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Metformin for Treatment of Overweight Induced by Atypical Antipsychotic Medication in Young People With Autism Spectrum Disorder
A Randomized Clinical Trial

Evdokia Anagnostou, MD; Michael G. Aman, PhD; Benjamin L. Handen, PhD; Kevin B. Sanders, MD; Amy Shui, MA; Jill A. Hollway, PhD; Jessica Brian, PhD; L. Eugene Arnold, MD; Lucia Capano, MD; Jessica A. Hellings, MD; Eric Butter, PhD; Deepali Mankad, MD; Rameshwari Tumuluru, MD; Jessica Kettel, MD; Cassandra R. Newsom, PsyD; Stasia Hadjiyannakis, MD; Naomi Peleg, MSc; Dina Odrobina, BMSc; Sarah McAuliffe-Bellin, MEd; Pearl Zakroysky, MPH; Sarah Marler, MA; Alexis Wagner, BS; Taylor Wong, BS; Eric A. Macklin, PhD; Jeremy Veenstra-VanderWeele, MD

IMPORTANCE Atypical antipsychotic medications are indicated for the treatment of irritability and agitation symptoms in children with autism spectrum disorder (ASD). Unfortunately, these medications are associated with weight gain and metabolic complications that are especially troubling in children and with long-term use.

OBJECTIVE To evaluate the efficacy of metformin for weight gain associated with atypical antipsychotic medications in children and adolescents with ASD (defined in the protocol as *DSM-IV* diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified), aged 6 to 17 years.

DESIGN, SETTING, AND PARTICIPANTS A 16-week, double-blind, placebo-controlled, randomized clinical trial was conducted at 4 centers in Toronto, Ontario, Canada; Columbus, Ohio; Pittsburgh, Pennsylvania; and Nashville, Tennessee. In all, 209 potential participants were screened by telephone, 69 individuals provided consent, and 61 participants were randomized to receive metformin or placebo between April 26, 2013, and June 24, 2015.

INTERVENTIONS Metformin or matching placebo titrated up to 500 mg twice daily for children aged 6 to 9 years and 850 mg twice daily for those 10 to 17 years.

MAIN OUTCOMES AND MEASURES The primary outcome measure was change in body mass index (BMI) *z* score during 16 weeks of treatment. Secondary outcomes included changes in additional body composition and metabolic variables. Safety, tolerability, and efficacy analyses all used a modified intent-to-treat sample comprising all participants who received at least 1 dose of medication.

RESULTS Of the 61 randomized participants, 60 participants initiated treatment (45 [75%] male; mean [SD] age, 12.8 [2.7] years). Metformin reduced BMI *z* scores from baseline to week 16 significantly more than placebo (difference in 16-week change scores vs placebo, −0.10 [95% CI, −0.16 to −0.04]; $P = .003$). Statistically significant improvements were also noted in secondary body composition measures (raw BMI, −0.95 [95% CI, −1.46 to −0.45] and raw weight, −2.73 [95% CI, −4.04 to −1.43]) but not in metabolic variables. Overall, metformin was well tolerated. Five participants in the metformin group discontinued treatment owing to adverse events (agitation, 4; sedation, 1). Participants receiving metformin vs placebo experienced gastrointestinal adverse events during a significantly higher percentage of treatment days (25.1% vs 6.8%; $P = .005$).

CONCLUSIONS AND RELEVANCE Metformin may be effective in decreasing weight gain associated with atypical antipsychotic use and is well tolerated by children and adolescents with ASD.

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Editorial

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Evdokia Anagnostou, MD, Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, 150 Kilgour Rd, Toronto, ON M4G 1R8, Canada (eanagnostou@hollandbloorview.ca).

The atypical antipsychotic medications risperidone and aripiprazole are the only treatments approved by the US Food and Drug Administration for use in autism spectrum disorder (ASD). Both medications improve irritability and agitation symptoms in children with ASD as young as 5 (risperidone) or 6 (aripiprazole) years.[1-6] Unfortunately, these medications also cause weight gain,[7,8] and greater cumulative exposure is also associated with increased diabetes risk.[9,10] Although weight gain may be reversible,[11,12] stopping these medicines often leads to relapse of irritability and agitation.[13] To our knowledge, no controlled studies have tested options for combating this weight gain in children with ASD.

