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BRIEF REPORT

Brief Report: Metformin for Antipsychotic-Induced Weight Gain in Youth with Autism Spectrum Disorder

Logan K. Wink[1] · Ryan Adams[1] · Ernest V. Pedapati[1] · Kelli C. Dominick[1] · Emma Fox[1] · Catherine Buck[1] · Craig A. Erickson[1]

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Abstract Antipsychotic treatment in youth with autism spectrum disorder (ASD) is becoming increasingly common, placing individuals at risk for antipsychotic-induced weight gain and associated complications. Metformin hydrochloride, a biguanide medication FDA-approved for treatment of type-2 diabetes in youth, may hold promise for treatment of antipsychotic-induced weight gain in youth with ASD. In this report we assess the long-term impact of metformin on antipsychotic-associated weight gain in a naturalistic sample of 53 youth with ASD. Results indicate that treatment with metformin stabilized BMI z-score over a nearly 2 year mean treatment period. Further work is indicated to determine the safety and efficacy of metformin treatment in youth with ASD, as well as predictors of response as a treatment for antipsychotic-induced weight gain.

Keywords Autism · Autism spectrum disorder · Metformin · Antipsychotic · Weight gain

Introduction

Aggression, self-injurious behavior, and severe tantrums (referred to as "irritability") are common targets of pharmacotherapy in youth with autism spectrum disorder (ASD) (Posey et al. 2008). Placebo-controlled trials have demonstrated the efficacy of atypical antipsychotics risperidone and aripiprazole for treatment of ASD-associated irritability, resulting in FDA-approval of these medications (McCracken et al. 2002; Owen et al. 2009). Unfortunately, risperidone and aripiprazole are both associated with antipsychotic-induced weight gain in youth with ASD (Martin et al. 2004; Wink et al. 2014). Additionally, youth with ASD are frequently treated with "off-label" psychotropic medications, often other antipsychotics, many of which are also associated with weight gain (Politte et al. 2014; Yoon et al. 2016). Psychotropic medication treatment in youth with ASD is becoming increasingly common (Park et al. 2016; Schubart et al. 2014), placing these individuals at particular risk for antipsychotic-induced weight gain and associated medical complications including obesity, dyslipidemia, and insulin resistance (Galling et al. 2016; Maayan and Correll 2011).

Metformin hydrochloride is a biguanide medication FDA-approved for treatment of type-2 diabetes in youth as young as 10 years old. Metformin decreases glucose absorption from the intestine, reduces hepatic glucose production, and increases the body's insulin sensitivity (Brufani et al. 2011). Metformin is generally considered a safe medication in pediatric populations, with gastrointestinal symptoms being the most common side effect and no severe adverse events documented in the pediatric literature (Brufani et al. 2011). Over the past decade, metformin has been studied as a potential treatment for antipsychotic-induced weight gain and associated sequelae (Correll et al. 2013). A recent meta-analysis demonstrated that metformin significantly reduces body-mass index (BMI) and insulin resistance compared to placebo in adults with schizophrenia or schizoaffective disorder (de Silva et al. 2016). Additionally, metformin was shown to be effective in treating antipsychotic-induced dyslipidemias in adults with schizophrenia (Wu et al. 2016).

✉ Logan K. Wink
logan.wink@cchmc.org

[1] Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Avenue MLC 4002, Cincinnati, OH 45229, USA

Metformin also may have a role in treating antipsychotic-induced weight gain in youth both with and without ASD. In a placebo-controlled trial of metformin in 39 youth treated with atypical antipsychotics targeting a variety of psychiatric disorders (including five participants with ASD), initial evidence suggests that metformin may mitigate antipsychotic-induced weight gain and measures of obesity including BMI z-score, waist circumference, and insulin-resistance (Klein et al. 2006). A single placebo-controlled trial of short-term metformin treatment in 61 youth age 6–17 years with ASD (mean dose to 1000 mg/day in youth age 6–9 years and 1587 mg/d in those age 10–17 years) targeting antipsychotic-induced weight gain, demonstrated significant reduction in BMI z-score in those treated with active drug compared to placebo over 16 weeks of treatment (Anagnostou et al. 2016).

In clinical practice, antipsychotic-induced weight gain is a significant concern for individuals with ASD and their caregivers. Our group's systematic reviews of naturalistic psychotropic medication treatment of individuals with ASD at two large sub-specialty clinics both demonstrated significant weight gain with second generation antipsychotics (Wink et al. 2014; Yoon et al. 2016), solidifying these concerns. The objective of this report is to assess the impact of long-term metformin on antipsychotic-induced weight gain in a naturalistic sample of youth with ASD to determine if naturalistic longer-term treatment mimics the effects seen in an initial short-term placebo-controlled trial in the field.

