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Cardiometabolic Outcomes in Children and Adolescents Following Discontinuation of Long-Term Risperidone Treatment

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Abstract

Objective: Second-generation antipsychotics (SGAs) cause weight gain and cardiometabolic abnormalities in children and adolescents. Less well-investigated is the outcome of these adverse events following SGA discontinuation, which we examined.

Methods: Medically healthy 7 to 17-year-old patients treated with risperidone for ≥6 months were enrolled and returned for follow-up, 1.5 years later. Treatment history was extracted from the medical and pharmacy records. Anthropometric and laboratory measurements were obtained at each research visit. Multivariable linear regression analysis and Fisher's exact test were used to compare participants who remained on risperidone at follow-up (Risp Cont Group) with those who had discontinued SGA treatment (SGA Disc Group) and those who had switched to another SGA (SGA Cont Group). Correlational analyses examined the association between change in age-sex specific body mass index (BMI) z score between study entry and follow-up and change in cardiometabolic outcomes.

Results: The sample consisted of 101 participants (93% male) with a mean age of 11.7 ± 2.6 years at study entry. The majority had an externalizing disorder and received 0.03 ± 0.02 mg/kg/day of risperidone, for 2.5 ± 1.6 years. At follow-up, 18% ($n = 18$) were in the SGA Disc Group and 9% ($n = 9$) were in the SGA Cont Group. BMI z score decreased in the SGA Disc Group, remained unchanged in the Risp Cont Group ($n = 74$), and increased in the SGA Cont Group. Importantly, the change in BMI z score between study entry and follow-up was significantly correlated with the change in systolic and diastolic blood pressure z scores, heart rate, waist circumference, percent body fat, inflammatory markers, fasting total insulin, homeostatic model assessment insulin resistance index (HOMA-IR), C-peptide, total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, triglycerides, triglycerides/HDL ratio, and leptin.

Conclusions: Following several years of treatment, risperidone discontinuation is associated with a reversal of the excessive weight gain, mediated by a negative energy balance, and a corresponding improvement in cardiometabolic parameters.

Introduction

Second-generation antipsychotic medications (SGAs) are widely used in children and adolescents (Crystal et al. 2009, Olfson et al. 2010, 2012). Although their introduction has allowed targeting of severe psychopathology, much has been written about their propensity to cause significant weight gain, predisposing to cardiovascular disease because of ensuing cardiometabolic abnormalities, such as insulin resistance and dyslipidemia (Newcomer 2005, Vitiello et al. 2009; De Hert et al. 2011; Bobo et al. 2013). However, in children and adolescents, SGAs are primarily prescribed for externalizing disorders, that is, attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders, in which symptoms of irritability and aggressive behavior predominate (Maglione et al. 2011; Olfson et al. 2010, 2012). Consequently, SGA use in this age group may be more time limited. Based on a randomized discontinuation trial examining the need for risperidone maintenance therapy in youth with disruptive behavior, it was estimated that 52.9% of those switched to placebo would remain relapse-free for the following 6 months (as compared with 70.7% of those continued on risperidone) (Reyes et al. 2006). Therefore, whereas risperidone was statistically more effective at preventing relapse, disruptive behavior remained well controlled in a substantial number of placebo-treated youths (Reyes et al. 2006),

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suggesting that many children and adolescents can tolerate discontinuing the SGA without clinical relapse. Clearly, however, this is not the case with all psychiatric disorders affecting youths; for example, discontinuing risperidone led to rapid resurgence of aggression in children and adolescents with autistic disorder, implying that treatment for extended periods in this condition is necessary (Research Units on Pediatric Psychopharmacology Autism Network 2005).

An increasing number of randomized clinical trials and observational studies have documented the magnitude of weight gain in SGA-treated youths following short- and long-term treatment (Correll et al. 2009; De Hert et al. 2011; Calarge et al. 2012a,b). Although reliable predictors of SGA-induced weight gain remain largely elusive, weight at the onset of treatment, prior SGA trials, the dose of certain SGAs, and perhaps some genetic variants may account for a portion of the interindividual susceptibility to this adverse event (Lipkovich et al. 2008a,b; Calarge et al. 2009c; Correll et al. 2009; Gebhardt et al. 2009; Gentile 2009; Calarge et al. 2012a; Gohlke et al. 2012; Malhotra et al. 2012; Mankoski et al. 2013). In contrast, much less is known about the reversibility of excessive weight after SGA discontinuation. The resistance of idiopathic obesity to behavioral and noninvasive medical interventions has been disappointing. Therefore, it would be of clinical interest to establish whether SGA discontinuation is associated with reversal of the excessive weight gain trajectory and of associated cardiometabolic abnormalities.

Suggestive evidence for normalization of weight following SGA discontinuation in youths comes from the study by Reyes et al. cited earlier (Reyes et al. 2006). Those youths who were randomized to placebo saw their elevated age-sex-specific weight z score nearly return to the baseline level. Similarly, in a small cohort, Lindsay et al. also showed that risperidone discontinuation led to a decrease in excessive body mass index (BMI) z score (Lindsay et al. 2004). However, in both studies, treatment with risperidone had lasted < 1 year, leaving unanswered whether risperidone discontinuation following long-term treatment would similarly be associated with a normalization of anthropometric outcomes. Furthermore, the impact of the resolution of excessive weight on cardiometabolic parameters was not assessed. Therefore, using data from an observational study that enrolled participants on chronic risperidone treatment, we examined the following questions: 1) Does continued risperidone treatment lead to additional developmentally inappropriate weight gain? 2) Does its discontinuation result in normalization of anthropometric and cardiometabolic parameters? 3) Are there baseline characteristics that may distinguish those who continue versus those who discontinue risperidone treatment?