Metformin hydrochloride, a biguanide drug approved for treatment of type 2 diabetes, increases insulin sensitivity and decreases intestinal glucose absorption and hepatic glucose production. Metformin has been studied for treatment of weight gain in the absence of diabetes in typically developing children.[14,15] In adults, metformin can stop or reverse weight gain associated with atypical antipsychotics.[16-18] Metformin significantly reduced body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) in a randomized clinical trial of 39 children aged 10 to 17 years who were receiving atypical antipsychotic medications,[19] similar to 2 open-label trials.[20,21] Results of a smaller randomized clinical trial failed to reach statistical significance.[22] Adverse events (AEs) in these studies were typically mild and largely confined to gastrointestinal (GI) symptoms, including diarrhea and nausea.[14-21]

Because atypical antipsychotic medications are often used in children with ASD and the mechanisms of weight gain are thought to include insulin resistance,[23] we sought to assess the safety, tolerability, and efficacy of metformin to decrease weight gain associated with the use of atypical antipsychotic medication in children with ASD. Unlike previous trials, we studied a younger age group that is at greater cumulative risk due to extended antipsychotic exposure. In addition, we focused exclusively on children with ASD who are less able to communicate potential AEs, thus meriting a separate assessment of safety and tolerability. We were concerned that GI AEs due to metformin[15] could overlap with GI symptoms that are already common in ASD,[24] potentially increasing irritability in children who cannot readily communicate discomfort.

Our specific hypotheses were that, at the end of 16 weeks, (1) metformin would ameliorate weight gain compared with placebo (primary outcome measure, BMI *z* score; secondary outcome measures, BMI, weight *z* score, and weight) and (2) metformin would be well tolerated based on AE rates and lack of worsening of the irritability/agitation targeted by atypical antipsychotic treatment.

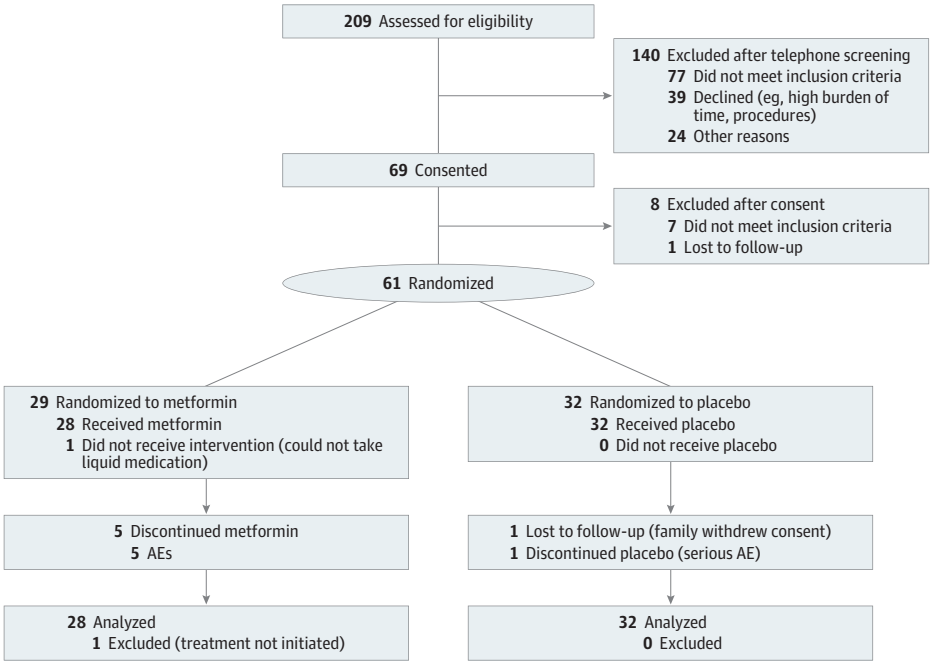
Key Points

Question What is the effect of metformin hydrochloride on weight gain associated with the use of atypical antipsychotics in children and adolescents with autism spectrum disorders?

Findings In this randomized clinical trial of 60 participants, metformin significantly reduced weight gain compared with placebo. Overall, metformin was well tolerated during 16 weeks of treatment.

Meaning In children and youth with autism spectrum disorder who are receiving atypical antipsychotics, metformin may be effective in decreasing weight gain.

Figure 1. CONSORT Flow Diagram



Methods

Study Design and Participants

This was a 16-week, randomized clinical trial testing the safety, tolerability, and efficacy of a liquid formulation of metformin hydrochloride (Riomet) in children and adolescents with ASD (**Figure 1**). The trial was conducted from April 26, 2013, to June 24, 2015. Participants were recruited through 4 academic sites participating in the Autism Speaks Autism Treatment Network. This trial was approved by the institutional review boards at each study site, and all participants or their legal guardians signed institutionally approved informed consent or assent forms according to the Helsinki agreement.[25] The full trial protocol is given in Supplement 1. Participants received financial compensation.

Inclusion criteria were age 6 to 17 years, 4 months; diagnosis of ASD (defined in the protocol as *DSM-IV* diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified) based on the Autism Diagnostic Observation Schedule[26] and *DSM-IV* clinical interview[27]; minimum of 1 month of therapy with a stable dose of an atypical antipsychotic with no plans to change; and a documented 7% or more increase in BMI since starting an atypical antipsychotic (within the past 12 months), or, if the BMI was in the 85th percentile or higher, a greater than 5% body weight increase per year since starting the medication, as documented by previous weight records.

