HHS Public Access

Author manuscript

J Ment Health Res Intellect Disabil. Author manuscript; available in PMC 2017 February 01.

Published in final edited form as:

J Ment Health Res Intellect Disabil. 2011 ; 4(1): 40–52. doi:10.1080/19315864.2010.542274.

Long-Term Aripiprazole in Youth With Developmental Disabilities Including Autism

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Abstract

We retrospectively reviewed clinic charts of 21 children and adolescents with developmental disabilities including autism spectrum disorders (ASD) treated consecutively with aripiprazole (ARI) for irritability and severe challenging behaviors. Data extracted include age, sex, and race; level of intellectual disability (ID); Diagnostic and Statistical Manual-IV diagnoses including comorbidity, ARI dosage, and treatment duration; other psychoactive medications and Clinical Global Impressions–Improvement (CGI-I) at baseline and end point; weight; height; and side effects. Body mass index (BMI) z scores are compared with Centers for Disease Control norms. Eleven boys and 10 girls with ID and/or ASD ages 8 to 18 years (mean age 13.4 years) received ARI; mean dose was 8.4 mg/day (range 2.5 to 15); average duration was 60.6 weeks (7 to 132). Eleven of 21 patients (52%) met CGI-I response of ≤ 2. ARI was well tolerated, including together with stimulants, divalproex, or less commonly other medications. Mean BMI was 23.8 ± 5.9 at baseline and 24.2 ± 5.2 at end. Mean BMI z score increase was 0.06 ± 0.67. Four individuals (19%) manifested early intolerable weight gain. In this long-term clinical sample, ARI was effective in 52% and well tolerated. ARI was mostly weight neutral; early weight gain was intolerable in 19%. Larger long-term outcome studies are warranted in this population.

Keywords

aripiprazole; autism; long-term; children; adolescents

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Aripiprazole (Abilify®; ARI) represents a new class of antipsychotic drug with novel presynaptic dopamine autoreceptor agonism as well as antagonism at postsynaptic D2 and D3 receptor sites (Burris et al., 2002; Yokoi et al., 2002) and has been increasingly studied in the population with developmental disabilities in the past several years. ARI is also a partial 5HT1a receptor agonist designed for a more favorable side effect profile in terms of reduced movement side effects, less appetite increase, and greater weight neutrality than other available atypical antipsychotics (Marder et al., 2003; Posey, Stigler, Erickson, & McDougle, 2008). In children and adolescents, ARI is indicated for the treatment of schizophrenia (ages 13–17 years) and for bipolar disorders (ages 10–17 years; Chang et al., 2007; Correll et al., 2009; Findling et al., 2008; Sanford & Keating, 2007) and for the treatment of irritability associated with autistic disorder in patients ages 6–17 years. Although the atypical antipsychotic risperidone is also Food and Drug Administration approved for irritability and severe behavior problems in children and adolescents with autism spectrum disorders (ASD), side effects including weight gain, prolactin elevation and associated complications may seriously limit risperidone tolerability in clinical practice in individuals with developmental disabilities including ASD (Findling et al., 2003; Hellings, Cardona, Zarcone, Ward, & Schroeder, 2004; Hellings, Zarcone, Crandall, Wallace, & Schroeder, 2001; Hellings et al., 2006; Malone, Gratz, Delaney, & Hyman, 2005; Martin et al., 2004). A recent industry-sponsored 8-week double-blind placebo-controlled trial of ARI dosed flexibly for irritability in children and adolescents with autistic disorder (Owen et al., 2009) found a mean weight gain of 2.0 kg on ARI and 0.8 kg for placebo at Week 8. The companion industry-sponsored 8-week fixed-dose placebo-controlled ARI study found no significant mean weight changes in comparison with placebo for groups receiving 5, 10, or 15 mg/day of ARI (Marcus et al., 2009).

Based on the profile of fewer movement disorder side effects than occur with classical antipsychotics such as haloperidol as well as the possibility of less weight gain, prescription of atypical antipsychotics including ARI is widespread for severe behavior problems in children and adolescents both with and without developmental disabilities (Cooper et al., 2006; McDougle, Stigler, & Posey, 2003). There is no evidence of ARI-associated QTc prolongation on electrocardiogram (Potkin et al., 2003), thus reducing cardiac arrhythmia concerns such as those associated with the atypical antipsychotic ziprasidone (Parikh, Kolevzon, & Hollander, 2008; Posey et al., 2008). Also, ARI does not produce prolactin elevation and normalizes prolactin in low doses, even when prescribed together with risperidone (Byerly et al., 2009; Hellings, Cardona, &Schroeder, 2010). Preliminary studies suggest that children experience side effects of atypical antipsychotics including weight gain more commonly than do adults and with greater severity (Correll et al., 2009). Also, a recent study by Ghaffari and coworkers (2009) found higher obesity rates in children ages 3 to 12 years with ASD currently receiving antipsychotics compared with past or nonusers of these medications. Therefore, ARI is a promising choice of antipsychotic treatment for these individuals if it proves relatively weight neutral in clinical practice.

