Published in final edited form as:
Expert Opin Pharmacother. 2011 March ; 12(4): 635–640. doi:10.1517/14656566.2011.557661.

Aripiprazole for the Treatment of Irritability Associated with Autism

Cristan A. Farmer, Ph.D. and **Michael G. Aman, Ph.D.**
The Ohio State University Nisonger Center

1. Introduction

Autistic disorder (autism) is a neurodevelopmental disorder that causes significant impairment in socialization and communication. Autism is one of five pervasive developmental disorders (PDD) named by the *Diagnostic and Statistical Manual-Fourth Edition* [1]: autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, Rett's disorder, and PDD not otherwise specified (NOS). Autism, Asperger's disorder, and PDD-NOS are often collectively referred to as autism spectrum disorders (ASDs). Some epidemiological studies suggest that the prevalence of ASD is as high as 1 in 150 [2], whereas autism is estimated to affect about 2.2/1000 [3,4]. Core symptoms that may be present in varying degrees in the subtypes of ASD include poor eye contact, social withdrawal, impaired social reciprocity, delayed or absent language, motor stereotypies, and intense and circumscribed interests. In addition to these core symptoms, individuals with ASDs frequently display accompanying psychiatric symptoms including anxiety, irritability, aggression, and inattention [5,6,7].

Despite their efficacy, behavioral interventions for such associated symptoms may be difficult to access for many families Pharmacologic intervention may aid in the implementation of behavioral approaches by reducing interfering symptoms associated with autism, such as hyperactivity and irritability. A recent survey found that about half of children with PDD were prescribed psychotropic medication [8], although this proportion is likely to have grown in the interceding years given evidence that psychotropic drugs have indeed grown in this population with time. Atypical antipsychotics have been a major area of focus in the pharmacological treatment of ASDs. Risperidone was the first atypical antipsychotic to receive a clinical indication for irritability associated with autism [9], but recent investigations have focused on other agents, including aripiprazole.

2. Introduction to aripiprazole and overview of the market

Aripiprazole is an atypical antipsychotic approved in 2009 by the FDA for the treatment of irritability associated with autistic disorder in pediatric patients aged 6–17 years. Aripiprazole also holds FDA-approved pediatric indications for the treatment of bipolar I disorder (10–17 years) and schizophrenia (13–17 years). The atypical, or second-generation, antipsychotics have lower risk of extrapyramidal symptoms (EPS) as compared with first-generation agents. Aripiprazole is sometimes referred to as a third-generation antipsychotic in order to distinguish it; while atypicals have varying levels of antagonism at the dopamine D_2 receptors, aripiprazole is also a partial *agonist* at both D_2 and serotonin 5-HT_{1A} receptors

Contact: Cristan Farmer, farmer.107@osu.edu.

Declaration of Interest: The second author has been a consultant to and received grant support from Bristol-Myers Squibb, the company that distributes aripiprazole. Additionally, they have been an unpaid consultant and received research support from Johnson & Johnson, which manufactures risperidone (a competitor of aripiprazole).

and an antagonist at serotonin 5-HT_{2A}. The effects at the D_2, 5-HT_{1A}, and 5-HT_{2A} receptors are hypothesized to be the mechanism of action for all indications [10]. There is mixed evidence that aripiprazole is relatively weight-neutral, which would represent a significant advantage over several other alternatives like risperidone [11].

3. Chemistry

Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. See Box 1.

4. Pharmacodynamics

Because it is both a partial antagonist and agonist at the D_2 and 5-HT_{1A} receptors, aripiprazole modulates the degree of blockade depending on the initial level in the CNS. It antagonizes the D_2 receptor site under hyperdopaminergic conditions but is an agonist under hypodopaminergic conditions [12]. This is the major difference between aripiprazole and the remainder of the atypical antipsychotics, and it is the likely mechanism of action for its efficacy. Aripiprazole also has high affinity for D_3 and 5-HT_{2A} receptors, and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic, histamine H_1 receptors, and serotonin reuptake sites. Antagonism at the 5-HT_{2A} receptor may be responsible for the reduced EPS, relative to the first-generation antipsychotics, by minimizing excessive dopaminergic blockade [13]. Partial agonism at 5-HT_{1A} has anxiolytic effects, and is also hypothesized to be associated with reduced risk of EPS [13]. The absence of affinity for cholinergic muscarinic receptors is associated with less sedation than found in several other second generation antipsychotics.

