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 4125 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.

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blindness: double (in treatment responders)</td>
<td>Age: over 18 years, average c. 41 years</td>
<td>2. Aripiprazole: dose 15 mg/day (n=106)</td>
<td>Unable to use the following:</td>
</tr>
<tr>
<td></td>
<td>Duration: 6 weeks, preceded</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>by &gt; 2-day wash-out period</td>
<td>History: acute relapse, response to clozapine, out-patient &gt; 3 months in the 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>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>Setting: hospital, North America</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carson et al (2000)</td>
<td>Allocation: randomised</td>
<td>Diagnosis: schizophrenia or schizoaffective disorder (DSM–IV)</td>
<td>1. Aripiprazole: dose 15 mg/day (n=103)</td>
<td>Leaving the study early</td>
</tr>
<tr>
<td></td>
<td>(method not described)</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>
</tr>
<tr>
<td></td>
<td>Blindness: double (no further details)</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>
</tr>
<tr>
<td></td>
<td>Duration: 4 weeks, preceded</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>Global state: CGI (no s.d. data) Mental state: BPRS, PANSS-derived BPRS score (no s.d. data) General functioning: CGI (no s.d.) 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>
</tr>
<tr>
<td></td>
<td>by &gt; 5-day wash-out period</td>
<td>Setting: hospital, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>Setting: mixed in- and out-patients, multinational</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(method not described)</td>
<td>n=310</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 Leaving the study early Unable to use the following: Global state: PANSS, CGI, PANSS-derived BPRS (no s.d. data) Adverse effects: change in weight, change in serum prolactin levels, SAS, AIMS, Barnes Akathisia Rating Scale, change in QTc interval, change in fasting plasma glucose, change in HbA1c, from baseline (no usable/s.d. data)</td>
</tr>
<tr>
<td></td>
<td>Blindness: double (no further details)</td>
<td>Age: mean c. 42 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 26 weeks, preceded</td>
<td>Gender: male, 174; female, 136</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>by 3- to 14-day wash-out period</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>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>Setting: mixed in- and out-patients, multinational</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Csernansky et al (2002)</td>
<td>Allocation: randomised</td>
<td>Diagnosis: schizophrenia (DSM–III–R)</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></td>
<td>(method not described)</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>
</tr>
<tr>
<td></td>
<td>Blindness: double</td>
<td>Gender: male, 91; female, 12</td>
<td>3. Placebo (n=35)</td>
<td>Mental state: BPRS change (no s.d. data) Global state: CGI severity scale (no usable data)</td>
</tr>
<tr>
<td></td>
<td>Duration: 4 weeks, preceded</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></td>
</tr>
<tr>
<td></td>
<td>by 3- to 7-day placebo wash-out period</td>
<td>Setting: in-patient, USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td>Consent: not described</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting: in-patient, USA</td>
<td>Loss: described</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniel et al</td>
<td>Allocation: randomised (method not described)</td>
<td>Diagnosis: schizophrenia (DSM-IV) n=307</td>
<td>1. Aripiprazole: dose 2 mg/day (n=59)</td>
<td>Leaving the study early</td>
</tr>
<tr>
<td>(2000)</td>
<td>Blindness: double</td>
<td>Age: 18–65 years, average c. 38 years. Gender: male, 247; female, 60</td>
<td>2. Aripiprazole: dose 10 mg/day (n=60)</td>
<td>Unable to use the following:</td>
</tr>
<tr>
<td></td>
<td>Duration: 4 weeks, preceded by 3- to 7-day wash-out period</td>
