



Semaglutide Injection, a GLP1 Agonist, Induced Depression and First Time Suicidal Ideation in a Female with Long-standing Anxiety

Kenneth Blum^{1,2,5,14,18,19*}, Alireza Sharafshah³, Chynna Fieleglman⁴, Kai-Uwe Lewandrowski^{5-7,14}, David Baron⁸, Alexander PL Lewandrowski⁹, Catherine A Dennen¹⁰, Albert Pinhasov², Abdalla Bowirrat², Nicole Jafari¹¹, Foojan Zeine¹², Rossano Kepler Alvim Fiorelli¹³, Sergio Schmidt¹⁴, Edward J Modestino¹⁵, Mark S Gold¹⁶, Debasis Bagchi¹⁷, Yatharth Mahajan¹⁸, Shaurya Mahajan¹⁸, Keerthy Sunder^{1,19}, Milan Makale²⁰, Kyriaki Z Thanos²¹, Kavya Mohankumar^{18,19}, Anand Swaroop²², Morgan P Lorio²³, Igor Elman^{2,24}, Panayotis K Thanos^{2,25} and Rajendra D Badgaiyan²⁶

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Kenneth Blum., et al.

¹Division of Addiction Research and Education, Center for Sports, Exercise, and Mental Health, Western University of Health Sciences, Pomona, CA, USA

²Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel

³Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

⁴Department of Psychology, St. John's University, Queens, NYC., NY, USA

⁵Division of Personalized Pain and Education, Center for Advanced Spine Care of Southern Arizona, Tucson AZ, USA

⁶Department of Orthopaedics, Fundación Universitaria Sanitas Bogotá D.C. Colombia

⁷Department of Orthopaedics, Universidade Federal do Estado do Rio de Janeiro and Department of Spine Surgery, Arizona University, School of Medicine, Tucson, AZ, USA

⁸Department of Psychiatry, Stanford University School of Medicine, Palo Alto, CA., USA

⁹Department of Biological Sciences, Dornsife College of Letters, Arts and Sciences, University of Southern California, Los Angeles, CA, USA

¹⁰Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA

¹¹Department of Applied Clinical Psychology, The Chicago School of Professional Psychology, Los Angeles, CA., USA

¹²Department of Health Science, California State University at Long Beach, Long Beach, CA., USA

¹³Department of General and Specialized Surgery, Gaffrée e Guinle University Hospital, Federal University of the State of Rio de Janeiro (UNIRIO)

¹⁴Post-Graduate Program in Neurology, Federal University of the State of Rio de Janeiro, Brazil

¹⁵Brain and Behavior laboratory, Cury College, Milton, MA.,USA

¹⁶Department of Psychiatry, Washington University, School of Medicine, St. Louis, MO, USA

¹⁷Department of Pharmaceutical Sciences, Texas Southern University College of Pharmacy, Houston, TX, USA

¹⁸Division of Clinical Neurology, The Blum Institute for Neurogenetics and Behavior, LLC., Austin, TX.,USA

¹⁹Division of Neuromodulation Research, Karma Doctors and Karma TMS, Palm Springs, CA, USA

²⁰Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA, USA

²¹Department of Psychology, University of Buffalo, NY, USA

²²Cepharm, Inc., Somerset, NJ, USA

²³Advanced Orthopedics, Altamonte Springs, FL, USA

²⁴Department of Psychiatry, Harvard University School of Medicine, Cambridge, MA., USA

²⁵Behavioral Neuropharmacology and Neuroimaging Laboratory on Addictions (BNNLA), Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, and Department of Psychology, University at Buffalo, Buffalo, NY, USA

²⁶Department of Psychiatry, Texas Tech University Health Sciences, School of Medicine, Midland, TX., USA

***Corresponding Author:** Kenneth Blum, Division of Addiction Research and Education, Center for Sports, Exercise, and Mental Health, Western University of Health Sciences, Pomona, CA, USA.