Methods

Participants

As previously described (Calarge et al. 2009a; Calarge et al. 2012a), the primary aim of this study was to investigate the cardiometabolic, hormonal, and skeletal adverse effects of risperidone during long-term use in children and adolescents. Therefore, 7–17-year-old patients treated with risperidone for ≥ 6 months were enrolled, irrespective of their primary psychiatric diagnosis or indication for risperidone. Concurrent treatment with additional psychotropics at study entry, but not with other antipsychotics, was allowed. Participants with neurological or medical conditions that could confound the cardiometabolic assessments were excluded (e.g., seizure disorder, hypothyroidism, dyslipidemia, diabetes) as were pregnant females and those receiving hormonal contraception. Eighteen months after study entry, the participants were invited to return for a follow-up research visit, at which time study entry assessments were repeated.

Procedures

This study was approved by the local Institutional Review Board. Written assent was obtained from children ≤ 14 years old and written consent was obtained from adolescents and parents or guardians.

Start and stop dates of each psychotropic, changes in the dosage and formulation, and the indication for risperidone were recorded from the medical and pharmacy records. All dosages of psychostimulants were expressed in methylphenidate equivalents for amphetamines ($\times 2$).

During the study entry and follow-up research visits, height was measured to the nearest 0.1 cm using a stadiometer (Holtain Ltd., UK) and weight was recorded to the nearest 0.1 kg using a digital scale (Scaletronix, Wheaton, IL) while the subjects were wearing indoor clothes without shoes. Vital signs were obtained with the subject in the sitting position, after 15 minutes of rest. Triceps and subscapular skinfold thickness was measured with a Lange skinfold caliper to the nearest 0.1 mm (Calarge et al. 2009a; Centers for Disease Control 2000). Waist circumference was measured to the nearest 0.1 cm with the measuring tape placed at the uppermost lateral border of the right iliac crest (Calarge et al. 2009a). The average of two measurements was used. In addition, the medical record was reviewed to extract all height and weight measurements, including the measurements closest (i.e., within 0–30 days) to when risperidone treatment was begun. When both were available, BMI (kg/m^2) was computed. As reported elsewhere (Calarge et al. 2012b), we observed excellent correlations between research-based anthropometric measurements and those recorded during clinical encounters falling within 1 month of the research visits.

Pubertal stage was evaluated by a physician. Independently, the participants, with parental help when necessary, completed a self-assessment form that included age-appropriate instructions and pictures depicting Tanner stages I–V. As interrater agreement between the physician and self-rating was high (Calarge et al. 2009a), self-rating was used for participants who declined to undergo this examination.

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), was generated based on a review of the psychiatric record, often supplemented by a clinical interview (conducted by C.A.C.), a standardized interview of the parent using the National Institute for Mental Health (NIMH) Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer et al. 2000), and the Child Behavior Checklist (Achenbach and Rescorla 2001).

At each of the research visits, a blood sample was obtained, after a 9 hour overnight fast, to measure glucose, total insulin, C-peptide, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, leptin, adiponectin, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), thyroid stimulating hormone (TSH), prolactin, and trough serum risperidone and 9-hydroxyrisperidone concentrations (referred to, henceforth, as risperidone concentration). Some of the assays were added at a later point in the study, making them available at study entry for a subsample. Low-density lipoprotein (LDL) cholesterol was estimated following Friedewald's equation (Friedewald et al. 1972). Measurements from participants who were either not fasting or whose fasting status was not recorded were excluded from the relevant analyses, except for prolactin, TSH, IL-6, and hsCRP.

Data analysis

To account for the natural growth observed in children and adolescents monitored over extended periods, weight and BMI measurements were converted into age-sex-specific z scores and percentiles using the 2000 Centers for Disease Control and Prevention normative data (Ogden et al. 2002). Overweight was defined as a BMI percentile between 85 and 95 and obese was defined as a BMI percentile ≥ 95. Blood pressure measurements were converted to age-sex-height-specific z-scores (Falkner and Daniels 2004). Body fat content was estimated using skinfold thickness measurements following Slaughter et al. (1988), and the homeostasis model assessment insulin resistance index (HOMA-IR) was estimated as: [insulin (μUI/mL) $\times$ glucose (mg/dL)]/405 (Matthews et al. 1985). A HOMA-IR cutoff of 4.39 was used to denote insulin resistance in adolescents (i.e., age >12 years) (Lee et al. 2006). The presence of metabolic syndrome was defined using cutoffs listed in Table 1, following Cook et al. (2003). Using the laboratory-determined normal ranges, hyperprolactinemia was defined as a prolactin concentration >15.2 ng/mL in males and >23.3 ng/mL in females.

