

## Efficacy and Tolerability of Pharmacotherapy Options for the Treatment of Irritability in Autistic Children

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**ABSTRACT:** Children with autism have a high rate of irritability and aggressive symptoms. Irritability or self-injurious behavior can result in significant harm to those affected, as well as to marked distress for their families. This paper provides a literature review regarding the efficacy and tolerability of pharmacotherapy for the treatment of irritability in autistic children. Although antipsychotics have not yet been approved for the treatment of autistic children by many countries, they are often used to reduce symptoms of behavioral problems, including irritability, aggression, hyperactivity, and panic. However, among antipsychotics, the Food and Drug Administration has approved only risperidone and aripiprazole to treat irritability in autism. Among atypical antipsychotics, olanzapine and quetiapine are limited in their use for autism spectrum disorders in children because of high incidences of weight gain and sedation. In comparison, aripiprazole and ziprasidone cause less weight gain and sedation. However, potential QTc interval prolongation with ziprasidone has been reported. Contrary to ziprasidone, no changes were evident in the QT interval in any of the trials for aripiprazole. However, head-to-head comparison studies are needed to support that aripiprazole may be a promising drug that can be used to treat irritability in autistic children. On the other hand, risperidone has the greatest amount of evidence supporting it, including randomized controlled trials; thus, its efficacy and tolerability has been established in comparison with other agents. Further studies with risperidone as a control drug are needed.

**KEYWORDS:** autism spectrum disorder, pervasive developmental disorders, Asperger's disorder, irritability, aripiprazole, risperidone

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### Introduction

Treatment for autism spectrum disorders (ASDs) or pervasive developmental disorders (PDDs), which are a wide spectrum of disorders including autism and Asperger's syndrome, includes therapeutic education regarding each symptom, arranging the environments of home or classroom, and pharmacotherapy. Pharmacotherapy is not curative, but rather serves as a treatment for secondary symptoms such as panic, hyperactivity, compulsion, and anxiety. Social impairment is best treated with behavioral therapy and social skills training.<sup>1</sup> Stachnik et al.<sup>2</sup> reported that among limited treatment options, non-pharmacologic approaches may be most beneficial, but

in some cases presenting with behavioral abnormalities, pharmacotherapy may be needed. To the author's knowledge, there has been little clear evidence assessing the adverse events of nonpharmacological interventions in ASDs,<sup>3,4</sup> although one report indicated that there were no adverse events in social skills training<sup>5</sup>

Irritability may be defined as an individual being abnormally sensitive, with a disposition or tendency to easily exhibit uncontrolled anger or aggression.<sup>6</sup> Children with autism and ASDs have a high rate of irritability and aggressive symptoms. In a study by Lecavalier,<sup>7</sup> up to 30% of children with autism have symptoms of irritability, including aggression



(24.5%), severe tantrums (30.2%), and deliberate self-injurious behavior (SIB) (16%). Horner et al.<sup>8</sup> reported in their review that a high ratio of children with autism who were 8 years of age or younger were found to exhibit severe problem behaviors including tantrums (76%), aggression (61%), SIB (11%), and stereotypy (5%). However, the prevalence of these behaviors, specifically in autism, has not been as systematically evaluated.<sup>9,10</sup> Irritability, aggression, and SIB can result in significant harm to those affected, and it can also lead to marked distress for the children's families.<sup>11</sup> In addition to its inherent potential dangerousness, irritability is frequently of sufficient severity to negatively impact the efficacy of educational and therapeutic interventions.<sup>12,13</sup> The treatment of irritability in ASDs or PDDs is multimodal and includes the use of behavioral and pharmacologic approaches.<sup>6,13</sup>

This paper provides a literature review regarding the efficacy and tolerability of pharmacotherapy for the treatment of irritability in autistic children. Although a significant amount of literature regarding pharmacotherapy for the treatment of irritability in autistic children has been published, there are some disagreements among the previous reports concerning the efficacy and safety of these treatments. Furthermore, the approved use of antipsychotics or other categories of agents to these young patients is limited in many countries. However, if there is a history of behavioral symptoms that occur in multiple settings and that do not respond to behavioral interventions, pharmacotherapy is often required.<sup>14</sup> This review focuses on the available evidence and clinical experience regarding pharmacotherapy for the treatment of irritability in autistic children. Medications used to treat the irritability will be discussed across categories of antipsychotics, antidepressants,  $\alpha$ -2 adrenergic agonists, antiepileptic drugs, and others.

## Literature Review

A literature review was conducted using the following PubMed search terms: "autistic spectrum disorder"; "pervasive developmental disorders"; and "autism" or "Asperger's disorder." The following limits were applied: randomized controlled trials (RCTs); "human trials"; and "English language." Additional articles were identified from reference information. Studies were selected based on the following inclusion criteria: 1) a sample population that included children and adolescents; and 2) at least one standardized assessment of irritability or aggression as a primary outcome measure of the study. Trials involving hormones or drugs not approved by either Health Canada or the United States Food and Drug Administration (FDA) were excluded from the analysis.

## Results

We identified 23 RCTs that met the criteria. Of these, 15 RCTs were conducted with antipsychotic agents (two with aripiprazole, four with risperidone, one with olanzapine, two with clozapine, and five with haloperidol), and nine RCTs were conducted with miscellaneous agents that included

antidepressants (one with clomipramine),  $\alpha$ -2 adrenergic agonists (one with clonidine, one with guanfacine), antiepileptic drugs (one with lamotrigine, one with levetiracetam), drugs with central nervous system actions (two with methylphenidate, one with amantadine), and nutritional supplements (one with L-carnitine). Haloperidol was an active control in two RCTs.

The pharmacotherapy of irritability in autistic children primarily encompasses atypical antipsychotics, which are emerging as the first-line pharmacologic treatment for this target symptom.<sup>13</sup> Although antipsychotics have not yet been approved for the treatment of autistic children by many countries, they are often used to reduce symptoms of behavioral problems including irritability, aggression, hyperactivity, panic, and SIB. However, among antipsychotics, the FDA has approved only risperidone and aripiprazole to treat irritability in autism.<sup>1,15</sup> Thus, aripiprazole and risperidone will be mainly discussed in this review.

