 [0.48, 1.22]
Subtotal (95% CI)	418	205		14.44	0.78 [0.55, 1.11]
Total events: 70 (Aripiprazole), 42 (Placebo)					
Test for heterogeneity: Chi² = 0.52, df = 2 (P = 0.77), I² = 0%					
Test for overall effect: Z = 1.38 (P = 0.17)					
05 headache					
Carson 2002 b	17/155	21/155		5.05	0.81 [0.44, 1.47]
Daniel 2004	32/235	2/62		1.18	4.22 [1.04, 17.13]
Oren 2005	13/175	7/88		2.71	0.93 [0.39, 2.26]
Potkin 2003	63/202	28/103		9.13	1.15 [0.79, 1.67]
Subtotal (95% CI)	767	408		18.08	1.11 [0.72, 1.72]
Total events: 125 (Aripiprazole), 58 (Placebo)					
Test for heterogeneity: Chi² = 4.87, df = 3 (P = 0.18), I² = 38.4%					
Test for overall effect: Z = 0.49 (P = 0.63)					
06 insomnia					
Carson 2002 b	67/155	63/155		12.54	1.06 [0.82, 1.38]
Oren 2005	10/175	9/88		2.82	0.56 [0.24, 1.32]
Potkin 2003	53/202	23/103		7.92	1.17 [0.77, 1.80]
Subtotal (95% CI)	532	346		23.27	1.04 [0.81, 1.34]
Total events: 130 (Aripiprazole), 95 (Placebo)					
Test for heterogeneity: Chi² = 2.33, df = 2 (P = 0.31), I² = 14.2%					
Test for overall effect: Z = 0.30 (P = 0.77)					
07 nausea					
Carson 2002 b	10/155	7/155		2.43	1.43 [0.56, 3.66]
Daniel 2004	17/235	3/62		1.58	1.50 [0.45, 4.94]
Oren 2005	10/175	2/88		1.04	2.51 [0.56, 11.23]
Potkin 2003	17/202	10/103		3.61	0.87 [0.41, 1.82]
Subtotal (95% CI)	767	408		8.66	1.23 [0.75, 2.01]
Total events: 54 (Aripiprazole), 22 (Placebo)					
Test for heterogeneity: Chi² = 1.95, df = 3 (P = 0.58), I² = 0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
08 vomiting					
Carson 2002 b	11/155	7/155		2.52	1.57 [0.63, 3.95]
Daniel 2004	9/235	2/62		1.03	1.19 [0.26, 5.36]
Potkin 2003	23/202	6/103		2.80	1.95 [0.82, 4.65]
Subtotal (95% CI)	592	320		6.35	1.66 [0.93, 2.98]
Total events: 43 (Aripiprazole), 15 (Placebo)					
Test for heterogeneity: Chi² = 0.34, df = 2 (P = 0.84), I² = 0%					
Test for overall effect: Z = 1.71 (P = 0.09)					
09 weight gain - > 7% over baseline					
Carson 2002 b	9/155	6/155		2.15	1.50 [0.55, 4.11]
Potkin 2003	22/202	2/103		1.14	5.61 [1.35, 23.39]
Subtotal (95% CI)	357	258		3.28	2.64 [0.70, 9.95]
Total events: 31 (Aripiprazole), 8 (Placebo)					
Test for heterogeneity: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%					
Test for overall effect: Z = 1.43 (P = 0.15)					
Total (95% CI)	5089	2957		100.00	1.08 [0.92, 1.26]
Total events: 598 (Aripiprazole), 329 (Placebo)					
Test for heterogeneity: Chi² = 34.44, df = 27 (P = 0.15), I² = 21.6%					
Test for overall effect: Z = 0.97 (P = 0.33)					