Based on our previous 5-year prospective study of risperidone, which also found excessive risperidone-associated weight gain in children and adolescents compared with adults (Hellings et al., 2001) as well as clinical experience, we tried ARI treatment in our outpatient and residential clinic settings for children and adolescents with intellectual

disabilities (ID) and/or ASD and severe behavior problems, including aggression and irritability. Following prescription of ARI for approximately a year (2005–2006), we reviewed patient charts retrospectively for ARI dosing, concomitant medications, efficacy, tolerability, and response. We hypothesized, based on our observations, that ARI is efficacious and tolerable in low doses mostly under 15 mg daily and that associated weight gain in the long term even together with other medications is less than that reported with some other atypical antipsychotics including olanzapine, quetiapine, and risperidone. Also, however, some children and adolescents in this population receiving ARI manifested significantly more weight gain than expected for growth early on in the course of treatment and at a rapid rate. Comparison of these findings with standardized Body Mass Index (BMI) *z* scores for age and gender provides clarification regarding observed weight changes.

METHODS

Approval for the retrospective chart review was obtained from the University of Kansas Human Subjects Committee. We reviewed clinic charts of children and adolescents with developmental disabilities including ASD treated consecutively with ARI by the same board-certified psychiatrist specializing in psychopharmacology (J.H.). Most patients received ARI together with other psychoactive medications, which is not uncommon in clinical practice. The following data was extracted from the charts: (a) age, sex, and race; (b) level of ID; (c) presence of ASD or other comorbid diagnoses based on *Diagnostic and Statistical Manual-IV*(*DSM-IV*) diagnostic criteria (American Psychiatric Association, 2000); (d) dates and hence duration of ARI treatment (baseline and end point); (e) weight and height at the visit initiating ARI treatment and at end time point; (f) ARI dosages and any other psychoactive medication prescribed; (g) Clinical Global Impressions–Improvement (CGI-I; Guy, 1976) rating of 2 (*Much Improved*) or 1 (*Very Much Improved*) at the end time point, as an indicator of response.

CGI ratings were performed routinely as part of each clinic visit and recorded in the chart by the treating psychiatrist. Unless used as monotherapy, ARI was started as an add-on to existing pharmacotherapy at 2.5 mg daily. Daily ARI dosing was increased as indicated for aggression or irritability in increments of 2.5 mg at the follow-up visits. This low titration increment was used in order to minimize possible sedation, akathisia, and gastrointestinal side effects associated with dose increases.

STATISTICAL ANALYSIS

BMI *z* scores were calculated on each patient by age and gender adjusted on the SAS macro program (Centers for Disease Control Web site: http://www.cdc.gov/nccdphp). Descriptive statistics were computed and two-sample tests and an analysis of covariance were performed on the data.

RESULTS

Twenty-one children and adolescents (11 boys and 10 girls) ages 8 to 18 years (mean age 13.4 years) at baseline received ARI without another concomitant antipsychotic. See Table 1

for patient demographics. Fifteen individuals lived in a local psychiatric residential treatment facility for children and adolescents with developmental disabilities and/or ASD, whereas 6 received treatment as outpatients of our specialty clinic. Eighteen of 21 had a comorbid attention-deficit/hyperactivity disorder (ADHD) diagnosis, 5 also with bipolar disorder. See Table 1 also for diagnoses, ARI dosing, and other concomitant medications. Although the original chart review included children and adolescents receiving other antipsychotics as well as ARI, most often for the purpose of tapering the previous antipsychotic, participants receiving any other concomitant antipsychotic are excluded from the current analysis, accounting for some intentional missing patient numbers in Table 1. Mean ARI dose was 8.4 mg/day (range 2.5 to 15mg/day), and average ARI treatment duration was 60.6 weeks (7 to 132 weeks). Ten patients (48%) received stimulants, whereas 8 received divalproex (38%). Other medications as detailed in Table 1 included clonidine, sertraline, lithium, oxcarbazepine, buspirone, and propranolol. Eleven of the 21 patients (52%) met the CGI-I response criterion of CGI-I ≤ 2. Mean ARI dose in the subgroup showing response was 8.2 mg/day (range 2.5 to 15 mg/day), similar to the overall mean dose. Overall, ARI was well tolerated; no serious adverse events occurred.