**Mechanism of action, metabolism, and pharmacokinetic profile.** *Atypical antipsychotics.* The atypical antipsychotics address both 5-hydroxytryptamine (5-HT) and dopamine (DA) function, and they may lead to fewer extrapyramidal symptoms (EPS), such as the antipsychotic-related dyskinesia, than typical antipsychotics. The 5-HT<sub>2</sub> antagonism has been hypothesized to underlie the lower incidence rate of EPS; therefore, atypical antipsychotics have been considered better and safer treatment options than typical antipsychotics.<sup>16,17</sup>

Chavez et al.<sup>18</sup> suggested that PDD is likely a heterogeneous disorder with a multifactorial etiology. The authors discussed the possible relationship between serotonin, DA, and norepinephrine and the observed clinical response to atypical antipsychotic treatment for autism, and they argued that the observed efficacy of atypical antipsychotics may be related to their ability to affect more than one neurotransmitter system.

The finding of hyperserotonemia<sup>19-21</sup> in a significant percentage of individuals with autism suggests that serotonin may be a potential target for pharmacotherapy. DA neurotransmitter deregulation may also occur in autism. DA is associated with certain functions including attention, motivation, and planning. If these areas of cognition are impaired and certain behaviors occur, such as aggression or irritability, then treatment with antipsychotic agents may result in modest improvements.<sup>22</sup>

*Aripiprazole.* Aripiprazole is indicated in the US for the treatment of schizophrenia and bipolar I disorder, and it has been used as an adjunctive treatment of major depressive disorder; in addition, it has been recently approved to treat irritability associated with autistic disorder in children and adolescents 5–16 years of age.<sup>9,10</sup> The efficacy and tolerability of aripiprazole, a dopamine D<sub>2</sub> partial agonist<sup>23</sup> that is distinctive from conventional antipsychotics, have been demonstrated in various psychiatric diseases. The mechanism of action underlying the effectiveness of aripiprazole in the treatment of ASDs has not been fully elucidated. A partial agonist effect on



dopamine D<sub>2</sub><sup>24–26</sup> and serotonin 5-HT<sub>1A</sub><sup>27,28</sup> receptors, and an antagonistic effect on serotonin 5-HT<sub>2A</sub><sup>29</sup> receptors, are proposed pharmacological activities that may be involved.

Aripiprazole has a time to maximum serum concentration (T<sub>max</sub>) of 2 hours in children and adolescents,<sup>30,31</sup> and a long serum half-life (T<sub>1/2</sub>) of 75 hours in adults.<sup>32</sup> Aripiprazole may be administered once daily, and its absorption does not appear to be affected by food. Steady-state concentrations are attained within 14 days of dosing. At steady-state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4, and aripiprazole may be subject to interactions with other drugs that are strong inhibitors or inducers of these enzymes. Aripiprazole does not have inhibitory or inducing effects on these or other CYP enzymes.<sup>31,32</sup> The pharmacokinetic parameters in children and adolescents with autistic disorders are consistent with those seen in adults after adjusting for weight.<sup>32–34</sup> The pharmacokinetic profile in a study conducted among children and adolescents with conduct disorder receiving 2–15 mg/day of aripiprazole for 14 days were linear, and the details for this study were as follows: mean maximum plasma concentration (C<sub>max</sub>), 21.8–194.2 ng/mL; median T<sub>max</sub> (time to C<sub>max</sub>), 2–4 hours; mean area under the plasma concentration time curve (AUC), 800–3879 ng\*hour/mL; mean weight normalized apparent oral total body clearance (CLT/F), 0.03–0.07 L/hour/kg.<sup>35</sup>

**Risperidone.** The pharmacodynamic effects of risperidone are thought to be mediated via dopamine D<sub>2</sub> and serotonin 5-HT<sub>2A</sub> receptor antagonism.<sup>36–39</sup> Risperidone and its active metabolite, 9-hydroxyrisperidone, have high in vitro binding affinity for these receptors, which results in significant inhibition of both serotonin and DA.<sup>36,37,39,40</sup> The neurotransmitter binding profile of risperidone may provide the putative mechanisms for its antipsychotic effects, and it may lead to the generally lower incidence rate of adverse effects experienced relative to older antipsychotic agents.<sup>41</sup>

Risperidone is absorbed rapidly and has a high bioavailability (70%).<sup>37,38,42,43</sup> The drug is 90% plasma protein bound and undergoes extensive hepatic metabolism, largely via cytochrome P450 (CYP) 2D6-mediated hydroxylation to 9-hydroxyrisperidone and, to a small extent, via N-dealkylation in adults.<sup>38,40</sup> Risperidone and its metabolites are eliminated largely via the urine and partly via the feces in adults.<sup>38,40</sup> In autistic children, peak plasma levels of risperidone and 9-hydroxyrisperidone were achieved ≈1 and 1–4 hours post-dose.<sup>37,38,42</sup> The mean terminal half-lives of risperidone and 9-hydroxyrisperidone in autistic children were ≈2 and 11–16 hours, which were 30%–35% lower than those in adults.<sup>42</sup>

**Olanzapine.** Olanzapine, a thienobenzodiazepine, exhibits a broad-based receptor profile including nanomolar binding affinity at several neurotransmitter binding sites.<sup>44</sup> It further displays mesolimbic DA selectivity<sup>45</sup> and a greater D<sub>4</sub> than

D<sub>2</sub> receptor affinity.<sup>46</sup> Olanzapine is uniquely associated with the release of both cortical DA and norepinephrine.<sup>47</sup> As with clozapine, the 5-HT-related behavioral activity of olanzapine is several orders of magnitude greater than its DA-mediated effects.<sup>48</sup> While not directly bound at the glutamatergic receptors, the preadministration of olanzapine antagonizes MK-801 and phencyclidine-induced behavioral disruptions mediated through the N-methyl-daspartate recognition site.<sup>49</sup> Olanzapine also possesses a muscarinic cholinergic profile and demonstrates anticholinergic activity.<sup>48,50,51</sup>

**Typical antipsychotics.** Research into the pharmacotherapy of autism and related disorders began in the 1960s.<sup>13</sup> Over time, as the typical antipsychotics (including chlorpromazine) were developed, investigators actively sought to determine their potential use in targeting the severe and often debilitating symptoms of aggression and SIB in autism.<sup>13</sup> The attention of investigators was shifting away from the low-potency antipsychotics due to their propensity to induce sedation and result in cognition-related adverse effects. Researchers were increasingly drawn toward antipsychotics with potent D<sub>2</sub> receptor antagonism, such as haloperidol, in their search for an effective treatment.<sup>13</sup>

**Efficacy in clinical studies.** *Aripiprazole.* Owen et al.<sup>10</sup> conducted an 8-week, placebo-controlled, randomized, double-blind trial (number [N] = 98) to evaluate the efficacy of aripiprazole for treating irritability in patients aged 6–17 years with autistic disorder who had tantrums, aggression, SIB, or a combination of these symptoms. Ninety-eight patients were randomly assigned (1:1) to flexibly dosed aripiprazole (target dosage: 5 mg/day, 10 mg/day, or 15 mg/day) or placebo. The mean improvement in the Aberrant Behavior Checklist–Irritability (ABC-I) subscale score from week 1 through week 8 was significantly greater in the aripiprazole group than in the placebo group. Although the Clinical Global Impression–Improvement (CGI-I) score was also significantly improved, clinically significant residual symptoms may still persist for some patients. The EPS-related adverse event rate was 14.9% for aripiprazole and 8.0% for placebo; however, no serious adverse events were reported.<sup>10</sup> These results suggested that aripiprazole was an effective treatment for irritability associated with autistic disorder, and the treatment was generally safe and well tolerated.