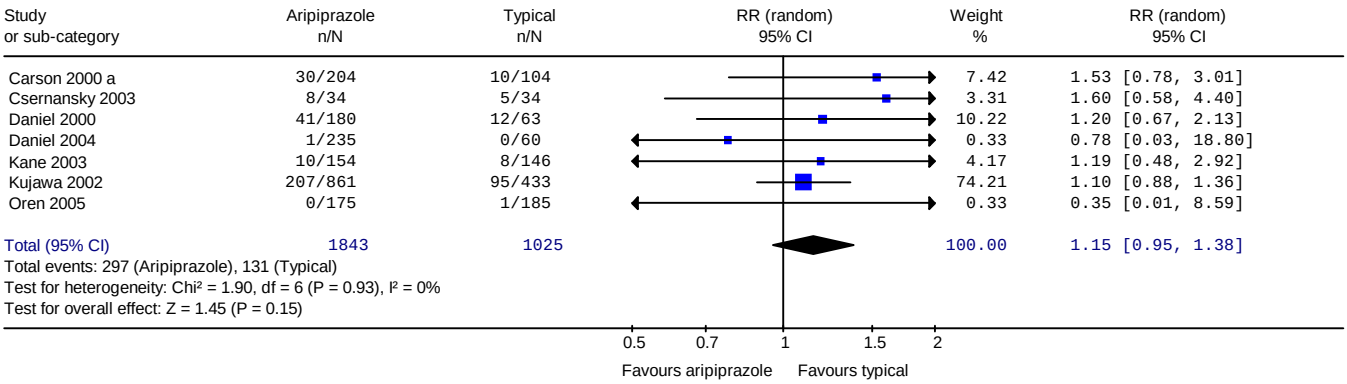




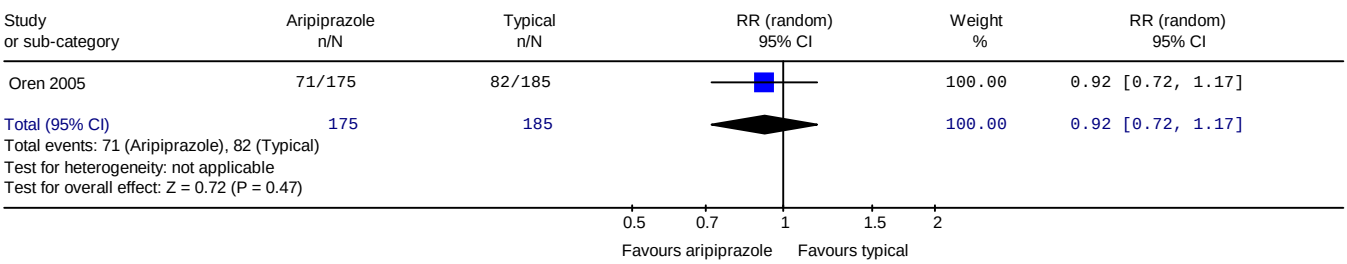
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 01 ARIPIPRAZOLE versus PLACEBO
Outcome: 08 Leaving the study early



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 01 Global state: 1. Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis



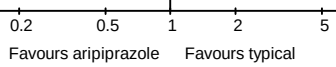
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 02 Global state: 2. Needing additional antipsychotic medication



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 03 Global state: 3. Needing additional benzodiazepines

Study or sub-category	Aripiprazole n/N	Typical n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Oren 2005	14/175	22/185		100.00	0.67 [0.36, 1.27]
Total (95% CI)	175	185		100.00	0.67 [0.36, 1.27]

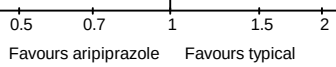
Total events: 14 (Aripiprazole), 22 (Typical)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.22 (P = 0.22)