Abstract

Mental illness affects approximately one in five children in the United States, with many individuals experiencing comorbid psychiatric conditions such as anxiety, depression, and substance use disorders. Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacologic treatment for generalized anxiety disorder, while benzodiazepines and certain SNRIs serve as second-line options. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for type 2 diabetes and weight management, have recently raised concerns due to their emerging neuropsychiatric side effects. Recent research has shown that GLP-1RAs modulate functional connectivity in key brain networks involved in mood regulation, including the default mode, salience, and frontoparietal networks. Adverse psychiatric outcomes such as mood instability, anxiety, and suicidal ideation have been reported in post-marketing surveillance and case studies, prompting regulatory review. This case report presents a 58-year-old female with a long history of anxiety who experienced a severe psychiatric decline, including insomnia, weight loss, and suicidal ideation, following semaglutide use for weight loss. Despite multiple medication trials, only repetitive transcranial magnetic stimulation (rTMS) achieved sustained symptom relief. The patient retrospectively attributed her decline to GLP-1 agonist exposure, describing the experience as traumatic. While most large-scale studies have not shown significant increases in suicidality with GLP-1RA use, growing evidence suggests the importance of pre-treatment psychiatric screening and genetic vulnerability assessment. This case underscores the potential for adverse neuropsychiatric outcomes in vulnerable individuals and supports the call for more rigorous investigation into the central effects of GLP-1RAs and personalized approaches to prescribing these medications.

Keywords: Semaglutide Injection; GLP1; Suicidal Ideation; Female; Long-standing Anxiety

Introduction

According to the Centers for Disease Control and Prevention (CDC), mental illness encompasses conditions that influence an individual's thoughts, emotions, mood, or behaviours. In the United States, nearly one in five children is affected by some form of mental illness [1]. Individuals with pre-existing mental health conditions, such as intellectual disability (HP:0001249), are frequently diagnosed with additional psychiatric disorders, including anxiety, mood disorders, substance use disorders, sleep disturbances, and antisocial personality disorders, highlighting the clinical importance of comorbidity in this population [2].

Comorbidity refers to the presence of two or more medical conditions within the same individual and is influenced by a range of factors, including genetic, biological, and environmental (epigenetic) contributors. It is associated with poorer health outcomes, challenges in disease management, and increased healthcare costs. In the U.S. alone, approximately 80% of Medicare expenditures are

allocated to patients with four or more chronic conditions, reflecting the widespread burden of comorbidity. The growing interest in this area of research stems from the complexity it introduces in diagnosing and treating co-occurring conditions, as overlapping symptoms can obscure clinical clarity and limit treatment efficacy [3].

Yeh, *et al.* [4] examined suicide mortality among 2,674 individuals who were patients at eight healthcare systems participating in the Mental Health Research Network between 2000 and 2013. These patients were compared to a matched control group of 267,400 individuals from the general population. The study assessed the prevalence of five psychiatric diagnoses, namely, anxiety disorders, ADHD, bipolar disorder, depressive disorders, and schizophrenia spectrum disorders, within the year preceding death. Among those who died by suicide, 51.3% had a documented psychiatric diagnosis, compared to only 12.7% in the control group. After adjusting for sociodemographic variables, the highest suicide

risk was observed among individuals with schizophrenia spectrum disorders, followed by those with bipolar disorder, depression, anxiety, and ADHD. Women with bipolar disorder exhibited a higher risk of suicide death than men. These findings underscore the need for proactive suicide screening and efforts to raise awareness about mental health conditions.

Anxiety

Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacological treatment for adults with generalized anxiety disorder (GAD) [5]. They are known for their proven efficacy, tolerability, and relatively mild side effect profile when compared to other treatments [6].

Fluoxetine, sertraline, and paroxetine have demonstrated efficacy in treating anxiety. Studies involving adults with GAD revealed that both sertraline and paroxetine significantly reduced anxiety symptoms. When paroxetine was compared to benzodiazepines, the latter produced more rapid symptom relief early in treatment, whereas paroxetine showed greater overall long-term efficacy [5].

