Aripiprazole for schizophrenia
Systematic review
H. G. EL-SAYEH, C. MORGANTI and C. E. ADAMS

Background Aripiprazole is an atypical antipsychotic that is reported to be effective in the treatment of schizophrenia.

Aims To investigate the effects of aripiprazole on patients with schizophrenia and schizophrenia-like psychoses by conducting a systematic review of randomised controlled trials (RCTs).

Method Database and manual searches and direct contact were used to identify relevant RCTs.

Results We included 10 randomised controlled studies (involving a total of 14125 patients), but study attrition was large and the standard of data reporting was poor. Compared with placebo, aripiprazole treatment was associated with a significant decrease in relapse rates, increased compliance with the study protocol, and a decrease in prolactin levels below the expected values. Compared with risperidone, aripiprazole caused less elevation of prolactin levels and less prolongation of the average QTc interval.

Conclusions Aripiprazole has been licensed despite the fact that few reliable data on this drug are publicly available. It may be effective for treatment of schizophrenia, but in terms of tolerability and global outcomes it shows little difference from existing antipsychotics.

Declaration of interest None. Funding detailed in Acknowledgements.

Atypical or second-generation antipsychotics are said to differ from conventional or typical antipsychotics in terms of their effects on the positive and negative symptoms of schizophrenia and on cognition, and in terms of their adverse effect profiles (Gelder et al, 2000). Aripiprazole is the prototype of a ‘third generation’ of antipsychotics – the so-called dopamine-serotonin-system stabilisers (Rivas-Vasquez, 2003). It is claimed to be at least as effective as haloperidol in the treatment of positive and negative symptoms of schizophrenia, and it may cause fewer adverse effects. Aripiprazole is reported to be useful in all phases of schizophrenia, and to enhance cognitive function (Rivas-Vasquez, 2003). In 2002 the drug was granted an appropriate status by the US Food and Drug Administration (FDA) for the treatment of schizophrenia (Dubitsky et al, 2002). It has been included in recent guidelines on schizophrenia treatment (American Psychiatric Association Work Group on Schizophrenia, 2004) and it is licensed for use in several other countries, including the UK. We here report the findings of a systematic review of randomised controlled trials (RCTs) of the effects of aripiprazole.

METHOD

Search strategy
We searched the Cochrane Schizophrenia Group’s register (August 2004) and we also hand-searched relevant journals and conference proceedings, and used several grey literature sources (including pharmaceutical industry materials and non-systematic internet searches). In addition, we inspected the references cited in identified studies for further trials and we examined the FDA website. We also contacted relevant authors and the manufacturers of aripiprazole (Bristol–Myers Squibb and Otsuka Pharmaceuticals). Full details have been published previously (El-Sayeh & Morganti, 2004).

Selection and inclusion criteria
We reliably selected RCTs that compared aripiprazole at any dose (the recommended target dose is 10–15 mg/day, range 10–30 mg/day) with any other antipsychotics or placebo in the treatment of people with schizophrenia or schizophrenia-like psychoses. Our primary outcome was relapse, but we also investigated a number of other outcomes, including death, mental state, cognitive functioning, adverse effects and quality of life. Before we viewed the data, we stipulated that outcome measures were to be categorised as short-term (up to 12 weeks), medium-term (13–26 weeks) or long-term (over 26 weeks). We assessed study quality using the criteria described in the Cochrane Reviewers’ Handbook 4.2.0 (Clarke & Oxman, 2003).

Data analysis
We analysed the data using RevMan version 4.2.3 (Cochrane Collaboration, Oxford, UK; see http://www.cc-ims.net/RevMan/current.htm), and we calculated random-effects relative risk (RR) and its 95% confidence interval by intention-to-treat analysis. Where possible, we calculated the number needed to treat (NNT) and the number needed to harm (NNH) (see http://www.nntonline.net). On the condition that more than 60% of participants were accounted for with respect to any given study outcome, everyone allocated to the intervention was counted, whether they completed the follow-up or not. It was assumed that those individuals who dropped out had a negative outcome (other than death). Continuous data were synthesised using weighted mean difference. Statistical heterogeneity was assessed by inspecting the relevant graph and was supplemented using the I-squared statistic (Higgins et al, 2003). If inconsistency was high (>75%), the data were not pooled, but were presented separately and the reasons for heterogeneity were investigated.

