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Metformin as a Possible Intervention for Cardiometabolic Risks in Pediatric Subjects Exposed to Antipsychotic Drugs

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Children and adolescents who are exposed to antipsychotic medication are at increased risk of weight gain and metabolic dysregulation. Metformin, which has demonstrated efficacy for these adverse treatment outcomes in adult samples, has been examined in pediatric samples, as well. Case reports, 2 uncontrolled studies, and 2 (out of 3) randomized controlled trials have demonstrated that metformin (1,000–1,700 mg/d) treatment for up to 16 weeks is associated with statistically and clinically significant weight loss. There is less consistent evidence, however, for benefits with metformin for glucose and lipid metabolism outcomes. The early institution of metformin in vulnerable patients merits consideration and study.

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Introduction

Children and adolescents may receive antipsychotic drugs on- or off-label for indications that include schizophrenia, bipolar disorder, autism spectrum disorder, tic disorders, and other conditions.[1] Antipsychotic drugs, however, are associated with cardiometabolic abnormalities. For example, in a systematic review and meta-analysis of randomized controlled trials (RCTs) of atypical antipsychotic drugs vs placebo in pediatric subjects, Almandil et al[2] identified 21 relevant studies (pooled N = 2,455). There were 14 studies for risperidone (N = 1,331), 3 for olanzapine (N = 276), and 4 for aripiprazole (N = 848). Mean increase in body weight, relative to placebo, was greatest with olanzapine (3.45 kg; 95% CI, 2.93–3.98 kg), intermediate with risperidone (1.77 kg; 95% CI, 1.35–2.20 kg), and least with aripiprazole (0.94 kg; 95% CI, 0.65–1.24 kg). Olanzapine was also associated with increased glucose and total cholesterol levels (2 RCTs).

In a large and extensive qualitative review, Martinez-Ortega et al[3] examined 71 intervention trials, 42 observational studies, and 14 literature reviews. They observed that, in children and adolescents treated with antipsychotic medications, younger age was associated with greater risk of antipsychotic-related weight gain; the risk seemed greatest with olanzapine and least with ziprasidone.

In another systematic review and meta-analysis, Galling et al[4] examined the risk of type 2 diabetes mellitus (T2DM) in children, adolescents, and young adults (aged 2–24 years) after exposure to antipsychotic treatment for at least 3 months. There were 13 studies that included 185,105 youth (mean age, 14.1 years; 59.5% male) who had received antipsychotics for 310,438 patient-years. The incidence rate of T2DM was 3.1 (95% CI, 2.4–3.8) per 1,000 patient-years. The risk of T2DM was higher with antipsychotic exposure relative to healthy controls as well as psychiatric controls. Greater cumulative risk of T2DM was associated with male gender, use of olanzapine, and longer antipsychotic exposure.

Metformin is perhaps the best established among pharmacologic and nonpharmacological inteventions that have been studied for the prevention or treatment of antipsychotic-related weight gain in adults.[5–7] In a systematic review and meta-analysis of the efficacy of metformin in the treatment of overweight and obesity in adolescents, Bouza et al[8] identified 9 RCTs that included 498 subjects with a mean age of 14.2 years and a mean body mass index (BMI) of 36.4. Metformin reduced the mean BMI by 1.42; improvements in fasting insulin and insulin sensitivity were also identified. The adverse event rate and the dropout rate due to adverse events did not differ between metformin and placebo groups.

Might metformin carry metabolic benefits in pediatric subjects exposed to antipsychotic drugs? This question was examined through a PubMed search conducted on August 31, 2016, with the keywords *metformin, child(ren)/adolescent(s),* and *schizophrenia/antipsychotic(s)*.

