Weight Gain and Metabolic Consequences of Risperidone in Young Children With Autism Spectrum Disorder

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Objective: We examine weight gain and metabolic consequences of risperidone monotherapy in children with autism spectrum disorder (ASD).

Method: This was a 24-week, multisite, randomized trial of risperidone only versus risperidone plus parent training in 124 children (mean age 6.9 ± 2.35 years; 105 boys and 19 girls) with ASD and serious behavioral problems. We monitored height, weight, waist circumference, and adverse effects during the trial. Fasting blood samples were obtained before treatment and at week 16.

Results: In 97 children with a mean of 22.9 ± 2.8 weeks of risperidone exposure, there was a 5.4 ± 3.4 kg weight gain over 24 weeks ($p < .0001$); waist circumference increased from 60.7 ± 10.4 cm to 66.8 ± 11.3 cm ($p < .0001$). At baseline, 59 of 97 children (60.8%) were classified as having normal weight; by week 24, only 25 of 85 (29.4%) remained in that group. Growth curve analysis showed a significant change in body mass index (BMI) *z* scores from pretreatment to week 24 ($p < .0001$). This effect was significantly greater for children with reported increased appetite in the first 8 weeks. From before treatment to week 16, there were significant increases in glucose ($p = .02$), hemoglobin A1c ($p = .01$), insulin ($p < .0001$), homeostatic model assessment–insulin resistance (HOMA-IR; $p < .001$), alanine aminotransferase ($p = .01$), and leptin ($p < .0001$). Adiponectin declined ($p = .003$). At baseline, 7 children met conventional criteria for metabolic syndrome; by week 16, 12 additional children were so classified.

Conclusion: Rapid weight gain with risperidone treatment may promote the cascade of biochemical indices associated with insulin resistance and metabolic syndrome. Appetite, weight, waist circumference, liver function tests, blood lipids, and glucose warrant monitoring.

Clinical trial registration information—Drug and Behavioral Therapy for Children With Pervasive Developmental Disorders; http://clinicaltrials.gov/; NCT00080145

Key words: autism spectrum disorder, risperidone, weight gain, metabolic syndrome, insulin resistance

J Am Acad Child Adolesc Psychiatry 2016;55(5):415–423.

Risperidone is approved for treating irritability in children with *DSM-IV*-defined autistic disorder.[1-3] In addition, risperidone has also demonstrated stable reductions in serious behavioral problems for up to 6 months with rapid return of symptoms with gradual discontinuation of treatment.[4,5] Although there is variability across pediatric patients, exposure to risperidone may cause weight gain and adverse metabolic consequences.[6-9] Weight gain and increased visceral adipose tissue may herald the emergence of insulin resistance and the metabolic syndrome.[10,11] The metabolic syndrome is a cluster of clinical indices including increased waist circumference, elevated glucose and triglycerides, reduced high-density cholesterol, and hypertension.[12] These alterations increase the risk of nonalcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease.[13,14] Weight gain with accumulation of visceral adipose tissue also affects the release of adiponectin and leptin. These cytokines are 2 of several secreted by adipocytes that play a role in glucose regulation, lipid metabolism, inflammation, and insulin sensitivity.[11,15] Adiponectin declines in obesity, which may contribute to insulin resistance and metabolic syndrome.[15,16] Lower levels of adiponectin are also associated with elevations in the inflammatory biomarker C-reactive protein.[15] Leptin, which plays a role in appetite regulation and energy expenditure, tends to increase with weight gain.[17]

Several studies have documented weight gain with olanzapine, risperidone, and aripiprazole in children, but few have examined the range of metabolic changes in risperidone-treated children with ASD.[18] In this study, we monitored weight, waist circumference, and body mass index (BMI), as well as lipids, hepatic transaminases, insulin, adiponectin, leptin, glucose, the homeostatic model assessment of insulin resistance (HOMA-IR), and glycosylated hemoglobin (HgA1c) in children with ASD treated with risperidone for up to 6 months. The children were participants in the Research Units on Pediatric Psychopharmacology (RUPP) Autism

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Network trial of risperidone alone versus risperidone plus parent training.[19,20]

METHOD

Design

The study design and primary results have been reported elsewhere.[19,20] Briefly, 124 medication-free children were randomly assigned to medication plus parent training (n = 75) or medication only (n = 49) for 24 weeks. The unbalanced randomization was based on the assumption that parents would prefer combined treatment. Participants were seen weekly for the first 8 weeks, then monthly until week 24. Blood pressure, pulse, height, and weight were measured at each visit. Adverse events were also systematically reviewed and documented at each visit. A fasting blood sample was collected at the pretreatment screening visit and week 16. We repeated the blood sample at week 16 to reduce participant assessment burden at the detailed endpoint visit (week 24).

