Aripiprazole for treating irritability in children & adolescents with autism: a systematic review

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Background & objectives: No clear therapeutic benefits of antipsychotics have been reported for the treatment of behaviour symptoms in autism. This systematic review provides an assessment of evidence for treating irritability in autism by aripiprazole.

Methods: The databases of MEDLINE/PubMed and Google Scholar were searched for relevant articles about the effect of aripiprazole in children with autism. The articles were searched according to the inclusion and exclusion criteria specified for this review. All the double-blind, controlled, randomized, clinical trials examining the efficacy of aripiprazole for treating children and adolescents with autism were included.

Results: From the 93 titles identified, 26 were irrelevant and 58 were evaluated for more details. Only five articles met the inclusive criteria. The evidence from precise randomized double blind clinical trials of aripiprazole for the treatment of autism in children and adolescents was convincing enough to recommend aripiprazole. Adverse effects were not very common and were usually mild.

Interpretation & conclusions: Current evidence suggests that aripiprazole is as effective and safe as risperidone for treating irritability in autism. However, further studies with larger sample size and longer duration are required.

Key words Aripiprazole - autism - children - clinical trial - irritability
Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone, is an atypical antipsychotic. It is approved for the treatment of bipolar I disorder (in children aged 10-17 yr), schizophrenia (in children aged 13-17 yr) and autism in children and adolescents by the Food and Drug Administration (FDA). There is strong evidence for its efficacy for treating tic disorder. In addition, there is some weak evidence for its efficacy for treating attention deficit hyperactivity disorder (ADHD). It is a partial agonist of serotonin (5-hydroxy tryptamine, 5-HT) 5-HT1A and dopamine D2 receptors. It is also a 5-HT2A receptor antagonist without considerable affinity at the cholinergic muscarinic receptor. Its serum half-life in adults is 72 h. Aripiprazole has only one active metabolite, dehydroaripiprazole. The half-life of this metabolite is about 94 hours in adults.

Autism is a complex neurodevelopmental disorder and its aetiology is not clearly known. At present, two medications including risperidone and aripiprazole are FDA approved for treatment of symptoms associated with autism. A 14-week, prospective, open-label study including 25 children with irritability and pervasive developmental disorder not otherwise specified and Asperger’s disorder reported that aripiprazole had no significant cardiac effects.

The aim of this systematic review was to evaluate the evidence from clinical trials of therapeutic intervention testing aripiprazole for autism in children and adolescents. A systematic review was conducted in May 2011 to determine the safety and efficacy of aripiprazole for patients with autism spectrum disorders (ASD). This study found two randomized controlled trials using aripiprazole for a duration of eight weeks to treat autism in children.

There was no study conducted on adult patients with autism. It was found that aripiprazole improved irritability in children with autism, but increased weight more than placebo. The current systematic review was aimed to update the evidence for administering aripiprazole for treating autism.

Material & Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to perform this systematic review.

Search strategy: Systematic literature searches were conducted to retrieve all randomized clinical trials (RCTs) of aripiprazole for treating pervasive developmental disorder. The databases of MEDLINE, Google Scholar, The Cochrane Library and Web of Science were searched up to 2013. The International Clinical Trials Registry Platform was also searched to find currently ongoing trials.

The terms for conducting the search were “aripiprazole+pervasive developmental disorder”, “autism+aripiprazole”, and “autistic disorder+aripiprazole”. Potentially relevant titles were selected and articles retrieved. A preliminary selection based on the titles was conducted. The references of the articles were also searched to find possible relevant articles. No language limitation was imposed.

Study inclusion criteria: All the randomized controlled clinical trials that investigated the effect of aripiprazole on irritability in pervasive developmental disorders were included. There were no age, publication date, and gender limitations. Any trial using a valid and reliable measurement to assess irritability was included. Intent-to-treat analysis was not an exclusion criterion.

Evaluation of validity: Methodological issues such as method of randomization, blinding of participants, and having any controlled groups were considered.

Data extraction: An extraction data sheet was designed. Study design, sampling, intervention, and adverse effects were extracted.

Results

The number of identified articles was 93 (Figure). Of these, 26 were found to be irrelevant. These studies had not examined the effect of aripiprazole on irritability in autism. The other reasons for exclusion were as follows: not a clinical trial, not double blind trials, post-hoc analyses, no control group, switching risperidone to aripiprazole, data re-analysis, assessed body mass index changes, prevention of irritability, and retrospective studies. One study reported antimanic effect of aripiprazole in patients with autism spectrum disorder and bipolar disorder. Another reported lack of any significant effect of aripiprazole on electrocardiographic data in pediatric patients. A post-hoc analysis reported quality of life of children with autism.

Only five articles met the inclusion criteria. In these trials, the effect of aripiprazole on patients with autism was investigated. The details of these studies are indicated in the Table. Only one trial compared...
The safety and efficacy of aripiprazole with another antipsychotic, risperidone, for treating children with autism. Only one systematic review was found concerning the effect of aripiprazole for treating autism in the Cochrane Library published in 2012. Searching Web of Science retrieved 83 titles, but these did not add to the titles retrieved from the two databases of PubMed/MEDLINE and Google Scholar.

In progress unpublished studies: There was one unpublished study in progress about the effect of aripiprazole for treating autism (NCT02069977) and there were two other studies that had not started recruiting patients yet (NCT00468130, and NCT00208533).

Discussion

In this systematic review, five published studies on the effect of aripiprazole on autism were reviewed. The best evidence from the randomized placebo controlled clinical trials confirmed that aripiprazole more than placebo reduced irritability in autism. The efficacy and safety of aripiprazole were comparable to risperidone for treating children and adolescents with autism. All these studies included children and adolescents. Therefore, it is not clear whether these results can be generalized to adult individuals with autism. This systematic review of double-blind controlled RCTs showed convincing evidence of effectiveness and, therefore, supported the recommendations for the use of aripiprazole for treating irritability associated with autism. Other reviews that included open label or retrospective trials also have shown similar results.