Table 1. Prevalence of Cardiometabolic Abnormalities in the Sample Grouped by Second-Generation Antipsychotic (SGA) Treatment Status at Follow-up[a]

	Risp Cont n = *74*	*SGA Cont* n = *9*	*SGA Disc* n = *18*	p *value*[b]
Waist circumference $\geq$90th percentile, *n* (%)				
At study entry	5 (7)	2 (25)	1 (6)	>0.20
At follow-up	7 (10)	4 (50)	1 (6)	**<0.02**
Systolic or diastolic blood pressure $\geq$90th percentile, *n* (%)				
At study entry	7 (10)	1 (11)	2 (11)	1.0
At follow-up	11 (16)	4 (44)	3 (17)	>0.10
Glucose $\geq$100 mg/dL, *n* (%)				
At study entry	7 (10)	0	4 (25)	>0.20
At follow-up	7 (11)	2 (22)	0	>0.10
Insulin $\geq$22 μIU/mL, *n* (%)				
At study entry	1 (2)	1 (13)	0	>0.20
At follow-up	3 (5)	0	1 (6)	1.0
HOMA-IR >4.39, *n* (%)[c]				
At study entry	2 (6)	0	0	1.0
At follow-up	2 (5)	1 (25)	1 (9)	>0.20
Triglycerides $\geq$110 mg/dL, *n* (%)				
At study entry	3 (4)	1 (13)	2 (13)	>0.20
At follow-up	9 (14)	4 (44)	2 (13)	***<0.09***
HDL Cholesterol $\leq$40 mg/dL, *n* (%)				
At study entry	6 (9)	1 (13)	0	>0.40
At follow-up	11 (17)	2 (22)	2 (13)	>0.80
$\geq$1 Metabolic syndrome criteria, *n* (%)[d]				
At study entry	16 (24)	3 (38)	6 (38)	>0.40
At follow-up	28 (44)	7 (78)	6 (38)	>0.10
Metabolic syndrome, *n* (%)[d]				
At study entry	2 (3)	0	0	1.0
At follow-up	4 (6)	2 (22)	0	***<0.1***

[a]Laboratory results are reported only for participants who were fasting: $n = 70$, 9, and 16, respectively, at study entry and $n = 66$, 10, and 16, respectively, at follow-up.

[b]Significant findings are bolded, and findings that are marginally significant are bolded and italicized.

[c]The homeostasis model assessment insulin resistance index (HOMA-IR) was defined categorically only in adolescent participants (i.e., age >12 years) (Lee et al. 2006).

[d]This variable includes abnormal waist circumference, systolic and diastolic blood pressure, glucose, triglycerides, and high-density lipoprotein (HDL) cholesterol as defined in this Table (Cook et al. 2003).

As will be detailed, most of the participants remained on risperidone at the follow-up visit (Risp Cont group, $n = 74$), one subgroup switched to another SGA (SGA Cont group, $n = 9$), and another subgroup discontinued all SGA treatment (SGA Disc group, $n = 18$). Fisher's exact test was used to compare categorical variables across the three groups at study entry and the follow-up visit, and multivariable linear regression analysis was used to compare continuous variables, while accounting for age and sex where appropriate. Variables not normally distributed were natural log transformed.

Between study entry and follow-up, a median 8 BMI measurements per participant were available (range 2–19, interquartile range: 6–10). Therefore, to model BMI z score change across the three SGA treatment groups, a hierarchical linear mixed model analysis was used to fit the trajectory of BMI z score over time by estimating a mean curve for BMI z score over time, across each SGA treatment group, from the individual curve of each subject. Thus, the model included both fixed and random effects for intercept and slope (i.e., time), to represent the mean curve and the random variation of each subject's curve from the mean curve, respectively. Informed by our previous work (Calarge et al. 2012a), the model included BMI z score at study entry, sex, treatment with selective serotonin reuptake inhibitors (SSRIs), weight-adjusted (mg/kg) daily dose of psychostimulants, and follow-up SGA treatment status, along with a time by follow-up SGA treatment status interaction effect. The latter interaction effect captures whether the trajectory of BMI z score over time differs across the three SGA treatment groups.

All hypothesis tests were two tailed and analyses utilized procedures from SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

Participant characteristics

Of 151 participants who entered the study, 108 (72%) returned for the follow-up visit after 1.49 ± 0.29 years. Of those, three were excluded from further analyses as their serum risperidone concentration at study entry or follow-up was below the detection limit, suggesting treatment nonadherence. Four other participants were excluded because of the onset of hypothyroidism ($n = 3$) or type 1 diabetes. Participants who returned for follow-up did not differ from those who dropped out of the study on multiple demographic and clinical characteristics including age, BMI z score or obesity status at study entry, and duration of risperidone treatment. However, those who returned for follow-up were more likely to be male (93% vs. 79%, $p < 0.02$), have an autism spectrum disorder (18% vs. 2%, $p < 0.02$), and have been receiving an antidepressant (63% vs. 40%, $p < 0.02$). In addition, they were less likely to have had a history of reported abuse or neglect (6% vs. 16%, $p = 0.05$).

At the follow-up visit, the majority (73%) had continued to take risperidone (Risp Cont Group), with 18% discontinuing all SGA treatment (SGA Disc Group) and 9% switching to another SGA (SGA Cont Group). The latter group included youths treated with different SGAs combined into a single group because of the small number of participants per drug (aripiprazole $n = 3$, ziprasidone $n = 2$, clozapine $n = 2$, quetiapine $n = 1$, and olanzapine $n = 1$). Tables 2 and 3 describe the demographic and clinical characteristics of the participants split into the three SGA treatment groups. No significant clinical differences existed across the three SGA treatment groups at study entry, except for a marginally higher rate of

Table 2. Demographic and Anthropometric Characteristics of the Sample Grouped by Second-Generation Antipsychotic Treatment Status at Follow-up