RESULTS

We identified over 400 citations, of which 54 reported 10 relevant studies (Table 1). All of these 10 studies were randomised, and all but one (Kern et al, 2001) were double-blind. However, none of them made the method of randomisation explicit or tested masking. Consequently they all carry a moderate risk of bias and may therefore overestimate the positive effects of
### Table 1 Characteristics of studies included in the review

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td></td>
<td>Blinding: double (in treatment responders)</td>
<td>Age: over 18 years, average age 41 years</td>
<td>2. Aripiprazole: dose 15 mg/day (n=106)</td>
<td>Unable to use the following:</td>
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<tr>
<td></td>
<td>Duration: 6 weeks, preceded by &gt; 2-day wash-out period</td>
<td>Gender: male, 327; female, 93</td>
<td>3. Aripiprazole: dose 20 mg/day (n=100)</td>
<td>Death: suicide and natural causes (incomplete data)</td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>History: acute relapse, response to previous neuroleptics other than clozapine, out-patient &gt; 3 months in past year, PANSS total score &gt; 60, and &gt; 4 on two defined PANSS criteria</td>
<td>4. Placebo (n=108)</td>
<td>Mental state: PANSS total score, PANSS-derived BPRS core score, PANSS negative sub-scale (no s.d. data)</td>
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<tr>
<td></td>
<td>Setting: hospital, North America</td>
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<tr>
<td>Carson et al (2000)</td>
<td>Allocation: randomised</td>
<td>Diagnosis: schizophrenia or schizoaffective disorder (DSM–IV) n = 414</td>
<td>1. Aripiprazole: dose 15 mg/day (n=102)</td>
<td>Leaving the study early</td>
</tr>
<tr>
<td>(method not described)</td>
<td>Blinding: double (no further details)</td>
<td>Age: mean c. 39 years</td>
<td>2. Aripiprazole: dose 30 mg/day (n=102)</td>
<td>Unable to use the following:</td>
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<tr>
<td></td>
<td>Duration: 4 weeks, preceded by &gt; 5-day wash-out period</td>
<td>Gender: male, 288; female, 126</td>
<td>3. Haloperidol: dose 10 mg/day (n=104)</td>
<td>Death: suicide and natural causes (incomplete data)</td>
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<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>History: acute relapse, mean age at first episode c. 22 years, mean number of previous hospitalisations c. 10</td>
<td>4. Placebo (n=106)</td>
<td>General functioning: CGI (no s.d.)</td>
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<td></td>
<td>Setting: hospital, USA</td>
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<td></td>
<td>Adverse effects: SAS, Barnes Akathisia Scale, AIMS, other outcome measures including changes in body weight, serum prolactin levels and QTc interval (no usable/s.d. data)</td>
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<tr>
<td>(method not described)</td>
<td>Blinding: double (no further details)</td>
<td>Age: mean c. 42 years</td>
<td>2. Placebo (n=155)</td>
<td>Adverse effects: adverse events above 10%, weight gain &gt; 7%, fasting plasma glucose &lt; 110 mg/dl, HbA₁c upper limit of normal, clinically significant laboratory measurements</td>
</tr>
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<td></td>
<td>Duration: 26 weeks, preceded by 3- to 14-day wash-out period</td>
<td>Gender: male, 174; female, 136</td>
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<td>Leaving the study early</td>
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<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>History: chronic stable, no significant worsening of symptoms in past 3 months, diagnosis for &gt; 2 years, mean baseline PANSS score c. 82</td>
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<td>Unable to use the following:</td>
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<tr>
<td></td>
<td>Setting: mixed in- and out-patients, multinational</td>
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<td></td>
<td>Global state: PANSS, CGI, PANSS-derived BPRS (no s.d. data)</td>
</tr>
<tr>
<td>Csernansky et al (2002)</td>
<td>Allocation: randomised</td>
<td>Diagnosis: schizophrenia (DSM–III–R) n = 103</td>
<td>1. Aripiprazole (OPC-14597): dose 5 mg on days 1+2, 10 mg on days 3+4, 15 mg on days 5+6, 20 mg on days 7–12, 30 mg on days 13–28 (n=34)</td>
<td>Leaving the study early</td>
</tr>
<tr>
<td>(method not described)</td>
<td>Blinding: double</td>
<td>Age: 18–65 years, average c. 36 years</td>
<td>2. Haloperidol: dose 5 mg on days 1+2, 10 mg on days 3+4, 15 mg on days 5+6, 20 mg on days 7–12, 30 mg on days 13–28 (n=34)</td>
<td>Unable to use the following:</td>
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<tr>
<td></td>
<td>Duration: 4 weeks, preceded by 3- to 7-day placebo wash-out period</td>