<td>History: acute relapse, BPRS score &gt; 36 and score of &gt; 2 on four criteria, antipsychotic medication taken for &gt; 72 hours before randomisation</td>
<td>3. Aripiprazole: dose 30 mg/day (n=61)</td>
<td>Global state: CGI (no s.d. data)</td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td></td>
<td>4. Haloperidol: dose 10 mg/day after 5 mg/day on days 1+2 (n=63)</td>
<td>Mental state: BPRS, PANSS (no s.d. data)</td>
</tr>
<tr>
<td></td>
<td>Setting: in-patient</td>
<td></td>
<td>5. Placebo (n=64)</td>
<td>General functioning: CGI (no s.d. data)</td>
</tr>
<tr>
<td>Kane et al</td>
<td>Allocation: randomised (method not described)</td>
<td>Diagnosis: schizophrenia (DSM-IV) n=300</td>
<td>1. Aripiprazole: dose 15–30 mg/day, average dose 28.8 mg/day (n=154)</td>
<td>Adverse effects: reported adverse effects, extrapyramidal side-effects,</td>
</tr>
<tr>
<td>(2003)</td>
<td>Blindness: double (during treatment phase)</td>
<td>Age: mean c. 42.1 years. Gender: male, 208; female, 92</td>
<td>2. Perphenazine: dose 8–64 mg/day, average dose 39.1 mg/day (n=146)</td>
<td>mean weight gain, mean prolactin levels (no usable data)</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td>History: treatment resistant, mean age at first hospitalisation 23 years, PANSS total score of &gt; 75 and score of &gt; 4 on two or more specified PANSS items, CGI severity of illness score of &gt; 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design: multicentre, parallel setting: unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kern et al</td>
<td>Allocation: randomised (method not described)</td>
<td>Diagnosis: schizophrenia or schizoaffective disorder n=256</td>
<td>1. Aripiprazole: dose 30 mg/day (n=128)</td>
<td>Leaving the study early</td>
</tr>
<tr>
<td>(2001)</td>
<td>Blindness: open-label</td>
<td>Age: 18–65 years, average c. 40 years. Gender: male, 164; female, 92</td>
<td>2. Olanzapine: dose 15 mg/day, after 10 mg/day on days 1–7 (n=127)</td>
<td>Mental state: response</td>
</tr>
<tr>
<td></td>
<td>Duration: 26 weeks</td>
<td>History: chronic stable, not hospitalised for &gt; 2 months before randomisation, previously on stable dose of antipsychotic for &gt; 2 months</td>
<td></td>
<td>Adverse effects: Quality of life: QLS scores</td>
</tr>
<tr>
<td></td>
<td>Design: multicentre, parallel setting: out-patient</td>
<td></td>
<td></td>
<td>Unable to use the following:</td>
</tr>
<tr>
<td></td>
<td>Setting: unknown</td>
<td></td>
<td>Adverse effects: spontaneously reported adverse effects occurring in &gt; 10% of participants, clinically significant weight gain</td>
<td>General state: PANSS-derived BPRS (no s.d. data)</td>
</tr>
<tr>
<td>Kujawa et al</td>
<td>Allocation: randomised (method not described)</td>
<td>Diagnosis: schizophrenia n=1294</td>
<td>1. Aripiprazole: dose 30 mg/day, with possibility of one-off dose decrease to 20 mg for tolerability (n=861)</td>
<td>Cognitive functioning: California Verbal Learning Test, Benton Visual</td>
</tr>
<tr>
<td>(2002)</td>
<td>Blindness: double</td>
<td>Age: 18–65 years, average c. 37 years. Gender: male, 758; female, 536</td>
<td>2. Haloperidol: dose 10 mg/day, with possibility of decrease to 7 mg for tolerability (n=433)</td>
<td>Retention Test, Wisconsin Card Sorting Test, Trail Making A and B,</td>
</tr>
<tr>
<td></td>
<td>Duration: 52 weeks</td>
<td>History: acute exacerbation, baseline PANSS score of 95, history of previous response to antipsychotic medication</td>
<td></td>
<td>Continuous Performance Test, verbal fluency, letter–number sequencing</td>
</tr>
<tr>
<td></td>
<td>Design: parallel, multicentre</td>
<td></td>
<td></td>
<td>from the WAIS-III, Grooved Pegboard Test (no usable s.d. data)</td>
</tr>
<tr>
<td></td>
<td>Setting: unknown, USA and Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
et al were noted to have had an acute relapse although the majority of the participants were randomised in the different studies. Patients in their thirties or forties. The Carson data up to 6 months (Kern 2002). Most of the studies were conducted in hospital, USA.

### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McQuade et al (2003)</td>
<td>Allocation: randomised (method not described)</td>
<td>Diagnosis: schizophrenia, n=317 Age: average c. 38 years Gender: male, 229; female, 88 History: acute relapse, mean age at first episode c. 25 years, mean time since current acute episode began c. 21 days</td>
<td>1. Aripiprazole: dose 15–30 mg/day (n=156) 2. Olanzapine: dose 10–20 mg/day (n=161)</td>
<td>Leaving the study early Unable to use the following: Global state: CGI (no usable data) Mental state: PANSS total score (no s.d. data) Adverse effects: mean change in weight (no s.d. data), clinically significant weight gain, serum prolactin levels, extrapyramidal side-effects, plasma lipids outside normal limits (no usable data)</td>
</tr>
</tbody>
</table>

PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; SAS, Simpson–Augus Scale; AIMS, Abnormal Involuntary Movement Scale; ECG, electrocardiogram; HbA1c, glycosylated haemoglobin; WAIS–III, Wechsler Adult Intelligence Scale version III.

Aripiprazole (Clarke & Oxman, 2003). Six of the studies reported data up to 12 weeks (Carson et al, 2000, 2002; Daniel et al, 2000; Adson et al, 2002; Kane et al, 2003; Potkin et al, 2003), three reported data up to 6 months (Kern et al, 2001; Carson et al, 2002; McQuade et al, 2003) and one reported data at 1 year (Kujawa et al, 2002).

Most of the studies were conducted in North America or Europe and involved between 103 (Csernansky et al, 2002) and 1294 (Kujawa et al, 2002) participants. Most of the participants were male inpatients in their thirties or forties. The majority had well-defined diagnoses of schizophrenia with little comorbidity. Such individuals represent a minority of patients in everyday care. However, we would also like to point out that there is variation in the clinical condition of the patients who were randomised in the different studies. Although the majority of the participants were noted to have had an acute relapse of schizophrenia, in some studies the 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 mg/day) (Dubinsky 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 RCTs, RR (leaving study for any reason)=0.68, 95% CI 0.55–0.86; NNT=4, 95% CI 6–11). However,
Aripiprazole showed no significant advantage over typical antipsychotics ($n=2213$, 5 RCTs, RR (leaving study 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% vs. 8%, 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 ($n=1348$, 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 ($n=2213$, 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, RR = 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

![Fig. 1](Comparison of aripiprazole with placebo in participants who left the study early for any reason.)

![Fig. 2](Comparison of aripiprazole 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 (NINH = 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 = 0.04, 95% CI 0.02–0.08; NNT = 4, 95% CI 3–5) and more serious adverse events are not reported. Large amounts of data could not be used for this review, partly because of data on adverse effects are available, the discretion to report only events which occur in more than 4% of patients. In accordance with the CONSORT statement (Moher et al., 2002). Therefore we can- not 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 patients 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.

### 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. Formalising 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.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Aripiprazole (n=834)</th>
<th>Atypical (n=1071)</th>
<th>RR (random) (95% CI)</th>
<th>Weight (%)</th>
<th>RR (random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc interval than 6 mg/day of risperidone (n=834)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (n=834)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (n=834)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3 Comparison of aripiprazole with other atypical antipsychotics with regard to adverse effects.
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 it 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**

We thank: Gill Rizzello, Mark Fenton and John Rathbone for help with the literature search and with the preparation and editing of this document.

The work received the intramural support of the University of Leeds and OsPEDA ne Guangda Ca’Granda.

**REFERENCES**


Aripiprazole for schizophrenia: Systematic review
H. G. El-Sayeh, C. Morganti and C. E. Adams
Access the most recent version at DOI: 10.1192/bjp.189.2.102

References
This article cites 11 articles, 3 of which you can access for free at:
http://bjp.rcpsych.org/content/189/2/102#BIBL

Reprints/permissions
To obtain reprints or permission to reproduce material from this paper, please write to permissions@rcpsych.ac.uk

You can respond to this article at /letters/submit/bjprcpsych;189/2/102

Downloaded from http://bjp.rcpsych.org/ on June 27, 2017
Published by The Royal College of Psychiatrists

To subscribe to The British Journal of Psychiatry go to:
http://bjp.rcpsych.org/site/subscriptions/