	Risp Cont n = *74*	*SGA Cont* n = *9*	*SGA Disc* n = *18*	p *value*[a]
Males, *n* (%)	70 (95)	8 (89)	16 (89)	> 0.30
Race/Ethnicity, *n* (%)				> 0.20
White	59 (80)	6 (67)	17 (94)	
African American	11 (15)	2 (22)	0	
Other	2 (3)	0	0	
Hispanic	2 (3)	1 (11)	1 (6)	
Age, years				
At study entry	11.8 ± 2.7	10.7 ± 2.5	11.5 ± 2.3	> 0.40
At follow-up	13.3 ± 2.7	12.3 ± 2.6	13.1 ± 2.3	> 0.50
Tanner stage, % I/II/III/IV/V				
At study entry	36/18/18/23/5	33/22/44/0/0	28/33/6/33/0	> 0.20
At follow-up	15/22/18/14/31	22/33/0/22/22	17/17/6/33/28	> 0.50
Anthropometric measures				
Body Mass Index *z* score				
At start of risperidone[b]	0.05 ± 1.03	−0.19 ± 1.41	0.25 ± 1.07	> 0.60
At study entry	0.36 ± 1.11	0.98 ± 1.41	0.66 ± 0.73	> 0.10
At follow-up	0.32 ± 1.11	1.66 ± 0.57	0.12 ± 0.92	**0.001**
Annual rate of change	−0.02 ± 0.34	0.40 ± 0.56	−0.35 ± 0.41	< **0.001**
Overweight, *n* (%)				
At Start of risperidone[b]	9 (17)	1 (14)	0	> 0.20
At study entry	13 (18)	2 (22)	4 (22)	> 0.70
At follow-up	10 (14)	2 (22)	2 (11)	> 0.70
Obese, *n* (%)				
At Start of risperidone[b]	2 (4)	0	2 (15)	> 0.10
At study entry	7 (10)	3 (33)	2 (11)	> 0.10
At follow-up	10 (14)	5 (55)	1 (6)	< **0.006**
Waist circumference, cm[c]				
At study entry	70.9 ± 13.9	75.6 ± 16.5	71.1 ± 10.1	> 0.20
At follow-up	75.1 ± 15.2	90.0 ± 11.9	70.7 ± 11.2	**0.0005**
Percent body fat[c]				
At study entry	19.4 ± 9.5	24.6 ± 14.3	21.7 ± 8.3	> 0.20
At follow-up	19.1 ± 10.2	30.1 ± 11.4	16.9 ± 8.9	< **0.007**
Heart rate, bpm[c]				
At study entry	85.7 ± 13.7	85.3 ± 10.2	85.3 ± 12.1	> 0.90
At follow-up	81.5 ± 13.1	83.9 ± 19.3	77.2 ± 14.2	> 0.30
Pulse pressure, mmHg[c]				
At study entry	46.0 ± 10.0	42.8 ± 9.8	47.7 ± 11.5	> 0.50
At follow-up	46.3 ± 11.0	52.0 ± 13.5	51.3 ± 13.0	< ***0.09***
Systolic blood pressure *z* score				
At study entry	−0.02 ± 0.95	−0.00 ± 0.98	0.38 ± 0.98	> 0.20
At follow-up	−0.19 ± 1.16	1.02 ± 1.96	0.21 ± 1.14	< **0.02**
Diastolic blood pressure *z* score				
At study entry	−0.15 ± 0.72	0.07 ± 0.79	0.04 ± 0.58	> 0.40
At follow-up	−0.18 ± 0.88	0.42 ± 0.89	−0.24 ± 0.75	> 0.10

Values are reported as mean ± sd or *n* (%).
[a]Significant findings are bolded and findings that are marginally significant are bolded and italicized.
[b]Data are available for *n* = 52, 7, and 13, across the three groups, respectively.
[c]Adjusted for age and sex.

disruptive behavior disorders in the Risp Cont Group and a significantly higher weight-adjusted dose of risperidone in the SGA Cont Group.

Anthropometric outcomes

As shown in Table 2, no significant between-group difference in BMI *z* score was observed either at the onset of risperidone treatment or at study entry. However, at the follow-up visit, the SGA Cont Group had a significantly higher BMI *z* score than the other two groups (both $p \leq 0.0005$), which did not differ from one another. Interestingly, the SGA Cont Group exhibited a greater increase in BMI *z* score between the onset of risperidone treatment and study entry than did the Risp Cont Group (least squares [LS] mean difference: 0.83, 95% confidence interval [CI]: 0.13, 1.54) and the SGA Disc Group (LS mean difference: 0.82, 95% CI: 0.00,

Table 3. Clinical Characteristics of the Sample Grouped by Second-Generation Antipsychotic (SGA) Treatment Status at Follow-up