Exclusion criteria were a history of intolerable AEs with metformin, previous use of metformin of sufficient dose and duration to determine response status, any serious medical illness requiring treatment or increasing the risk of lactic acidosis, use of medication with unacceptable interactions with metformin, planned procedure requiring contrast medium, pregnancy at screening, current use of medication for target symptoms of appetite or weight loss, or inability to tolerate blood work.

Screening Assessments

Diagnostic assessment included the Autism Diagnostic Observation Schedule[26] and *DSM-IV* interview[27]; cognitive assessment was performed using the Stanford-Binet, 5th Edition, Abbreviated Battery[28] or Mullen Scales of Early Learning[29]; and behavior was evaluated by the caregiver-completed Aberrant Behavior Checklist.[30] A comprehensive medical and developmental assessment included vital signs, height, weight, physical examination, review of medical and psychiatric history including Safety Monitoring Uniform Report Form,[31,32] review of concomitant therapies, and clinical laboratory tests (liver function, metabolic panel, serum lactate, fasting glucose, hemoglobin A_{1c}, insulin, vitamin B_{12}, lipid panel, and complete blood cell count). Urine or blood pregnancy testing was conducted for girls of child-bearing potential.

Study Intervention

All participants and caregivers received brief counseling and informational handouts regarding diet and exercise before they began the trial. Metformin hydrochloride (Riomet) and matching placebo were donated by Ranbaxy Pharmaceuticals Ltd. Metformin was dispensed as a liquid suspension of 100 mg/mL, with placebo matching the appearance, smell, and taste of metformin. For 6- to 9-year-old children, the dosage was started at 250 mg with their evening meal for 1 week, followed by the addition of 250 mg at breakfast for 1 week. At the week 2 visit, if the previous dose had been well tolerated, it was increased to 500 mg twice daily. For 10- to 17-year-old participants, treatment was started following the same schedule as used with the children, but at the week 4 visit, if the drug had been well tolerated, the dose was increased to 850 mg twice daily. The dosing strategy was based on previous pediatric trials of metformin.[15,19] If AEs occurred, the study physician (including E.A., K.B.S., J.A.H., L.E.A., L.C., D.M., R.T., J.K., and J.V.-V.) had the option to decrease the dose in multiples of 50 mg and rechallenge once the AE was resolved, with higher doses administered in multiples of 50-mg units.

All treatment was double-blinded. Randomization was conducted by the data coordinating center via permuted blocks stratified by age group (6-9 vs 10-17 years) and site using random block sizes of 2 and 4. An autogenerated email with randomization identification was sent to the site once a participant successfully enrolled. Only the investigational pharmacy at each site and unblinded staff at the data coordinating center had access to the treatment assignment.

Primary Outcome

The primary efficacy measure was change from baseline to week 16 in body mass index (BMI) *z* score calculated from the 2000 Centers for Disease Control and Prevention (http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm) age- and sex-normed growth charts at week 16. Height and weight were measured at baseline and 2, 4, 8, 12, and 16 weeks after treatment initiation.

Secondary Outcomes

Secondary outcomes included (1) changes in other body variables (absolute and relative change in weight, absolute BMI, and abdominal and hip circumference) and (2) changes in fasting metabolic variables (eTable 1 and eTable 2 in Supplement 2). The Homeostasis Model Assessment of Insulin Resistance[33] was used to integrate fasting glucose and insulin values in a composite measure of metabolic risk.

Safety Assessments

Safety was assessed with the Safety Monitoring Uniform Report Form,[31,32] which was slightly modified to assess rare AEs previously reported with metformin,[14-22] which was administered by a clinician at every visit. Clinical laboratory tests were repeated at week 16.

Given concern that children with ASD may be unable to report AEs verbally and could manifest physical discomfort with increased irritability/agitation,[34-36] we examined the effect of metformin vs placebo on irritability/agitation by caregiver ratings on the Aberrant Behavior Checklist Irritability subscale.[29,37] The Clinical Global Impression Scale–Improvement,[38] based on change in global symptoms, including behavioral and physical functioning, was also administered at every visit as a measure of tolerability.[31]

Statistical Analysis

A sample size of 90 participants was originally planned, assuming a pooled, among-person SD of 0.6 for a 16-week change in BMI *z* score. Interim blinded analysis of change in BMI *z* scores indicated an effective SD of only 0.16, and the sample size was reduced to 60 for 80% power to detect a difference of 0.12, which would be a difference in weight change of approximately 3.0 kg in our sample. The interim analysis was of blinded data analyzed as a single sample only and thus did not affect our type I error rate.[39]

Safety, tolerability, and efficacy analyses used a modified intent-to-treat sample comprising all participants who received at least 1 dose of medication. The primary efficacy end point was 16-week change from baseline in BMI *z* scores. All participants in the modified intent-to-treat sample were included in the analysis. Secondary analysis included all participant randomized, including 1 individual who did not receive medication (intent to treat).

