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Case Report | Internal Medicine

Liraglutide-Induced Depression with Suicidality in an Obese Adult: A Case Report

Feras M. Almarshad[1*], Dushad Ram[1]

Abstract

Obesity is a major health issue worldwide. Treating adults with obesity often involves lifestyle and diet changes and sometimes medication. Liraglutide is a drug that is being closely studied for treating obesity. However, the potential side effects of liraglutide, particularly its impact on mood and the development of depression, may be of concern. Given the frequent co-occurrence of obesity and depression, it is important to understand how obesity treatments like liraglutide might affect a person's mood. A 47-year-old schoolteacher with no personal or family history of mental illness or chronic physical condition sought help for his steadily increasing weight. Despite having a sedentary job and reporting no major stress or substance use, he did not attempt to change his diet or activity level, occasionally experiencing sleep difficulties. He was overweight, with a body mass index of 42. The patient was diagnosed with adult obesity and prescribed liraglutide, diet changes, and exercise. Initially, he lost weight, but he also developed depressive symptoms, including fatigue, loss of interest, sleep disturbances, and suicidal ideation. Following cessation of liraglutide treatment, his depression symptoms got better, but his weight slightly increased. This case sheds light on the possible link between liraglutide and depression in managing obesity. It is crucial for healthcare providers to be aware of potential mental health side effects of obesity drugs like liraglutide. Although the exact reasons behind these mood changes are not fully understood, this case emphasizes the need for careful observation and decision-making in treatment. Understanding these issues can help balance the benefits and risks of liraglutide and ensure better care and treatment options for people with obesity.

[1] *Department of Medicine, College of Medicine, Shaqra University, Shaqra, Saudi Arabia*

***Corresponding author**: falmarshad@su.edu.sa

Introduction

Obesity, a global epidemic, has a profound health implication, affecting 39% of the world's population [1]. The management of obesity in adults has changed significantly over time in terms of lifestyle modifications, dietary changes, and pharmacological interventions [2]. Various pharmacological options are available now. Among them, liraglutide, glucagon-like peptide-1 (GLP-1) receptor agonist, has emerged as a promising treatment for obesity [2, 3] by promoting satiety and reducing food intake [4]. Despite its effectiveness as an antiobesity agent, liraglutide has raised concerns about potential side effects [5]. Regarding psychological side effects, though not depression per se, depressive symptoms and mood disturbances were documented in a subset of patients during initial clinical trials [6], though another report could not confirm this [7]. It is to be noted that depression is not only a debilitating mood disorder but also a major public health concern often linked to obesity [8]. The bidirectional relationship between obesity and depression has been reported, suggesting that each condition exacerbates the other [9]. Given the intertwined nature of both disorders, it is imperative to understand the possible impact of antiobesity medications, such as liraglutide, on mood, as they may be encountered in routine practice.

This case report aims to shed light on emerging concerns regarding liraglutide-induced depression in the context of obesity management. It may provide an understanding of the complex relationship between liraglutide, obesity, and depression, which in turn may help in informed treatment decision-making, better patient care, and the overall understanding of the risks and benefits of liraglutide in the management of obesity.

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Case Report

First Visit

Patient Information

A 47-year-old male schoolteacher of upper socioeconomic status from an urban background, with no past history of chronic medical, surgical, or mental illness, nor any family history of such conditions, presented with a continuous steady increase in weight over the past few years, without any fluctuation in weight over time. He was a non-vegetarian, who consumed meals three times a day and had never tried to modify his diet or employ other methods to control his weight. He considered complaints non-urgent, thus he deferred early consultation with his internal medicine physician.

Medical History

There were no other associated symptoms except for intermittent sleep disturbance. Apart from being a sedentary worker, there was no history of substance use, intake of other medications, or stress related to the workplace. Family members were supportive towards him. He has never been treated for gaining weight.

Clinical Findings

Upon physical examination, his height measured 170 cm, his weight was 124 kg, resulting in a body mass index (BMI) of 42. His investigation report revealed an glycated haemoglobin (HbA1c) level of 5.9%, total cholesterol of 223 mg/dL, low-density lipoprotein (LDL) cholesterol of 135 mg/dL, and triglyceride level of 130 mg/dL. His other investigations for complete hemogram, liver function test, thyroid function test, electrocardiogram (ECG), leptin, and ghrelin were within normal limits. An abdominal ultrasound revealed a mild fatty liver.