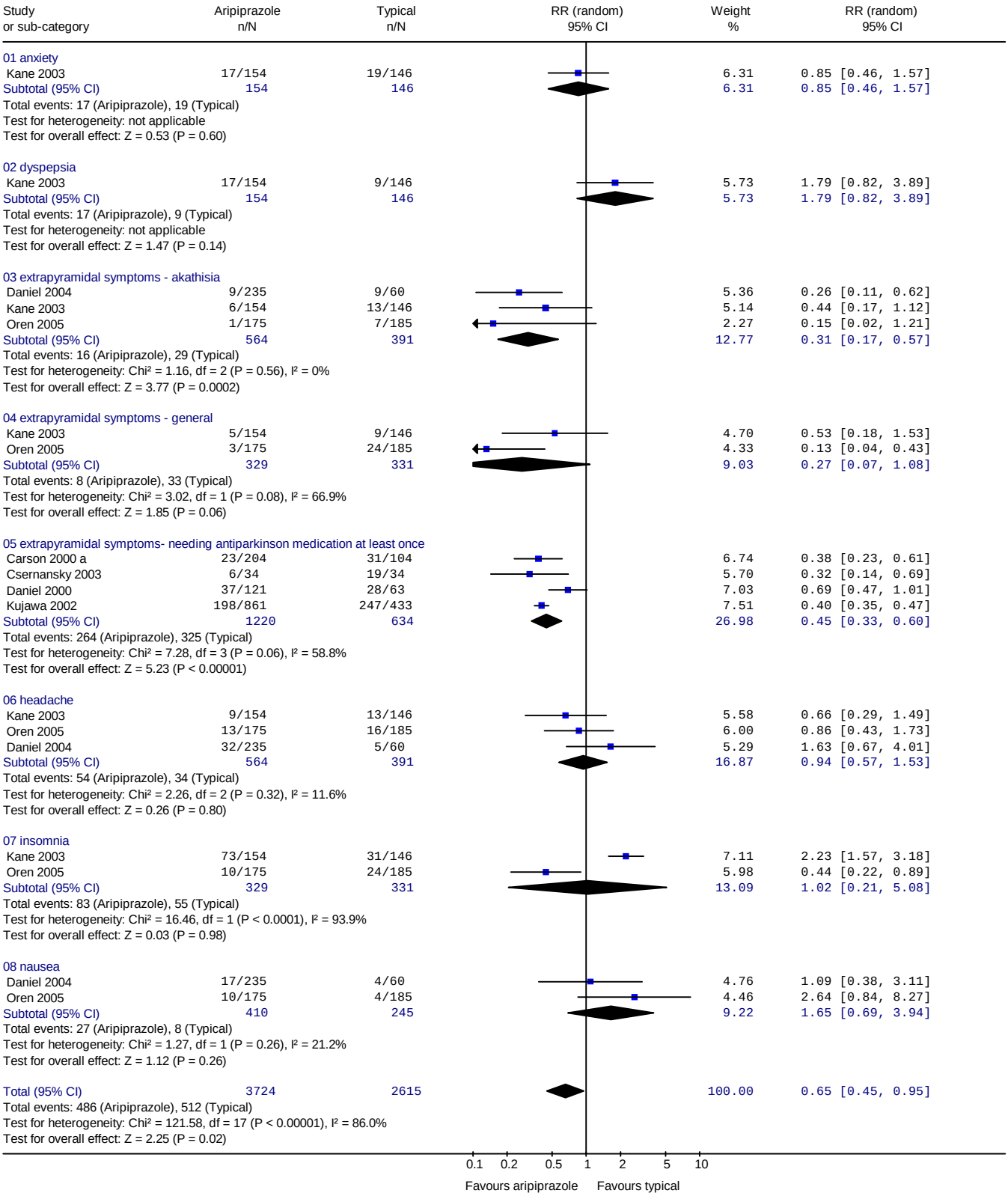
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 04 Mental state: Treatment response (defined by CGI or PANSS)

Study or sub-category	Aripiprazole n/N	Typical n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Kane 2003	39/154	30/146		100.00	1.23 [0.81, 1.87]
Total (95% CI)	154	146		100.00	1.23 [0.81, 1.87]

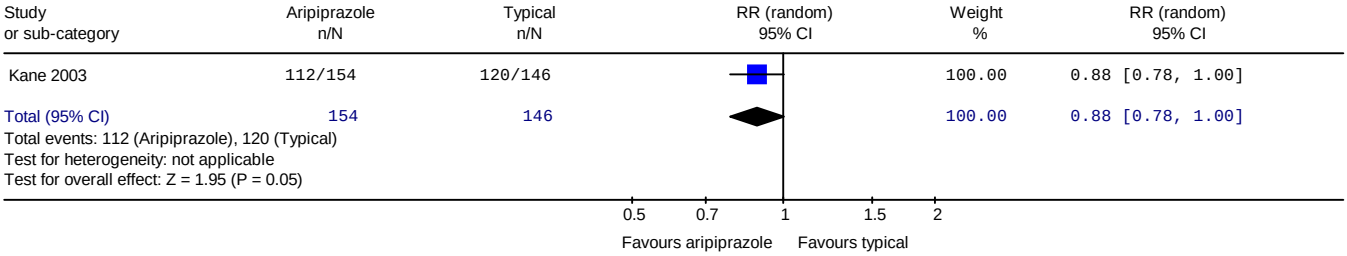
Total events: 39 (Aripiprazole), 30 (Typical)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