Methods

As part of a larger comprehensive assessment of medication management in ASD, we analyzed clinical data describing individuals with ASD treated by the Behavioral and Developmental Neuropsychiatry group within the Division of Child and Adolescent Psychiatry at XXXX (XXXXX). From the XXXXX electronic medical records, we identified individuals with ASD between the ages of 2 and 20 years (to align with CDC growth charts, http://www.cdc.gov/growthcharts/background.htm) who were clinically treated with metformin and at least one antipsychotic by our investigators (XXX, XXX, and XXX) between July 2012 and February 2016. For each included individual, demographic data including race, psychiatric co-morbidities, known genetic disorders, and reported presence of intellectual disability (ID) was collected. ASD diagnoses were made via Autism Diagnostic Observation Schedule testing and physician evaluation including review of DSM-IV or DSM-5 criteria (as applicable). All participants in this study were treated with metformin due to weight gain and/or increased appetite thought by their provider to be potentially related to antipsychotic treatment. Titration of metformin was performed based on clinical assessment and clinician judgement, with upward titration based on ongoing weight and/or appetite concerns.

For this review, we defined "baseline" as the date metformin was prescribed to each study participant, and collected baseline data including age, BMI, concomitant psychotropic medications, and metformin starting dose at treatment initiation. We defined study "endpoint" as the date metformin was stopped by the participant or the final data collection point available for an individual (the date data collection was initiated). We again collected data including age, BMI, concomitant psychotropic medications, and final metformin dose at this final time point. To provide frame of reference regarding BMI-trajectory, we collected BMI data at 6 and 12 months prior to metformin initiation when available. To account for developmental growth and gender, we transformed all BMI values into BMI z-scores based on CDC growth charts. We calculated duration of metformin treatment for all participants.

Paired sample *t*-tests were used to evaluate change in BMI z-score from baseline to final data point during metformin treatment. McNemar tests examined if there were significant changes in the frequency of concomitant psychotropic drug use from the initial time point to the final time point for each category of drug. A series of repeated ANOVA's tested age, sex, duration of treatment, dose (initial and final), and concomitant drug category as possible moderators of BMI z-score change. A repeated measures ANOVA was utilized to test if there were differences in BMI z-score at 6 and 12 months prior to the initial dose of metformin and the BMI Z-score at the initial dose time point. This project was approved by the CCHMC Institutional Review Board.

Results

Fifty-three individuals meeting inclusion criteria were identified. The majority of included subjects were male (81.1%), Caucasian (88.7%), and were diagnosed with cognitive impairment (66.0%) and a disruptive behavior disorder (94.3%) (Table 1). Over 9% of participants suffered from a known genetic syndrome including Soto Syndrome, Ehler's Danlos, Tuberous Sclerosis, and Fragile X Syndrome. The mean age of participants was 13.5 (SD = 2.8) years at initiation of metformin treatment, and the mean duration of treatment with metformin was 1.94 (SD = 1.8) years (Table 2). Seventy-two percent of study participants (N = 38) continued to take metformin at the final available clinical record review and 15 subjects stopped metformin use during the period in which treatment was reviewed (4 due to weight loss/decreased appetite, 4 due to gastrointestinal side effects, 1 due to

Table 1 Demographic and diagnostic data (N = 53)

Descriptive factor	Percent (%)
Gender, male	81.1
Race, white	88.7
Cognitive impairment	66.0
Known genetic disorder	9.4
Disruptive behavior disorder	94.3
Anxiety disorder	56.6
ADHD	22.6
Mood disorder	18.7
Sleep disorder	5.6
Movement disorder	5.6
Pica	3.8

Genetic disorders: Soto Syndrome, Ehler's Danlos, Tuberous sclerosis, Fragile X syndrome

Disruptive behavior disorder: intermittent explosive disorder, disruptive behavior disorder, oppositional defiant disorder, aggression, self-injurious behavior

Anxiety disorder: anxiety disorder not otherwise specified (NOS), generalized anxiety disorder, obsessive compulsive disorder, post-traumatic stress disorder, adjustment disorder

Mood disorder: major depressive disorder, depressive disorder NOS, mood disorder NOS, bipolar disorder

Sleep disorder: insomnia, sleep disorder NOS

Movement disorder: tic disorder, Tourette's syndrome

Table 2 Metformin information (N = 53)