Marcus et al.<sup>9</sup> conducted an 8-week, double-blind, randomized, placebo-controlled trial (N = 218) in children and adolescents aged 6–17 years with autistic disorder and who exhibited behaviors such as tantrums, aggression, and self-injury. Patients were randomly assigned to one of four groups (aripiprazole 5 mg/day, 10 mg/day, or 15 mg/day, and placebo). After 8 weeks, all aripiprazole dose groups exhibited significantly greater improvements in the caregiver-rated ABC-I score than did the placebo group. The clinician-rated CGI-I score was also significantly improved. The most common adverse event leading to discontinuation was sedation (23.6%). Two serious adverse reactions occurred: presyncope (5 mg/day)



and aggression (10 mg/day).<sup>9</sup> In this trial, aripiprazole was highly effective and well tolerated in children and adolescents with autistic disorder complicated by irritability.

Findling et al.<sup>52</sup> conducted a multicenter, double-blind, randomized, placebo-controlled, relapse-prevention trial (N = 85) in the long-term maintenance treatment of pediatric patients (aged 6–17 years) with irritability associated with autistic disorder. In Phase 1, single-blind aripiprazole was flexibly dosed (2–15 mg/day) for 13–26 weeks. Patients with a stable response ( $\geq 25\%$  decrease in the ABC-I subscale score and a rating of “much improved” or “very much improved” on the CGI-I) for 12 consecutive weeks were randomized into Phase 2 to continue aripiprazole or switch to placebo. In this study, the difference in time to relapse between aripiprazole and placebo was not statistically significant ( $P = 0.097$ ); the Kaplan–Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo (hazard ratio = 0.57; number needed to treat = 6). However, the authors concluded that both the hazard ratio and the number needed to treat suggest that some patients will benefit from maintenance treatment.<sup>52</sup>

*Risperidone.* In two 8-week, randomized, double-blind trials (n = 101<sup>53</sup> and n = 55<sup>54</sup>) in autistic children and adolescents (aged 5–17 years), patients receiving oral risperidone (mean modal dosage of 1.37–1.96 mg/day) had significantly greater improvements from baseline in irritability scores than those receiving placebo. In modified intent-to-treat analyses, parent-rated ABC-I subscale scores were reduced by 56.9%<sup>53</sup> and 65.0%<sup>54</sup> from baseline in the risperidone groups versus a decrease of 14.1%<sup>53</sup> and 34.7%<sup>54</sup> respectively, in the placebo groups. There were also significantly greater improvements from baseline for some of the other ABC subscale scores (stereotypic behavior, lethargy/social withdrawal, and/or hyperactivity/noncompliance) in the risperidone groups than in the placebo groups, and a significantly higher proportion of patients in the risperidone groups achieved a positive response.<sup>53,54</sup>

In the 8-week, randomized, double-blind, placebo-controlled trial, a risperidone/placebo solution (0.01–0.06 mg/kg/day) was administered to 79 children (aged 5–12 years) with PDD. Subjects taking risperidone (mean dosage: 0.04 mg/kg/day; 1.17 mg/day) experienced a significantly greater mean decrease on the irritability subscale of the ABC compared with those taking placebo. With respect to the study endpoint, risperidone-treated subjects exhibited a 64% improvement over baseline in the irritability score, which was almost double that noted among the placebo-treated subjects (31%). Risperidone-treated subjects also exhibited significantly greater decreases across the other four subscales of the ABC; on the conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the Nisonger Child Behavior Rating Form (parent version); and on the Visual Analog Scale of the most troublesome symptom. More risperidone-treated subjects (87%) showed global improvement in their condition compared with the placebo group (40%). Somnolence, the most frequently reported

adverse event, was noted in 72.5% (risperidone) versus 7.7% of subjects (placebo).<sup>55</sup>

The benefits of up to 6 months of risperidone treatment (mean dosage = 1.96 mg/day), in terms of the mean ABC-I subscale scores and clinician-rated CGI-I scores, were maintained in an open-label extension and double-blind, placebo-controlled, discontinuation trial (n = 63).<sup>56</sup> Efficacy was also maintained in the longer term, according to secondary endpoints, including changes from baseline across most of the other mean ABC subscales,<sup>56</sup> and in the parent-rated modified Ritvo–Freeman Real Life Rating Scale, the validated clinician-rated Children’s Yale–Brown Obsessive Compulsive Scale, and the clinician-rated Maladaptive Behavior Domain of the Vineland Adaptive Behavior Scales (MBD-VABS) scores.<sup>57</sup>

*Olanzapine.* In a double-blind, placebo-controlled, pilot trial conducted among children (aged 6–11 years) with ASDs, it was found that at mean doses of  $10 \pm 2.04$  mg/day of olanzapine was effective at globally improving autistic features based on the CGI-I (–2.25 on olanzapine versus –1.1 on placebo) and response rate (50% on olanzapine versus 20% on placebo). It was once again observed that olanzapine increased weight, appetite, and sedation.<sup>58</sup>

*Typical antipsychotics (haloperidol).* One team of researchers<sup>59–63</sup> conducted several placebo and active controlled trials of haloperidol in children and adolescents with autism and associated irritability. While symptoms of irritability, maladaptive behavior, stereotypy, and withdrawal improved in many of the haloperidol trials, the side effect burden was high and included sedation, acute dystonia, and withdrawal dyskinesias.<sup>59–63</sup> In an RCT of Remington et al.<sup>64</sup> the authors compared clomipramine, haloperidol, and placebo in 36 patients with autism over the course of 7 weeks. Subjects ranged in age from 10–36 years (mean = 16.3 years) and 24 subjects were less than 18 years of age. Haloperidol was administered in a daily dose of 13 mg/day. Although no significant difference was found in the ABC-I subscale of aggression and SIB with haloperidol as compared to placebo, only haloperidol proved superior to baseline on a global measure of autistic symptom severity, as well as on specific measures for irritability and hyperactivity. Ten of the 33 subjects prematurely discontinued haloperidol treatment due to “behavioral problems” (n = 3), fatigue/lethargy (n = 5), depression (n = 1) and dystonia (n = 1).<sup>64</sup>