5. Pharmacokinetics and Metabolism

Peak plasma concentration of aripiprazole is reached within 3–5 hours of oral administration, and steady state concentration is achieved within 14 days in both children and adults [13]. The average elimination half-life is 75 hours for aripiprazole and 94 hours for its metabolite, dehydro-aripiprazole, although the metabolite is not thought to contribute to clinical effects [10]. The absolute bioavailability of aripiprazole is 87%. It is greater than 99% protein-bound, and is eliminated primarily through hepatic metabolism with P450 enzymes CYP2D6 and CYP3A4. Therefore, it is necessary to consider the influence of genetic variations on an individual's ability to metabolize aripiprazole. Carbamazepine and oxcarbazepine, CYP3A4 inducers, interact significantly with aripiprazole, and may well require that the aripiprazole dose be increased. Valproate has no clinically important interaction with aripiprazole. Coadministration with some SSRIs, including fluoxetine and fluvoxamine, may require a lower dose of aripiprazole because drug plasma exposure may be significantly increased.

6. Clinical Efficacy

6.1 Retrospective and open trials

Retrospective reports were the first to point towards the efficacy of aripiprazole in treating irritability associated with autism spectrum disorders. Two chart reviews [14,15] of a total of 66 children with a PDD or developmental disability indicated improvement on the Clinical Global Impressions (CGI) scale in 29 cases (44%), with final doses ranging from 1.25 mg to 30 mg. Stigler and colleagues completed a series of open-label studies. The first, a naturalistic open trial in five males (5–18 years) with PDD and maladaptive behaviors, showed positive response in all participants [16]. The children received an average daily dose of 12.0 mg per day. Weight change ranged from −30 to +1 pounds, though this net weight loss was likely due to discontinuation of other atypical antipsychotics immediately

preceding the trial. This study was followed by a 14-week prospective open-label study in 25 children with PDD-NOS or Asperger's disorder, aged 5–17 years [17]. The mean endpoint dose was 7.8 mg (range 2.5–15 mg per day). Twenty-two of the children (88%) completed the study, all of whom were considered a responder based on CGI and *Aberrant Behavior Checklist* [18] (ABC) ratings. Positive effects were also observed on secondary outcome measures, including the *Vineland Adaptive Behavior Scales* [19] and the *Children's Yale-Brown Obsessive Compulsive Scale* [20] (CYBOCS). Age- and sex-adjusted body mass index increased from 20.3 (SD = 6.1) to 21.1 (SD = 5.7) over the course of the trial. Mild ($n = 8$) and moderate ($n = 1$) instances of EPS were reported, but no severe or serious adverse events were reported.

6.2 Randomized controlled trials

Two Phase-III trials of aripiprazole for irritability associated with autistic disorder (*not* ASDs) have been published. In an eight-week double-blind study [21], 218 children were randomized in a ratio of 1:1:1:1 to aripiprazole (5, 10, or 15 mg per day) or placebo. Participants were aged 6–17 years ($M = 9.7$ years), met criteria for autistic disorder, and exhibited problem behaviors such as irritability, self-injurious behavior, agitation, or some combination of the three. Scores of 4 or higher on the CGI Severity scale and 18 or higher on the caregiver-rated ABC Irritability subscale at baseline were required for inclusion. All subjects randomized to aripiprazole were initiated at 2 mg per day for the first week, which was titrated to 5 mg for Week 2. Subsequently, participants were titrated in 5 mg increments to the respective randomized dose, where appropriate. In this fixed-dose study, no dose adjustments were permitted. Subjects unable to tolerate the randomized dose were discontinued from the study.

Out of 368 children enrolled in the study, 218 were randomized to double-blind treatment with placebo ($n = 52$), 5 mg aripiprazole ($n = 53$), 10 mg aripiprazole ($n = 59$), or 15 mg aripiprazole ($n = 54$). A total of 178 children completed the study, with completion rates in the placebo, 5 mg, 10 mg, and 15 mg groups of 73.1%, 83.0%, 83.1%, and 87.0%, respectively. No participants in the aripiprazole groups discontinued due to lack of efficacy; the most common reason for withdrawal across all treatment groups was adverse events.

