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Aripiprazole Decreases Irritability in 12 out of 14 Youth with Autism Spectrum Disorders

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To The Editor:

Autism is a neurodevelopment disorder characterized by lifelong impairments. Youth with autism spectrum disorders (ASDs) are often prescribed medication treatments to help with maladaptive behaviors (Campbell et al 1978; Cohen et al. 1980; Naruse et al. 1982; Anderson et al. 1984; McDougle et al. 1998; Aman et al. 2005; Chavez et al. 2007; Doyle and McDougle 2012). Both aripiprazole and risperidone have been approved by the United States Food and Drug Administration (FDA) to treat the irritability of autism, and short-term studies have demonstrated safety and preliminary efficacy. In 2006, the FDA approved risperidone for the treatment of irritability in youth with autism based on two, 8 week randomized controlled trials (McCracken et al. 2002; Shea et al. 2004). The FDA then approved aripiprazole in 2009 for treating irritability in youth with autism, who were between the ages 6 and 17 years (Owen et al. 2009).

Aripiprazole has a unique mechanism of action, as it has a combination of partial agonism at the D2 and 5-HT1A receptors and antagonism at the 5-HT2A receptor. In addition, aripiprazole only has moderate H1 affinity, which may lessen attendant weight gain and sedation compared with other medications in the class. We conducted an open-label study of aripiprazole in youth with ASDs over a 12 week period, to test its effectiveness and safety in youth 7–14 years of age. The protocol was institutional review board (IRB) approved by the Cambridge Health Alliance (trial registered at NCT00308074). Parents signed informed consent and youth signed assent forms prior to enrollment. Whereas in prior registration 8 week studies, doses ranged from 2.5 to 15 mg/day, we permitted a daily maximum of 20 mg/day in divided doses. Our study permitted flexible dosing allowing for 2.5–5 mg uptitration on a weekly basis to reduce irritability, with a goal of prescribing the lowest effective dose to minimize side effects.

The study population was boys or girls between the ages of 6 and 17 years with a diagnosis of autism, Asperger's disorder, or pervasive developmental disorder, not-otherwise-specified (PDD NOS) based on American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) and confirmed using both the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord and Le Couteur 1994; American Psychiatric Association 2000). To be included in this study, a subject had to have a minimum score of 18 on the irritability subscale of the Aberrant Behavior Checklist-Irritability (ABC-Irritability) subscale (which has a maximum of 45 points). All subjects had at least a score of moderate on the Clinical Global Impressions Scale-Severity (CGI-S) to be included. Exclusion criteria included any other significant Axis I disorder, estimated intelligence quotient (IQ) < 50, significant medical or neurologic illness, requiring other psychotropic medications that could not be safely tapered, or inability to manage blood draws. To be rated a clinical responder, a subject had to have both a 25% reduction of the ABC-Irritability (Aman et al. 1985) and a score of 1 or 2 (very much improved or much improved) on the Clinical Global Impressions-Improvement Scale (CGI-I). We used several safety measures, such as the Monitoring of Side Effects System (MOSES), laboratory tests, vital signs, and weight, to monitor for adverse effects on a weekly basis.

We report here on 14 children and adolescents, 8 of whom were males (age 13 ± 1.3 years) and 4 of whom were females (age 12 ± 2.3 years). Overall, 87.5% were treatment responders, and the average end-point dose was 10.4 ± 5.3 mg at week 12 (see Table 1). Although all subjects experienced improvement in CGI-I scores from first to final visits, the mean end-point CGI-I score was 1.78 ± 1.58. There were two youth who did not meet response criteria. One had a 25% change in ABC-I but a CGI-Irritability score of 3, and the other had a CGI-I score of 1, but did not have at least 25% reduction in ABC-Irritability. All families chose to continue aripiprazole at the end of this open label study, lending further evidence of the real-world effectiveness of this treatment. Treatment did not raise prolactin levels (they decreased -3.6 [95%CI: -5.5, -1.8] $p = 0.001$), but aripiprazole was associated with 2.6 kg (95%CI: 1.3, 3.8) weight gain (average starting weight was $42.6 \text{ kg} \pm 3.7$, and end-point weight was $45.2 \text{ kg} \pm 3.7$ [$p = 0.0006$]). Liver functions were not elevated, nor were Hg A1C or blood pressure, at end-point. One subject had abnormal involuntary movements that were not tardive dyskinesia and were nonepileptiform in nature. There were no episodes of neuroleptic malignant syndrome or tardive dyskinesia observed. Youth were likely to report sedation, however. Although this study was limited by the sample size and was not placebo controlled or randomized, it was intensive in nature in terms of systematically assessing response and side effects.