*Antidepressant (clomipramine).* In an RCT by Remington et al.<sup>64</sup> subjects were randomized to receive flexible doses of clomipramine 100–150 mg/day, haloperidol 1–1.5 mg/day, or placebo. In those patients who were able to complete a full therapeutic trial, clomipramine proved comparable to haloperidol in terms of improvement compared with baseline. However, significantly fewer individuals receiving clomipramine versus haloperidol were able to complete the trial (37.5% versus 69.7%) for reasons related to both side effects and efficacy or behavior problems.<sup>64</sup>

*$\alpha$ -2 adrenergic agonists.* Clonidine. A trial by Fankhauser et al.<sup>65</sup> used transdermal clonidine at doses of 0.16–0.48 mg/day



in a 4-week double-blind, placebo-controlled, cross-over study of children and young adults aged 5–33 years. In the trial, the patch reduced symptoms including impulsivity, hyperarousal, and self-stimulating behavior.<sup>65</sup>

**Guanfacine.** In a double-blind, placebo-controlled, cross-over trial of eleven children aged 5–9 years with autism and/or intellectual disabilities for 6 weeks involving a maximum dose of 3 mg/day of guanfacine, Handen et al.<sup>66</sup> noted benefits in hyperactivity and comorbid symptoms. About 45% of children had a 50% reduction in ABC hyperactivity. The CGI-I ( $P = 0.005$ ), Parent ABC Hyperactivity subscale ( $P = 0.025$ ), and Teacher ABC Hyperactivity subscale ( $P = 0.005$ ) were found to have statistically significant differences between the guanfacine and placebo groups.<sup>66</sup>

**Antiepileptic drugs.** Lamotrigine. In the blinded study conducted by Belsito et al.<sup>67</sup> among 28 children (aged 3–11 years) with autism without epilepsy, the study showed no difference between lamotrigine and placebo on the ABC, the Autism Behavior Checklist, the VABS, the Pre-Linguistic Autism Diagnostic Observation Schedule, or the Childhood Autism Rating Scale (CARS) at a final dose of 5 mg/kg per day.<sup>67</sup>

**Levetiracetam.** In a double-blind, placebo-controlled trial of levetiracetam conducted with 20 children (aged 5–17 years) presenting with irritability and autism, Wasserman et al.<sup>68</sup> compared an average dose of 862.5 mg to placebo. The authors reported no difference between the drug and placebo in terms of the patients' mood and their scores on the irritability scales on the ABC, CY-BOCS, or Conners scales (long version for parent and teacher).<sup>68</sup>

**Psychostimulants (methylphenidate).** Quintana et al.<sup>69</sup> conducted a 4-week trial of ten patients with autistic disorder (aged 7–11 years). Patients were randomized to receive methylphenidate immediate-release (IR) 10 mg twice daily for 1 week, followed by methylphenidate IR 20 mg twice daily for 1 week, or placebo in a crossover design. At the endpoint, patients receiving methylphenidate had a statistically significant reduction in the Conners Teacher Questionnaire, the ABC-total, ABC-I, and ABC-hyperactivity scores (–0.5, –28.2, –7.8, and –13.4, respectively) compared to patients receiving placebo (–0.3, –17.8, –4.6, and –5.7, respectively). A statistically significant moderate reduction in hyperactivity symptoms was also observed.<sup>69</sup> Handen et al.<sup>70</sup> conducted the second RCT of methylphenidate in 13 children diagnosed with autism or PDD not otherwise specified with symptoms of attention-deficit hyperactivity disorder over 7 days using a double-blind, placebo-controlled, cross-over design. Subjects ranged in age from 5.6–11.2 years (mean = 7.4 years). Methylphenidate was administered in low (0.3 mg/kg) and high (0.6 mg/kg) doses two to three times daily. As compared to placebo, subjects who received methylphenidate showed significant improvements on the Hyperactivity Index of the Conners, IOWA Conners Teacher Rating Scale, and the Hyperactivity and Inappropriate Speech subscale on the ABC.<sup>70</sup>

**Antiparkinsonian medication (amantadine).** In a double-blind, placebo controlled, 5-week trial by King et al.<sup>71</sup> which was conducted among 39 children (aged 5–19 years) with autism, there were statistically significant improvements in the absolute changes in clinician-rated ABC–Community Version (ABC-CV) scores for hyperactivity (amantadine –6.4 versus placebo –2.1;  $P = 0.046$ ) and inappropriate speech (–1.9 versus 0.4, respectively;  $P = 0.008$ ) in the amantadine-treated group. Although the differences between groups were not statistically significant on the parent-rated ABC-CV, the active medication helped reduce symptoms of irritability and aggression in 47% of the children versus 37% of those on placebo. In terms of CGI-I score, 53% of those on amantadine improved versus 25% of those on placebo ( $P = 0.076$ ).<sup>71</sup>

**Carnitine (L-carnitine).** Geier et al.<sup>72</sup> conducted a 3-month trial of 30 patients with ASDs (aged 3–10 years) who were randomized to receive either L-carnitine (50 mg/kg/day) or placebo. Patients who received L-carnitine had a statistically significant change in CARS score (–2.03) compared to patients who received placebo. A statistically significant reduction in the modified CGI-I score (–0.69) was observed with L-carnitine treatment compared to placebo, while a non-statistically significant reduction in the parent-rated Autism Treatment Evaluation Checklist total score was observed with L-carnitine compared to placebo.<sup>72</sup>

The reported clinical and safety outcomes of RCTs in children and adolescents with autism and irritability referenced above are summarized in Table 1.