All doses of aripiprazole were associated with significantly greater improvement than placebo on the primary outcome measures. On the caregiver-rated ABC Irritability subscale, the mean change in the placebo group was −8.4, compared to −12.4 ($p = 0.032$), −13.2 ($p = 0.008$), and −14.4 ($p = 0.001$) for the 5, 10, and 15 mg aripiprazole groups, respectively. Significant differences between placebo and aripiprazole groups on the ABC Irritability subscale were observed as early as Week 1 for the 15 mg group and at Week 2 for the other active drug groups. Significant advantage for aripiprazole was also observed on CGI Improvement; the mean rating in the placebo group (3.3) was significantly higher (worse) than 5 mg (2.6, $p = 0.03$), 10 mg (2.5, $p < 0.001$), and 15 mg (2.5, $p < 0.001$). However, only the aripiprazole 5 mg group differed from placebo in the proportion of children designated "responders" by the blinded clinician (55.8% versus 34.7%, $p = 0.034$). Response rates in the 10 mg and 15 mg groups were not significantly different from placebo (49.2% and 52.8%, respectively). The relatively high placebo response rate may have been due to the random assignment ratio; caregivers knew that each child had a 75% chance of receiving active medication.

A similar study, with flexible dosing instead of fixed, was also reported [22]. Patients were 6–17 years of age ($M = 9.3$ years) with autistic disorder and irritability as assessed by caregiver-completed ABC Irritability subscale and clinician-rated CGI-Severity. Participants were randomized at a 1:1 ratio to placebo or aripiprazole, which was initiated at 2 mg per day and titrated up to a maximum of 15 mg per day. Dose adjustments were incremental at

2, 5, 10, or 15 mg. No dose increases were permitted after Week 6; decreases for tolerability were permitted at the discretion of the investigator at any time.

Of the 164 children who were enrolled, 98 were randomized: 51 were randomized to placebo and 47 to aripiprazole. The completion rate in the aripiprazole group was higher than placebo (83.0% versus 70.6%); lack of efficacy was the most common reason for discontinuation in the placebo group (11.8%), while adverse events was most common reason for the active group (10.6%). Aripiprazole doses during the last week of treatment were distributed as follows: 2 mg per day ($n = 2$, 5%), 5 mg per day ($n = 13$, 33%), 10 mg per day ($n = 16$, 41%), and 15 mg per day ($n = 8$, 21%).

Aripiprazole was associated with more improvement than placebo on the ABC Irritability subscales (−12.9 vs. −5.0, $p < 0.001$) and CGI Improvement (2.2 vs. 3.6, $p < 0.001$). A significantly greater proportion of children in the aripiprazole group were classified as responders at the end of the trial (52.5% vs. 14.3%, $p < 0.001$); this effect was significant beginning at Week 2. Improvement on secondary measures, including the CYBOCS and other subscales of the ABC, was also noted.

Data from the fixed-dose and flexible-dose studies were pooled for post-hoc analyses. A line-item analysis of the ABC revealed that improvements on the Irritability subscale were largely due to reductions in behaviors related to tantrums [23]. Although the studies were not designed to assess the impact of aripiprazole on hyperactivity, the line-item analysis revealed that there were significant and substantial effects on the ABC Hyperactivity subscale. This reduction in hyperactivity when children are selected for irritable behavior may be useful clinically, though the use of an antipsychotic drug *for hyperactivity alone* is rarely recommended.

A 52-week extension of these trials has been completed, and the results were presented at a scientific meeting [24]. The extension was open-label and flexibly dosed; it included participants who received aripiprazole in the first two trials ($n = 174$), those who received placebo ($n = 70$), and *de novo* participants ($n = 86$). Those who received prior aripiprazole maintained improvements observed during the initial trial. The *de novo* group experienced more improvement than the prior placebo group, likely due to some degree of placebo-induced improvement in the prior blinded trial, though both groups were at levels comparable to the prior aripiprazole group at the *end* of the extension.

7. Safety and Tolerability

In general, weight gain, hyperglycemia, and dyslipidemia are recognized as common adverse events associated with atypical antipsychotics. Greenaway and Elbe [11] published a review of aripiprazole use in child and adolescent psychiatry and noted that the most common side effect was sedation/somnolence. EPS and akathisia developed in 8–28% of the patients included in the review, but those effects were usually mild or moderate in severity. Additionally, the review found that four large, randomized, controlled trials (non-ASD) found no significant increases in weight or body mass index.