	Risp Cont n = *74*	*SGA Cont* n = *9*	*SGA Disc* n = *18*	p *value*[a]
Disruptive behavior disorder, *n* (%)	68 (92)	7 (78)	14 (78)	***<0.09***
Attention-deficit/hyperactivity disorder, *n* (%)	65 (88)	7 (78)	17 (94)	>0.30
Anxiety disorder, *n* (%)	23 (31)	3 (33)	5 (28)	1.0
Depressive disorder, *n* (%)	3 (4)	0	2 (11)	>0.20
Autism spectrum disorder, *n* (%)	12 (16)	2 (22)	5 (28)	>0.40
Tic disorder, *n* (%)	17 (23)	3 (33)	5 (28)	>0.70
Pharmacotherapy				
Duration of risperidone treatment, years[b]				
At study entry	2.64 ± 1.65	1.97 ± 1.58	1.91 ± 1.34	>0.10
At follow-up	4.05 ± 1.70	2.47 ± 1.60	2.39 ± 1.52	**<0.0001**
Risperidone dose, mg/kg/d[b]				
At study entry	0.03 ± 0.02	0.04 ± 0.02	0.02 ± 0.02	**<0.02**
At follow-up	0.03 ± 0.02	—	—	—
Psychostimulants, *n* (%)				
At study entry	52 (70)	4 (44)	14 (78)	>0.20
At follow-up	59 (80)	5 (56)	11 (61)	>0.10
α_2-agonists, *n* (%)				
At study entry	23 (31)	4 (44)	4 (22)	>0.50
At follow-up	25 (34)	6 (67)	5 (28)	>0.10
Antidepressants, *n* (%)				
At study entry	45 (61)	6 (67)	14 (78)	>0.40
At follow-up	43 (58)	8 (89)	10 (56)	>0.10
Mood stabilizers, *n* (%)				
At study entry	5 (7)	0	0	>0.70
At follow-up	6 (8)	0	2 (11)	>0.60

[a]Significant findings are bolded and findings that are marginally significant are bolded and italicized.
[b]Adjusted for age and sex.

1.64), which did not differ from each other (LS mean difference: 0.01, 95% CI: −0.53, 0.56).

After adjusting for age and sex, the SGA Disc Group gained significant weight (+5.0 kg, 95% CI: 1.6, 8.3) between study entry and follow-up, which was not different ($p > 0.20$) from the weight gained by the Risp Cont Group (+6.9 kg, 95% CI: 4.4, 9.4) but it was significantly less ($p < 0.0001$) than that gained by the SGA Cont Group (+17.5 kg, 95% CI: 13.1, 21.9). However, whereas the BMI in the SGA Disc Group did not significantly change (−0.36 kg/m^2, 95% CI: −1.30, 0.58) between study entry and follow-up, after adjusting for age and sex, that of the other two groups significantly increased (Risp Cont Group: +0.93 kg/m^2, 95% CI: 0.23, 1.64 and SGA Cont Group: +3.99 kg/m^2, 95% CI: 2.76, 5.23). Taking age-appropriate growth into account, this translated into a reversal of the age-sex-specific BMI *z* scores in the SGA Disc Group to the pre-risperidone level (−0.54, 95% CI: −0.80, −0.28), the maintenance of the BMI *z*

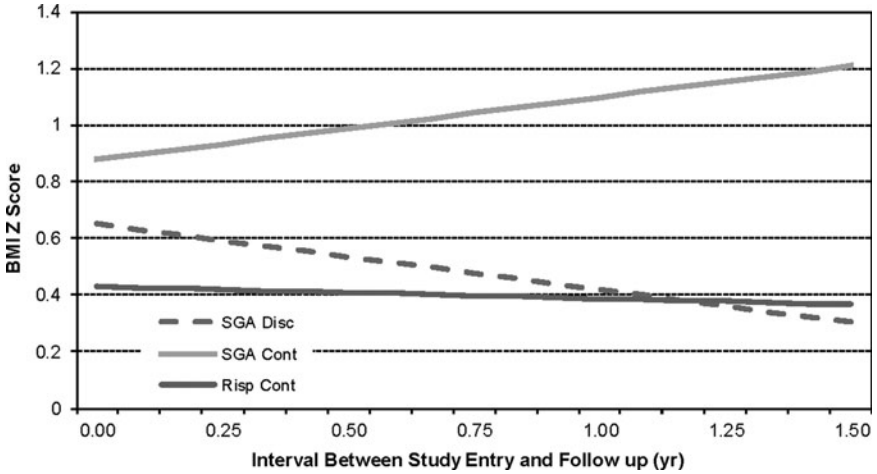

FIG. 1. Trajectory of body mass index (BMI) *z* score across those who remained on risperidone, switched to another second-generation antipsychotic (SGA), or discontinued SGAs

scores in the Risp Cont Group (-0.04, 95% CI: −0.16, 0.09), and a further increase in BMI z scores in the SGA Cont Group (+0.68, 95% CI: 0.31, 1.04). After adjusting for BMI z score at study entry ($\beta = 0.91$, $p < 0.0001$), male sex ($\beta = -0.00$, $p > 0.90$), SSRI treatment ($\beta = -0.17$, $p < 0.0001$), and the weight-adjusted dose of psychostimulants ($\beta = -0.18$, $p < 0.0001$), there was a significant time by SGA treatment group interaction effect whereby the BMI z score significantly decreased over time in the SGA Disc Group ($\beta = -0.19$, $p < 0.004$) but significantly increased in the SGA Cont Group ($\beta = 0.26$, $p < 0.003$) compared with the Risp Cont Group (Fig. 1).

The differential trajectory in BMI z score over time translated into nearly triple the rate of overweight and obesity in the SGA Cont Group (78%) compared with the other two groups (27% for the Risp Cont Group and 17% for the SGA Disc Group, respectively, $p = 0.004$). As would then be expected, at follow-up, the SGA Cont Group also had significantly larger waist circumference and percent body fat as well as higher age-sex-height-specific systolic blood pressure z score (Table 2). The change in BMI z score between study entry and follow-up in the entire sample was positively correlated with change in systolic and diastolic blood pressure z scores (Spearman's $\rho = 0.20$, $p < 0.06$ and $\rho = 0.26$, $p < 0.02$, respectively) and, after adjusting for age and sex, with heart rate (Spearman's $\rho = 0.28$, $p < 0.006$), waist circumference (Spearman's $\rho = 0.74$, $p < 0.0001$), and percent body fat (Spearman's $\rho = 0.62$, $p < 0.0001$).

