The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Metformin for the treatment of antipsychotic-induced metabolic disturbances in people with intellectual and developmental disabilities

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Individuals with intellectual and developmental disabilities are additionally burdened by an increased risk of metabolic comorbidities.[1–3] A contributing factor to this risk is the high rate of antipsychotic use in this population; these psychotropic medications are highly associated with serious metabolic adverse effects.[4–6] Despite the well-established association, there is presently a lack of effective treatment options for antipsychotic-induced metabolic disturbances in people with intellectual and developmental disabilities.

This situation is best exemplified by a 28-year-old female who was referred to the Adult Neurodevelopmental Services Mental Health and Metabolic Clinic at the Centre for Addiction and Mental Health in Toronto, Canada, which is a clinical service that has been established to address gaps in current care and treat adults with intellectual and developmental disabilities experiencing antipsychotic-related weight gain and other metabolic aberrations. This patient had a diagnosis of autism spectrum disorder, mild intellectual disability and obsessive-compulsive disorder, and was prescribed risperidone for the treatment of challenging behaviours.

The patient gained more than 23 kg (50 lb) in the 6 months after starting antipsychotic treatment, positioning her in the class I level of obesity classifications. This adverse effect was causing substantial distress for the patient and was of great concern to her family as well. A comprehensive metabolic assessment showed that she met criteria for metabolic syndrome, including abdominal obesity, elevated blood sugar and high triglyceride levels. The patient was advised on the importance of lifestyle modifications, including diet and exercise. Serial review of these factors was conducted at each follow-up visit. The patient reported her attempts to improve her diet; however, she expressed concerns over her ability to engage in exercise as she felt out of breath very quickly and she had limited access to a gym to go frequently.

After 2 months of no improvement, various pharmacological interventions were proposed to help with the patient's metabolic health, including metformin, topiramate and liraglutide, all of which have shown effectiveness in treating antipsychotic-induced weight gain. After careful consideration, metformin was chosen for several reasons, namely that it is the best-researched agent with the most evidence of weight loss in severe mental illness; the patient had a history of glaucoma, meaning that topiramate was contraindicated; and liraglutide was very expensive, not covered by her drug plan and involved injections, which made the patient very apprehensive. Before prescribing metformin, fasting bloodwork — as well as measures of B_{12}, folate and hepatic and renal enzymes — were collected, which showed she would be an ideal candidate. The patient was informed that these investigations would be repeated on a yearly basis to ensure continued safety. The patient was started on 500 mg at bedtime and titrated up to 2000 mg/d. Before starting metformin, the patient's weight was 89.9 kg and her body mass index (BMI) was 33.3 kg/m^2. Twelve months of metformin treatment resulted in weight loss of 18 kg, which brought her BMI down to 26.4 kg/m^2, which is classified as overweight but not obese. Furthermore, the patient's overall metabolic profile improved and she no longer met criteria for metabolic syndrome; her fasting glucose, hemoglobin A_{1c} and low-density lipoprotein cholesterol decreased, and her high-density lipoprotein cholesterol increased slightly. Her waist circumference still met the criterion for metabolic syndrome (> 102 cm), but was an improvement from before she started metformin (120 cm). Furthermore, the patient did not report any tolerability concerns except for mild gastrointestinal upset, which was managed by slowing the up-dose titration rate for metformin.

Prescribing adjunctive pharmacological interventions to address antipsychotic-induced weight gain is becoming increasingly popular in other patient populations, such as for patients with schizophrenia,[7] particularly in the case of limited uptake or effectiveness of lifestyle interventions. Unfortunately, people with intellectual and developmental disabilities who are treated with antipsychotics are systematically excluded from clinical trials, hindering the development of evidence to help guide safe and effective treatment in this population. Metformin is a safe, first-line biguanide antihyperglycemic agent used for treating type 2 diabetes; it has recently been recommended for the treatment of antipsychotic-induced weight gain for patients with severe mental illness.[8–10] It also has added benefits for people with symptoms of polycystic ovarian syndrome.[11] In diabetes, metformin acts by decreasing gluconeogenesis in the liver and increasing glucose uptake in peripheral tissues, such as the skeletal muscle.[12] Although the

mechanisms by which metformin may ameliorate antipsychotic-induced weight gain remains elusive, it is possible that its effects on body weight may be secondary to its insulin-sensitizing effects. In addition, metformin is believed to act on some of the pathological alterations of antipsychotic agents on various neurotransmitter systems and the gut microbiota, which may contribute to its weight loss effects in this population.[13,14] Furthermore, preclinical evidence has shown that antipsychotic agents and metformin both affect appetite through opposing actions in the hypothalamus.[15]