Case Reports

There have been a few case reports on the use of metformin to treat antipsychotic-related weight gain. These are of small relevance now that the results of uncontrolled and controlled prospective studies have

Clinical Points

- Children and adolescents may receive antipsychotic medication for various indications. These patients are at risk of weight gain and other adverse cardiometabolic changes.
- A small body of research suggests that pediatric subjects who gain weight with atypical antipsychotics could lose some of this weight with adjunctive treatment with metformin (1,000–1,700 mg/d). It is not clear, however, whether glucose and lipid metabolism also improves.
- It may be better to start metformin cotherapy earlier, rather than later; that is, before, rather than after considerable and potentially irreversible weight gain. This, however, needs to be empirically examined in randomized controlled trials.

been published. However, these are referenced here for completeness. Weaver et al[9] reported a 17-year-old girl with schizoaffective disorder whose clozapine-related progressive weight gain stabilized after the introduction of metformin (1,000 mg/d). Salau et al[10] reported that metformin (250 mg/d) slowed but did not reverse aripiprazole-related weight gain in a 13-year-old boy with autism spectrum disorder.

Uncontrolled Studies

In 1 uncontrolled study, Morrison et al[11] recruited 19 patients (63% male), aged 10–18 (mean, 14.1) years, who were receiving risperidone, olanzapine, quetiapine, or valproate separately or in combination and who had gained much weight with these medications. All patients were treated with metformin 1,500 mg/d for 12 weeks. Three patients dropped out between weeks 4 and 8, and 4 more dropped out between weeks 8 and 12. Weight loss was observed in 15 (79%) patients. The mean weight loss in observed cases was 0.9 kg at 4 weeks, 1.1 kg at 8 weeks, and 2.9 kg at 12 weeks. Four patients continued metformin for a longer period, losing 4–13 kg at the time of the last follow-up. Although metformin was associated with loose stools in 6 patients on some occasions, in none of these 19 patients did dropout occur due to adverse events.

In another uncontrolled study, Shin et al[12] identified 11 patients (64% male), aged 10–18 (mean, 14) years, who had gained weight with atypical antipsychotic drugs. All patients were treated with metformin in a dose that was gradually up-titrated to up to 2,000 mg/d Only 5 (45.5%) patients completed the study; the reasons for dropout in the remaining patients were mainly administrative in nature. Weight gain was arrested with metformin treatment; whereas both weight and waist circumference decreased, neither change reached statistical significance. There was a significant fall in serum triglycerides, which was greater with longer duration of treatment, but no significant change in other metabolic parameters, including HDL cholesterol, LDL cholesterol, blood sugar, and insulin levels.

Randomized Controlled Trials

Three RCTs have examined benefits with metformin in pediatric samples exposed to antipsychotic drugs.

Klein et al. These authors[13] described a 16-week RCT of adjunctive metformin in 38 psychiatrically heterogeneous patients (55% male), aged 10–17 (mean, 13) years, who had gained > 10% (mean, about 10 kg) of baseline body weight during up to 12 months of treatment with olanzapine, risperidone, or quetiapine. Most patients were receiving other psychotropic drugs, as well; these drugs were kept stable during the course of the study. The dose of metformin was gradually raised to 1,700 mg/d. All patients also received nutritional counseling.

Three metformin patients dropped out: 1, due to diabetes at baseline; another, due to continued weight gain associated with metformin noncompliance; and a third, due to the need for medication change. Five placebo patients dropped out: 2 because of diabetes (1, at baseline) and 3 because of the need for medication change.

Placebo patients gained a mean of 4 kg, whereas metformin patients maintained the same weight. BMI decreased by 0.4 units with metformin but increased by 1.1 with placebo. Relative to placebo, metformin was associated with significant reduction in age-adjusted standardized weight scores. Relative to placebo, metformin also significantly reduced waist circumference and improved insulin sensitivity. The need for glucose tolerance testing was significantly lower with metformin. Adverse events, including diarrhea, did not differ between the 2 groups.