Cardiometabolic outcomes

The change in age-sex-specific BMI z score between the two research visits (i.e., at study entry and follow-up) was significantly correlated with the age-sex-adjusted change in a number of cardiometabolic outcomes including total insulin (Pearson's $\rho = 0.26$, $p < 0.03$), HOMA-IR (Pearson's $\rho = 0.22$, $p < 0.07$), C-peptide (Pearson's $\rho = 0.38$, $p < 0.03$), total cholesterol (Pearson's $\rho = 0.25$, $p < 0.03$), LDL cholesterol (Pearson's $\rho = 0.33$, $p < 0.004$), HDL cholesterol (Pearson's $\rho = -0.25$, $p < 0.03$), triglycerides (Pearson's $\rho = 0.25$, $p < 0.03$), and triglycerides/HDL ratio (Pearson's $\rho = 0.24$, $p < 0.04$). It was also correlated with change in leptin (Pearson's $\rho = 0.55$, $p < 0.0001$), IL-6 (Pearson's $\rho = 0.38$, $p < 0.02$), and hsCRP (Spearman's $\rho = 0.27$, $p < 0.08$).

When compared across the three SGA treatment groups, several significant or marginally significant differences in the cardiometabolic parameters emerged, with the SGA Cont group being different from the two other groups, which did not differ from each other (Tables 1 and 4). In addition, whereas total cholesterol increased between the two research visits in the SGA Cont Group (+14.5 mg/dL), it decreased in the Risp Cont Group (−2.7 mg/dL, $p < 0.05$) and the SGA Disc Group (−9.4 mg/dL, $p < 0.02$). Similarly, the change in LDL cholesterol was larger in the SGA Cont Group than in the other two groups (+18.8 mg/dL vs. −1.4 mg/dL and −4.6 mg/dL, both $p < 0.003$). Overall, there was a marginally higher rate of metabolic syndrome in the SGA Cont Group at follow-up (Table 1).

Hormonal outcomes

Prolactin concentration was higher at follow-up in the Risp Cont Group than in the other two groups (both $p < 0.007$). In fact, although there was no difference across the three SGA treatment groups in the rate of hyperprolactinemia at study entry ($p > 0.60$), none of the participants in either the SGA Disc or the SGA Cont Group had this hormonal abnormality at follow-up, whereas 47% of those in the Risp Cont Group did ($p < 0.0001$). On the other hand, TSH concentration did not differ among the three groups. However, whereas ~14% of the participants had a TSH above the laboratory-determined cutoff for normal of 4.20 μIU/mL at study entry, similarly distributed across the SGA treatment groups ($p > 0.80$), 7% had elevated TSH at follow-up, all in the Risp Cont Group. Nonetheless, this difference was not significant ($p > 0.40$). It is of note that the highest TSH value was 8.91 μIU/mL; notably, however, participants with hypothyroidism were excluded from the analyses as described earlier.

Discussion

To our knowledge, this is the largest observational study to date monitoring metabolic outcomes in children and adolescents treated with SGAs for several years. Using a largely overlapping sample, we previously reported that substantial weight gain occurs following the initiation of risperidone treatment (Calarge et al. 2009a) and identified clinical, pharmacological, and genetic variables that may moderate weight gain (Calarge et al. 2009c, Calarge et al. 2012a). We further proposed that the rate at which weight is gained impacts the severity of cardiometabolic abnormalities (Calarge et al. 2012b). The primary finding of the current analysis is that after an initial mean 2.4 years of treatment, risperidone continuation is associated with persistence of excessive weight, whereas risperidone discontinuation leads to the normalization of weight. This is not to say that the SGA Disc Group actually lost weight between study entry and follow-up. In fact, they gained weight, but at a lower rate, commensurate with necessary gain for normal growth and development. This allowed them to achieve a negative energy balance and their age-sex-specific BMI z scores to normalize. We further found that change in BMI z score over the study period impacted cardiometabolic parameters in predictable ways.

A comprehensive assessment of factors associated with SGA treatment continuation is beyond the aims of this study. Across multiple variables, summarized in Tables 1–4, no significant differences were identified between the Risp Cont and SGA Disc Groups, whether at the onset of risperidone treatment or study entry. On the other hand, the SGA Cont group appears to have been receiving a higher weight-adjusted dose of risperidone at study entry and to have had a larger increase in BMI z score since the initiation of risperidone. These two characteristics may be related in light of evidence suggesting that weight gain during risperidone treatment is dose dependent (Correll et al. 2009; Gentile 2009). However, neither the cumulative exposure period to risperidone nor the cumulative dose of risperidone over that period differed across the three SGA treatment groups (data available from the authors). This is consistent with our prior finding that the dose effect of risperidone on weight gain attenuates over time, as excessive weight plateaus (Calarge et al. 2012a). It is of note that whereas discontinuing risperidone was attributed by the physician or the family to weight gain in 56% of the SGA Cont Group, this was the case for only 6% of the SGA Disc Group ($p < 0.0002$). In contrast, 31% of the SGA Disc Group reported that risperidone was no longer necessary as a reason for discontinuation compared to none of the SGA Cont Group ($p < 0.0002$). This suggests that various considerations, including clinical improvement, underlie the decision to discontinue SGA treatment. In contrast, the decision to switch to an alternate SGA agent appears to be primarily motivated by adverse events, in particular weight gain. Our data show that substitution with another SGA provides no improvement in weight status at best and, in many instances, it is actually associated with additional weight gain. In fact, the participants who switched SGAs exhibited varying degrees of change in BMI z score between study entry and follow-up depending upon the alternative SGA they were