Medical Diagnosis

A diagnosis of adult obesity was made.

Treatment

A collaborative decision was made to initiate outpatient treatment, commencing with liraglutide at a dosage of 0.6 mg, escalating by 0.6 mg per week until reaching a daily dose of 3 mg, along with diet modification and regular exercise. He was advised to return after completing one month on 3 mg of liraglutide.

Outcome

The patient reported no immediate side effects with the medication. Within weeks of reaching 3 mg, he noticed visible weight loss, and after four months, his body weight was 96 kg, and his BMI reduced to 33; however, there was no further decrease in BMI thereafter. The patient developed symptoms of generalized fatiguability that increased in severity over weeks and was gradually accompanied by loss of interest and decreased cognitive ability (slowness). He started skipping duties as a teacher from school initially, but when he started experiencing significant sleeplessness and recurrent thoughts of death, he eventually ceased attending work altogether.

Second Visit

The patient consulted his internal medicine physician and underwent a detailed evaluation. His investigation revealed an HbA1c level of 5.1%, total cholesterol of 195 mg/dL, LDL cholesterol of 116 mg/dL, and triglyceride levels of 118 mg/dL. A hemogram, liver function test, renal function test, thyroid function test, and electrolyte levels in the ECG were all within normal limits. A mental status examination revealed that the patient exhibited impaired personal care, reported slowness in thinking and physical activity, and was depressed. He expressed hopelessness regarding the future, feeling helpless and worthless due to his inability to fulfill his work and other responsibilities. While the patient voiced thoughts that death might be preferable to disability, he did not exhibit active suicidal ideation or plans, nor any delusions or hallucinations. The patient demonstrated a fifth-grade level of insight. He underwent assessment using the Zung Self-Rating Depression Scale, yielding a score of 68, indicative of a moderate level of depression.

Diagnosis

A diagnosis of adult obesity and medication-induced depressive disorder was made as per the criteria laid down in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Treatment

Considering the absence of apparent risk factors for developing a psychiatric disorder, ongoing medication was suspected to have contributed to this condition. Hence, liraglutide was discontinued, and the patient was advised to continue with diet modification and regular exercise. He was urgently referred to a psychiatrist and scheduled for an appointment in one month's time.

Outcome

Due to social and personal reasons, the patient did not consult a psychiatrist and returned for follow-up after one month. Since the previous visit, he had discontinued medication and was not adhering to dietary modifications or regular exercises. The patient did not report any withdrawal symptoms after discontinuing the medication, and on mental status examination, his personal care was adequate. Except for mild fatigability, he did not mention any slowing of activities or thoughts, and was a little anxious but not depressed. There were no feelings of hopelessness, helplessness, or worthlessness. The patient did not express any thoughts of death, suicidal ideation or plans, nor did he exhibit any delusions or hallucinations, with insight grade six. He was assessed using the Zung Self-Rating Depression Scale, yielding a score of 45, suggestive of no depression. However, he gained weight (102 kg), and his BMI increased to 35 from 33. Further investigation revealed cholesterol levels of 200 mg/dL, LDL levels of 122 mg/dL, and triglyceride levels of 126 mg/dL, while all other parameters remained within normal limits. He was advised to continue with diet modification and regular exercise. According to the World Health Organisation - Uppsala Monitoring Centre (WHO-UMC) causality assessment system, depression was deemed to be caused by liraglutide, as

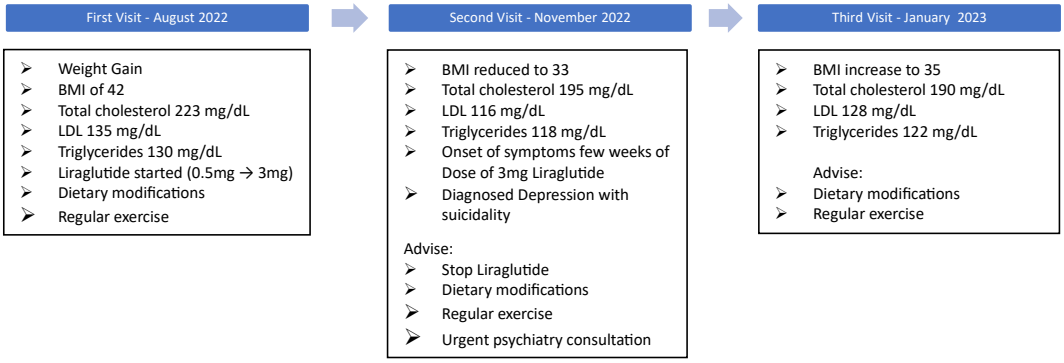

Figure 1. Case Timeline.