**Safety. Aripiprazole.** EPS. In randomized, double-blind, placebo-controlled trials of autism in childhood and adolescence, the occurrence of EPS was more frequent in the aripiprazole group than in the placebo group, and salivation, tremor, and dystonia were observed.<sup>72,73</sup> However, the degree of EPS was considered to be mild to moderate.<sup>72,73</sup>

**Akathisia.** No consensus has been reached regarding the occurrence rate of akathisia in patients taking aripiprazole. The occurrence rate of this side effect was comparable between the aripiprazole and placebo groups among those with autistic disorders.<sup>9,10</sup> To the author's knowledge, the prevalence of akathisia in autistic children receiving aripiprazole has not yet been clearly reported; however, akathisia occurred at a higher rate in child and adolescent patients receiving a higher dose of aripiprazole for the treatment of schizophrenia<sup>73</sup> and bipolar I disorder.<sup>74</sup>

**Serum prolactin.** Serum prolactin was significantly reduced after aripiprazole administration compared with baseline, and it was also significantly lower in the aripiprazole group than in the placebo group in randomized, double-blind, placebo-controlled trials on autism.<sup>9,10</sup>

**QT prolongation.** Contrary to ziprasidone,<sup>75–77</sup> no changes were evident in blood pressure, heart rate, electrocardiography, or QT interval in any of the double-blind, placebo-controlled trials for aripiprazole conducted among children and adolescents with autistic disorder,<sup>9,10</sup> or in those conducted with adolescents with schizophrenia.<sup>73</sup>

Table 1. Summary of RCTs in autistic children.

AGENT	REFERENCE	STUDY DESIGN	SUBJECTS (N)	AGE (YEARS)	DURATION	DOSSAGE	CLINICAL OUTCOMES	TOLERABILITY
Aripiprazole	Owen et al. (2009)	Placebo-controlled, randomized, double-blind trial	Autistic disorder who had tantrums, aggression, or self-injury (98)	6–17	8 weeks	5, 10, 15 mg/day and placebo	Improvements in ABC-I subscale score (aripiprazole -12.9 vs. placebo -5.0; $P < 0.001$ ) and CGI-I score (2.2 vs. 3.3; $P < 0.001$ ). Clinically significant residual symptoms may still persist for some patients.	No serious adverse events. Discontinuation due to adverse events: APZ; 10.6%, placebo; 5.9%. EPS; APZ; 14.9%, placebo; 8.0%. Mean weight gain: APZ; 2.0 kg, placebo; 0.8 kg.
Aripiprazole	Marcus et al. (2009)	Randomized, placebo-controlled, parallel-group study	Autistic disorder who had tantrums, aggression, or self-injury (218)	6–17	8 weeks	5, 10, or 15 mg/day and placebo	Improvements in ABC-I subscale scores (aripiprazole 5 mg/day, -12.4; 10 mg/day, -13.2, 15 mg/day -14.4 vs. placebo, -8.4; all $P < 0.05$ ) and CGI-I score (Placebo 3.3, aripiprazole 5 mg/day 2.6, $P = 0.003$ ; 10 mg/day 2.5, $P < 0.001$ ; 15 mg/day 2.5, $P < 0.001$ ).	Sedation (23.6%). Serious adverse events: presyncope (0.46%), aggression (0.46%).
Aripiprazole	Findling et al (2014)	Multicenter, double-blind, randomized, placebo-controlled, relapse-prevention trial	Autistic disorder (85)	6–17	13–26 weeks in phase 1 (single blind) and 12 weeks in phase 2 (double-blind, placebo-controlled)	2–15 mg/day and placebo	No difference in time to relapse between aripiprazole and placebo ( $P = .097$ ). Kaplan-Meier relapse rates at week 16:35% for aripiprazole, 52% for placebo (hazard ratio = 0.57; number needed to treat = 6).	Phase 1: weight increase (25.2%), somnolence (14.8%), vomiting (14.2%). Phase 2: (aripiprazole vs. placebo), upper respiratory tract infection (10.3% vs. 2.3%), constipation (5.1% vs. 0%), movement disorder (5.1% vs. 0%).
Risperidone	McCracken et al (Research Units on Pediatric Psychopharmacology Autism, Network) (2002)	Multisite, randomized, double-blind trial	Autistic disorder (101)	5–17	8 weeks	0.5–3.5 mg/day	Responders (25% decrease in the Irritability score and a rating of much improved or very much improved on the CGI-I scale) (risperidone 69% vs. placebo 12%; $P < 0.001$ )	Average weight gain of $2.7 \pm 2.9$ kg, (vs. Placebo, $0.8 \pm 2.2$ ; $P < 0.001$ ) increased appetite, fatigue, drowsiness, dizziness, drooling
Risperidone	Pandina et al. (2007)	Double-blind, placebo-controlled trial	Autism (55)	5–12	8 weeks	$1.37 \pm$ mg/day	Improvements in ABC-I (risperidone, $-13.4 \pm 1.5$ vs placebo, $-7.2 \pm 1.5$ ; $P < 0.05$ )	Somnolence (74%)



Risperidone	Shea et al. (2004)	Randomized, double-blind, placebo-controlled trial	Autism and other PDD (79)	5–12	8 weeks	0.01–0.06 mg/kg/day	64% improvement over baseline in ABC-I (risperidone, $-12.1 \pm 5.8$ vs. placebo, $30.7\%$ , $-6.5 \pm 8.4$ ; $P < 0.001$ ). Decreases in other 4 ABC subscales: conduct problem, insecure/ anxious, hyperactive, overly sensitive subscales of the Nisonger Child Behavior Rating Form (parent version); the Visual Analog Scale of the most troublesome symptom (all $P < 0.05$ , compare with placebo).	Somnolence (72.5%), increases in weight (2.7 kg), pulse rate, and systolic blood pressure
Risperidone	Research Units on Pediatric Psychopharmacology Autism, Network (2005)	Two-part study: Part I, consisted of 4-month open-label treatment; Part II, randomized, double-blind, placebo-substitution study of risperidone withdrawal.	Autism accompanied by severe tantrums, aggression, and/or SIB who showed a positive response in an earlier 8-week trial (63)	5–17	8 weeks	1.96 mg/day	The relapse rates were 62.5% for gradual placebo substitution and 12.5% for continued risperidone (Yates's corrected $\chi^2 = 6.53$ , $df = 1$ , $P = 0.01$ )	
Risperidone	McDougle et al. (2005)	Double-blind, placebo-controlled trial	Autism (101)	5–17	8 weeks		Greater reduction in the overall in RFRLRS, subscales for sensory motor behaviors, affectual reactions, and sensory responses. Greater reductions in scores on CYBOCS (risperidone 15.51 to 11.65; placebo, 15.18 to 14.21; significant interaction between study group and time; $F = 8.21$ , $df = 1$ , $P = 0.005$ ) and MBD-VABS was maintained for 6 months	
Olanzapine	Hollander et al. (2006)	Double-blind placebo-controlled study	PDD (11)	6–14	8 weeks	10 $\pm$ 2.04 mg/day	Improvement in CGI-I (olanzapine $-2.25$ vs. placebo $-1.1$ ; significant linear trend $\times$ group interaction; $P = 0.012$ ) (response rate 50%)	Weight gain ( $7.5 \pm 4.8$ lbs vs. placebo $1.5 \pm 1.5$ lbs)