During the acute phase (first 8 weeks), 2 treatment-blinded clinicians followed up each participant: an independent evaluator who monitored therapeutic response, and a treating clinician who adjusted the risperidone dose and monitored adverse effects. After week 8, the treating clinician could consult with the behavior therapist for urgent clinical matters. The independent evaluator remained blinded for the entire study. The weight-based, twice-daily risperidone dose was gradually increased over the first 4 weeks. For children weighing 14 to 20 kg, the maximum dose was 1.75 mg/day.

TABLE 1 Baseline Demographic and Clinical Characteristics of Children With Autism Spectrum Disorder (ASD) in a Randomized Trial of Risperidone Only Versus Risperidone Plus Parent Training

Characteristic	Full Sample (N = 124) n (%)	Participants Included in Analysis (n = 97) n (%)	Participants Not Included in Analysis (n = 27)[a] n (%)
Age, y			
4–6	63 (50.8)	48 (49.5)	15 (55.6)
7–10	50 (40.3)	39 (40.2)	11 (40.7)
11–13	11 (8.9)	10 (10.3)	1 (3.7)
Tanner stage <3	119 (96.0)	92 (94.8)	27 (100)
Tanner stage ≥3	5 (4.0)	5 (6.2)	0
Diagnosis			
Autistic disorder	81 (65.3)	64 (66.0)	17 (63.0)
Asperger disorder	8 (6.4)	7 (7.2)	1 (3.7)
PDD-NOS	35 (28.2)	26 (26.8)	9 (33.3)
Race/ethnicity			
White/non-Hispanic	93 (75.0)	75 (77.3)	18 (66.7)
Hispanic	9 (7.3)	7 (7.2)	2 (7.4)
African American	18 (14.5)	13 (13.4)	5 (18.5)
Asian	2 (2.4)	2 (2.1)	1 (3.7)
Native American	1 (0.8)	0 (0)	1 (3.7)
IQ <70[b]	53 (42.7)	43 (44.3)	10 (40.0)
IQ ≧70	69 (55.6)	54 (55.7)	15 (60.0)
Clinical Global Impression—Severity			
Moderate	39 (31.5)	26 (26.8)	13 (48.2)
Marked	52 (41.9)	46 (47.4)	6 (22.2)
Severe	32 (25.8)	24 (24.7)	8 (29.6)
Extreme	1 (0.8)	1 (1.0)	0 (0)
	Mean [95% CI]	**Mean [95% CI]**	**Mean [95% CI]**
Vineland Adaptive Scales			
Communication	59.2 [54.5–64.0]	59.0 [54.0–63.9]	61.1 [42.6–79.6]
Daily living	45.3 [41.4–49.2]	44.9 [40.6–49.3]	46.6 [37.1–56.0]
Socialization	62.3 [58.4–66.3]	62.5 [58.3–66.8]	60.8 [48.2–73.4]
Aberrant Behavior Checklist			
Irritability	29.5 [28.3–30.7]	29.5 [28.2–30.8]	29.5 [26.6–32.3]
Social withdrawal	15.9 [14.4–17.5]	15.7 [13.9–17.5]	16.8 [13.5–20.0]
Hyperactivity	35.6 [34.1–37.1]	35.3 [33.6–37.1]	36.7 [33.6–39.8]
Stereotypy	8.8 [7.8–9.7]	9.2 [8.1–10.3]	7.2 [5.1–9.2]
Inappropriate speech	6.0 [5.3–6.6]	6.2 [5.5–7.0]	5.1 [3.7–6.6]

Note: PDD-NOS = pervasive developmental disorder not otherwise specified.

[a] *Fifteen participants dropped out before week 14, and 12 participants switched to aripiprazole at week 8.*

[b] *IQ missing for 2 participants.*