Subjects treated with aripiprazole tolerated the medication well, and the results presented here show a slightly higher magnitude of symptom reduction than the 2012 Cochrane Collaborative meta-analysis regarding aripiprazole for ASDs (Ching and Pringsheim 2012). This may be because our protocol allowed for higher doses (up to 20 mg/day) and was slightly longer in duration; 12 weeks as opposed to 8. This is in comparison with data pooled from 316

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Table 1. Symptom Ratings at Baseline and End-Point Over 12 Weeks

	Baseline Mean ± SE	*End-point Mean ± SE*	*Change Mean (95%CI)*	p *value*
YBOCS				
Severity	3.0 ± 0.5	1.8 ± 0.4	−1.2 (−2.4, −0.0)	0.04
Reliability	0.9 ± 0.1	0.9 ± 0.1	0.0 (−0.3, 0.3)	0.9
Obsessions	7.2 ± 1.8	6.2 ± 1.5	−1.0 (−4.9, 2.9)	0.6
Compulsions	9.3 ± 1.6	4.6 ± 1.4	−4.7 (−7.7, −1.7)	0.006
Total	15.9 ± 2.6	10.2 ± 2.0	−5.7 (−10.6, −0.8)	0.03
ABC				
Irritability	24.5 ± 2.9	6.8 ± 2.0	−17.7 (−22.0, −13.3)	< 0.0001
Lethargy	15.0 ± 2.7	5.1 ± 1.4	−9.9 (−16.2, −3.6)	0.005
Stereotypy	8.1 ± 1.8	1.8 ± 0.8	−6.4 (−10.1, 2.7)	0.003
Hyperactivity	27.9 ± 3.2	6.7 ± 1.9	−21.2 (−26.9, −15.6)	< 0.0001
Inappropriate speech	6.4 ± 1.0	2.2 ± 0.6	−4.3 (−5.9, −2.7)	< 0.0001
BPRS				
Total	69.0 ± 4.7	36.1 ± 4.1	−32.9 (−44.7, −21.1)	< 0.0001

YBOCS, Yale–Brown Obsessive Compulsive Scale; ABC, Aberrant Behavior Checklist; BPRS, Brief Psychiatric Rating Scale.

children (taken from two randomized placebo- controlled trials of 8 weeks' duration by Shea et al. [2004] and Owen et al. [2009]). In that pooled study, they noted that ABC-irritability subscale scores decreased by 6.17 (95%CI: 9.07,-3.26), although they only observed a weight gain of 1.13 kg (95% CI: 0.71, 1.51) in 8 weeks. Doses in the Owen study were most likely to be 15 mg by the end of the study (26 of the 36 youth were at this dose at end-point). Doses in the Ching pooled data were described in terms of impact on the ABC-Irritability scores (5 mg/day, reduced by −12.4; 10 mg/day, reduced by −13.2; 15 mg/day, reduced by −14.4; versus placebo, −8.4; all $p < .05$). Across the studies in the Cochrane review, common side effects included weight gain, sedation, and tremor (relative to placebo), which are similar to our findings. We conclude that over 12 weeks, more symptom reduction is possible in this population, but with it may come metabolic risks, such as weight gain.

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