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Semaglutide and exacerbation of psychogenic non-epileptic activity: A case report

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Abstract

Background: Semaglutide, a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA), is widely used for the treatment of type 2 diabetes and obesity and has demonstrated benefits in metabolic and emerging psychiatric indications. However, concerns have arisen regarding potential neuropsychiatric side effects, including mood disturbances and suicidality. To date, no known cases have linked semaglutide to Psychogenic Non-Epileptic Attacks (PNEA), a subtype of functional neurological disorder.

Case presentation: We present the case of a 58-year-old African American woman with a history of PNEA, post-traumatic stress disorder, traumatic brain injury, and type 2 diabetes who developed a marked exacerbation of her seizure-like episodes approximately 13 weeks after initiating semaglutide therapy. Prior to treatment, her PNEA episodes were infrequent and brief. Following semaglutide initiation, she experienced daily episodes lasting up to 35 minutes, accompanied by depressive symptoms. Neurological workup was negative, and EEG showed no epileptiform activity. Upon discontinuation of semaglutide and titration of antidepressant therapy, the patient experienced complete resolution of her functional seizures and significant improvement in mood.

Discussion: Although semaglutide is not known to cause PNEA, its ability to modulate central neurotransmission, particularly dopamine signaling and stress response pathways, raises the possibility of adverse neuropsychiatric effects in vulnerable individuals. This case parallels other reports of mood disturbances associated with GLP-1 RAs and expands the scope of potential neurologic effects. Additionally, it highlights the contrast between semaglutide's emerging psychiatric applications and its rare but serious adverse events.

Conclusion: This case may represent the first reported association between semaglutide and PNEA exacerbation. Clinicians should be aware of potential neurologic and psychiatric side effects in patients with a history of functional neurological disorders or mood instability. Close monitoring and individualized risk assessment are warranted, particularly in those with complex neuropsychiatric histories.

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Introduction

Semaglutide is a Glucagon-Like Peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes and, at higher doses, for obesity management. It mimics endogenous GLP-1, enhancing insulin secretion, inhibiting glucagon, delaying gastric emptying, and promoting satiety via central mechanisms [1,2]. These effects contribute to improvements in glycemic control, weight loss, and cardiovascular outcomes.

Beyond metabolic benefits, semaglutide shows promise in neuropsychiatric indications. Preliminary studies have shown reductions in alcohol intake and binge eating behavior through modulation of central reward circuits, prompting clinical interest in GLP-1 Receptor Agonists (GLP-1 RAs) for substance use disorder, including alcohol, cocaine, and nicotine dependence [3-10]. Additionally, semaglutide has been shown to reduce pro-inflammatory neurobiological markers such as Tumor Necrosis Factor Alpha (TNF-α) and Interleukin-6 (IL-6), lower stress hormone levels such as corticosterone, inhibit Nuclear Factor-kappa B (NF-κB) signaling, and increase Brain-Derived Neurotrophic Factor (BDNF) expression. Taken together, these changes may indicate a multifaceted neuroprotective and antidepressant-like effect [11]. The agent has also demonstrated putative neuroprotective benefits in preclinical mouse models of Alzheimer's disease through mediation of various neuroinflammatory pathways [12].

Despite these promising findings, concerns have emerged regarding adverse psychiatric effects. Mood disturbances, including depressive symptoms and suicidality, have been observed in case reports and pharmacovigilance analyses, with emerging evidence from real-world data and regulatory reviews [13-18]. In contrast, other reports deny a significant difference in neurologic or psychiatric adverse outcomes in patients taking semaglutide compared to patients taking other glucose-lowering drugs, such as sitagliptin, empagliflozin, or glipizide [19-22]. Additionally, among participants free of serious mental illness, weekly semaglutide was not proven to raise psychiatric-event risk [22].

Psychogenic Non-Epileptic Attacks (PNEA) are episodes that clinically resemble epileptic seizures but occur without corresponding electrographic changes on EEG [13]. PNEA is classified under the umbrella of Functional Neurological Disorders (FND), which are characterized by abnormal nervous system functioning without identifiable structural pathology. These episodes are often triggered or exacerbated by psychological stress and are frequently associated with underlying psychiatric comorbidities such as anxiety, depression, Post-Traumatic Stress Disorder (PTSD), and personality disorders [23]. The pathophysiology of PNEA is complex and multifactorial, involving alterations in emotion regulation, stress response pathways, including the Hypothalamic-Pituitary-Adrenal (HPA) axis, and dopaminergic signaling within brain regions such as the limbic system, prefrontal cortex, and basal ganglia [24]. This report presents the first documented case of semaglutide-associated exacerbation of PNEA in a patient with prior stable functional neurologic symptoms, highlighting the need for awareness of potential neuropsychiatric risks in vulnerable populations.

Case presentation

A 58-year-old African American woman with a history of obesity, type II diabetes, traumatic brain injury, cervical stenosis, PTSD, and PNEA presented to the emergency room with seizure-like activity. She was diagnosed with PNEA two years prior to this admission, following the death of her brother. These attacks led the patient to seek treatment with therapy, which she had participated in for over a year. Although the events would still occur, they were limited to only one event per six months on average. Each episode would typically last between 15-60 seconds. Upon presentation in the emergency room, the patient had a witnessed episode in which both upper limbs were moving in a circular fashion in front of her body, appearing as if she was climbing a ladder with her arms, while her head was turned to the side with forcibly closed eyelids, eyelid fluttering, and teeth chattering. There were no focal or generalized tonic-clonic movements and no clear automatisms. The episode lasted around 6 minutes. The patient was able to recall the episode's events and did not display any postictal signs.