<td>Gender: male, 91; female, 12</td>
<td>3. Placebo (n=35)</td>
<td>Mental state: BPRS change (no s.d. data)</td>
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<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>History: acute relapse, BPRS score &gt; 30 and score of &gt; 4 on two of four positive symptoms, evidence of previous response to antipsychotic medication</td>
<td></td>
<td>Global state: CGI severity scale (no usable data)</td>
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<td></td>
<td>Setting: in-patient, USA</td>
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<td></td>
<td>Consent: not described</td>
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<td>Loss: described</td>
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<tr>
<td>Study</td>
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Age: 18–65 years, average c. 38 years  
Gender: male, 247; female, 60  
History: acute relapse, BPRS score > 36 and score of > 2 on four criteria, antipsychotic medication taken for > 72 hours before randomisation  
Allocation: randomised (method not described)  
Blindness: double  
Setting: in-patient | 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 on days 1+2  
(n=63)  
5. Placebo (n=64) | Leaving the study early  
Unable to use the following:  
Global state: CGI (no s.d. data)  
Mental state: BPRS, PANSS (no s.d. data)  
General functioning: CGI (no s.d. data)  
Adverse effects: reported adverse effects, extrapyramidal side-effects, mean weight gain, mean prolactin levels (no usable data) |
Age: mean c. 42.1 years  
Gender: male, 208; female, 92  
History: treatment resistant, mean age at first hospitalisation 23 years, PANSS total score of > 75 and score of > 4 on two or more specified PANSS items, CGI severity of illness score of > 4  
Allocation: randomised (method not described)  
Blindness: double (during treatment phase)  
Setting: unknown, USA and Europe  
Duration 6 weeks, preceded by 14-day patient screening, 2-day neuroleptic wash-out, 4–6 weeks' confirmation of treatment resistance, 2- to 10-day neuroleptic wash-out  
Design: multicentre, parallel | 1. Aripiprazole: dose 15–30 mg/day, average dose 28.8 mg/day  
(n=154)  
2. Perphenazine: dose 8–64 mg/day, average dose 39.1 mg/day  
(n=146) | Leaving the study early  
Mental state: response  
Adverse effects: Quality of life: QLS scores  
Unable to use the following:  
Mental state: PANSS-derived BPRS (no s.d. data)  
Adverse affects: AIMS, Barnes Akathisia Rating Scale, SAS, mean prolactin levels, ECG changes, vital signs, body weight (no usable/s.d. data) |
| Kern et al (2001)    | Allocation: randomised (method not described) | Diagnosis: schizophrenia or schizoaffective disorder  
Age: 18–65 years, average c. 40 years  
Gender: male, 164; female, 92  
History: chronic stable, not hospitalised for > 2 months before randomisation, previously on stable dose of antipsychotic for > 2 months  
Allocation: randomised (method not described)  
Blindness: open-label  
Setting: out-patient  
Duration: 26 weeks  
Design: multicentre, parallel  
Setting: unknown | 1. Aripiprazole: dose 30 mg/day  
(n=128)  
2. Olanzapine: dose 15 mg/day, after 10 mg/day on days 1–7  
(n=127) | Adverse effects: spontaneously reported adverse effects occurring in > 10% of participants, clinically significant weight gain  
Unable to use the following:  
Adverse effects: mean change in weight, median change in serum cholesterol levels (no s.d. data)  
Age: 18–65 years, average c. 37 years  
Gender: male, 758; female, 536  
History: acute exacerbation, baseline PANSS score of 95, history of previous response to antipsychotic medication  
Allocation: randomised (method not described)  
Blindness: double  
Setting: unknown, USA and Europe  
Duration: 52 weeks  
Design: parallel, multicentre  | 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 of decrease to 7 mg for tolerability  
(n=433) | Leaving the study early  
Unable to use the following:  
Global state: response (no usable data)  
Mental state: PANSS total score, PANSS negative sub-scale score, MADRS total score, PANSS depression item, PANSS depression/anxiety cluster, PANSS negative sub-scale score (no s.d. data)  
Adverse effects: SAS, Barnes Akathisia Rating Scale, AIMS, body weight, serum prolactin levels, vital signs, ECG changes (no usable/s.d. data) |
Although the majority of the participants were randomised in the different studies. However, we would also make our findings more rather than less heterogeneity, and the fact that it could interpret the findings of the meta-analysis. Any participants had chronic stable schizophrenia or treatment-resistant schizophrenia. Any interpretation of the findings of the meta-analyses must take into account this clinical heterogeneity, and the fact that it could make our findings more rather than less applicable to everyday care.