In the fixed-dose study of aripiprazole in autistic disorder [21], 21 children of the 218 randomized withdrew due to adverse events (AEs). The placebo group lost four children (7.7%) due to AEs, and the 5, 10, and 15 mg aripiprazole groups lost $n = 5$ (9.4%), $n = 8$ (13.6%), and $n = 4$ (7.4%), respectively. Discontinuation as a result of AEs occurred for eight participants in the flexible-dose study [22] [placebo $n = 3$ (5.9%), aripiprazole $n = 5$ (10.6%)].

Robb et al. [25] conducted a pooled analysis of the safety data from the two large trials, with a total *N* of 313 ($n = 212$ aripiprazole, $n = 101$ placebo). Most adverse events (AEs) in the trials were mild or moderate. The median time to resolution for AEs was generally less than 20 days; sedation had a median time to resolution of 19 days in the active treatment group (compared to 8.5 days for placebo), and extrapyramidal disorder was resolved at a median of 17 days in the active group. For all AEs that occurred at a rate of greater than 5%, peak incidence of onset was at Weeks 1 or 2, with a few exceptions including tremor (Week 3), extrapyramidal disorder (Week 4) and drooling (Week 5). Overall, 20.8% of the participants treated with aripiprazole and 9.9% of the placebo group reported EPS, with no differences observed as a function of age. Change in body weight was 1.6 kg for the children treated with aripiprazole compared to 0.5 kg for the placebo group ($p < 0.001$), and changes in body mass index were +0.7 and +0.2 ($p < 0.001$), respectively. The proportion of participants with clinically-significant weight gain (>7% of baseline weight) was 29% in the aripiprazole group and 5.6% in the placebo group. In both studies, aripiprazole treatment was associated with *decreased* prolactin levels. No treatment-emergent changes in ECG were observed.

Safety/tolerability data were presented at a scientific meeting on the 52-week extension [26]. As expected, the *de novo* group ($n = 86$) and those who received a previous trial of placebo ($n = 70$) experienced more AEs than the group previously exposed to aripiprazole ($n = 174$). Weight gain was the most common AE, followed by vomiting. Some AEs led to discontinuation, including aggression (2.1%), increased weight (2.1%) and EPS (0.6%). EPS occurred in 15% of patients across the groups. After at least 9 months of treatment, aripiprazole was associated with 0.33 SD of increased weight (transformed to Z-scores, a standardized measure of distance from the group mean), relative to normal growth.

8. Regulatory Affairs

Aripiprazole was approved in late 2009 for the treatment of irritability associated with autistic disorder in pediatric patients aged 6 to 17 years, including symptoms of aggression towards others, deliberate self-injury, temper tantrums, and “quickly-changing moods.” Prescribing information released by the company was recently updated with special considerations for treating childhood disorders, recommending that aripiprazole be used in conjunction with a “total treatment program” [10] including multiple modes of treatment.

9. Conclusion

Autism is often associated with maladaptive behaviors that are frequently treated pharmacologically, often with the atypical antipsychotic risperidone. Risperidone, like other atypical antipsychotics, is associated with increased prolactin and significant weight gain, so there is sufficient impetus to identify another treatment with a side effect profile that may be more favorable for such patients. Aripiprazole has demonstrated efficacy relative to placebo for treating irritability associated with autistic disorder. The most commonly observed side effects of aripiprazole in children with autistic disorder were somnolence, weight gain, and EPS. However, in most cases, these effects were not serious or severe. Although a direct comparison to risperidone in this population is not yet available, the current data suggest that aripiprazole may have a more favorable side effect profile for many patients. The treatment effects observed for aripiprazole were not as dramatic as those seen in risperidone trials, but this may be an artifact of study design. The fixed-dose study likely had an increased rate of placebo response due to the relatively low chance (25%) of placebo assignment, a design feature which was known to caregivers. Aripiprazole was effective compared to placebo at doses of 5 mg, 10 mg, and 15 mg per day, and the data pointed to little additional benefit to increasing the dose past 10 mg. Although aripiprazole is only *approved* for treating children

with autistic disorder within the PDDs, it is likely that children across the autism spectrum will benefit similarly from treatment.