	M (*SD*)	Range
Age initial	13.5 (2.8)	7.7–18.2
Duration (years)	1.94 (1.8)	0.3–6.3
Start dose	718.87 (370.7)	250–2000
Final dose	1175.47 (555.9)	250–2000
Initial Z-BMI	1.86 (0.6)	0.42–3.07
Final Z-BMI	1.81 (0.7)	0.43–3.5

noncompliance, and 6 did not have sufficient clinical documentation to explain reason for discontinuation). Metformin doses ranged from 250 to 2000 mg daily, with mean starting dose of 719 mg (SD = 370.7) and mean final dose 1175 mg daily (SD = 555.9 mg). Metformin dose increased significantly for participants between baseline (date metformin was prescribed) and final data point capture (paired sample *t*-value = 6.15, p < 0.001). All participants were treated with an antipsychotic throughout duration of metformin treatment, and nearly half received concomitant psychotropic drug treatment with an antidepressant, non-stimulant ADHD medication (including alpha-2 agonists), or a sleep aid (Fig. 1, see "Appendix" section for complete drug list by category). There was no change in frequency of concomitant

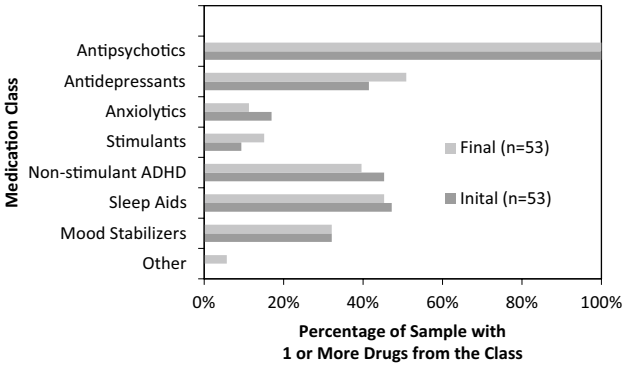

Fig. 1 Frequency of participants taking at least one psychotropic drug from each category at initial and final time points. See "Appendix" section for complete medication list by class

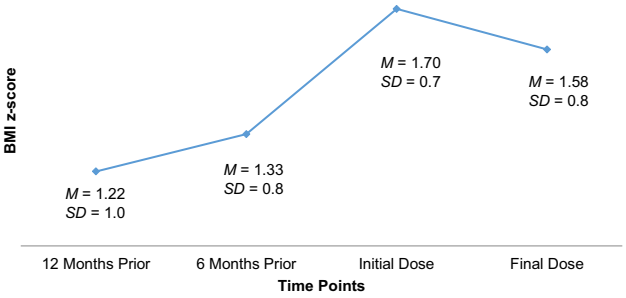

Fig. 2 Linear and cubic change from tests of within subject contrasts for Z-BMI from 12 months prior to initial dose to the final dose

medications by drug class over duration of study (all McNemar tests *ps* > 0.15).

The majority of study participants were significantly overweight, with mean baseline BMI z-score of 1.86 (SD = 0.6, range 0.42–3.07), and mean final BMI z-score of 1.81 (SD = 0.7, range 0.43–3.5) (Table 2). However, there was no significant change in BMI z-score between time points (*t*-value = 0.50, p ns). None of the variables tested (age, gender, duration on metoformin, dose (initial and final), concomitant drug category) were found to moderate change in BMI z-score.

A subset of participants (N = 33) had BMI data available for time points 6 and 12 months prior to starting treatment with metformin. For these participants we tested differences in BMI z-scores 12 months prior to starting metformin, 6 months prior to the initial dose, at the initial dose, and at the final dose. A repeated measures ANOVA found significant differences in BMI z-scores between these four time points (F(3, 96) = 7.10, p = 0.01). Tests of within subjects contrasts found significant linear (F(1, 32) = 9.37, p < 0.01) and cubic effects (F(1, 32) = 16.67, p < 0.001) but not quadratic effect (F(1, 32) = 1.65, p ns) in change in BMI z-score across the four time points (Fig. 2). Overall there

was a linear increase in BMI z-score from 12 months prior to the initial dose and then a decrease in BMI z-score from the initial dose to the final dose that resulted in the cubic effect.