Aripiprazole was compared with placebo in 6 studies (encompassing a total of 1628 patients), with haloperidol in 4 studies \( (n=1913) \), with perphenazine in 1 study \( (n=300) \), with olanzapine in 2 studies \( (n=573) \) and with risperidone in 1 study \( (n=301) \). Aripiprazole was given over a wide range of doses \( (2–30 \text{ mg/day}) \) (Dubitsky et al, 2002). Two studies reported deaths (Carson et al, 2000; Adson et al, 2002) but did not supply usable outcomes, although data were available on the FDA website. We found no usable data on service outcomes, general functioning, behaviour, engagement with mental health services, satisfaction with treatment, economic outcomes or cognitive functioning. Although relapse was the primary outcome measure for this review, only one study that compared aripiprazole treatment with placebo (Carson et al, 2002) provided data on this outcome, and relapse in that study was defined by changes in rating scale scores, not by re-hospitalisation rates as are commonly used. Seven of the 10 studies that were included reported data in terms of both a last-observation-carried-forward (LOCF) analysis and an observed-cases analysis (where observed cases are defined as those who completed the trial). We could not use the LOCF data because of the high drop-out rates reported in the studies as well as the tendency to report mean figures without providing a measure of variance.

More participants who were allocated to aripiprazole completed the studies compared with those allocated placebo \( (n=1658, 6 \text{ RCTs, RR (leaving study for any reason)} = 0.68, 95\% \text{ CI 0.55–0.86; NNT=4, 95\% \text{ CI } 6–11) \). However,
Aripiprazole showed no significant advantage over typical antipsychotics ($n=2,213$, 5 RCTs, RR (leaving for any reason by 12 weeks) $=0.90$, 95% CI 0.76–1.05; see Fig. 1). In total, 52% of participants left these 3 studies early. If an LOCF analysis were to have been used, this would have meant that large assumptions would have to be made about the outcomes of over half the participants. Before we viewed the data, we had stated that making such assumptions for over 40% of participants rendered the outcomes impossible to interpret. In the comparison with the other atypical antipsychotic medications, 53% of the patients who were allocated aripiprazole treatment left the studies before the end of the trial, compared with 58% of the patients in the comparison groups ($n=618$, 2 RCTs, RR (leaving for any reason) $=1.05$, 95% CI 0.93–1.19). When drop-out was due to adverse effects, again we found no significant difference between aripiprazole and other atypical antipsychotics ($n=618$, 2 RCTs, 5% 6.2%, RR=0.78, 95% CI 0.42–1.42).