To date, only a single open-label study has shown the effectiveness of metformin in reducing weight and improving glycemic control and insulin resistance in 16 individuals with type 2 diabetes, obesity and intellectual and developmental disabilities (4 of whom were on antipsychotic medications).[16] Metformin has been found to reduce antipsychotic-induced weight gain in a randomized trial of children and youth with autism spectrum disorders.[17] However, this evidence has yet to be extended to adults or those with other intellectual and developmental disabilities who are also prescribed antipsychotic agents. To this point, a single clinical case-series of 11 patients showed a mean weight loss of 11.1 (standard deviation 12.30) kg after 6 months of treatment with metformin.[18]

The use of metformin has no serious safety concerns; the most common adverse effect is gastrointestinal intolerance (e.g., nausea, vomiting, diarrhea, bloating), which can be minimized by slower titration schedules, taking the drug with meals and switching to the extended-release formulation, if possible.[12] There is a rare risk of lactic acidosis with extreme overdose;[19] therefore, metformin is usually discouraged for patients with severe liver, kidney or cardiovascular dysfunction.

Overall, the metabolic adverse effects of antipsychotic use in individuals with intellectual and developmental disabilities is a largely neglected issue. Clinically meaningful weight loss is associated with many favourable outcomes, including reduced rates of cardiometabolic comorbidities and improved quality of life.[20–22] Emphasizing metabolic monitoring and exploring the therapeutic potential of early intervention with metformin can contribute to the development of guidelines and implementation strategies to address a recalcitrant health problem in this extremely vulnerable population.

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References

1 Vancampfort D, Schuch F, Van Damme T, et al. Metabolic syndrome and its components in people with intellectual disability: a meta-analysis. *J Intellect Disabil Res* 2020;64:804-15.

2 Florio T, Trollor J. Mortality among a cohort of persons with an intellectual disability in New South Wales, Australia. *J Appl Res Intellect Disabil* 2015;28: 383-93.

3 Heslop P, Glover G. Mortality of people with intellectual disabilities in England: a comparison of data from existing sources. *J Appl Res Intellect Disabil* 2015; 28:414-22.

4 Stogios N, Smith E, Bowden S, et al. Metabolic adverse effects of off-label use of second-generation antipsychotics in the adult population: a systematic review and meta-analysis. *Neuropsychopharmacology* 2021;47:664-72.

5 Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacol* 2011;21:517-35.

6 Smith E, Stogios N, Au E, et al. The metabolic adverse effects of antipsychotic use in individuals with intellectual and/or developmental disability: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2022;146:201-14.

7 Agarwal SM, Stogios N, Ahsan ZA, et al. Pharmacological interventions for prevention of weight gain in people with schizophrenia. *Cochrane Database Syst Rev* 2022;10:CD013337.

8 Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. *CMAJ* 2020;192:E875-91.

9 *Guidelines for the management of physical health conditions in adults with severe mental disorders.* Geneva: World Health Organization. 2018.

10 Cooper SJ, Reynolds GP, Barnes T, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol* 2016;30: 717-48.

11 Johnson NP. Metformin use in women with polycystic ovary syndrome. *Ann Transl Med* 2014;2:56.

12 Nasri H, Rafieian-Kopaei M. Metformin: current knowledge. *J Res Med Sci* 2014;19: 658-64.

13 Luo C, Wang X, Huang H, et al. Effect of metformin on antipsychotic-induced metabolic dysfunction: the potential role of gut-brain axis. *Front Pharmacol* 2019;10:371.

14 Reynolds GP, McGowan OO. Mechanisms underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol* 2017;31:1430-6.

15 Lv WS, Wen JP, Li L, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. *Brain Res* 2012;1444:11-9.

16 Komori T, Yoshida F, Nakamura J, et al. Metformin ameliorates treatment of obese type 2 diabetic patients with mental retardation; its effects on eating behavior and serum leptin levels. *Exp Clin Endocrinol Diabetes* 2004;112:422-8.

17 Anagnostou E, Aman MG, Handen BL, et al. Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: a randomized clinical trial. *JAMA Psychiatry* 2016;73:928-37.

18 Stogios N, Hahn M, Lunsky Y, et al. Addressing metabolic comorbidity in individuals with intellectual and developmental disability on antipsychotics: a clinical case series. *J Clin Psychopharmacol* 2023;43:60-3.

19 Flory J, Lipska K. Metformin in 2019. *JAMA* 2019;321:1926-7.

20 Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess* 2004;8:1-182.

21 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393-403.

22 Chen CK, Chen YC, Huang YS. Effects of a 10-week weight control program on obese patients with schizophrenia or schizoaffective disorder: a 12-month follow up. *Psychiatry Clin Neurosci* 2009;63: 17-22.