Table 4. Cardiometabolic and Hormonal Laboratory Tests in the Sample Grouped by Second-Generation Antipsychotic Treatment Status at Follow-up[a]

	Risp Cont n = *74*	*SGA Cont* n = *9*	*SGA Disc* n = *18*	p *value*[b]
Glucose, mg/dL				
At study entry	91.4 ± 9.9	91.3 ± 4.0	91.6 ± 8.5	> 0.90
At follow-up	89.6 ± 10.3	91.4 ± 25.0	90.0 ± 5.0	> 0.80
C-peptide, ng/mL				
At study entry	1.7 ± 0.7	1.8 ± 0.8	1.5 ± 0.2	> 0.60
At follow-up	1.8 ± 0.9	2.7 ± 0.8	1.8 ± 0.7	**0.002**
Insulin, μIU/mL				
At study entry	6.9 ± 5.0	8.2 ± 6.5	6.3 ± 3.1	> 0.60
At follow-up	7.2 ± 6.9	10.0 ± 3.6	7.6 ± 6.1	< ***0.06***
HOMA-IR[c]				
At study entry	1.58 ± 1.20	1.86 ± 1.54	1.46 ± 0.75	> 0.60
At follow-up	1.57 ± 1.59	2.40 ± 1.52	1.68 ± 1.39	< ***0.06***
Total cholesterol, mg/dL				
At study entry	156.6 ± 26.4	148.5 ± 12.5	164.6 ± 28.6	> 0.20
At follow-up	155.4 ± 24.6	162.8 ± 19.2	163.7 ± 38.7	> 0.70
LDL cholesterol, mg/dL				
At study entry	86.5 ± 22.0	78.4 ± 19.1	94.4 ± 26.6	> 0.20
At follow-up	86.4 ± 19.5	95.6 ± 24.3	95.1 ± 29.2	> 0.30
HDL cholesterol, mg/dL				
At study entry	59.3 ± 14.9	55.9 ± 15.5	55.5 ± 12.6	> 0.30
At follow-up	55.5 ± 15.7	49.3 ± 8.8	52.5 ± 16.5	> 0.10
Triglycerides, mg/dL				
At study entry	59.9 ± 73.2	71.4 ± 40.1	73.6 ± 49.5	< ***0.07***
At follow-up	70.1 ± 67.0	94.8 ± 54.6	77.2 ± 56.7	< ***0.10***
Triglycerides/HDL cholesterol				
At study entry	1.23 ± 1.98	1.41 ± 0.90	1.48 ± 1.27	< ***0.08***
At follow-up	1.61 ± 2.34	2.10 ± 1.46	1.68 ± 1.61	< ***0.08***
Leptin, ng/mL				
At study entry	4.8 ± 4.5	7.5 ± 5.7	6.3 ± 6.1	> 0.20
At follow-up	5.6 ± 5.7	15.5 ± 9.9	4.6 ± 5.1	< **0.002**
Adiponectin, μg/mL				
At study entry	16.3 ± 6.9	12.5 ± 6.1	14.6 ± 7.1	> 0.30
At follow-up	13.3 ± 6.1	9.3 ± 3.4	14.8 ± 8.9	**0.05**
Interleukin-6, pg/mL				
At study entry	1.16 ± 0.87	1.03 ± 0.92	0.84 ± 0.50	> 0.40
At follow-up	1.20 ± 1.30	1.40 ± 0.98	1.13 ± 1.10	> 0.70
hs CRP, mg/L				
At study entry	0.86 ± 1.86	0.24 ± 0.12	0.37 ± 0.39	> 0.90
At follow-up	0.81 ± 1.87	1.30 ± 1.61	0.50 ± 1.2	> 0.10
Thyroid stimulating hormone, μIU/mL				
At study entry	2.7 ± 1.3	2.4 ± 1.1	2.2 ± 1.2	> 0.20
At follow-up	2.7 ± 1.3	2.7 ± 1.2	1.9 ± 0.7	> 0.10
Prolactin, ng/mL				
At study entry	21.5 ± 15.3	28.7 ± 14.8	22.4 ± 17.3	> 0.50
At follow-up	18.2 ± 14.1	6.7 ± 6.2	5.8 ± 3.1	< **0.0001**

[a]All analyses were adjusted for age and sex. Except for high sensitivity C-reactive protein (hs CRP), interleukin 6, thyroid stimulating hormone, and prolactin, laboratory results are reported only for participants who were fasting: $n = 67$, 8, and 16, respectively, at study entry and $n = 63$, 9, and 16 at follow-up. Interleukin-6, hs CRP, and adiponectin were added while the study was ongoing, making them available for 34, 4, and 5 participants, respectively, at study entry.

[b]Significant findings are bolded and findings that are marginally significant are bolded and italicized.