(Continued)



Table 1. (Continued)

AGENT	REFERENCE	STUDY DESIGN	SUBJECTS (N)	AGE (YEARS)	DURATION	DOSSAGE	CLINICAL OUTCOMES	TOLERABILITY
Haloperidol & Clomipramine	Remington et al. (2001)	Latin square design	Autistic disorder (36)	10–36	7 weeks	clomipramine 100–150 mg/day, haloperidol 1–1.5 mg/day	Only haloperidol proved superior to baseline a global measure of autistic symptom severity on CARS (Repeated-measures univariate analyses of variance followed by post hoc comparisons using Scheffé's $F$ , $P < 0.05$ ), as well as specific measures for irritability ( $P < 0.05$ ) and hyperactivity ( $P < 0.05$ ) on ABC.	Clomipramine was not better tolerated than placebo. Fatigue, tachycardia, tremors, insomnia, nausea and vomiting, decreased appetite, diaphoresis
Clonidine	Fankhauser et al. (1992)	Double-blind placebo-controlled cross over study	Autistic males (9)	5–33	4 week	0.16–0.48 mg/day	Reduction of impulsivity, hyperarousal, and self-stimulating behavior. A significant difference from placebo treatment on a subscale (sensory responses) of the Ritvo-Freeman Real Life Rating Scale (analyses of variance: $P < 0.05$ ), the CGI-I ( $P < 0.0001$ ) and the therapeutic effect item of CGI ( $P = 0.0003$ ).	Sedation, hypotension, fatigue, decreased activity
Guanfacine	Handen et al. (2008)	Double-blind, placebo-controlled cross over trial	Autism and/or intellectual disabilities (11)	5–9	6 weeks	$\leq 3$ mg	45% of children had a 50% reduction in the ABC hyperactivity. The CGI-I (Independent-sample t-test: $P = 0.005$ ), Parent ABC Hyperactivity subscale ( $P = 0.025$ ), and Teacher ABC Hyperactivity subscale ( $P = 0.005$ ) were found to have statistically significant differences between guanfacine and placebo groups.	Sedation, irritability
Lamotrigine	Beisito et al. (2001)	Double-blind, placebo-controlled, parallel group study	Autism (28)	3–11	18 weeks	5.0 mg/kg/day	No significant differences in improvements between lamotrigine or placebo on the Autism Behavior Checklist, the ABC, the PL-ADOS, Vineland Adaptive Behavior scales or the CARS. (Repeated measures analysis of variances )	Insomnia, hyperactivity





Levetiracetam	Wasserman et al. (2006)	Double-blind, placebo-controlled trial	Autism (20)	5–17	10 weeks	862.5 ± 279.19 mg	No difference between drug and placebo in CGI-I ( $t = 0.350$ , $df = 13.621$ , $P = 0.765$ ), nor in the mood and the irritability scales on the ABC, CY-BOCS or Conners' scales.	Agitation, aggression
Methylphenidate	Quintana et al. (1995)	Double-blind crossover study	Autistic disorder (10)	7–11	2 weeks	20 or 40 mg/day	Significant reduction in the Conners Teacher Questionnaire (Methylphenidate $1.3 \pm 0.7$ vs. placebo $1.5 \pm 0.3$ , $t = 2.69$ , $P = .02$ ), ABC-total ( $42.0 \pm 18.3$ vs. $52.4 \pm 22.5$ , $t = 2.43$ , $P = .04$ ), ABC-I ( $4.0 \pm 3.8$ vs. $7.2 \pm 6.3$ , $t = 3.23$ , $P = .01$ ), and ABC-hyperactivity ( $12.1 \pm 9.4$ vs. $19.8 \pm 17.9$ , $t = 2.82$ , $P = .02$ ), as compared to placebo.	decreased appetite, irritability, insomnia, stomachache, headache
Methylphenidate	Handen et al. (2000)	Double-blind, placebo-controlled, crossover design	Autism or PDD-NOS with symptoms of ADHD (13)	5.6–11.2	over 7 days	0.3 or 0.6 mg/kg	Significant improvement on the Hyperactivity Index of the Conners (Repeated-measures analyses of variance followed by post hoc comparisons: $P < 0.001$ ), IOWA Conners Teacher Rating Scale ( $P = 0.004$ ), and Hyperactivity ( $P = 0.003$ ) and Inappropriate Speech ( $P = 0.001$ ) on ABC, as compared to placebo.	Social withdrawal, dullness, sadness, irritability, skin picking.
Amantadine	King et al. (2001)	Double-blind, placebo controlled	Autism (39)	5–19	5 weeks	5.0 mg/kg/day	No differences between groups parent-rated ABC-CV. Significant improvements in absolute changes in clinician-rated ABC-CVs for hyperactivity (amantadine $-6.4$ versus placebo $-2.1$ ; $P = .046$ ) and inappropriate speech ( $-1.9$ versus $0.4$ ; $P = .008$ ). Higher CGI scale ratings (53% improved versus 25%; $P = .076$ ).	Insomnia, somnolence
L-carnitine	Geier et al. (2011)	Randomized controlled trial	ASD (30)	3–10	3 month	50 mg/kg/day	Significant Reduction in CAPS (contrast between groups: $-2.03$ , 95% CI = $-3.7$ to $-0.31$ ; $P = 0.02$ ) score and modified CGI-I ( $-0.69$ , 95% CI = $-1.1$ to $-0.06$ ; $P = 0.03$ ).	Well tolerated with adverse effects of irritability, stomach discomfort