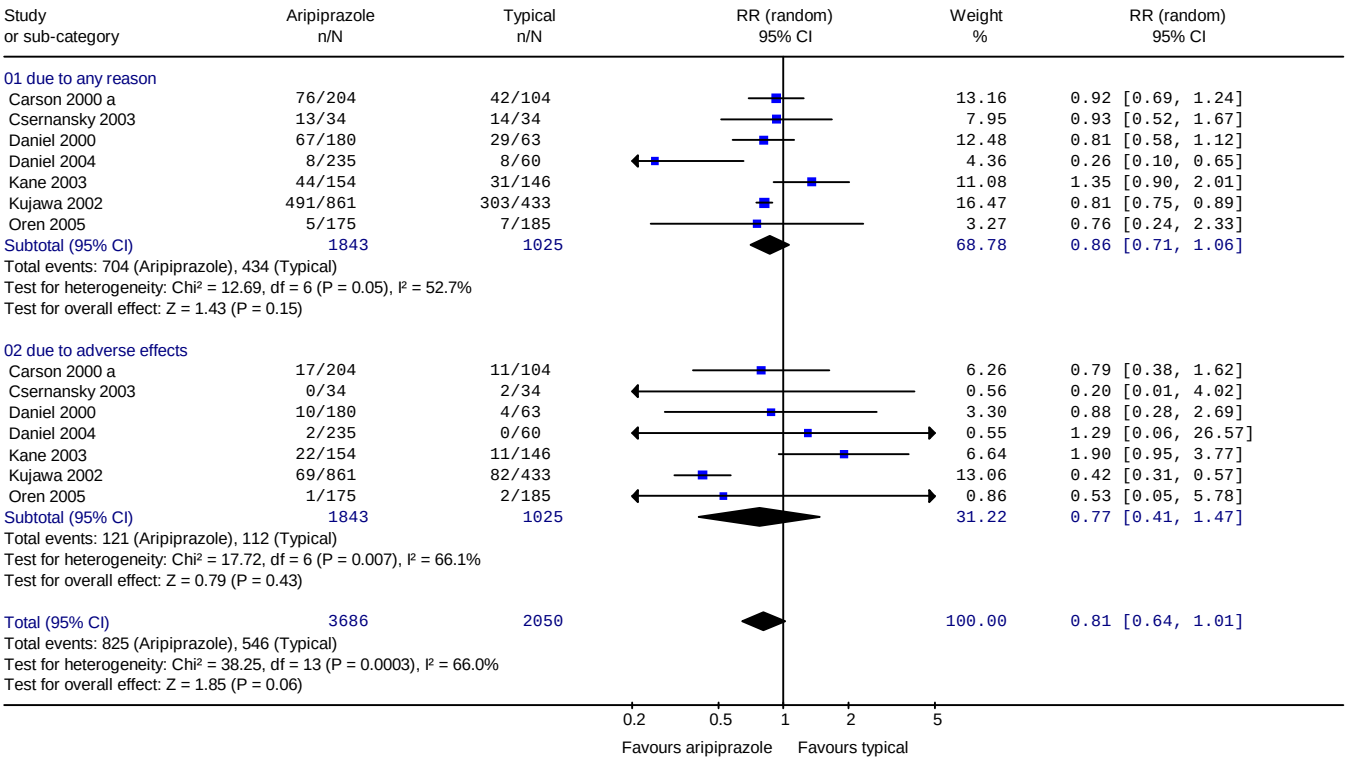
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 05 Adverse effects: Clinically important specific adverse effects



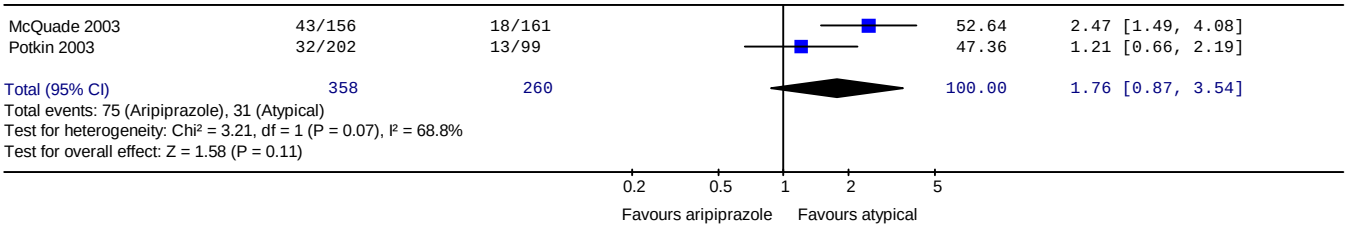
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 06 Quality of life: No clinically important improvement in quality of life (defined by QLS score)



