A Case of Semaglutide-Induced Euphoria in a Patient With Bipolar Disorder

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As glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed, their neuropsychiatric effects are of growing interest. GLP-1 receptors are diffusely present in the CNS and known to modulate mood.[1] However, the original clinical trials of GLP-1RAs excluded patients with mood disorders and prior suicidality.[2,3] While some have studied the incidence of depression, anxiety, and suicidality in GLP-1RA users, the variety of mood effects of these agents in patients with mood disorders are not fully known.[4,5] Herein, we report what is to our knowledge the first case of transient euphoria, accompanied by anxiolysis and cognitive slowing, following semaglutide in a patient with bipolar disorder.

Case Report

Ms S is a 77-year-old woman with bipolar II disorder, diagnosed in 1997 by *DSM-IV* criteria, with 1 remote suicide attempt and remote cannabis use. Since 1997, she was treated at various points with valproate, risperidone, and olanzapine for mood stabilization, along with sertraline and later venlafaxine for depressive symptoms. In the past 5 years, she has been euthymic on venlafaxine 225 mg/day and trazodone 12.5 mg/night. She has not had known affective instability while on antidepressants alone.

In November 2024, Ms S was started on semaglutide 0.25 mg weekly for obesity by her internist. Within a few hours of her first semaglutide injection, she experienced euphoria and anxiolysis, without use of other substances. She described giggling excessively, feeling calm, and cognitively slowed. She likened the experience to cannabis ingestion in her youth. The euphoria subsided by morning, but mild anxiolysis persisted for 2 days following the injection. After the subsequent injection a week later, euphoria, anxiolysis, and cognitive slowing recurred with the same time course. She had no manic symptoms. With the third and fourth injections, these symptoms did not recur. Instead, Ms S experienced significant fatigue without depressive symptoms or suicidality and subsequently stopped the treatment.

Discussion

Since reports to the European Medicines Agency of depression and suicidality in patients taking GLP-1RAs, large studies have demonstrated conflicting results regarding the association of these drugs with mood disturbance and suicidality.[4–6] Some have even shown antidepressant and anxiolytic effects of GLP-1RAs with chronic use, with putative mechanisms of serotonergic signaling modulation, reduced neuroinflammation, and induced neurogenesis and synaptic plasticity.[7–10] However, to our knowledge, this is the first report of GLP-1RA-induced acute euphoria, in addition to anxiolysis and cognitive slowing.

Using the Naranjo Adverse Drug Reaction Probability Scale, Ms S's episodes of euphoria reached a score of 7, indicating that they were probable adverse drug reactions to semaglutide.[11] While these episodes were pleasant and did not include mania, they interfered with functioning, making them relevant to prescribers. The episodes were transient, which suggests they may occur primarily in the beginning of treatment, although studies are needed to determine whether this is the case.

While proposing a mechanism for Ms S's euphoria is speculative, one possibility may be the modulation of dopaminergic pathways in the ventral tegmental area (VTA), involved in reward processing.[12] GLP-1RAs acutely increase dopamine signaling in the VTA, which could cause acute pleasure and euphoria.[12] GLP-1RAs also upregulate VTA presynaptic dopamine-2 (D2) receptor transcription, ultimately reducing VTA dopaminergic signaling over time.[1] This might partially explain the reduction in hedonic food-seeking from GLP-1RAs and might explain why Ms S's euphoric episodes waned with repeated GLP-1RA administration.[1,12] One might also hypothesize that Ms S's primary mood disorder and prior exposure to D2-blocking agents predisposed to her mood effects of GLP-1RAs by altering baseline dopaminergic signaling in the VTA. However, mechanistic research is needed to support these hypotheses. With the growing use of GLP-1RAs, clinicians should be alert to their possible neuropsychiatric effects including euphoria.

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