Weight gain, metabolic consequences. Aripiprazole causes less weight gain because it has a low affinity for histamine H1 receptors, and it is a partial agonist of serotonin 5-HT<sub>2C</sub> receptors, which are associated with weight gain and obesity.<sup>27,28,78</sup> Additionally, because of the low affinity for the histamine H1 receptors, the incidence of oversedation is low.<sup>78</sup> Furthermore, aripiprazole has almost no affinity for muscarinic M1 receptors, so it has few anticholinergic effects, such as constipation, dry mouth, urinary retention, or effects on cognitive function.<sup>79</sup> In the nonrandomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study, Correll et al.<sup>79</sup> evaluated the effects of olanzapine, quetiapine, risperidone, and aripiprazole on body composition and metabolic parameters in 338 pediatric and adolescent patients who were treated for 12 weeks without prior antipsychotic medication exposure. The patients' weight increased significantly in the antipsychotic treatment groups; aripiprazole caused the least amount of weight gain. Furthermore, serum total cholesterol, triglycerides, and nonhigh-density lipoprotein cholesterol (total cholesterol minus high-density lipoprotein cholesterol) increased significantly with olanzapine, quetiapine, and risperidone, but not with aripiprazole.<sup>79</sup>

On the other hand, in a long-term, placebo-controlled trial conducted with autistic children by Findling et al.<sup>52</sup> aripiprazole patients gained an average of 1.6 kg of weight gain, which was more than the weight gained by placebo recipients. Therefore, careful monitoring of weight should be performed over the course of treatment with aripiprazole, although aripiprazole causes less weight gain in comparison with other atypical antipsychotics.

**Risperidone.** In a pooled descriptive analysis of short-term clinical trials,<sup>38</sup> the most common treatment-emergent adverse events (ie, those occurring in >1.0% of patients receiving risperidone [n = 76] and at a rate that was at least twice that in the placebo group [n = 80]) were somnolence, increased appetite, fatigue, upper respiratory tract infection, increased saliva, constipation, dry mouth, tremor, and dystonia. The most common of these was somnolence, which was generally transient in nature.<sup>38</sup>

**EPS.** There was a higher incidence of adverse events associated with EPS in the risperidone group than in the placebo group in a pooled analysis of short-term trials evaluating risperidone treatment.<sup>38</sup> In clinical trials, tardive dyskinesia occurred in two of 1,885 children and adolescents with autistic disorder or other psychiatric disorders receiving risperidone, with these cases resolving upon discontinuation of treatment.<sup>38</sup>

**Serum prolactin.** Eight children (28%) of 25 young autistic children (22 males and three females; age range, 3.9–7 years; mean age, 4.10 years) during treatment with risperidone (dosage range: 0.25–0.90 mg/day; mean dosage 0.52 mg/day) had prolactin levels (30 ng/mL) higher than two times the upper limit after 10 weeks of treatment.<sup>80</sup> In double-blind

trials, 49% of children and adolescents receiving risperidone had elevated serum prolactin levels, while 2% of patients did in the placebo group.<sup>38,81</sup> Monitoring of prolactin during treatment with risperidone may be warranted.<sup>80</sup>

**Weight gain and growth/sexual maturation.** Risperidone treatment was associated with weight gain in short- and longer-term trials,<sup>53,56</sup> with these increases being in excess of developmentally expected norms, and which follow a curvilinear trajectory and decelerate over time.<sup>82</sup> There was no correlation between serum leptin levels and weight gain in 63 children and adolescents with autistic disorder receiving risperidone for up to 6 months. Serum leptin change does not reliably predict risperidone-associated weight gain.<sup>82</sup>

The long-term effects of risperidone on growth and sexual maturation remain to be fully evaluated.<sup>36,38</sup> In a retrospective analysis of pooled data from five clinical trials conducted with 572 evaluable children (aged 5–15 years) with disruptive behavior disorders receiving risperidone for up to 1 year, there were no statistically significant or clinically relevant effects on growth, or on the onset or progression of puberty.<sup>38</sup>

**Olanzapine.** Common adverse events included sedation and weight gain.<sup>6</sup> Rhinitis, “glazed eyes,” constipation, and insomnia were also reported.<sup>58</sup> Although olanzapine is a potentially effective treatment for irritability in autism because the risk of adverse events, including EPS, appears to be low, the increase in weight and appetite associated with olanzapine use may well be a limiting factor in its use and in its investigation for use in ASD.<sup>58,83–88</sup>

**Typical antipsychotics (haloperidol).** The most commonly reported adverse events were constipation, blunted affect, rigidity, dystonia, insomnia, increased appetite, depression, fatigue, and upper respiratory tract infection.<sup>6,89</sup> A study by Perry et al.<sup>62</sup> enrolled 60 children (age range, 2.3–7.9 years) with autism who were responders to haloperidol. The subjects were randomized to continuous or discontinuous (5 days on and 2 days off) treatment with haloperidol for 6 months, after which they all received 4 weeks of placebo. Although all were reversible, three youth developed dyskinesias during haloperidol treatment and nine developed withdrawal dyskinesias during the placebo period.<sup>62</sup> Another study by Campbell et al.<sup>63</sup> prospectively monitored the emergence of tardive dyskinesia and withdrawal dyskinesia in 118 children with autism aged 2.3–8.2 years. The youth received 6 months of haloperidol followed by 1 month of placebo, after which the need for another cycle of haloperidol treatment followed by placebo was assessed. In this study, 40 of 118 (33.9%) subjects developed dyskinesias, primarily reversible withdrawal dyskinesias. Of the individuals on a higher mean dosage (3.4 mg/day) of haloperidol during the study, nine of ten (90%) developed dyskinesias.<sup>63</sup>

**Clomipramine.** In one RCT, clomipramine was not better tolerated than placebo.<sup>64</sup> The adverse events included fatigue, tachycardia, tremors, insomnia, nausea and vomiting, decreased appetite, and diaphoresis.<sup>64</sup>



*$\alpha$ -2 adrenergic agonists.* Clonidine. The side effects noted in the two clonidine trials included sedation, hypotension, fatigue, and decreased activity.<sup>65,90</sup>

Guanfacine. The side effects noted in the two guanfacine trials were sedation and irritability.<sup>66,91</sup>

*Antiepileptic drugs.* Lamotrigine. In one study, the most notable side effects were insomnia and hyperactivity, at a final dose of 5 mg/kg per day. None of the children enrolled in the trial were withdrawn due to skin rash (a potentially serious adverse effect of lamotrigine treatment).<sup>67</sup>

Psychostimulants (methylphenidate). In one RCT, adverse effects of decreased appetite, irritability, insomnia, stomachache, and headache were reported.<sup>69</sup> In another RCT, five of 13 children experienced severe side effects, including social withdrawal, dullness, sadness, irritability, and skin picking. These side effects caused three subjects to be discontinued from the study.<sup>70</sup>