The FDA has also approved citalopram and escitalopram for the treatment of anxiety disorders, including GAD. In three placebo-controlled trials, escitalopram demonstrated superior efficacy. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has also shown significant benefits for anxiety and is FDA-approved for treating GAD in children and adolescents [5,7].

Although SNRIs such as venlafaxine have been found to reduce anxiety, SSRIs are generally preferred due to their broader efficacy and quicker symptom relief [5]. Comparative studies found fluoxetine and fluvoxamine to be more effective than sertraline and venlafaxine, with better tolerability. Fluoxetine, fluvoxamine, and paroxetine were more widely accepted by patients, with fluvoxamine demonstrating particularly high acceptability. SSRIs, excluding sertraline, were identified as the most effective and well-tolerated, while venlafaxine showed lower efficacy and acceptance [8].

Benzodiazepines are typically considered second-line pharmacologic options for adults with anxiety [25], and they are the most

frequently prescribed non-SSRI agents [6]. They are effective in alleviating anxiety symptoms; however, their use is associated with a dose-dependent risk of sedation, tolerance, confusion, and elevated mortality [9]. While co-prescribing benzodiazepines with antidepressants may hasten symptom relief, benzodiazepines alone have not been shown to improve long-term outcomes and are associated with higher risks of dependence and adverse effects [10].

Additionally, benzodiazepines carry the potential for withdrawal symptoms, dependence, and cognitive side effects such as fatigue, jitteriness, tremors, and sweating [5,11]. They act as allosteric modulators of the GABAA receptor. Although alprazolam is the only benzodiazepine FDA-approved for GAD, others like diazepam and clonazepam are effective. However, their prescription is often limited due to concerns about abuse and dependency [5].

An alternative herbal remedy is *Passiflora incarnata* Linnaeus, a plant genus comprising approximately 520 species, mainly found in Central and South America, with limited distribution in North America, Southeast Asia, and Australia. Traditionally used in Europe and North America as a sedative and treatment for anxiety and insomnia, *Passiflora incarnata* remains a subject of interest in herbal medicine [12].

Glucoregulatory Function and GLP-1 Receptor Agonists

GLP-1 receptor agonists offer significant benefits in obesity management by enhancing postprandial insulin secretion, promoting satiety, and delaying gastric emptying [13,14]. Studies have consistently shown their effectiveness in lowering HbA1c levels and reducing cardiovascular risk in patients with pre-existing atherosclerotic cardiovascular disease (ASCVD) [15-18].

Moreover, GLP-1 receptor agonists have been associated with reduced mortality in patients with type 2 diabetes and cardiovascular disease [19]. Emerging research suggests that GLP-1 receptors also play a role in the regulation of the dopaminergic mesolimbic system, which may influence addictive behaviours such as alcohol consumption. Although the appetite-suppressing effects of GLP-1 receptor agonists are well-established [20], their impact on alcohol use disorder (AUD) remains complex and under investigation [21].

Notably, Farokina, *et al.* [22] examined genetic variants of the GLP-1R gene and their influence on brain connectivity in relation to AUD severity. At rs6923761, three isochorismate synthase (ICs) proteins showed significant genotype \times AUDIT score interactions within brain networks, two within the anterior salience network and one within the visuospatial network. At rs1042044, four ICs showed similar interaction effects, three within the dorsal default mode network and one in the basal ganglia network. In both SNPs, individuals with the variant allele and high AUDIT scores exhibited stronger within-network connectivity.

These findings highlight how genetic variations in GLP-1R are associated with differential brain network activity in individuals with varying AUD severity. The results are especially relevant given the roles of the salience and default mode networks in the neurobiology of addiction and AUD. Ongoing research continues to explore GLP-1R as a promising pharmacotherapeutic target for AUD.