Anagnostou et al. These authors[14] described a 4-center, 16-week, North American RCT of metformin augmentation in 60 children and adolescents (age, 6–17 years) with autism spectrum disorder. The mean age of the sample was 12.8 years. The sample was 75% male. All subjects were on a stable dose of atypical antipsychotic medication (mostly risperidone or aripiprazole), and all had gained > 7% of baseline BMI within the past year. These subjects were randomized to receive metformin or placebo. Metformin was slowly up-titrated to 1,000 mg/d in children aged 6–9 years and 1,700 mg/d in those aged 10–17 years. Treatment adherence was > 95% in both groups.

Metformin was associated with significantly greater weight loss (mean difference, 2.73 kg; 95% CI, 1.43–4.04 kg; effect size, 1.13) and significantly greater reduction in BMI (by 0.96 units; 95% CI, 0.45–1.46 units; effect size, 1.01) than placebo. The BMI standardized scores reduced more with metformin than with placebo (mean difference, 0.10; 95% CI, 0.04–0.16; effect size; 0.82). Waist-hip ratio change did not differ significantly between the 2 groups, nor did metabolic outcomes, including lipid levels, fasting glucose, fasting insulin, and insulin sensitivity.

Irritability and clinical global ratings did not differ significantly between the 2 groups. Adverse events were greater with metformin than with placebo and resulted in dropout in 5 metformin patients (agitation, n = 4; sedation, n = 1) but no placebo patient. Gastrointestinal adverse events were reported during 25% vs 7% of treatment days in metformin vs placebo groups, respectively.

Arman et al. Negative results have also been reported. Arman et al[15] described a 12-week RCT in which metformin

(1,000 mg/d) or placebo were used as add-on treatments in 49 children and adolescents with schizophrenia, all of whom received risperidone (6 mg/d). Only 32 patients completed the study. Metformin did not attenuate risperidone-related weight gain.

Safety and Tolerability

Whereas most of the studies reviewed in earlier sections reported that metformin was well tolerated, 1 study[14] reported significantly more adverse events with metformin; the commonest adverse event was gastrointestinal disturbance, something that is well known. The use of an extended-release formulation may improve the tolerability of the drug.[16]

Hypersensitivity reactions may occur with almost any drug, and metformin is no exception. In this context, a Type 1 hypersensitivity reaction was described to have developed within 10 minutes of metformin exposure in a 10-year-old boy who was advised the drug for the treatment of risperidone-related abnormal weight gain. The reaction subsided shortly after the administration of oral diphenhydramine.[17] There is no certainty, however, that the hypersensitivity was due to metformin and not to the excipients in the medication.

Concluding Notes

Risperidone, aripiprazole, olanzapine, paliperidone, and quetiapine are atypical antipsychotics that carry approvals for pediatric use. Ziprasidone and lurasidone are more weight-neutral than these antipsychotics; however, neither ziprasidone nor lurasidone has a pediatric label, as yet. Both merit consideration and study in pediatric samples to determine whether they are effective in children and adolescents without carrying the risk of development of adverse cardiometabolic changes.

In antipsychotic-exposed pediatric subjects who do experience increase in weight and indices of metabolic dysregulation, metformin appears to be safe and effective; the effect size for weight is large, judging from the largest RCT conducted to date.[14] There is no clear evidence, however, that glucose and lipid metabolic outcomes also show favorable changes. There may be a case for the early institution of metformin treatment in pediatric subjects who show evidence of weight gain with antipsychotic treatment; it is overly optimistic to expect substantial benefits with metformin after there has been considerable weight gain and metabolic dysregulation. The early use of metformin in antipsychotic-exposed pediatric samples therefore merits study. The ideal dose and duration of treatment are other issues on which more clarity is needed. It is unclear whether dietary advice and exercise would also be of benefit; results in adult samples have not been overly encouraging.[6] Nevertheless, this is also a subject for future investigation.

Topiramate may also improve weight and metabolic outcomes in pediatric subjects who receive antipsychotic drugs. McDougle[18] provided a discussion on the use of both ziprasidone and topiramate in the context of atypical antipsychotic-induced weight gain.

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