[c]The homeostasis model assessment insulin resistance index.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

prescribed (aripiprazole, $n=3$, BMI z score change $=0.2\pm0.2$; ziprasidone, $n=2$, $\Delta=0.0\pm0.1$; clozapine, $n=2$, $\Delta=2.0\pm1.5$; quetiapine, $n=1$, $\Delta=0.5$; and olanzapine, $n=1$, $\Delta=1.0$); however, none actually had a decline in BMI z score. Therefore, it appears that children and adolescents who gain substantial weight on risperidone are equally likely to gain excessive weight on other SGAs.

The cardiovascular sequelae of excessive weight are well established (Wormser et al. 2011). Moreover, weight loss interventions have been shown to improve cardiovascular parameters (Norris et al. 2005; Rucker et al. 2007; De Miguel-Etayo et al. 2013). Therefore, it was not surprising to see all cardiometabolic markers, including blood pressure, insulin resistance, lipid parameters, and even inflammatory markers, change in correlation with the change in BMI z score. It is reassuring that despite maintaining excessive weight for several years, participants who discontinued risperidone saw their BMI z score normalize and the change was associated with an improvement in a host of cardiometabolic markers. This is consistent with findings from clinical trials switching youth and adults from one SGA to another with the potential to cause less weight gain, as well as with findings from weight loss interventions in which idiopathic obesity had been present presumably for years (Norris et al. 2005; Rucker et al. 2007; Rosenheck et al. 2009; Mukundan et al. 2010).

We and others have found prolactin concentration to be closely tied to the dose of risperidone (Kinon et al. 2003; Calarge et al. 2009b). At follow-up, prolactin concentration was strongly correlated with risperidone concentration (Pearson's $\rho=0.56$, $p<0.0001$) and the change in prolactin between study entry and follow-up was strikingly different across the three SGA treatment groups. Consistent with our previous findings and those of others (Findling et al. 2003; Kinon et al. 2003; Calarge et al. 2009b), hyperprolactinemia persisted in $\sim$50% of the risperidone-treated children and adolescents, even after nearly 4 years of treatment. To what extent this may adversely impact health and development requires further investigation, particularly in light of some preclinical and clinical evidence, including from our laboratory, suggesting that hyperprolactinemia is inversely associated with bone mass (Calarge et al. 2010, 2013).

Thyroid dysfunction has been associated with both psychopathology and the use of antipsychotic medications, particularly quetiapine (Greenspan et al. 2005; Kelly and Conley 2005; Bou Khalil and Richa 2011; Dickerman and Barnhill 2012). Although we did not find significant differences in TSH concentration across the three SGA treatment groups, it is concerning that three participants were excluded from the analysis because of hypothyroidism, and several participants, restricted to the Risp Cont Group, continued to show elevated TSH. Therefore, further research is necessary to investigate this preliminary finding and examine whether it is related to SGAs or the underlying psychopathology.

Our findings are important in many respects as reviewed; nonetheless, their interpretation must take into account several shortcomings. First, the study is observational, suggesting that a variety of uncontrolled factors could explain the differences we observed. Further, the participants had already received risperidone for a minimum of 6 months before entering the study. Therefore, it is unclear how our findings may apply to patients who had received SGA treatment, risperidone or otherwise, for a shorter period of time before discontinuing it. As discussed earlier, participants in the SGA Cont Group switched from risperidone to one of several SGAs with clearly different potential to cause weight gain and cardiometabolic abnormalities. Merging them into a single group was done for practical, as opposed to scientific, reasons, because of the small sample size. Clearly, this would influence the findings related to that group, but should not affect the results from the correlational analyses examining the association between change in BMI z score and cardiometabolic parameters. It should also not affect the findings related to the SGA Disc Group, a primary focus of this report. An additional related factor is that the discontinuation of risperidone and, in the SGA Cont Group, the initiation of the new SGA treatment, occurred at different times for different participants. Therefore, further anthropometric and metabolic changes may still take place for at least some participants who have not reached their new ''homeostatic'' set point. Finally, of those who entered the study, 28% did not return for follow-up. This significant attrition may also have impacted our findings, particularly as these participants differed in certain demographic and clinical characteristics (e.g., females) from those who completed the follow-up.

Conclusions

In sum, SGA treatment appears to alter the homeostatic set point controlling energy balance whereby, despite interindividual variability, on average, the new equilibrium corresponds to a higher BMI than is appropriate for age and sex. This new threshold seems stable over time, at least for risperidone, as more extended treatment does not appear to lead to further excessive weight gain. However, discontinuation of the treatment results in a return to the baseline BMI z score whereas switching to another SGA is associated with a varying magnitude of BMI change, depending upon the propensity of the particular new SGA to cause weight gain. Idiopathic obesity responds to weight loss interventions, but the benefits subside over the intermediate term. It is, therefore, reassuring that the discontinuation of risperidone, particularly after years of use, is associated with largely spontaneous resolution of the excessive weight and a favorable change in cardiometabolic parameters.

Clinical Significance

Children and adolescents who discontinued risperidone lost the excessive, age-inappropriate, weight they had gained on it. Further, this was associated with an improvement in multiple cardiometabolic parameters. Such findings are somewhat reassuring, particularly considering that the participants had been in treatment for an extended period. Nonetheless, because no demographic or clinical characteristic at study entry helped predict who might discontinue risperidone by follow-up, clinicians must remain vigilant about following recommended guidelines for monitoring in order to minimize the potential cardiovascular sequelae of SGAs, especially when treatment is needed for years.

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