GLP-1 Receptor Agonists for Clozapine-Induced Weight Gain:

A Case Report With the Dual GLP-1/GIP Agonist Tirzepatide

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Olanzapine and clozapine are among the most effective antipsychotics, with clozapine being the only US Food and Drug Administration (FDA)–approved option for treatment-resistant schizophrenia. However, their high metabolic risks, including weight gain, diabetes, and lipid abnormalities,[1] deter treatment adherence[2] and increase cardiovascular disease risk and related mortality,[3,4] making it challenging for clinicians to balance psychiatric and physical health. Incretin mimetics including glucagon-like peptide-1 (GLP-1) agonists and GLP-1/gastric inhibitory polypeptide (GIP) dual agonists have revolutionized obesity treatment[5] and offer hope for patients with serious mental illness. While GLP-1 agonists have shown effectiveness in managing antipsychotic-induced weight gain,[6–8] the potential of newer GLP-1/GIP dual agonists, particularly for clozapine-induced weight gain, remains unknown. We describe a patient with schizophrenia who effectively reversed substantial clozapine-induced weight gain using tirzepatide, followed by weight regain after insurance-related discontinuation.

Case Report

Mr A, a white man, developed psychosis at the age of 20 years, characterized by thought broadcasting and paranoid delusions. After ineffective trials of paliperidone and olanzapine, he was diagnosed with treatment-resistant schizophrenia and started on clozapine at age 21 years, titrated to 650 mg/day (trough level: 381 ng/mL) over 4 months. His psychotic symptoms partially remitted, allowing him to maintain daily function. However, his unhealthy diet and inactive lifestyle continued.

Despite starting metformin proactively, titrated to 1,000 mg twice daily, concurrently with clozapine to mitigate metabolic side effects, Mr A gained 60 lb within a year (191–251 lb, body mass index [BMI]: 27–36 kg/m^2), worsening social isolation and self-esteem. He also developed hyperlipidemia (triglycerides: 473 mg/dL, low-density lipoproteins [LDLs]: 132 mg/dL), obstructive sleep apnea, and an increasing hemoglobin A1c (HgA1c) (4.9–5.4). Frustrated, he considered stopping clozapine.

To address obesity and associated comorbidities, Mr A's endocrinologist initiated tirzepatide 2.5 mg weekly subcutaneously via a preapproval promotional program with affordable access through his commercial insurance. After 6 months, he lost 35 lb, and his tirzepatide dose was increased to 5 mg weekly. Despite unchanged lifestyle habits, he returned to his preclozapine weight (191 lb, BMI: 27 kg/m^2) after 10 months, reversing clozapine-induced weight gain and resolving obstructive sleep apnea. His HgA1c decreased to 5.0, though hyperlipidemia persisted (triglycerides: 156 mg/dL and LDL: 181 mg/dL). With his weight stabilized, he chose to remain on clozapine. His psychiatric symptoms remained stable throughout treatment, with no reported adverse effects from tirzepatide.

Post-FDA approval, Mr A's insurance denied coverage after the promotional program ended, resulting in abrupt tirzepatide discontinuation and a 17-lb regain over 3 months, despite starting topiramate 100 mg nightly and phentermine 100 mg twice daily. The patient later restarted tirzepatide at 2.5 mg weekly, paying out of pocket, and weight loss resumed.

Discussion

This case demonstrates the successful use of a GLP-1/GIP dual agonist for treating clozapine-induced obesity. Although metformin is the standard first-line preventive measure,[9–11] it failed to avert significant weight gain, whereas tirzepatide fully reversed it.

Rapid weight regain after tirzepatide discontinuation aligns with findings on other GLP-1 agonists,[12,13] emphasizing the need for maintenance treatment and reliable access through consistent insurance coverage, affordability, and supply to sustain benefits. This is a health equity issue, given increased medical mortality in patients treated with clozapine. Few if any patients with serious mental illness can manage obesity with diet and exercise alone,[14] and many experience adverse social determinants of health that impede treatment adherence and access. Continued access to incretin mimetics may further help clozapine patients maintain psychiatric stability via supporting adherence to clozapine—psychiatric stability being the basis for better medical health outcomes.

Further research is needed to understand the long-term effectiveness, risks, and patient-specific predictors of GLP-1 agonists

in managing antipsychotic-induced weight gain. Cost-effective early interventions should also be explored to prevent weight gain and related comorbidities in high-risk individuals.

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