Worth the Weight? The Challenges of Administering the Glucagon-Like Peptide 1 Receptor Agonist Semaglutide With Long-Term Olanzapine Use in a Patient With Schizophrenia

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We present a case report on the challenges of using the glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide in a patient with schizophrenia and severe, olanzapine-induced weight gain that was resistant to alternative weight treatments.

Case Report

The patient, a 6-ft/1.83-m 39-year-old African-American man, was first diagnosed with schizophrenia in 2008, beginning treatment at our center in 2013 (Table 1). By 2015, he had cycled through numerous antipsychotics, with limited efficacy/tolerability, including >40 lb/18 kg weight gain. He began olanzapine in 2015, with the dose gradually increased to 30 mg. He responded well, obtaining employment as a peer counselor and rising to a supervisory level. Despite a trial of metformin, he gained an additional >60 lb/27 kg by late 2020 and was cross-titrated to paliperidone. Over the next 14 months, he lost 23 lb/10.4 kg but decompensated concurrent to self-discontinuing his medications and lost his job. He resumed olanzapine but continued to gain weight despite 2 separate trials of olanzapine-samidorphan, reaching a peak of 375.1 lb/170.1 kg in June 2023. While his serum glucose was generally within normal limits, he began to develop medical complications, including elevated cholesterol/triglycerides, prediabetes, sleep apnea, and hypertension, prompting trials of metabolically friendly antipsychotics, referral to a sleep apnea specialist and endocrinologist, and discussions of an exercise program/dietary changes.

His full adherence with these recommendations was unclear. The next few months led to some weight loss, but alternative antipsychotics were ineffective for his symptoms and poorly tolerated, and we agreed to resume olanzapine 30 mg in August 2023 in combination with semaglutide. Ozempic was started due to Wegovy being on back order and was gradually titrated to 2 mg. Due to an unexpected change in the patient's Medicare plan, Ozempic treatment was interrupted in January 2024 for 3 months. The patient's weight increased by >20 lb/9.1 kg, reaching a new high. Attempts to contest coverage denial, including a probate hearing, were unsuccessful. After exhausting all coverage options, we successfully obtained no-cost coverage directly through a patient assistance program. Ozempic was resumed, and with the exception of a ~3-week interruption due to his roommate accidentally moving the Ozempic to the freezer, he remains on it as of February 2025, with a weight loss of 25 lb/11.3 kg (6.5%) since resuming it.

Discussion

Our experience speaks to several complications of the long-term management of antipsychotic-induced weight gain and the use of GLP-1R agonists in schizophrenia. First, his limited response/tolerability of metabolically neutral antipsychotics, high functioning, and >100 lb of weight gain on olanzapine exemplifies the tradeoffs of balancing efficacy and metabolic liability in schizophrenia treatment. Olanzapine is an effective[1] and tolerable,[2] yet metabolically challenging, antipsychotic.[3] Olanzapine can lead to mean increases >20 lb over the first year,[4] which may be higher in African-Americans[5] and may be dose-dependent,[6] suggesting that our patient's experience is typical. He required high-dose olanzapine,[7] which may have attenuated the impact of olanzapine-samidorphan, metformin, and semaglutide. The recent approval of xanomeline/trospium chloride provides another metabolically neutral option.[8]

Second, using a self-administered, off-label, weekly injection with highly specific storage requirements in a condition with potential cognitive impairment created logistical issues that required frequent re-education, management, and surveillance by our team, particularly given his sensitivity to even brief nonadherence. Finally, this case adds to an ongoing debate on the long-term ethics[9,10] of antipsychotics and GLP-1R use. There is limited literature on semaglutide in schizophrenia,[11,12] but it is highly effective for weight in the general population,[13] and studies of older GLP-1R agonists suggest efficacy[14–16] in schizophrenia. During treatment, in addition to balancing efficacy and tolerability of

Table 1.