Weight gain in some individuals was marked, as described later. Weight measurements were available for all patients. Both weight and height measurements were available for 19 of the 21 patients. Mean baseline BMI was 23.8 ± 5.9 and mean end BMI was 24.2 ± 5.2. BMI *z* scores increased by a mean of + 0.06; range ± 0.67. See Figure 1 for a scatter plot of the BMI *z* scores over time. Changes in BMI were not significantly different between ARI responders and nonresponders. Rates of BMI *z* score change were not significantly related to age, gender, ARI dose, or duration. Four individuals (19%) experienced significant increases in appetite and weight. Patients 30 and 31 in Table 1 are noteworthy; ages 11 and 9 years, respectively, both were White females. Their parents/guardians discontinued the ARI due to marked weight gain in spite of good response and CGI-I ratings of *Much Improved,* not wanting to pursue dietary intervention due to possible worsening of irritability and aggression. Patient 30 gained 7.0 kg in 24 weeks on ARI plus sertraline, and Patient 31 gained 8.6 kg in 33 weeks on ARI monotherapy. Both patients had refused height measurements at clinic visits and were therefore not included in BMI calculations.

DISCUSSION

Individuals prescribed ARI had failed all prior attempts at behavioral and psychological interventions. Although many participants had a comorbid diagnosis of ADHD, antipsychotics are not indicated for this. Antipsychotics are more effective for severe aggression, repetitive behaviors, anxiety disorders, and mood stabilization. Although mild cases with such problems may respond to applied behavior analytic approaches and psychological interventions alone, for more severe cases appropriate medications often improve the success of such strategies.

Review of this case series found ARI treatment was effective in 52% of cases and in low doses in children and adolescents with developmental disabilities and multiple comorbidities. The sample studied comprises relatively treatment-resistant individuals, notably youths with developmental disabilities in residential treatment and those consulting

at a tertiary referral center. Most patients already received psychiatric medications at presentation. In many cases the feasibility of tapering off existing medications is low if the patients are aggressive or self-injurious and the current medications may be partially effective. Aripiprazole, added gradually, was well tolerated including together with other medications, most often stimulants, apart from excessive weight gain in 19%. Information regarding the lack of serious adverse events is important because in severe cases of aggression and irritability, medication is used in add-on fashion as discussed. The optimum mean ARI dose clinically was 8.4 mg/day or 0.15 mg/kg/day, similar to that of the Stigler, Posey, and McDougle (2004) and Valicenti-McDermott and Demb (2006) case review findings.

The lack of long-term weight gain in most individuals after a mean of 60.6 weeks of ARI treatment is noteworthy because several other psychoactive and antiseizure medications in common use are associated with weight gain, including divalproex, clonidine, lithium, and antidepressants. Also, individuals in this population may receive long-term divalproex or other antiseizure medications for seizures. Concomitant medications decrease concentration-to-dose ratios (C:D ratios) of ARI if they induce the cytochrome P4503A4 enzyme whereas CYP2D6 inhibitor drug combinations may increase the C:D ratio by as much as 45% (Waade, Christensen, Rudberg, Refsum, & Hermann, 2009). Clinicians need to be cognizant of drug interactions at all times, especially when serving this population that often has difficulty verbalizing side effects. For individuals receiving atypical antipsychotics and other medications causing weight gain, practitioners are now required to monitor for metabolic syndrome indicators of weight, height, BMI, fasting lipids, blood glucose, blood pressure, and pulse.

Although it may be argued that food availability is less at a residential facility, food hoarding, snacking, frequent birthday parties, home visits, and eating out all increase food availability there. Four individuals manifested serious acute weight gain after ARI treatment began, 1 of whom received ARI as monotherapy. Dietary intervention was not considered feasible in these cases partly also related to the rapid rate of weight gain and problematic appetite increase. In the risperidone study follow-up performed by the Research Units in Pediatric Psychopharmacology (RUPP) group (Martin et al., 2004), early weight gain at 1 month of treatment predicted ongoing weight increase. The RUPP researchers postulated that leptin receptors may be desensitized by an atypical antipsychotic effect of reducing adipocyte feedback on the satiety center. Genetic factors including 5HT2C receptor gene polymorphisms may also predispose to antipsychotic-induced weight gain (Reynolds, Zhang, & Zhang, 2002). In general, the atypical antipsychotics clozapine, olanzapine, risperidone, and quetiapine are associated with the greatest weight gain side effects. Weight gain is established as a serious potential complication of risperidone treatment, which in children and adolescents can be ongoing in the population with ID and/or ASD (Hellings et al., 2010; Hellings et al., 2001), especially in children and adolescents. Excessive weight gain is associated with medical complications including Type 2 diabetes, cardiovascular disease, hypertension, stroke, sleep apnea, arthritis, and carcinoma of multiple types. Type 2 diabetes and the associated cardiovascular complications may have a more malignant and rapid course in children and adolescents than occurs in adults (Correll et al., 2009). Genetic predisposition including maternal obesity during pregnancy, food access, dietary content,