The proportion of participants experiencing AEs classified by the MedDRA (http://www.meddra.org/) system organ class and preferred term was compared between treatments by using the Fisher exact test with estimated odds ratios and exact 95% confidence intervals. Effects of metformin on primary and secondary efficacy outcomes were estimated from shared-baseline, random-slope, linear mixed models with fixed effects of stratum × visit (categorical) and stratum × treatment × postbaseline visit interaction, and random participant-specific intercepts and slopes with unstructured covariance. The mean model was unstructured in time, whereas the covariance model assumed participant-specific linear deviations from the means. The shared-baseline assumption, enforced by omitting a treatment main-effect term, reflected the true state of the population before randomization and adjusts for chance differences at baseline.[40] Effects of treatment assignment on 16-week change were estimated by linear contrasts of the baseline and week 16 least-square means using the observe stratum frequencies. Effect sizes (ESs) for treatment differences were calculated relative to the pooled SD for 16-week change among participants who completed the trial. The primary end point was tested at 2-tailed $\alpha = .05$. The secondary end points and analyses were considered exploratory, without adjustment for multiple comparisons. To assess whether GI AEs mediated benefit from metformin, we calculated the number of days that participants experienced any of the following symptoms: abdominal discomfort or pain, diarrhea, eructation, flatulence, nausea, vomiting, and gastroenteritis. We tested whether total duration of GI AEs mediated the treatment effect by using a causal model for direct and indirect effects.[41] The total natural indirect effect for GI AEs was taken as a measure of mediation.

Results

Participants

Sixty-one participants were randomized and 60 initiated treatment, 28 (7 [25%] female) received metformin and 32 (8 [25%] female) received placebo, and the mean (SD) age was 12.8 (2.7) years (Figure 1, **Table 1**, and eTable 3 in Supplement 2). One participant randomized to receive metformin refused liquid medication and therefore withdrew without ever taking treatment. This participant was included only in the secondary ITT analysis.

At baseline, the placebo group had a higher IQ than the metformin group (mean [SD], 84 [20] vs 69 [25]) and was receiving more psychotropic medications (53% vs 36% were taking ≥3 medications) (Table 1 and eTable 4 in Supplement 2).

In children aged 6 to 9 years, the mean final dose in both the metformin and placebo groups was 1000 mg/d. In those aged 10 to 17 years, the mean final dose in the metformin group was 1587 mg/d and in the placebo group, 1674 mg/d ($P = .24$). Adherence was excellent in both groups (96% of doses taken in both groups, with ranges of 75%-100% in the metformin group and 85%-100% in the placebo group).

Primary Outcome

To account for anticipated growth and differences in typical BMI across childhood, we used changes in BMI standardized to age- and sex-based norms (*z* scores). Metformin was superior to placebo in reducing weight gain associated with atypical antipsychotics, as assessed by change from baseline to week 16 BMI *z* scores (metformin vs placebo difference, −0.010 [95% CI, −0.16 to −0.04]; ES, 0.82; $P = .003$) (**Table 2**, **Figure 2**, and pretreatment and posttreatment values in eTable 5 in Supplement 2). Participants receiving placebo experienced no change over 16 weeks in BMI *z* scores (0.02 [95% CI, −0.03 to 0.06]); however, those receiving metformin experienced a substantial reduction compared with baseline (−0.08 [95% CI, −0.13 to −0.04]). Three of 28 participants (11%) in the metformin group experienced 8% to 9% declines in BMI. No other participants experienced more than a 5% decline in BMI during the 16-week treatment period. Benefit from metformin did not differ significantly by study site ($P = .91$) (eTable 6 in Supplement 2).

Secondary Outcomes

A similar pattern of differences between the treatment and placebo group was observed when examining weight *z* scores (ES, 1.04), BMI (ES, 1.01), weight (difference, 2.7 kg; ES, 1.13), BMI percentiles (ES, 0.47), and weight percentiles (ES, 0.65) (Table 2 and Figure 2). Baseline BMI was positively but weakly associated with percentage change in BMI ($r = 0.11$; $P = .39$) (eFigure in Supplement 2). No significant differences were noted in changes of any of the metabolic variables studied (eTable 5 in Supplement 2). Intent-to-treat analysis, including 1 participant who never received the study medication, did not lead to meaningful changes in the results (eTable 7 in Supplement 2).