There were significantly fewer relapses among patients who were given aripiprazole compared with those who were allocated placebo (relapse by 12 weeks: $n=310$, 1 RCT, RR $=0.59$, 95% CI 0.45–0.77; NNT=5, 95% CI 4–8; relapse by 26 weeks: $n=310$, 1 RCT, RR $=0.66$, 95% CI 0.53–0.81; NNT=5, 95% CI 4–8). This study defined relapse as either a Clinical Global Impression (CGI; Guy, 1976) rating of minimally worse, or a Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987) rating of moderately severe on hostility or uncooperativeness on two successive days, or an increase in total PANSS score of 20% or more compared with the score at randomisation (Carson et al, 2002). Patients who were allocated aripiprazole were at less risk of poor compliance with the study protocol because of lack of efficacy, deterioration or psychosis. Significantly fewer patients who were allocated aripiprazole compared with those who were given placebo experienced this deterioration ($n=1,348$, 5 RCTs, RR (by about 12 weeks) $=0.66$, 95% CI 0.49–0.88; NNT=15, 95% CI 10–41). No difference was found between aripiprazole and either the typical antipsychotic drugs haloperidol and perphenazine ($n=2,213$, 5 RCTs, RR=1.1, 95% CI 0.91–1.32) or the atypical antipsychotic drugs olanzapine and risperidone for this same global outcome ($n=618$, 2 RCTs, RR=1.76, 95% CI 0.87–3.54).

Aripiprazole had a favourable effect compared with placebo on a range of adverse effects, including headache ($n=615$, 2 RCTs, RR=1.04, 95% CI 0.76–1.43), anxiety ($n=615$, 2 RCTs, RR=0.86, 95% CI 0.53–1.39), weight gain ($n=615$, 2 RCTs, RR=2.64, 95% CI 0.70–9.95), extrapyramidal side-effects ($n=615$, 2 RCTs, RR=1.63, 95% CI 0.15–17.55) and changes in QTc interval (aripiprazole 20 mg ($n=204$, 1 RCT, 95% CI $=-3.19$ to 9.19). Aripiprazole did appear to be significantly superior to placebo in terms of the number of patients who showed a rise in serum prolactin level to at least 23 ng/ml in one short study ($n=305$, RR=0.32, 95% CI 0.13–0.81; NNT=14, 95% CI 11–50) (Porkin et al, 2003). Because of high drop-out rates and under-reporting in the included studies, we could only derive data on adverse effects for aripiprazole compared with typical antipsychotics from a single study which used a perphenazine control (Kane et al, 2003). The results suggest that there is little significant difference in specific adverse effects between aripiprazole and this typical antipsychotic (Fig. 2), apart from the finding of significant adverse effects with aripiprazole compared with typical antipsychotics with regard to adverse effects.
that patients who were allocated aripiprazole required less antiparkinsonian medication (NNT=4, 95% CI 3–5) and more often experienced insomnia (NNHI=4, 95% CI 3–9). No outcomes were available to allow comparison of aripiprazole with typical antipsychotic medication with regard to changes in the QTc interval.

When combined, two trials that compared aripiprazole with other atypical antipsychotics failed to show any difference between the new drug and the other atypicals for the outcome of weight gain of 7% or more above baseline (n=556, RR=0.49, 95% CI 0.12–1.94) (Fig. 3). Aripiprazole treatment at a dose of 20 mg/day resulted in significantly less change in QTc interval than risperidone in the short term (n=200, 1 RCT, weighted mean difference 6.0, 95% CI −3.11 to 1.11), and this remained true for higher doses of aripiprazole. Treatment with aripiprazole was associated with significantly less risk of an increase in prolactin levels above normal compared with risperidone (n=446, 1 RCT, weighted mean difference 0.04, 95% CI 0.02–0.08; NNT=2, 95% CI 1–2.5), but the clinical implications of this are unclear. Overall there appeared to be few differences between aripiprazole and other atypical antipsychotics, but more well-designed and adequately reported studies are needed to demonstrate whether this is indeed the case.

Eight people who were allocated aripiprazole are known to have died in open-label extension arms of two of the studies (total n=834) (Carson et al., 2000; Adson et al., 2002). However, the authors note that the causes of these eight deaths included suicide. The people who were randomised in these two trials were experiencing an acute relapse of schizophrenia, and this may partly explain the observed mortality figures. None of these deaths occurred in the randomised controlled phase of these trials.