caloric expenditure by exercise, and epigenetics are important factors that may influence weight gain (Bouchard et al., 2010). At the same time, restricted food preferences in this population combined with violent and destructive behavior associated with frustration may discourage parents of these children and adolescents from trying dietary interventions to address even serious weight gain. Although prospective studies of a drug as monotherapy are superior to case series examining dosing, efficacy, and side effects, long-term clinical studies are important because a majority of children and adolescents in clinical practice with ID and ASD receive combination treatments rather than monotherapy. Although concomitant stimulants caused decreased appetite and weight loss, in clinical practice 30 to 50% of children with developmental disabilities receive stimulant treatment; therefore, this sample is representative of clinical practice.

Limitations of the study include the retrospective design, small sample size, lack of metabolic indicators, lack of systematic side effect rating using questionnaires, and lack of height measurements in two cases with serious acute weight gain. Also, doses of concomitant medications were not deliberately held constant during the period of observation. Because this is a chart review, there was no blinding of ratings nor any control group. Another case series of shorter duration examining clinical ARI treatment after 6.1 ± 4.5 months in 32 children and adolescents (24 of whom met criteria for ASD and 18 with ID) ages 5 to 19 years found good efficacy for aggression and self-injury in 56% of cases (Valicenti-McDermott & Demb, 2006). The poorest response was observed in the 13 cases with a comorbid diagnosis of ADHD, even with concomitant medications. Mean optimum daily maintenance dose, after 6–15 months of treatment, was 10.6 ± 6.9 mg/day or 0.27 mg/kg/day. Although sedation was the most frequent side effect, overall weight gained as indicated by BMI *z* scores was significant but also greatest in children under 12 years of age. Mean BMI increased from 22.5 to 24.1 ($p = .003$). As noted under Results, although the current study statistical analysis did not find a correlation between excessive early weight gain and young age, 1 individual in the analysis (Participant 26) age 8 years and 2 other females not in the analysis under 12 years also gained weight markedly (Participants 30 and 31). Stigler and coworkers' (2004) brief 14-week open prospective study of ARI monotherapy in 13 outpatient children and adolescents with Asperger's syndrome or pervasive developmental disorder not otherwise specified found similar results. Ten of 13 participants manifested sedation; 7 of 13 participants gained weight and 2 participants lost weight (range −2.1 to +7.7 lb in 14 weeks).

Four individuals manifested metabolic syndrome (see Table 1); however, all were obese prior to starting ARI. Two individuals had received risperidone treatment prior to the ARI trial, and another 3 had received risperidone in the distant past. A pooled analysis of the effects of ARI on metabolic measures in child and adolescent placebo-controlled trial participants without IDD was recently carried out by the pharmaceutical manufacturer (Baker et al., 2009). Changes in fasting plasma glucose, total cholesterol, and triglycerides were not statistically significant. Participants receiving ARI in this pooled analysis gained a mean of 1.6 kg versus 0.3 kg for participants receiving placebo ($p < .001$).

CONCLUSIONS

In this retrospective chart review of a long-term clinical sample, ARI was effective in 52% of cases for irritability and severe behavior problems in youth with IDD and/or ASD at a mean dose of 8.4 mg/day. ARI was well tolerated together with other medications, including stimulants and divalproex. In this small sample, ARI was mostly weight neutral, although early appetite increase and weight gain were intolerable in 19%. Larger long-term prospective clinical studies are warranted in this population.