Discussion

In this naturalistic sample of youth with ASD treated with antipsychotic medication at our tertiary care treatment center, treatment with metformin stabilized study participant's BMI z-score over a nearly 2 year mean treatment period. These results are striking when compared with the upward climb in BMI z-score recorded in the subset of participants with BMI data from the 12 months prior to metformin initiation. Although our review does not demonstrate weight loss in the total group of study participants, as was described in the randomized metformin controlled trial from Anagnostou et al. (2016) the long-term stabilization of BMI z-score in our participants is promising and suggests that the addition of metformin had a potential meaningful impact on the participant's overall health. Furthermore, the clinical treatment described in this retrospective review aligned remarkably with Anagnoustou's controlled trial, with our mean metformin dose of 1175 mg/day versus Anagnostou's reported mean dose of 1293.5 mg/day, and our 72% metformin continuation rate at study completion versus Anagoustou's rate of 83% of metformin participants continuing on treatment throughout the trial (Anagnostou et al. 2016). This underscores the clinical relevance and potential tolerability of metformin for treatment of antipsychotic-induced weight gain in youth with ASD.

As always, our study results must be considered in context of the study's limitations. Though the naturalist sample provides us with a "real world" feel for the impact of metformin in clinical care, the study design has flaws. The sample represents individuals seeking care at a tertiary care center, and therefore may not be representative of individuals who receive care in community centers. The frequency of concomitant medication use did not change over the course of the study, however we did not collect data on antipsychotic or concomitant medication dosage changes and therefore cannot ascertain the impact of such changes on BMI Z-score in study participants. We have no data on study participants' diet, exercise regimen, or lifestyle during the study duration, though participants were obese at baseline and remained obese at study conclusion. We do not have specific data on tolerability of metformin or adverse effects during treatment, however 72% of participants remained on drug at final data collection time point, indicating that metformin was relatively well tolerated. Additionally, though we have access to metabolic labs such as lipids and insulin levels for some participants at some time points, the available data is not sufficient to draw any conclusions regarding the impact of metformin on these measures in our sample. Detailed safety lab monitoring, as well as additional anthropometric measures such as waist circumference, will be meaningful to include in future work.

Further work is indicated to determine the safety and efficacy of metformin as a treatment for antipsychotic-induced weight gain in youth with ASD. However, this study adds to the growing body of evidence supporting the use of metformin for this indication in clinical practice. Future study which potentially incorporates life style modifications, comprehensive long-term metformin use safety, and measure of potential impact on lipid metabolism and insulin-resistance are needed.

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Author Contributions LKW was involved in all aspects of this research including conceptualization, design, execution, and composition of the manuscript. RA completed the statistical design and analysis for this project. EVP and KCD were involved in project conceptualization and reviewed the manuscript in detail. CB and EF completed all data collection and were involved in manuscript review. CAE was involved in all aspects of the project including conceptualization, execution, and manuscript completion.

Compliance with Ethical Standards

Conflict of interest The authors report no direct conflicts of interest with this report. Dr. Wink's current research is supported by the Simons Research Foundation, Autism Speaks, Roivant Sciences Ltd, and Cures Within Reach. Dr. Wink has served as a past consultant for Otsuka. Dr. Pedapati receives research support from the Cincinnati Children's Hospital Research Foundation. Dr. Erickson is a consultant to and holds equity in Confluence Pharmaceuticals and is a consultant to Neurotrope and Fulcrum. Dr. Erickson is a past consultant to Alcobra Pharmaceuticals, the Roche Group, and Novartis. Dr. Erickson holds non-related IP held by CCHMC and Indiana University. Dr. Erickson receives or has received research grant support from the John Merck Fund, Indiana University School of Medicine, Cincinnati Children's Hospital Medical Center, Autism Speaks, the United States Department of Defense, the Simons Foundation, the United States Centers for Disease Control, the National Fragile X Foundation, The Roche Group, Neuren Pharmaceuticals, the National Institutes of Health, and Roivant Sciences Ltd. Dr. Adams, Dr. Dominick, Ms. Fox, and Ms. Buck have no conflicts to report.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent As this work was a chart review study, need for informed consent by participants was waived by our IRB.

Appendix

Complete Drug List by Category

Antipsychotics: aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, thioridizine, ziprasidone.

Antidepressants: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, sertraline.

Anxiolytics: buspirone, clonazepam, hydroxyzine, lorazepam, propranolol.

Stimulants: amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamphetamine, methylphenidate, methylphenidate ER.

Non-stimulant ADHD Medications: atomoxetine, clonidine, guanfacine, guanfacine ER.

Sleep Aids: diphenhydramine, melatonin, ramelteon, trazodone, zolpidem.

Mood Stabilizers/Anti-epileptics: clobazam, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproic Acid.

Other: acamprosate, *n*-acetylcysteine, riluzole.

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