Regarding side effects, aripiprazole in children and adolescents seemed to be safe. Many of the adverse effects reported were of mild nature. Serious adverse effects were rare. Because, the number of RCTs is very limited, larger studies need to be conducted to show if it is totally safe. One of the limitations of this review is potential incompleteness of the reviewed evidence. Publication bias cannot be ignored. The four major databases of PubMed/MEDLINE, Google Scholar, the Cochrane Library, and Web of Science were searched. In addition, we also searched International Clinical Trials Registry Platform to find ongoing trials.

In conclusion, the current evidences support the efficacy and safety of aripiprazole for treating irritability in autism in children and adolescents.
<table>
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<tr>
<th>Study</th>
<th>Patients condition</th>
<th>Design</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Main outcome measures</th>
<th>Main results</th>
<th>Main adverse effects</th>
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</thead>
<tbody>
<tr>
<td>Ghanizadeh et al</td>
<td>Children with autism spectrum disorders</td>
<td>8 wk randomized double blind controlled clinical trial</td>
<td>59 patients</td>
<td>Aripiprazole versus risperidone</td>
<td>Irritability subscale and adverse effects</td>
<td>The efficacy of aripiprazole (mean dose 5.5 mg/day) and risperidone (mean dose 1.12 mg/day) were not different.</td>
<td>The rates of adverse effects were not significantly different between the two groups.</td>
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<tr>
<td>Ribb et al</td>
<td>Data were pooled from two previous studies</td>
<td>8 wk, randomized, double blind, multicenter, parallel-group trials</td>
<td>313 (aripiprazole 212, placebo 101)</td>
<td>Aripiprazole (2-15 mg/day fixed dose and 5-15 mg/day flexibly dose)</td>
<td>Adverse events</td>
<td>Aripiprazole is safe and well tolerated in 6 to 17 years old children with irritability associated with autism</td>
<td>Discontinuations due to adverse events with aripiprazole versus placebo were, overall, 10.4 versus 6.9 per cent. Subjects 6-12 yr: 10.8 versus 5.1 per cent, Subjects 13-17 yr: 8.9 versus 13.6 per cent. Common adverse events with aripiprazole versus placebo included sedation (20.8 vs 4.0%), fatigue (16.5 vs 2.0%), vomiting (13.7 vs 6.9%), increased appetite (12.7 vs 6.9%), somnolence (10.4 vs 4.0%), and tremor (9.9 vs 0.0%). Most adverse events were mild or moderate. Only fatigue showed a dose-response relationship (P&lt;0.05). Mean body weight change (last observation carried forward, 1.6 vs 0.4 kg) was higher with aripiprazole than placebo (P&lt;0.001). The extrapyramidal symptom-related adverse event: aripiprazole versus placebo was 20.8 vs 9.9 per cent.</td>
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<td>Marcus et al</td>
<td>These two studies were from the same sample of patients</td>
<td>Double blind, randomized, placebo-controlled, parallel group design</td>
<td>218 children, 6 to 17 yr of age assigned to one of the treatment conditions</td>
<td>Aripiprazole 5, 10, or 15 mg/day placebo</td>
<td>Aberrant Behavior Checklist (ABC)-Irritability subscale</td>
<td>Aripiprazole more than placebo reduced autism symptoms at week 8 for all doses</td>
<td>182 out of 216 patients experienced at least one mild to moderate adverse effect. The most common adverse effects leading to withdrawal were: sedation, drooling, and tremor. The most common extrapyramidal symptoms (20%) were tremor, extrapyramidal disorder, and akathisia. Discontinuation rates due to adverse events: 7.7 per cent for placebo and 9.4 per cent for aripiprazole. The two serious adverse events: presyncope (5 mg/day) and aggression (10 mg/day).</td>
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<tr>
<td>Marcus et al</td>
<td>Randomized placebo-controlled parallel-group fixed-dose study</td>
<td>218 children, 6 to 17 yr of age</td>
<td>Aripiprazole (5, 10, or 15 mg/day) or placebo</td>
<td>Aripiprazole decreased ABC checklist score more than placebo</td>
<td>Extrapyramidal symptoms: 14.9 per cent for aripiprazole and 5.9 per cent for placebo.</td>
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<tr>
<td>Owen et al</td>
<td>As mentioned above</td>
<td>98 children and adolescents (age 6-17 yr) with autistic disorder</td>
<td>Flexibly dosed aripiprazole (target dosage: 5, 10, or 15 mg/day) or placebo</td>
<td>Aripiprazole decreased ABC checklist score more than placebo</td>
<td>Discontinuation rates due to adverse effects: 10.6 per cent for aripiprazole and 5.9 per cent for placebo.</td>
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**Main results**:
- **Marcus et al**: 70 children, 6 to 17 yr of age were randomized to aripiprazole (5, 10, or 15 mg/day) or placebo. Aripiprazole decreased ABC checklist score more than placebo.
- **Owen et al**: 98 children and adolescents (age 6-17 yr) with autistic disorder were flexibly dosed on aripiprazole (target dosage: 5, 10, or 15 mg/day) or placebo. Aripiprazole decreased ABC checklist score more than placebo.

**Main adverse effects**:
- Extrapyramidal symptoms: 14.9 per cent for aripiprazole and 5.9 per cent for placebo.
- Discontinuation rates due to adverse effects: 10.6 per cent for aripiprazole and 5.9 per cent for placebo.

**References**


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