Safety

There was no significant difference between the groups in change from baseline to week 16 on the Aberrant Behavior Checklist Irritability subscale (ES, 0.01; $P = .94$) or the Clinical Global Impression Scale Improvement Scale (ES, 0.11; $P = .91$). There was 1 serious AE. A participant with a history of hospital admissions for aggression who was randomized to receive placebo was admitted for aggression. The serious AE

Table 1. Baseline Characteristics

Characteristic	Metformin (n = 28)	Placebo (n = 32)	*P* Value
Sex, No. (%)			
Male	21 (75)	24 (75)	>.99
Female	7 (25)	8 (25)	
Race, No. (%)			
Asian	2 (7)	2 (6)	.77
Black or African	3 (10)	1 (3)	
White	22 (79)	28 (88)	
Other/multiracial	1 (4)	1 (3)	
Ethnicity, No. (%)			
Hispanic	0	2 (6)	.49
Non-Hispanic	28 (100)	29 (94)	
Age, mean (SD), y	12.9 (2.85)	12.7 (2.64)	.77
IQ, mean (SD)	68.9 (25.14)	84.1 (20.30)	.02
Primary caregiver educational level, No. (%)			
Some college or less	10 (37)	12 (37)	.37
College degree	7 (26)	14 (44)	
Graduate degree	10 (37)	6 (19)	
Annual household income, No. (%), $			
<50 000	9 (33)	12 (397)	.71
50 000-99 999	12 (44)	8 (26)	
≥100 000	6 (22)	11 (35)	
BMI category, No. (%)[a]			
Normal weight	1 (4)	0	.41
Overweight	4 (14)	4 (12)	
Obese	23 (82)	28 (88)	
BMI *z* score, mean (SD)	2.05 (0.49)	2.12 (0.39)	.57
Weight *z* score, mean (SD)	2.15 (0.70)	2.21 (0.59)	.87
CGI-Severity, mean (SD)	4.71 (0.71)	4.53 (0.80)	.35
ABC irritability, mean (SD)	17.5 (11.2)	21.8 (9.7)	.12
Psychotropic medications, No. (%)[b]			
1	6 (21)	8 (25)	.39
2	13 (46)	7 (22)	
3	3 (11)	9 (28)	
4	5 (18)	5 (16)	
5	1 (4)	3 (9)	
Antipsychotic medications, No. (%)			
Risperidone	19 (689)	12 (38)	.09
Aripiprazole	7 (25)	16 (50)	
Quetiapine	0	1 (3)	
Olanzapine	1 (4)	1 (3)	
Ziprasidone	1 (4)	1 (3)	
Iloperidone	0	1 (3)	
Risperidone dosage, mean (SD), mg/d	2.0 (1.4)	2.0 (1.2)	.97
Aripiprazole dosage, mean (SD), mg/d	9.6 (6.6)	10.2 (6.0)	.81

Abbreviations: ABC, Aberrant Behavior Checklist; BMI, body mass index; CGI, Clinical Global Impression.

[a] Normal weight, 15th to less than 85th percentile; overweight, 85th or greater to less than 95th percentile; and obese, 95th or greater percentile.

[b] Includes medications affecting behavior: stimulants, nonstimulants, antidepressants and antianxiety medications, antipsychotics, and mood stabilizers (eTable 4 in Supplement 2).

was determined to be unrelated to the study drug. One other participant receiving placebo was lost to follow-up when the participant withdrew consent after the dose of the atypical antipsychotic medication was increased following an outburst at school. Five participants in the metformin group discontinued treatment: 4 owing to agitation (determined to be possibly related to the study drug in 3 and unrelated in 1, at weeks 1, 5, and 8, with 2 at week 8) and 1 owing to sedation (at week 10).

Adverse events occurring in more than 5% of participants in either group (>1 participant) are listed in **Table 3**. Overall, abnormal feces was the only statistically significant differ-

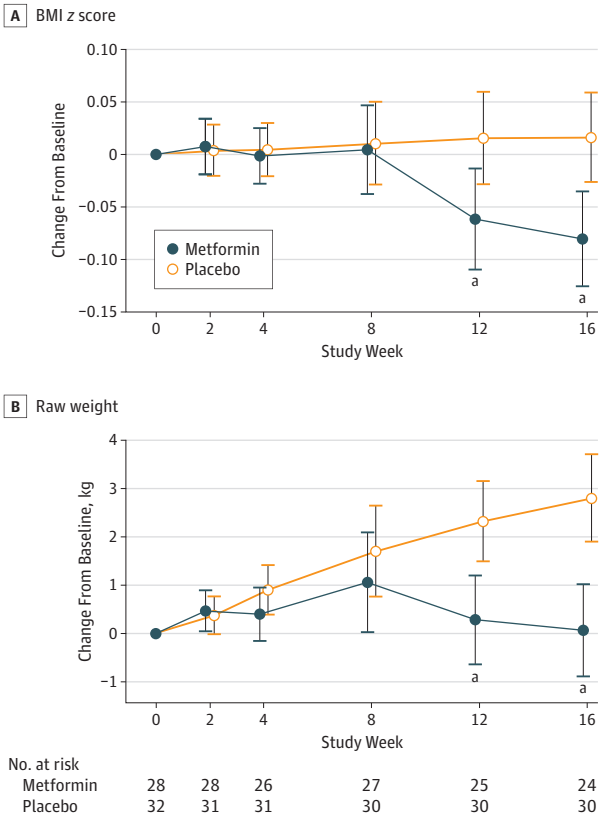
Table 2. Effect of Metformin vs Placebo on Primary/Secondary Measures: Anthropometric Measurements and Irritability[a]