The patient was admitted to the hospital, and the events continued to occur 1-3 times daily, with a similar presentation as the initial attack in the emergency department, though at times there was also lower extremity involvement with periodic kicking. The longest episode was reported to last 35 minutes. After a neurological workup, including EEG, did not reveal any significant abnormalities, psychiatry was consulted. The patient's psychotropic medications included duloxetine 40 mg daily and gabapentin 600 mg twice daily, both primarily prescribed for pain due to cervical stenosis, although there was some suspected added mood benefit that the patient reported with duloxetine. As the patient reported stable pain control, she felt these medications did not require adjustment. However, she did report some worsening mood, stating, "I feel like I'm depressed for the first time" and recalled signs of depression over the previous 6 weeks. These depressive symptoms had intensified until 1 week prior to presentation, when her seizure-like activity began to worsen, prompting her to present to the hospital. On exam she endorsed anhedonia, loss of concentration, poor sleep, decreased appetite, and feelings of helplessness and hopelessness, which she attributed to her worsening seizure-like episodes. The patient denied any safety concerns and was help-seeking. Ultimately the patient's duloxetine was increased to address suboptimally controlled mood symptoms.

Notably, the patient had been started on semaglutide injections 13 weeks prior to hospitalization and was titrated up over a 10 week span to a weekly dose of 2 mg at time of admission.Noting the timeline and correlation with worsening mood and PNEA, the patient and her medical providers elected to discontinue semaglutide. The patient was followed closely by mental health throughout the hospitalization and was discharged after 1 week with follow up in a functional neurologic disorder clinic. The patient's PHQ-9 score in the hospital was 17. Six months after discontinuing semaglutide, she scored a 3, and notably, had 3 months of no seizure-like activity, with the last episode lasting just 45 seconds. No other medication changes had occurred in this period of time. She reported being the "best I've ever been".

Discussion

This case illustrates an association between semaglutide use and exacerbation of PNEA. A Naranjo Adverse Drug Reaction Probability Scale yields a total score of 5, indicating that this reaction is probable [25]. Although semaglutide has demonstrated efficacy for metabolic control and holds promise

for neuropsychiatric conditions, its central activity may also present psychiatric and neurologic risks.

GLP-1 receptors are located in the hypothalamus, hippocampus, and mesolimbic system—regions involved in regulating mood, cognition, and reward processing. GLP-1 RAs like semaglutide can influence central dopaminergic pathways, particularly in the ventral tegmental area and nucleus accumbens, where they may alter dopamine release and receptor activity. These changes can affect motivation and reinforcement signaling, which are relevant to both substance use and mood disorders [5,26]. In the hypothalamus, GLP-1 RAs can modulate Corticotropin-Releasing Hormone (CRH) expression and impact the HPA axis, potentially influencing cortisol levels and stress reactivity. Additionally, GLP-1 signaling has been shown to affect the expression of pro-inflammatory cytokines such as TNF-α and IL-6, and neurotrophic factors like BDNF, which are implicated in the pathophysiology of depression and functional neurological symptoms [11,12]. In some individuals, these neurochemical shifts may increase susceptibility to psychiatric symptoms, particularly in the presence of trauma history, affective disorders, or functional neurological disorders. Pharmacogenomic variability in GLP-1 receptor pathways may further influence individual sensitivity to these central effects, contributing to variable psychiatric and neurological outcomes across patients [24,27].

Although no previous cases of semaglutide-induced PNEA have been reported, increasing attention has been drawn to other neuropsychiatric effects [13-15]. Registry and pharmacovigilance data support an association between semaglutide and psychiatric events, including suicidality, especially in those with preexisting psychiatric conditions [16-18,28,29].

The potential for semaglutide to influence both therapeutic and adverse outcomes through central GLP-1 receptor activity underscores the complexity of its neuropsychiatric profile. While studies have explored the benefits of semaglutide in substance use disorder, binge eating and even cognitive function, this case adds a cautionary perspective [3,4,12,30-33]. The interplay between GLP-1 receptor activity in the brain and individual vulnerability, whether structural, genetic, or psychiatric, requires further investigation. This case highlights the need for monitoring of central nervous system effects of GLP-1 receptor agonists more closely in at-risk populations.

Conclusion & recommendations

This case represents what may be the first documented association between semaglutide and the exacerbation of PNEA. The patient's symptoms began after initiation and titration of semaglutide and resolved following its discontinuation, alongside increased duloxetine dose. While semaglutide is widely regarded as safe and effective for glycemic and weight control and is under investigation for psychiatric benefits, clinicians must remain vigilant regarding its potential neuropsychiatric and neurologic side effects [1-4,11-17,20,21]. This is especially important in individuals with a history of psychiatric illness or functional neurological symptoms.

In practice, careful pre-treatment assessment and close follow-up are advisable when prescribing semaglutide to patients with complex neuropsychiatric histories. Further research is warranted to clarify the mechanisms underlying these effects and to identify those at greatest risk. Until then, individualized risk–benefit evaluation, patient education, and prompt adverse event reporting remain critical to safe prescribing practices.

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