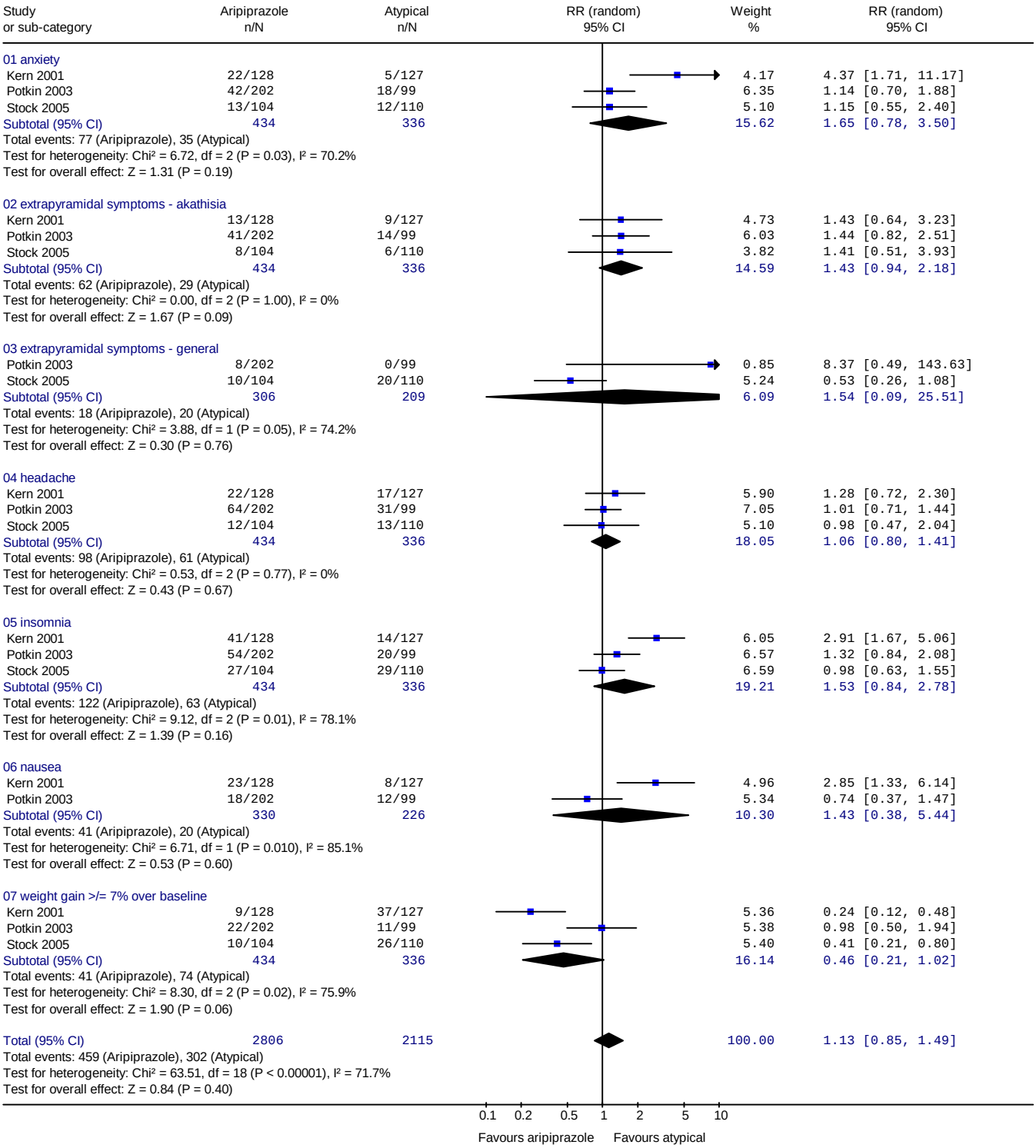
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 02 ARIPIPRAZOLE versus TYPICAL ANTIPSYCHOTICS
Outcome: 07 Leaving the study early