	Metformin (n = 28)		Placebo (n = 32)		Treatment Difference		
Characteristic	16-wk Change (95% CI)	*P* Value	16-wk Change (95% CI)	*P* Value	16-wk Change (95% CI)	Effect Size	*P* Value
BMI *z* score	−0.08 (−0.13 to −0.04)	<.001	0.02 (−0.03 to 0.06)	.45	−0.10 (−0.16 to −0.04)	0.82	.003
Weight *z* score	−0.10 (−0.15 to −0.05)	<.001	0.04 (−0.01 to 0.08)	.15	−0.13 (−0.20 to −0.06)	1.04	<.001
BMI raw	−0.43 (−0.80 to −0.06)	.02	0.52 (0.18 to 0.87)	.004	−0.95 (−1.46 to −0.45)	1.01	<.001
Weight raw, kg	0.07 (−0.88 to 1.02)	.89	2.80 (1.90 to 3.70)	<.001	−2.73 (−4.04 to −1.43)	1.13	<.001
BMI percentile, %	−0.84 (−1.47 to −0.21)	.01	0.025 (−0.58 to 0.63)	.93	−0.87 (−1.66 to −0.07)	0.47	.03
Weight percentile, %	−1.11 (−1.90 to −0.32)	.006	0.309 (−0.44 to 1.06)	.41	−1.42 (−2.50 to −0.34)	0.65	.01
Waist-hip ratio, %	0.23 (−1.10 to 1.55)	.73	0.51 (−0.76 to 1.77)	.43	−0.28 (−1.96 to 1.40)	0.07	.74
ABC irritability	−0.95 (−3.16 to 1.27)	.40	−0.99 (−3.08 to 1.10)	.35	0.05 (−2.94 to 3.03)	0.008	.98

Abbreviations: ABC, Aberrant Behavior Checklist; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Results were obtained from linear contrasts of estimates from the shared-baseline, linear mixed model described in the Methods section.

Figure 2. Metformin Effect on Body Mass Index (BMI) *z* Score and Weight Change



Estimates of means for the treatment and placebo groups at each visit. Error bars indicate 95% CIs.

[a] Significant difference at each visit.

ence in AEs between the groups (4 of 28 [14%] receiving metformin vs 0 of 32 receiving placebo; *P* = .04). There was a nonsignificant increase in GI AEs in the metformin group compared with the placebo group (23 [82%] receiving metformin vs 19 [59%] receiving placebo; *P* = .09) (Table 3). Participants receiving metformin experienced GI AEs during a significantly higher percentage of treatment days (25.1% vs 6.8%; *P* = .005).

Blinding Assessment

Both clinicians and participants were asked to guess whether the participant was taking metformin or placebo at the end of 16 weeks. The rate of guessing participant assignment correctly did not differ significantly between the metformin and placebo groups for either clinician (metformin: guessed metformin, 8%; placebo, 15%; uncertain, 77%; placebo: guessed metformin, 10%; placebo, 24%; uncertain, 66%) or participant (metformin: guessed metformin, 32%, placebo, 36%, uncertain, 32%; placebo: guessed metformin, 14%, placebo, 61%, uncertain, 25%) guesses. Among caregivers who guessed (excluding those who were uncertain), caregivers of placebo participants more often guessed correctly (17 of 21 [81%]; odds ratio, 3.8 [95% CI, 0.7 to 2.15]; *P* = .09). Correct guessing by caregivers did not predict change in the primary outcome measure (16-week change in BMI *z* score among placebo correct guessers, −0.001; among placebo incorrect guessers, −0.025; difference, 0.023 [95% CI, −0.08 to 0.12]; *P* = .65).

Post Hoc Analysis

Baseline variables differing substantially between groups included aripiprazole use (metformin, 7 [25%]; placebo, 16 [50%]), risperidone use (metformin, 19 [68%]; placebo, 12 [38%]), and mean [SD] full-scale IQ (metformin, 69 [25]; placebo, 84 [20]). There was no evidence that any of these findings confounded the association between randomized treatment assignment and changes in BMI *z* scores: use of aripiprazole (interaction ES, 0.3; *P* = .61), use of risperidone (interaction ES, 0.26; *P* = .64), age (interaction ES, 0.001 per year; *P* = .91), full-scale IQ (interaction ES, 0.005 per unit; *P* = .71), and number of psychotropic medications (interaction ES, 0.09 per medication; *P* = .68).