10. Expert Opinion

Regardless of the pharmacological agent employed, there will always be some patients who do not respond to an established medicine, such as risperidone. Therefore, the positive clinical data for aripiprazole and its FDA approval are welcome developments for practitioners and patients alike. The data in the Marcus et al. study [21] suggested that aripiprazole may have a relatively flat response curve across doses ranging from 5 to 15 mg for young people with autism, although the placebo response rate was quite high as well. In the flexibly dosed study, nearly 80% of participants assigned to aripiprazole were titrated to 10 mg or less in their last week. This suggests that dosing can be kept quite simple for children with autism. Despite its pharmacokinetic profile, many (if not most) clinicians dose risperidone twice daily in children with ASDs [27]. Due to its longer half-life, aripiprazole is dosed once daily in children with autism, and simplified dosing is a relative advantage.

Another relative advantage for aripiprazole compared with risperidone is in the apparent lack of prolactin elevation. Indeed, prolactin sometimes *declines* with aripiprazole, and it would be helpful to know if this has any negative (or positive) implications beyond an association with sexual side effects (e.g., the possibility of effects on growth). More research on the implications of any prolactin changes would be welcome. Like risperidone, aripiprazole may cause a degree of somnolence in many children with ASDs. As numerous young people with ASD experience sleep disorder, this side effect can often be used to advantage by strategic timing of dosing. Occasional activation with aripiprazole may be a disadvantage in many children with ASD; this can often be avoided by starting with 2 mg/day for at least a week and by dosing in the morning if necessary. In a very small percentage of children treated with risperidone, initial daytime somnolence does not seem to decline with passage of time; such children may benefit by a trial of aripiprazole.

On the face of it, aripiprazole does not have quite the positive clinical impact on average that was reported for risperidone by the Research Units on Pediatric Psychopharmacology Autism Network [28]. This may reflect a real difference in clinical efficacy, or it may be ascribed in part to greater cross-site variation by investigators involved in industry-sponsored trials, such as in the pivotal autism aripiprazole investigations. What is much needed at this juncture is a head-to-head comparison of aripiprazole and risperidone in young people with ASD. Fortunately, a large multi-site clinical trial to do just this is underway in South Carolina, led by Dr. C. Lindsay DeVane (Medical University of South Carolina). In addition to conducting a careful clinical comparison of the two drugs, this team will examine a host of biomarkers to determine if they have predictive utility for clinical response and/or adverse events.

Abbreviations used (in order of appearance)

PDD	pervasive developmental disorder
NOS	not otherwise specified
FDA	Food and Drug Administration
EPS	extrapyramidal symptoms
CGI	Clinical Global Impressions (scale)
ECG	electrocardiogram

ABC	Aberrant Behavior Checklist (scale)
CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale
AE	adverse event
CNS	central nervous system
SD	standard deviation