Antiparkinsonian medication (amantadine). In the RCT, patients reported adverse effects of insomnia and somnolence more often.<sup>71</sup>

Carnitine (L-carnitine). In the RCT, L-carnitine was generally well tolerated, with adverse effects of irritability and stomach discomfort.<sup>72</sup>

**Place in therapy.** *Aripiprazole.* Greenaway and Elbe<sup>31</sup> concluded in their review that in children and adolescents, aripiprazole appears to have minimal impact on the patients' metabolic profile compared to most other atypical antipsychotics, and that aripiprazole may represent an important alternative for some children and adolescents who have experienced poor efficacy or significant metabolic adverse effects with their current antipsychotic treatment regimen.<sup>31</sup> Their arguments are reconciled with other reports in that aripiprazole is generally safe and well tolerated in the treatment of irritability in autistic disorders.<sup>9,10,92-95</sup> Aripiprazole also improves qualitative disorders in interpersonal interactions, including communication skills and motivation.<sup>94,95</sup>

In summary, compared with other antipsychotics, aripiprazole causes fewer adverse events that can lead to drug discontinuation (for example, EPS, weight gain, and sedation). Therefore, aripiprazole is associated with excellent treatment compliance and is a promising drug to improve treatment outcomes in ASDs.

*Risperidone.* Risperidone had a clinically manageable tolerability profile, with most adverse events being of mild to moderate intensity. There are some aspects of treatment, such as weight gain, somnolence, hyperprolactinemia, hyperglycemia, and EPS that require monitoring, and the long-term safety of risperidone in children with autistic disorder remains to be fully determined.<sup>36,37</sup>

*Olanzapine.* Although olanzapine may be a promising treatment that is well tolerated for the treatment of some behavioral symptoms (irritability, hyperactivity/noncompliance, and lethargy/withdrawal) associated with ASDs, the risk of significant weight gain remains a concern.<sup>58,83-88</sup> The non-RCT

or short period trial limits the ability to make inferences about common side effects such as weight gain, lipidemia, and tardive dyskinesia. Further long-term RCTs of olanzapine are required.

*Clozapine.* The dearth of reports on the use of clozapine in ASDs is most likely due to its potential to cause life-threatening agranulocytosis, as well as its propensity to lower the seizure threshold. Frequent blood draws and cardiovascular monitoring, which are difficult procedures for children with autism, also make this atypical antipsychotic a less than ideal candidate.<sup>96</sup> Patients with an impaired ability to communicate and those with cognitive impairments would likely encounter difficulty tolerating weekly to biweekly venipuncture to monitor white blood cell counts.<sup>97</sup>

*Typical antipsychotics (haloperidol).* Although potentially beneficial, the current role of haloperidol is limited to treatment-refractory patients due to concerns regarding its associated adverse effects, including frequently observed EPS.<sup>13</sup>

*$\alpha$ -2 adrenergic agonists.* Although clonidine and guanfacine are well tolerated in RCTs,<sup>65,66</sup> the efficacy and long-term safety for the irritability of autism remains to be fully determined.

*Antiepileptic drugs.* Due to the finding of increased insomnia and hyperactivity,<sup>67</sup> lamotrigine is not a first-line agent to control irritable and aggressive symptoms in a population of children who frequently complain of insomnia and hyperactivity.<sup>96</sup> The findings of increased aggression<sup>68,98</sup> make levetiracetam a final option in the treatment of children with autism, unless the child has refractory epilepsy.<sup>96</sup>

*Psychostimulants (methylphenidate).* The two RCTs<sup>69,70</sup> produced significant results, but their sample sizes were small and the study duration was relatively short.<sup>11</sup>

*Antiparkinsonian medication (amantadine).* In the RCT of King et al.<sup>71</sup> clinician-rated improvements were noted in behavioral ratings following treatment with amantadine; however, parents did not report statistically significant behavioral changes with amantadine.

*Carnitine (L-carnitine).* L-carnitine was proposed as a potential treatment for patients diagnosed with ASD to improve mitochondrial dysfunction. L-carnitine therapy administered for 3 months significantly improved several clinical measurements of ASD severity, but subsequent studies are recommended.<sup>72</sup>

*Clomipramine.* In the RCT, clomipramine did not seem to be more effective, nor was it better tolerated in comparison with haloperidol or placebo.<sup>64</sup>

## Limitations

This study has some limitations. First, RCTs investigating the efficacy and tolerability of pharmacotherapy for the treatment of irritability in autistic children are still limited. Conclusions drawn from such studies must be evaluated with caution, and further accumulation of controlled studies is needed. Second, studies evaluating the long-term consequences of treatment are limited. Further investigations



will provide the answers to these problems, which are fundamental for clinicians.

## Conclusion

This paper reviewed the pharmacological profile and outcomes of previous clinical studies of pharmacotherapy for the treatment of irritability in autistic children. The four risperidone RCTs and the two aripiprazole RCTs reported statistically significant improvements in primary outcome measures. Thus, the bulk of positive RCT evidence regarding the pharmacotherapy treatment of irritability in autism pertains to the FDA-approved antipsychotics risperidone and aripiprazole. RCTs supporting the efficacy of several alternative and adjunctive agents may afford additional treatment options when optimal antipsychotic doses fail to control symptoms or cause intolerable adverse effects.<sup>6</sup>

Among atypical antipsychotics, olanzapine<sup>58,85–87</sup> and quetiapine<sup>99–101</sup> are limited in their use for ASDs among children because of the drugs' high incidences of weight gain and sedation. In comparison, aripiprazole<sup>79,102,103</sup> and ziprasidone<sup>104,105</sup> cause less weight gain and sedation, although there was no obvious trend in favor of aripiprazole regarding weight gain in a long-term observation study,<sup>52</sup> and no RCTs have been conducted regarding the use of ziprasidone among autistic children. Furthermore, the potential QTc interval prolongation with ziprasidone has been reported.<sup>75–77</sup> Contrary to ziprasidone, no changes were evident in the QT interval in any trials for aripiprazole.<sup>9,10,73</sup> However, head-to-head comparison studies are needed to support the idea that aripiprazole may be a promising drug that can be used to treat irritability in autistic children. On the other hand, risperidone has the greatest amount of evidence to support it (including RCTs); thus, its efficacy and tolerability have been established in comparison with other agents. Further studies with risperidone as a control drug are thus needed.

## Author Contributions

Conceived the concept: EK. Analyzed the data: EK. Wrote the first draft of the manuscript: EK. Made critical revisions: EK. The author reviewed and approved of the final manuscript.

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