We were concerned that the apparent benefit of metformin might only be the result of increased GI discomfort. We found, however, that participants experiencing more days with GI symptoms experienced insignificantly greater (rather than smaller) increases in BMI and weight. The total natural

Table 3. Adverse Events[a]

MedDRA System Organ Class	Preferred Term	Participants, No. (%)		P Value	Estimated OR (95% CI)
		Metformin (n = 28)	Placebo (n = 32)		
Ear and labyrinth disorders	Overall	0	3 (9)	.24	0 (0-1.9)
Gastrointestinal disorders[b]	Abdominal discomfort	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Abdominal pain	3 (11)	3 (9)	>.99	1.16 (0.14-9.436)
	Abdominal pain, upper	3 (11)	4 (13)	>.99	0.84 (0.11-5.52)
	Abnormal feces	4 (14)	0	.04	Infinity (1.09-infinity)
	Chapped lips	1 (4)	2 (6)	>.99	0.56 (0.009-11.3)
	Constipation	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Diarrhea	17 (61)	13 (41)	.20	2.26 (0.71-7.24)
	Flatulence	3 (11)	3 (9)	>.99	1.16 (0.14-9.44)
	Nausea	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Vomiting	8 (29)	4 (13)	.20	2.80 (0.63-14.3)
	Overall	23 (82)	19 (59)	.09	3.15 (0.84-13.2)
General disorders and administration site conditions	Fatigue	6 (21)	6 (19)	>.99	1.18 (0.27-5.12)
	Irritability	7 (25)	7 (22)	>.99	1.19 (0.30-4.70)
	Product taste abnormal	3 (11)	0	.10	Infinity (0.69-infinity)
	Pyrexia	3 (11)	1 (3)	.33	3.72 (0.27-201.5)
	Overall	13 (46)	14 (44)	>.99	1.11 (0.36-3.48)
Infections and infestations	Ear infection	2 (7)	1 (3)	.59	2.39 (0.12-145.1)
	Gastroenteritis	3 (11)	1 (3)	.33	3.72 (0.27-201.5)
	Otitis media	2 (7)	1 (3)	.59	2.39 (0.12-145.1)
	Sinusitis	1 (4)	2 (6)	>.99	0.56 (0.009-11.3)
	Upper respiratory tract infection	6 (21)	11 (34)	.39	0.52 (0.13-1.90)
	Overall	14 (50)	19 (59)	.60	0.68 (0.22-2.14)
Injury, poisoning and procedural complications	Overall	4 (14)	5 (16)	>.99	0.90 (0.16-4.74)
Investigations	Blood insulin level increased	2 (7)	2 (6)	>.99	1.15 (0.08-16.9)
	Blood triglyceride level increased	1 (4)	2 (6)	>.99	0.56 (0.009-11.34)
	Overall	4 (14)	5 (16)	>.99	0.90 (0.160-4.736)
Metabolism and nutrition disorders	Decreased appetite	8 (29)	4 (13)	>.99	2.80 (0.63-14.28)
	Increased appetite	0	4 (13)	>.99	0 (0-1.22)
	Overall	8 (29)	8 (25)	.78	1.20 (0.33-4.41)
Musculoskeletal and connective tissue disorders	Back pain	0	2 (6)	.49	0 (0-3.95)
	Pain in extremity	2 (7)	1 (3)	.59	2.39 (0.12-145.10)
	Overall	4 (14)	7 (22)	.52	0.60 (0.11-2.73)
Nervous system disorders	Dizziness	2 (7)	1 (3)	.59	2.39 (0.12-145.10)
	Headache	5 (18)	6 (19)	>.99	0.94 (0.20-4.278)
	Somnolence	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Overall	12 (43)	10 (31)	.43	1.65 (0.51-5.43)
Psychiatric disorders	Affect lability	0	3 (9)	.24	0 (0-1.92)
	Aggression	5 (18)	2 (6)	.24	3.26 (0.47-36.5)
	Anger	4 (14)	1 (3)	.18	5.17 (0.46-262.50)
	Anxiety	1 (4)	3 (9)	.62	0.36 (0.007-4.5)
	Depressed mood	0	2 (6)	.49	0 (0-3.95)
	Initial insomnia	4 (14)	2 (6)	.40	2.50 (0.32-29.41)
	Middle insomnia	2 (7)	1 (3)	.59	2.39 (0.12-145.10)
	Overall	14 (50)	13 (41)	.60	1.462 (0.47-4.59)
Reproductive system disorders	Overall	1 (4)	2 (6)	>.99	0.56 (0.009-11.3)

(continued)

Table 3. Adverse Events[a] (continued)

MedDRA System Organ Class	Preferred Term	Participants, No. (%)		P Value	Estimated OR (95% CI)
		Metformin (n = 28)	Placebo (n = 32)		
Respiratory, thoracic and mediastinal disorders	Cough	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Nasal congestion	3 (11)	2 (6)	.66	1.80 (0.19-22.92)
	Rhinorrhea	2 (7)	4 (13)	.68	0.54 (0.05-4.17)
	Sneezing	2 (7)	3 (9)	>.99	0.74 (0.06-7.07)
	Overall	8 (29)	12 (38)	.59	0.67 (0.19-2.25)
Skin and subcutaneous tissue disorders	Rash	4 (14)	2 (6)	.40	2.50 (0.32-29.41)
	Overall	6 (21)	8 (25)	.77	0.82 (0.20-3.20)

[a] Only adverse events occurring in more than 5% of participants with each group are reported.