Case Presentation

Patient overview

The patient is a 58-year-old female with a long-standing history of anxiety, which has been managed with 10 mg of fluoxetine for approximately 18 years. She also suffers from restless leg syndrome (RLS), which has been controlled through iron supplementation. Family history reveals a genetic predisposition to anxiety, as both of her daughters have been diagnosed with anxiety disorders. Her son struggles with Substance Use Disorder, anxiety, insomnia, and depression.

Initial presentation and GLP-1 medication use

In January 2024, the patient began using semaglutide, a GLP-1 receptor agonist, purchased from an online provider. Although fluoxetine was listed on her intake form, the provider did not inquire further or offer counseling regarding potential interactions or side effects. After administering three 0.25 mg injections, the patient noted disturbances in her sleep. Uncertain whether this was due to her RLS or the medication, she discontinued the semaglutide injections and sought advice from a specialist for her RLS. Following recommendations to increase iron intake, her RLS symptoms improved.

Discontinuation of fluoxetine and subsequent medication trial

In July 2024, the patient stopped taking fluoxetine to help with her RLS symptoms with guidance that the fluoxetine might be exacerbating her condition. She chose to revisit semaglutide injections in August 2024 and resumed treatment, again receiving no counseling about mental health concerns. Initially starting with 0.25 mg doses, she gradually increased to 0.5 mg after four weeks. However, the patient soon experienced worsening sleep disruptions and a decline in mood, prompting her to discontinue the semaglutide on October 6, 2024.

Psychiatric intervention and treatment adjustments

On October 16, 2024, the patient experienced a significant breakdown following several nights of poor sleep and heightened anxiety. She sought psychiatric care and restarted fluoxetine on October 23, 2024. Despite these efforts, she continued to struggle with poor sleep, increased anxiety, and depressive symptoms. Fluoxetine failed to alleviate her symptoms, even after dosage increases and an appropriate time period.

The treatment plan was adjusted, and the patient was switched to duloxetine, but this medication also proved ineffective. Next, gabapentin was introduced to address sleep disturbances and daily anxiety, followed by 100 mg of trazodone to improve sleep. Despite these interventions, the patient's condition worsened, and she began experiencing suicidal ideation, along with a significant 25-pound weight loss.

In an attempt to address these issues, the psychiatrist transitioned her to 15 mg of mirtazapine to support sleep and appetite, while also starting sertraline. After an appropriate trial, sertraline was deemed ineffective, and the patient was switched to venlafaxine. A regimen of 150 mg of venlafaxine, 25 mg of buspirone, and 15 mg of mirtazapine were prescribed.

Repetitive transcranial magnetic stimulation (rTMS)

On April 4, 2025, the patient began repetitive transcranial magnetic stimulation (rTMS) therapy. By the two-third point of treatment, she began to experience an improvement in her symptoms.

Current status

The patient is currently taking 150 mg of venlafaxine and 15 mg of mirtazapine daily. She reports improvement in her anxiety and depressive symptoms; she expressed that she has never experienced such intense anxiety, accompanied by both mental and physical symptoms, for such an extended period. Additionally, the patient noted that she has never experienced suicidal ideation or prolonged insomnia before and attributes the significant damage to her mental health from the GLP-1 drugs. Patients have expressed fear that she could regress again and begin to experience increasing symptoms again once she has completed the rTMS. She likes the experience of PTSD.

Summary

The mechanistic influence of glucagon-like peptide-1 (GLP-1) and its receptor agonists (GLP-1RAs) on brain functional activity remains insufficiently explored. Psychiatric disorders are often characterized by dysregulated functional connectivity across neural circuits underpinning clinical symptoms. Recent studies suggest that GLP-1 and GLP-1RAs modulate connectivity within several key brain networks, including the dorsal default mode network (DMN), visuospatial network, right frontoparietal network, and the salience network. Additionally, GLP-1 agonism has been associated with decreased connectivity in regions such as the hypothalamus, lateral orbitofrontal cortex, and amygdala. These findings underscore the need for further research into the neural circuits modulated by GLP-1 receptor signaling and how such modulation may impact cognitive processes and psychopathology in psychiatric conditions [23].

