

Ranitidine, Metformin, and Topiramate: Managing Weight Gain in a Clozapine-Treated Patient With Schizoaffective Disorder

To the Editor: Clozapine is an extremely effective antipsychotic reserved for treatment-resistant schizophrenia due to side effects such as agranulocytosis, cardiomyopathy, and significant weight gain.^{1,2} Clozapine-induced weight gain has been reported at 4.1 kg during the first 18 weeks of therapy.³ A 16-week, double-blind, multidosage clozapine study suggested clozapine-induced weight gain to be a dose-dependent phenomenon. Increasing the dose of clozapine from 300 mg/d to 600 mg/d was associated with an average weight gain of 2 kg.⁴

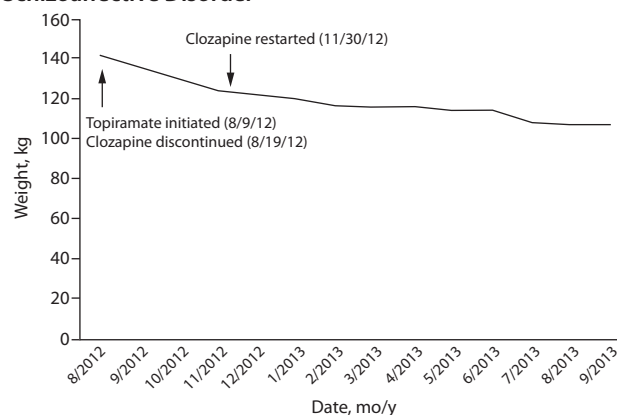
As body mass index (BMI) increases, the risk of comorbidities associated with diabetes and coronary heart disease (CHD) increase. The prevalence of type 2 diabetes in schizophrenia and that in schizoaffective disorder are reported to be approximately 13% and 50%, respectively.⁵ CHD risk doubles in women with a BMI between 25 kg/m² and 29 kg/m² and triples with a BMI > 29 kg/m² as compared to a BMI < 21 kg/m².⁶ Diet and exercise are effective at preventing weight gain, but single-handedly they can be insufficient for short-term weight loss.⁷ Furthermore, sedation and fatigue resulting from clozapine can lead to a 20% decrease in energy expenditure, making diet and exercise more difficult to incorporate.⁸

Patients with schizophrenia are not candidates for many US Food and Drug Administration (FDA)-approved weight loss therapies due to potential worsening of psychosis. In an attempt to manage antipsychotic-induced weight gain, several novel therapies have been studied, including ranitidine, metformin, and topiramate. In an open-label study, ranitidine 300 mg/d was shown to be effective in reducing weight gain by 75% over 16 weeks in patients taking olanzapine.⁹ Studies looking at other H₂ receptor antagonists have not been as promising.^{10,11} The Diabetes Prevention Program showed that metformin was associated with reduced body weight and a 31% reduced incidence of type 2 diabetes.¹² In a double-blind study, metformin was shown to reduce body weight by 3.0 kg over 16 weeks in patients with schizophrenia or schizoaffective disorder.¹³ A recent study looking at topiramate augmentation in clozapine-treated patients with schizophrenia showed a 2.6-kg weight reduction after 12 weeks of therapy.¹⁴

Case report. Ms A, a 33-year-old woman, was diagnosed with DSM-IV schizoaffective disorder, bipolar type. Her fasting lipid profile and blood hemoglobin A_{1c} level were both within the respective normal ranges. She also struggled with episodic pyrosis. She received treatment with clozapine 400 mg/d for schizoaffective disorder, but continued to have significant weight gain. Ms A's previous facility reported her weight to be 135 kg (BMI = 51.6 kg/m²) in June 2011 and 142 kg (BMI = 58.0 kg/m²) in June 2012 while taking clozapine.

When she was transferred to our facility, she weighed over 140 kg in August 2012. Clozapine was tapered off after the metabolic and cardiovascular risks were determined to outweigh the psychiatric benefit. After clozapine was discontinued and topiramate 200 mg/d was added, the patient experienced a 12% (17.3 kg) weight reduction within 3 months. Unfortunately, Ms A's psychosis began to steadily worsen to the point that, slightly longer than 3 months after it had been discontinued, clozapine was restarted at 12.5 mg/d. During the next 16 days, it was titrated to 300 mg/d, at which dose it was continued. The main concern was Ms A's prior history of significant weight gain based on her previous trial of clozapine and apprehension of reversing metabolic and cardiovascular benefits achieved with her BMI reduction of 8 kg/m² since clozapine discontinuation. An informed decision was made to adjunctively start both metformin 1,000 mg/d and ranitidine 300 mg/d while continuing topiramate

Figure 1. Change in Weight Over Time in a Patient With Schizoaffective Disorder



200 mg/d in an attempt to manage clozapine-induced weight gain. After clozapine was restarted, Ms A continued to lose weight at a steady rate (Figure 1).

After 4 months of treatment with this combination, Ms A lost 8.2 kg, which is greater than studies of topiramate, metformin, and ranitidine would suggest individually. She has now been on a combination of clozapine, topiramate, metformin, and ranitidine for 9 months with a total body weight reduction of 24% (34.5 kg). These therapies have been trialed individually for weight loss in recent reports, but to our knowledge this combination has not been studied.

Over one third of adults struggle with obesity in the United States.¹⁵ The health risks associated with obesity include type 2 diabetes, cancer, asthma, gallbladder disease, and cardiovascular diseases.¹⁶ An estimated 30%–60% of patients on clozapine therapy are expected to have weight gain ≥ 7% of their initial body weight.¹⁷ This necessitates the need for practitioners to be cognizant of available treatment options to prevent health risks associated with clozapine-induced weight gain.

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