Selected Medication Regimen and Metabolic Parameters

Start date	Antipsychotic	Adjunctive weight loss medication	Weight, lb (kg)	Other metabolic values	Notes on medication changes
2008–2015	Trials of paliperidone, perphenazine, haloperidol decanoate, aripiprazole, quetiapine		218.0 (98.9)		Stopped for side effects/efficacy, limited details of doses/trial length available
March 2015	Quetiapine (200 mg) and olanzapine (10 mg) qhs		260.0 (117.9)	HbA1c = 5.7%	Stopped for side effects/efficacy
May 2015	Olanzapine (20 mg) qhs		268.8 (121.9)		
July 2015	Olanzapine (30 mg) qhs		278.2 (126.2)		Dose increased for efficacy
January 2017		Metformin (1,000 mg) bid; started July 2016	293.7 (133.2)		Unclear on adherence for metformin—discontinued late 2017
February 2018			319.8 (145.1)		
December 2020	Paliperidone (6 mg)		323.0 (146.5)		Switched from olanzapine due to weight concerns
August 2021	Olanzapine (30 mg) qhs → no medication		312.0 (141.5)		Switched back to olanzapine for efficacy. Patient self-discontinued olanzapine sometime between August 2021 and April 2022
April 2022	Olanzapine (30 mg)		301.2 (136.6)		
May 2022	Olanzapine (15 mg) + combination olanzapine 15 mg/samidorphan 10 mg qhs		311.7 (141.4)		
December 2022	Olanzapine (30 mg) qhs		333.2 (151.1)		Stopped combination olanzapine 15 mg/samidorphan 10 mg for lack of efficacy for weight attenuation and self-reported side effects
April 2023	Olanzapine (15 mg) + combination olanzapine 15 mg/samidorphan 10 mg		360.0 (163.3)		Resumed combination olanzapine 15 mg/samidorphan 10 mg
June 2023	Separate, brief trials of aripiprazole (10–15 mg) and lumateperone 42 mg		375.1 (170.1)	HbA1c = 6.2% Cholesterol: 168 mg/dL Triglyceride: 182 mg/dL	Stopped combination olanzapine 15 mg/samidorphan 10 mg for lack of efficacy for weight attenuation. Referred to specialists and recommended lifestyle interventions
August 2023	Olanzapine (30 mg)	Began Ozempic titration from 0.25 q week	366.4 (166.2)		Stopped aripiprazole and lumateperone due to nausea/akathisia
November 2023		Began Ozempic 2 mg q week	366.2 (166.1)	WC = 55.5 in/141.0 cm	
January 12, 2024		NA	358.8 (162.7)	WC = 55 in/139.7 cm	Stopped Ozempic for insurance change
March 29, 2024		Resumed Ozempic titration from 0.25 q week	381.4 (173.0)	WC = 55.3 in/141.5 cm HbA1c = 6.2%	Weight peaked at 384.8 (174.8) in May 2024
June 28, 2024		Began Ozempic 2 mg q week	381.0 (172.8)		
October 8, 2024		Ozempic 2 mg q week	375.4 (170.3)	WC = 53.5 in/141.5 cm	Ozempic placed in freezer accidentally. Estimated last dose mid to late October 2024
November 13, 2024		Ozempic 2 mg q week	374.8 (179.0)	WC = 52.75 in/134.0 cm, HbA1c = 5.8%	Resumed Ozempic
January 2025			362.8 (164.6)	WC = 53.3 in/141.5 cm	
February 2025			356.4 (161.7)	WC = 53 in/134.6 cm HbA1c = 5.9% Cholesterol: 98 mg/dL Triglyceride: 73 mg/dL	

Abbreviations: HbA1c = hemoglobin A1c, NA = not applicable, WC = waist circumference.

olanzapine itself, we faced treatment/dosage decisions on using semaglutide as a weight-loss–branded formulation (Wegovy, maximum dose 2.4 mg) or not (Ozempic, maximum dose 2 mg) and shifting coverage for off-label use. While successful, use of the patient assistance program is not a viable solution for everyone. Two controlled studies with semaglutide in schizophrenia are ongoing,[17,18] which we hope will inform expanded coverage of semaglutide in federal insurance programs.

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