**DISCUSSION**

**Limitations of data on deaths**

Despite the eight deaths reported in the results section above, this research finding has not been widely disseminated. Also, on the FDA website, a number of additional deaths are reported in those known to be allocated to aripiprazole in various trials. However, we have been informed by the pharmaceutical company in question that these deaths did not occur in trials relevant to this review. We are in continued dialogue with Bristol-Myers Squibb, and hope to gain further clarification on these and other data. Not disseminating clear information regarding these people’s outcome, we argue, breaks that unspoken contract that occurs between researchers and trial participants at the point of gaining informed consent. Formulating the contract of informed consent, public registration of all future trials before randomisation and clearer dissemination of trial data are all essential steps in rectifying this situation.

**Other data limitations**

Many of the data used in this review were obtained from conference proceedings and posters, making extraction difficult and double-counting likely. No serious published attempt was made to give each study a unique identifier. A total of 16 relevant studies, including a number of Japanese phase II and phase III studies, were only available on the FDA website and could not be included because the data were incomplete (Dubitsky et al., 2002). Therefore we cannot include these studies without the express assistance of the pharmaceutical companies who own the material. Multiple requests for further information on the highlighted FDA-identified trials have been made by telephone, by e-mail and in person. It is unlikely that patients who gave their informed consent would have understood that their results would remain undisclosed and would therefore not help to inform the care of other people with schizophrenia.

These studies were not designed to provide results of great relevance to everyday care. They were designed in line with the stipulations of the drug regulatory authorities. The majority of trials included well-defined study participants with little comorbidity. The typical antipsychotic drugs of comparison reported in this review were occasionally of such a nature or used at such a dose that they distanced these trials even further from everyday practice. The outcomes are remarkably few in number, of limited duration and poorly reported, and they take little account of the CONSORT statement (Moher et al., 2001), or else they carry such assumptions as to render them meaningless. Accordingly, findings from these studies are difficult to translate into meaningful decisions about patient care. Where complete data on adverse effects are available, the decision to report only events which occur in at least 5–10% of participants means that rare serious adverse events are not recorded. Large amounts of data could not be used for this review, partly because of the poor quality of reporting. Many studies failed to provide standard deviations when reporting mean changes in a particular outcome measure. Other studies failed to report outcomes in more than 40% of randomised patients. In accordance with our protocol (see above section on data analysis), we believe that including data from this population would involve making too many assumptions about final outcomes.
and that these data should not be used until further information has been obtained.

**Recommendations and implications**

We recommend that there should be greater compliance with CONSORT guidance in future studies. The allocation of unique study identifiers numbers to minimise confusion, performing an intention-to-treat analysis on all outcomes, and clear presentation of all study data are critical to this process.

This systematic review suggests that aripiprazole does not differ significantly from some typical or other atypical antipsychotics in terms of several global outcomes and adverse effects. However, it does not appear to cause hyperprolactinaemia, an adverse effect that is commonly seen with the typical antipsychotics and even with some of the other atypical antipsychotics. There appeared to be no significant difference in prolongation of the QTc interval compared with placebo, but there was less change in the QTc interval in one study that compared aripiprazole with other atypical antipsychotics (risperidone, n=200 patients). No data were available on the effect on QTc interval compared with typical antipsychotics. Aripiprazole may cause more insomnia than typical antipsychotics, but is perhaps also associated with less need for antiparkinsonian medication. However, the authors acknowledge that because of the lack of available evidence, and the limited numbers of comparator drugs that were used in these trials, further studies using a wider range of comparator drugs may be required before the results can be generalised to an antipsychotic class (either typical or atypical) as a whole.

Aripiprazole is an interesting compound with a novel mechanism of antipsychotic action, but its real effects are unclear, partly as a consequence of the requirements of both the regulatory authorities and the pharmaceutical industry. This review effectively demonstrates why large, long, well-designed, well-conducted and adequately reported pragmatic RCTs should be part of the regulatory authority’s requirements. It also illustrates the way in which clinicians, recipients of care, policy makers and even those who work in the pharmaceutical industry are compromised by the limitations of using explanatory trials as the sole basis for allowing a drug to be given a national licence.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