Emerging data have also raised concerns regarding potential neuropsychiatric side effects. In one recent study, albeit based on trend-level findings, GLP-1RAs were associated with mood instability, increased risk-taking behaviour, and chronic pain [24]. The rising clinical use of GLP-1 receptor agonists, primarily for glycaemic control in type 2 diabetes, weight loss, and cardiovascular and renal protection, has prompted a growing need for thorough safety monitoring. In July 2023, the European Medicines Agency initiated an investigation into reports of suicidal ideation and self-harm potentially associated with GLP-1RAs. Although meta-analyses of

randomized controlled trials have not demonstrated an increased risk of suicidality, these trials were not specifically designed to evaluate psychiatric outcomes, and the relatively low frequency of these events has limited statistical power to detect meaningful differences [25].

Multiple pharmacovigilance analyses and regulatory reports have described incidents of suicidal thoughts and self-injurious behaviour linked to GLP-1RA usage [26]. However, findings remain mixed. While some disproportionality analyses have shown elevated reporting rates compared to other antihyperglycemic agents, no definitive causal relationship has been established [27]. Notably, semaglutide has been linked to several rare but concerning adverse events, including suicidal ideation, hair loss, and even vision impairment [28].

In a recent investigation by Lu, *et al.* [29], researchers identified eight potential neuropsychiatric adverse events associated with GLP-1RAs. For the first time, signals were detected for migraine, olfactory disturbances, and sensory abnormalities. Moreover, positive signals for suicide-related events with semaglutide use were observed, particularly in weight-loss populations. Large-scale registry and administrative database studies have similarly suggested a potential association between GLP-1RA treatment and elevated suicidality risk [30].

Nonetheless, the bulk of population-based studies have failed to consistently establish a statistically significant increase in suicide risk. Many, however, include cautionary interpretations. A comprehensive meta-analysis including over 107,000 patients (data up to 2024) found no significant association between GLP-1RA treatment and psychiatric adverse events compared to placebo [31].

Complementing these population findings, our laboratory conducted *in silico* enrichment analysis that identified links between GLP-1 receptor activity and depressive phenotypes involving dopaminergic pathways. These computational and gene-level studies provide converging evidence suggesting that GLP-1R agonism may contribute to depressive-like phenotypes [32,33].

Conclusion

While the efficacy and safety of GLP1-agonists continue to be investigated and for the most part show positive clinical outcomes and even safety profiles, there seems to be a rising concern of adverse effects including depression, mood changes and suicidal ideation. Certainly, our laboratory published on a to be confirmed genetic pathway for both depression and suicidal ideation. This case report just highlights an experience of female experiencing a terrible experience involving GLP1 agonistic therapy for weight loss. Our basic tenant is because of the established mechanism linked to an attenuation of dopamine release at the brain reward circuit via enhanced GABA activity causing an unwanted hypodopaminergia, DNA identification seems clinically advisable prior to prescribing. In addition, attending physicians should obtain a history of patient's mental health events prior to prescribing.

Author Contributions

Conceptualization, KB; writing-original draft preparation, KB; writing-review and editing, KB, AS, CF, KUL,DB,APLL, CAD, KM and PKT. References were annotated by YM and SM. The second draft was edited by AP,AB, NJ,FZ, RKAF, SS,EJM, MSG, DB, KS, MM, KZK, AS, MPL, IG,RDB. All authors have read and agreed to publish this version of the manuscript.

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Data Availability Statement

The data availability is contained within the manuscript.

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Conflicts of Interest

KB owns domestic and foreign patents on GARS and KB220 that are assigned to either Synaptamine Inc. or TranspliceGen Holdings LLC. Other authors declare no conflict of interest.

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