11. Bibliography

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, DC: American Psychiatric Association; 2000.
2. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators and Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMQR Surveill Summ. 2007; 56:12–28.
3. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children: conformation of high prevalence. Am J Psychiatry. 2005; 162:1133–1141. [PubMed: 15930062]
4. Fombonne E, Zakarian R, Bennett A, et al. Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations. Pediatrics. 2006; 118:e139–e150. [PubMed: 16818529]
5. Lecavalier L. Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. J Autism Dev Disord. 2006; 36:1101–1114. [PubMed: 16897387]
6. Kanne M, Mazurek M. Aggression in children and adolescents with ASD: Prevalence and risk factors. J Autism Dev Disord. 2010 published online 20 October 2010. 10.1007/s10803-010-1118-4
7. Farmer C, Aman M. Aggressive behavior in a sample of children with autism spectrum disorders. Res Autism Spec Dis. 2010; 5(1):317–323.
8. Aman M, Lam K, Van Bourgondien M. Medication patterns in patients with autism: Temporal, regional, and demographic influences. J Child Adolesc Psychopharmacol. 2005; 15:116–126. [PubMed: 15741793]
9. Janssen. Risperidone [package insert]. Titusville, NJ: 2009. July revision
10. Otsuka Pharmaceutical Company, Ltd. Aripiprazole [package insert]. Tokyo, Japan: 2009. November revision
11. Greenaway M, Elbe D. Focus on aripiprazole: A review of its use in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry. 2009; 18:3.
12. Erickson C, Stigler K, Posey D, McDougle C. Aripiprazole in autism spectrum disorders and Fragile X Syndrome. Neurotherapeutics. 2010; 7:258–263. [PubMed: 20643378]
13. DeLeon A, Patel N, Crimson M. Aripiprazole: A comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther. 2004; 26(5):649–666. [PubMed: 15220010]
14. Valicenti-McDermott M, Demb H. Clinical effects and adverse reactions of off-label use of aripiprazole in children and adolescents with developmental disabilities. J Child Adolesc Psychopharmacol. 2006; 16(5):549–560. [PubMed: 17069544]
15. Masi G, Cosenza A, Millepiedi S, Muratori F, Pari C, Salvadori F. Aripiprazole monotherapy in children and young adolescents with pervasive developmental disorders: A retrospective study. CNS Drugs. 2009; 23(6):511–521. [PubMed: 19480469]
16. Stigler K, Posey D, McDougle C. Case Report: Aripiprazole for maladaptive behavior in pervasive developmental disorders. J Child Adolesc Psychopharmacol. 2004; 14(3):455–463. [PubMed: 15650503]
17. Stigler K, Diener J, Kohn A, Li L, Erickson C, Posey D, McDougle C. Aripiprazole in pervasive developmental disorder not otherwise specified and Asperger's disorder: A 14-week, prospective, open-label study. J Child Adolesc Psychopharmacol. 2009; 19(3):265–274. [PubMed: 19519261]

18. Aman, M.; Singh, N. Aberrant Behavior Checklist Manual. East Aurora, NY: Slosson Educational Publications; 1986.

19. Sparrow, S.; Cicchetti, D.; Balla, D. Vineland Adaptive Behavior Scales, Second Edicition, Survey Interview Form/Caregiver Rating Form. Linovia, MN: Pearson Assessments; 2005.

20. Scahill L, Riddle M, McSwiggin-Hardin M, et al. Children's yale-Brown Obsessive Compulsive Scale: Reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997; 36:844–852. [PubMed: 9183141]

21*. Marcus R, Owen R, Kamen L, Manos G, McQuade R, Carson W, Aman M. A double-blind, randomized, placebo-controlled study of fixed-dose aripiprazole in children and adolescents with autistic disorder. J Am Acad Child Adolesc Psychiatry. 2009; 48(11):1110–1119. Randomized controlled trial. [PubMed: 19797985]

22*. Owen R, Sikich L, Marcus R, Corey-Lisle P, Manos G, McQuade R, Carson W, Findling R. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009; 124(6):1533–1540. Randomized controlled trial. [PubMed: 19948625]

23. Aman M, Kasper W, Manos G, Mathew S, Marcus R, Owen R, Mankoski R. Line-item analysis of the Aberrant Behavior Checklist: Results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. J Child Adolesc Psychopharmacol. 2010; 20(5):415–422. [PubMed: 20973712]

24. Findling, R.; Marcus, R.; Kamen, L., et al. 52-week open-label study of the safety and tolerability of aripiprazole flexibly dosed in the treatment of irritability in children and adolescents with autistic disorder. Poster presented at the 48th Annual Meeting of American College of Neuropsychopharmacology; Hollywood, FL. December 2009;

25. Robb A, Anderson C, Bellocchio E, et al. Safety and tolerability of aripiprazole in the treatment of irritability associated with autistic disorder in pediatric subjects. Prim Care Companion J Clin Psychiatry. In Press.

26. McCollough, M.; Owen, R.; Corey-Lisle, P., et al. A 52-week safety and tolerability study of aripiprazole for the treatment of irritability in pediatric patients (6–17 years) with autistic disorder. Poster presented at the 163rd Annual Meeting of the American Psychiatric Association; New Orleans, LA. May 2010;

27. Aman M, Vinks A, Remmerie B, et al. Plasma pharmacokinetic characteristics of risperidone and their relationship to saliva concentrations in children with psychiatric or neurodevelopmental disorders. Clin Ther. 2007; 29(7):1476–1486. [PubMed: 17825699]

28. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone in children with autism and serious behavioral problems. New Engl J Med. 2002; 347:314–321. [PubMed: 12151468]