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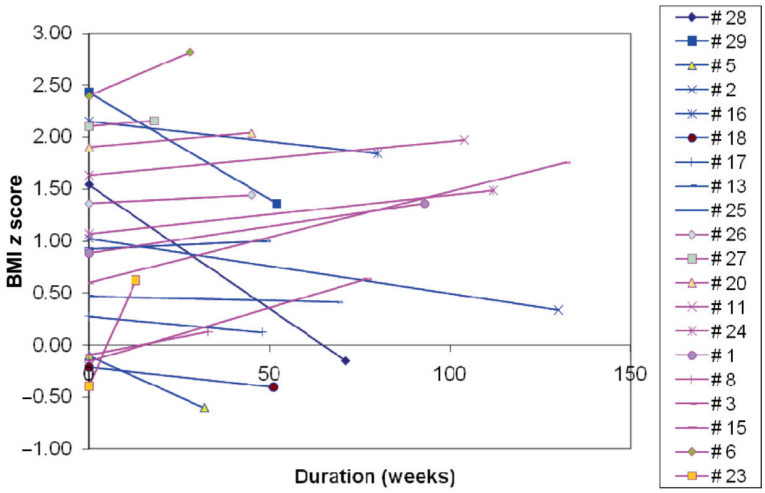

FIGURE 1.

Subject-specific BMI *z* score change and duration of treatment. Figure available in color online.

TABLE 1

Patient Demographics, Diagnosis, and Medications

Participant	Age (years at start)	Race and Gender	Autism spectrum or ID diagnosis	Other comorbid diagnoses	ARI dose mg/day	Other medications	Metabolic syndrome	Prior risperidone
Residential patients								
1	12	WM	Mild ID	ADHD, Bipolar M.D.	7.5	Focalin DVP	−	−
2	12	WM	PDD-NOS Mild ID	ADHD, Bipolar M.D.	7.5	Mixed amphetamine salts, AMI, DVP	−	+
3	12	WM	Unspecified ID	ADHD	10	Mixed amphetamine salts, guanfacine, AMI	−	−
5	13	WF	Mild ID	ADHD, PTSD	15	Clonidine, Li, AMI, DVP	−	−
6	13	WF	Mild ID	ADHD, PTSD	10	MPH, DVP, AMI, sertraline	−	Distant past
8	14	WF	Mild ID	Dysthymic Disorder	10	atomoxetine, Trazodone, DVP	+	−
11	14	WM	Unspecified ID	ADHD, Bipolar M.D.	5	Carbamazepine	−	−
13	14	WM	PDD-NOS Mild ID	ADHD, Bipolar M.D.	10	DEX, clonidine, DVP	−	−
15	14	WF	PDD-NOS Mild ID	ADHD, PTSD, Bipolar M.D., Epilepsy	15	Tiagabine, DVP	+	+
16	15	WM	Asperger's syndrome Mild ID	ADHD, Phonological D/O	15	Concerta, clonidine, oxcarbazepine	−	−
17	15	WF	Autistic D/O Unspecified ID	ADHD, IED, PMDD	5	Buspirone, Sertraline	+	−
18	15	WF	B.I.F.	ADHD, trichotillomania	2.5	Propranolol	−	−
20	16	AAF	Mild ID	ADHD	10	Mixed amphetamine salts, atomoxetine, oxcarbazepine	−	−
23	18	WM	PDD-NOS Mild ID	ADHD, PTSD, enuresis	10	AMI, fluoxetine	−	−
24	18	WM	Mild ID	IED, enuresis, encopresis	5	Clonidine	+	−
Outpatients								
26	8	WM	Autistic D/O Unspecified ID	ADHD, OCD	7.5	Dexedrine	−	−
27	12	F	PDD-NOS Mild ID	ADHD, OCD	2.5	DVP, escitalopram	−	Distant past
28	12	WM	Asperger's B.I.F.	ADHD, OCD	5	MPH, sertraline	N/A	Distant past
29	15	WM	Asperger's	ADHD, ODD	5	Concerta, clonidine	N/A	−

Participant	Age (years at start)	Race and Gender	Autism spectrum or ID diagnosis	Other comorbid diagnoses	ARI dose mg/day	Other medications	Metabolic syndrome	Prior risperidone
30	11	F	PDD-NOS B.I.F.	ADHD	5	sertraline	N/A	+
31	9	F	PDD-NOS Mild ID	OCD	5	–	N/A	–

Note. AA = African American; ADHD = attention-deficit/hyperactivity disorder; AMI = amitriptyline; ARI = aripiprazole; B.I.F. = borderline intellectual functioning; Bipolar M.D. = bipolar mood disorder; DEX = dextroamphetamine; D/O = disorder; DVP = divalproex; F = female; ID = intellectual disability; IED = intermittent explosive disorder; Li = lithium; M = male; MPH = methylphenidate; MR = mental retardation; N/A = not available; OCD = obsessive compulsive disorder; ODD = oppositional defiant disorder; PDD-NOS = pervasive developmental disorder, not otherwise specified; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; RIS = risperidone; W = White