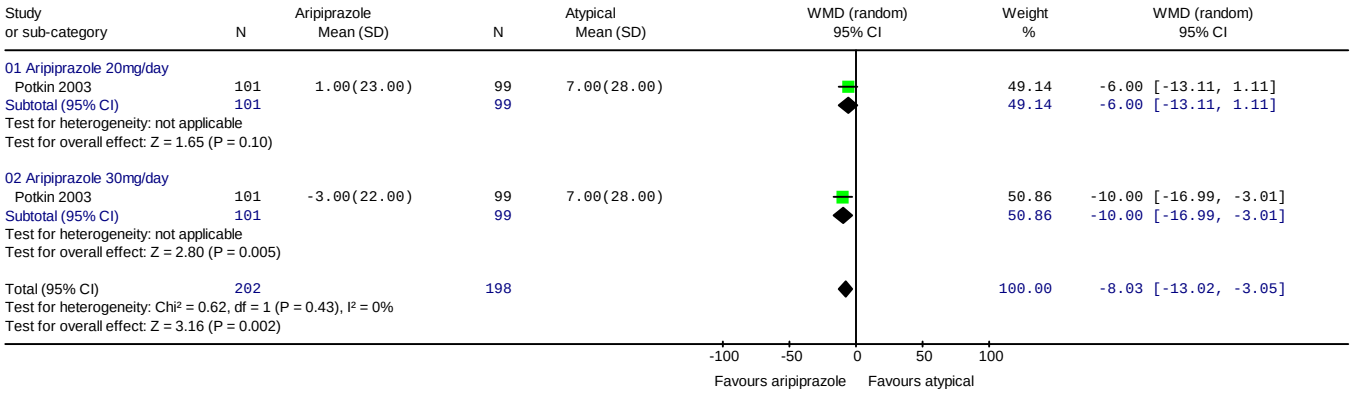
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
Outcome: 01 Global state: Poor compliance with study protocol due to lack of efficacy, deterioration or psychosis



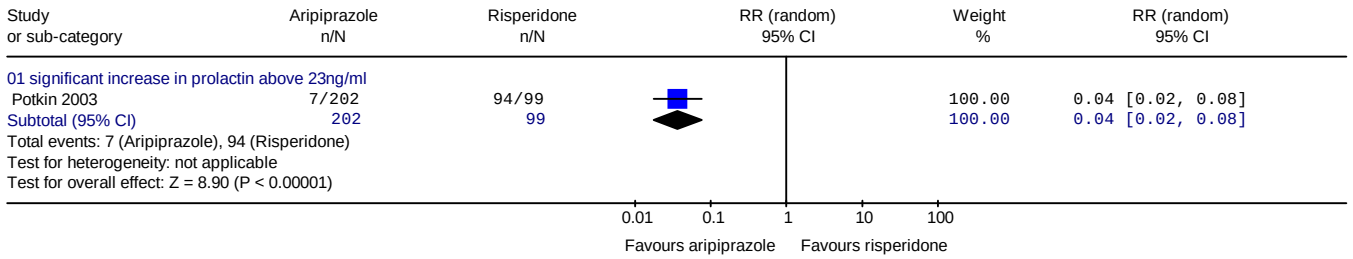
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
Outcome: 02 Adverse effects: 1. Clinically important specific adverse effects



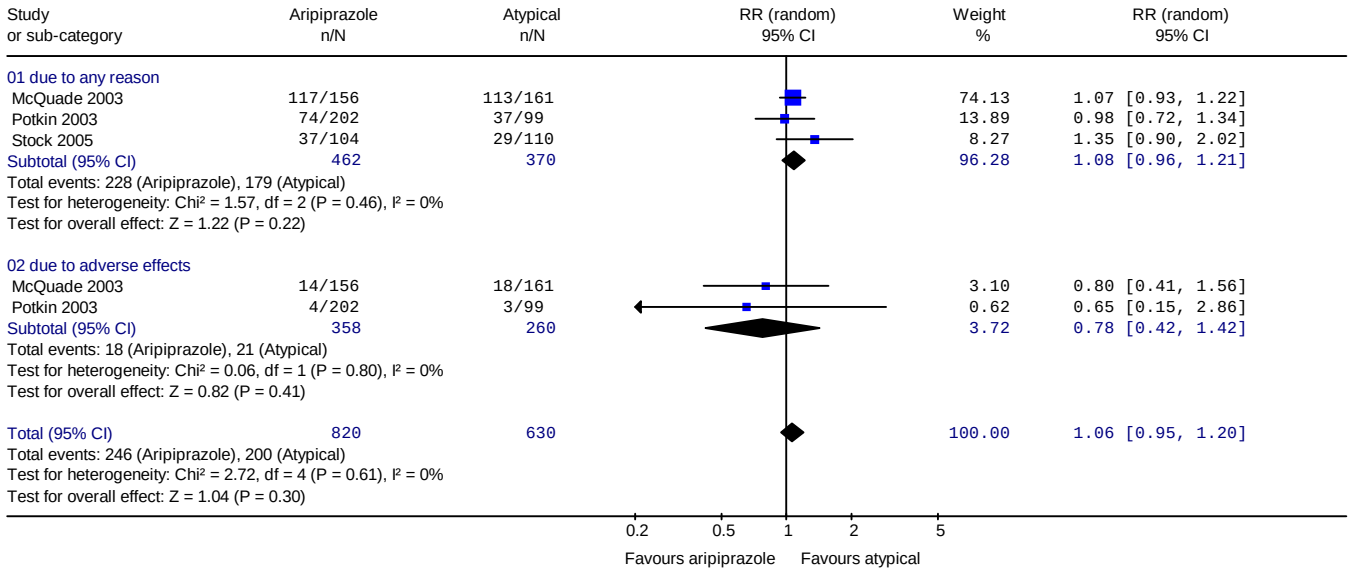
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
Outcome: 03 Adverse effects: 2. Average change in QTc interval (ms) from baseline