[b] In MedDRA categories (http://www.meddra.org/) that include an expected adverse event, all adverse events meeting the 5% cutoff are reported.

indirect effect mediated by GI AEs were gains of 0.007 for BMI *z* scores (95% CI, −0.027 to 0.042; *P* = .68) and 0.11 kg for weight (95% CI, −0.57 to 0.80; *P* = .75).

Discussion

Atypical antipsychotic medications are US Food and Drug Administration–approved for use in children at a younger age in ASD than in any other condition; however, to our knowledge, no previous studies have examined treatment or prevention of weight gain in children with ASD who receive these medications. Metformin was superior to placebo in managing established weight gain associated with atypical antipsychotics in this population. Children receiving placebo continued to gain weight during the study, as expected for age (BMI *z* score increase negligible), whereas BMI *z* scores decreased in the metformin group (Figure 2). The large effect size of BMI *z* score changes in this study is comparable to that observed in the Klein et al[19] pediatric pilot trial of metformin in children receiving atypical antipsychotics. The benefits from treatment in our sample were not clear until after 8 weeks of treatment (Figure 2), which was also consistent with previous pediatric RCTs[15,19] of metformin targeting weight gain in children and youth. Other strategies to reduce weight gain associated with atypical antipsychotic use in adults include sibutramine hydrochloride and topiramate, but the AE profiles of these drugs are not trivial.[42] In children, stimulants failed to reduce weight gain associated with atypical antipsychotics.[43] In addition, nutritional counseling has previously shown little benefit for children and adolescents receiving atypical antipsychotic medications,[19] and food selectivity may make this particularly challenging in the ASD population.[26] However, metformin was not only effective, it was well tolerated in our participants. Although there was nonsignificant increase in GI distress in the metformin group, GI AEs were not responsible for any treatment discontinuation, and we found no evidence that the benefit on BMI was due to GI AEs.

There are some important limitations to this study. First, the length of metformin treatment may have been inadequate to capture metabolic benefits. Furthermore, the length of the study was too short to evaluate whether initial improvements will be maintained. The small sample size yielded too little precision in our estimates to discount possible effects for metabolic and behavioral outcomes. In addition, although we had reliable information on the length of time that participants were stable on their current dose, we did not have reliable information on the length of overall exposure to antipsychotic medications. We also did not evaluate the benefit of lifestyle modifications, although brief counseling regarding diet and exercise was provided to all participants. Behavioral interventions targeting weight in youth with ASD have not been tested. Combined programs that compared metformin with placebo with all participants receiving vigorous and continuous lifestyle supports might produce different results. Finally, this study addressed only the benefit of metformin added to an atypical antipsychotic after children had already gained significant weight. The trial did not address the question of whether coadministration of metformin at the onset of atypical antipsychotic use prevents initial weight gain, which is a question for future research.

Conclusions

In this RCT, metformin was well tolerated and effective at managing weight gain associated with atypical antipsychotic use in children and adolescents with ASD. These findings have important implications for children in whom the benefits of atypical antipsychotics for treating irritability and agitation symptoms are difficult to balance with the substantial weight gain that often accompanies their use.

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Author Affiliations: Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada (Anagnostou, Brian, Capano, Mankad, Peleg, Odrobina); Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (Anagnostou, Brian, Capano, Mankad); Nisonger Center, The Ohio State University, Columbus (Aman, Hollway, Arnold, Hellings, Wagner, Wong); Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Handen, Tumuluru, Kettel, McAuliffe-Bellin); Department of Psychiatry, Vanderbilt University, Nashville, Tennessee (Sanders, Marler); Biostatistics Center, Massachusetts General Hospital, Boston (Shui, Zakroysky, Macklin); Department of Psychology, Nationwide Children's Hospital, Columbus, Ohio (Butter); Department of Pediatrics and Psychology, The Ohio State University, Columbus (Butter); Department of Pediatrics, Vanderbilt University, Nashville, Tennessee (Newsom); Department of Pediatrics, CHEO Research Institute, University of Ottawa, Ottawa,

Ontario, Canada (Hadjiyannakis); Department of Medicine, Harvard Medical School, Boston, Massachusetts (Macklin); Department of Psychiatry and Sackler Institute for Developmental Psychobiology, Columbia University, New York, New York (Veenstra-VanderWeele); New York State Psychiatric Institute, New York (Veenstra-VanderWeele); Center for Autism and the Developing Brain, New York Presbyterian Hospital, White Plains, New York (Veenstra-VanderWeele).

Author Contributions: Dr Anagnostou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Anagnostou, Aman, Handen, Hollway, Butter, Hadjiyannakis, Veenstra-VanderWeele.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Anagnostou, Aman, Handen, Sanders, Macklin, Veenstra-VanderWeele.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Shui, Macklin.
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Study supervision: Anagnostou, Aman, Handen, Sanders, Veenstra-VanderWeele.

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