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ASCP Corner

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Cardiovascular Health in Severe Mental Illness: Potential Role for Metformin

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Severe mental illnesses (SMI) such as schizophrenia and bipolar disorder are associated with very high rates of metabolic disorders, including obesity, diabetes, and metabolic syndrome.[1–3] The etiology of this comorbidity is multifactorial, encompassing genetic predisposition, environmental factors such as poor nutrition and sedentary lifestyles, and medication side effects. Antipsychotic drugs, used routinely in the treatment of SMI, contribute significantly to this risk.[4,5] Indeed, a recent large Danish cohort study found that patients with schizophrenia are inherently 3 times more likely to have type 2 diabetes than the general population, and this risk was exacerbated by antipsychotics, both first and second generation, by a further 3 times.[6] Much of this risk is accrued early, with rates of obesity approaching 50% and prediabetes in excess of 15% within less than 6 months of starting treatment.[7]

Patients with schizophrenia spectrum disorders have a 20% lower life expectancy and die 15–20 years earlier than the general population, largely due to the several-fold increased risk of cardiovascular disease and type 2 diabetes.[8–10] As such, schizophrenia is associated with more disability than cancer and many other physical illnesses.[11,12]

Beyond increased cardiovascular mortality, weight gain negatively impacts self-esteem and quality of life[13–15] and is the most distressing side effect reported by callers to mental health helplines.[16] Furthermore, antipsychotic-induced metabolic effects contribute to medication noncompliance[16] and have also been correlated with worse cognition,[17,18] a core symptom domain that has yet to be effectively addressed by treatment.

In 2004, the American Diabetes Association/American Psychiatric Association consensus document was published, which detailed, for the first time, metabolic monitoring guidelines for antipsychotic use.[19] Other guidelines have since been published; however, modifications have been limited in most of them, with monitoring and lifestyle changes remaining the methods of choice for addressing metabolic risk.[16] While lifestyle interventions such as diet and exercise or other methods like cognitive behavioral therapy may show some efficacy,[20,21] more recent large-scale studies have raised questions about the clinical and cost-effectiveness of this approach.[22,23] These factors have perhaps contributed to the low rates of treatment for metabolic comorbidities in SMI.[7,24–27]

It is generally accepted that achieving clinically meaningful weight loss (ie, 5% of body weight) carries many benefits, including reduced rates of cardiovascular disease[28] and type 2 diabetes,[29,30] and improved quality of life.[31] Therefore, an early adoption of adjunctive pharmacologic interventions is warranted to address this concerning problem. Intervening earlier may also produce more favorable results, as it is easier to prevent weight gain than to precipitate weight loss and associated metabolic perturbations.[32]

Metformin, a biguanide antihyperglycemic and first-line pharmacologic treatment for type 2 diabetes, is now recommended in the Mental Health section of the Canadian Obesity Guidelines,[33] as well as guidelines from the World Health Organization[34] and UK,[16] for the treatment of antipsychotic-induced weight gain in conjunction with lifestyle modification. The major mechanism of action involves suppression of hepatic glucose production (via adenosine monophosphate–activated protein kinase [AMPK] activation), in addition to increased glucose utilization in the gut.[35] Sixty years of clinical experience and trial data have yielded almost no serious safety concerns, except for the very rare occurrence of lactic acidosis in the context of severe liver, heart, or kidney dysfunction, and/or extreme overdose.[35]

Metformin should be started with 500 mg twice a day or 850 mg once a day, with meals; dosage should be increased in increments of 500 mg weekly or 850 mg every 2 weeks, up to 2,000 mg/d, given in divided doses.[36] Higher doses may be used if tolerated/required; clinical trials have examined doses as high as 2,550 mg/d.[35,37] Gastrointestinal adverse effects are common with metformin and include nausea, vomiting, abdominal discomfort, flatulence, and diarrhea. These can be minimized by using gradual dose up-titration, administration of the drug with meals, and use of a time-release/extended-release formulation. Adverse effects are often temporary, and prescribers should work with patients

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to find an optimum dose. Annual monitoring of creatinine and serum B_{12} levels (metformin can impair vitamin B_{12} absorption) is recommended.[38]

Metformin has been studied extensively for treating antipsychotic-related weight gain and has the most evidence supporting efficacy and safety in this role.[39,40] Efficacy may be higher earlier in the course of illness (average weight loss: 5.18 kg) as compared to patients with more long-standing illness (average weight loss: 2.22 kg). Furthermore, in line with its use as a first-line antidiabetic agent, metformin in patients with schizophrenia has been associated with adaptive changes in fasting insulin levels and insulin resistance in normoglycemic individuals.[39] It has also been shown to improve dysglycemia and insulin sensitivity in patients with comorbid diabetes or prediabetes.[41] Improvements have been found in other metabolic parameters as well, including triglycerides (mean change: −21.01 mg/dL) and total cholesterol levels (mean change: −14.40 mg/dL).[42] These effects would have significant implications in improving the overall cardiometabolic profile of patients. Notably, no significant differences in side effects or dropout frequency in comparison to placebo have been reported.[40,42]

In a recent Cochrane meta-analysis (Agarwal et al, under review; see protocol[43]), metformin was found to be effective in preventing weight gain as well (average weight difference: 4.03 kg), especially in combination with agents with a high metabolic liability, such as olanzapine. Again, no significant difference in side effects or dropout frequency in the metformin arm versus placebo was noted. More recent work supports metformin's efficacy in preventing weight gain when started together with clozapine.[44,45] Metformin also reduces the risk of developing diabetes and is associated with modest weight loss among high-risk patients with prediabetes.[35,46]

Alternative pharmacologic agents have also been investigated to ameliorate antipsychotic-induced weight gain. A combination of olanzapine and samidorphan (OLZ/SAM) is now available in the United States for the treatment of schizophrenia or bipolar disorder in adults.[47] This agent offers the therapeutic efficacy of olanzapine while also mitigating olanzapine-induced weight gain through opioid receptor antagonism; it is presently the only FDA-approved drug for this specific indication. A recent evidence-based review of the pharmacokinetics, safety, and efficacy of OLZ/SAM indicates that the effectiveness of the agent is equivalent to that of olanzapine, along with the advantage of lesser weight gain.[47] This single-tablet combination also has the added benefit of reducing pill burden. However, although OLZ/SAM has been demonstrated to mitigate some of the increase in waist circumference generally observed with olanzapine alone, thus denoting less of an increase in the mass of "metabolically active" fat tissue, it has not been found to improve any laboratory parameters. Other compounds that have demonstrated promising preliminary findings for treatment of antipsychotic-induced weight gain include bupropion[48]; miricorilant, which is a novel selective glucocorticoid modulator[49]; topiramate[50]; and glucagon-like peptide-1 receptor agonists.[51] The evidence for these agents is still quite limited, and their role in prevention of antipsychotic-induced weight gain has not been comprehensively studied.

To summarize, monitoring alone is clearly not enough, and the field must move to actively mitigate the onset and progression of metabolic abnormalities. Relatively inexpensive options such as adjunctive metformin are a good start. It is time we get to it.

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