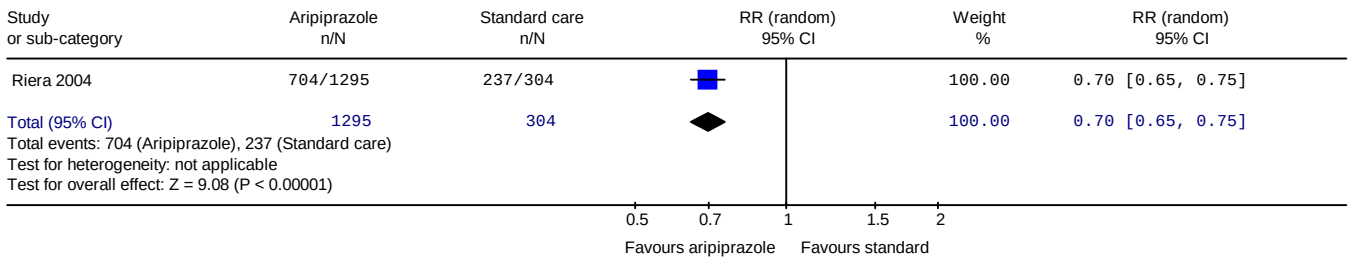
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
Outcome: 04 Adverse effects: 3. Physiological (serum) measures



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 03 ARIPIPRAZOLE versus ATYPICAL ANTIPSYCHOTICS
Outcome: 05 Leaving the study early



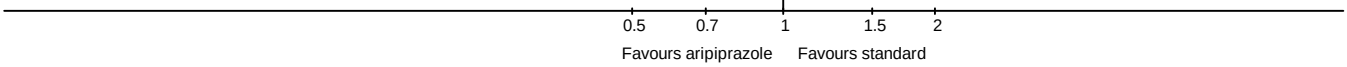
Review: Aripiprazole for schizophrenia (For publication)
Comparison: 04 ARIPIPRAZOLE versus STANDARD CARE
Outcome: 01 Global state: Not responded



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 04 ARIPIPRAZOLE versus STANDARD CARE
Outcome: 02 Satisfaction with treatment: Not satisfied with care

Study or sub-category	Aripiprazole n/N	Standard care n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Riera 2004	688/1295	240/304		0.00	0.67 [0.62, 0.73]
Total (95% CI)	1295	304		0.00	0.67 [0.62, 0.73]

Total events: 688 (Aripiprazole), 240 (Standard care)
Test for heterogeneity: not applicable
Test for overall effect: Z = 10.03 (P < 0.00001)



Review: Aripiprazole for schizophrenia (For publication)
Comparison: 04 ARIPIPRAZOLE versus STANDARD CARE
Outcome: 03 Leaving the study early

Study or sub-category	Aripiprazole n/N	Standard care n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 due to any reason					
Riera 2004	453/1295	131/304		100.00	0.81 [0.70, 0.94]
Subtotal (95% CI)	1295	304		100.00	0.81 [0.70, 0.94]

Total events: 453 (Aripiprazole), 131 (Standard care)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.74 (P = 0.006)