the symptoms were associated with its use and there was no evidence to attribute it to any other medical condition or medications (as the symptoms improved upon withdrawal of the medication) and the clinical response to withdrawal was clinically reasonable.

Third Visit

The patient visited his internal medicine physician one and a half months after his last follow-up. No depressive symptoms were reported or observed. The Zung Self-Rating Depression Scale yielded a score of 38, indicating an absence of depression. There were no further increases in weight, and he did not present with any other physical or psychological concerns. Upon assessment, his BMI remained at 35, with cholesterol levels measuring 190 mg/dL, LDL levels at 128 mg/dL, and triglyceride levels at 122 mg/dL. Other investigations were within normal limits. He was advised to continue with diet modification and regular exercise and to report immediately if he experiences any psychological symptoms.

Case Timeline

The timeline of clinical episode is depicted on Fig. 1.

Discussion

This case report of liraglutide-induced depression represents a rare occurrence, which makes it unique and noteworthy. The relationships between liraglutide and mood symptoms appear not straightforward. Studies using an animal model suggest that liraglutide may exhibit anxiogenic effects and cognitive improvement but does not necessarily produce an antidepressant effect [10], while others have documented antidepressant effects [11], probably via improving hippocampal neural plasticity [12]. The literature suggests that liraglutide is safe for depression [13] and improves mood, cognitive function, and eating behaviour [14], and the anti-obesity properties are not affected by the presence of psychiatric symptoms [15]. A review and meta-analysis suggest that it significantly reduces depressive symptoms in diabetic patients [16]. Animal studies suggest that the underlying mechanisms may involve the activation of the GLP-1 receptor, which suppresses microglial proptosis by promoting mitophagy, thereby reducing depression-like symptoms in diabetic mice [17] and promoting glycogen synthase kinase-3 beta (GSK-3β) phosphorylation [18]. Reports of liraglutide-associated depression are limited, particularly among individuals with obesity and comorbid diabetes. Initially, the study examining its safety revealed a link with depressive symptoms [7]. A recent pharmacovigilance report suggests that GLP-1 receptor agonists may be associated with more severe depressive symptoms and suicidality [19], particularly among females [7, 19].

While the exact mechanisms underlying these adverse effects remain unclear, it is postulated that the influence on neurobiological pathways, appetite regulation, and neurotransmitters may contribute to mood changes. Long-term adaptive changes, rather than the enhancement of monoaminergic signalling [20], and glucocorticoid resistance, rather than high levels of glucocorticoids [21], are possible mechanisms. Reviews on medications associated with depression have identified several medications with different mechanisms that may cause depression in some patients [22].

An initial animal study has observed that liraglutide exhibits the capacity to permeate into the brain stem, lateral septum, and hypothalamus. Within these regions, it ostensibly interacts directly with an array of GLP-1 receptor isoforms, thereby influencing the neural circuitries implicated in regulating feeding behaviour, reward processing, and energy homeostasis [23, 24]. The activation of GLP-1 receptors is associated with an augmentation of dopaminergic neuronal activity through a presynaptic modality within the ventral tegmental area (Fig. 2) [25]. This receptor stimulation is also linked to an upregulation of dopamine transporter expression on the neuronal membrane, contributing to a decrement in extracellular dopamine concentrations within the synaptic junctions in the brain lateral septum and striatal regions [26, 27]. Dopamine is implicated in the immediate reinforcement and reward mechanisms, and alterations in the reward circuitry are recognized as pivotal factors in the aetiology of anhedonia and other depressive symptomatology [28].

However, such effect is also confounded by the frequent association of depression with obesity, diabetes, and past history of depression or other psychiatric disorders. Therefore, these medications should be used cautiously and closely monitored in patients with a history or factors for depressive disorders. Hence, in patients with a history or

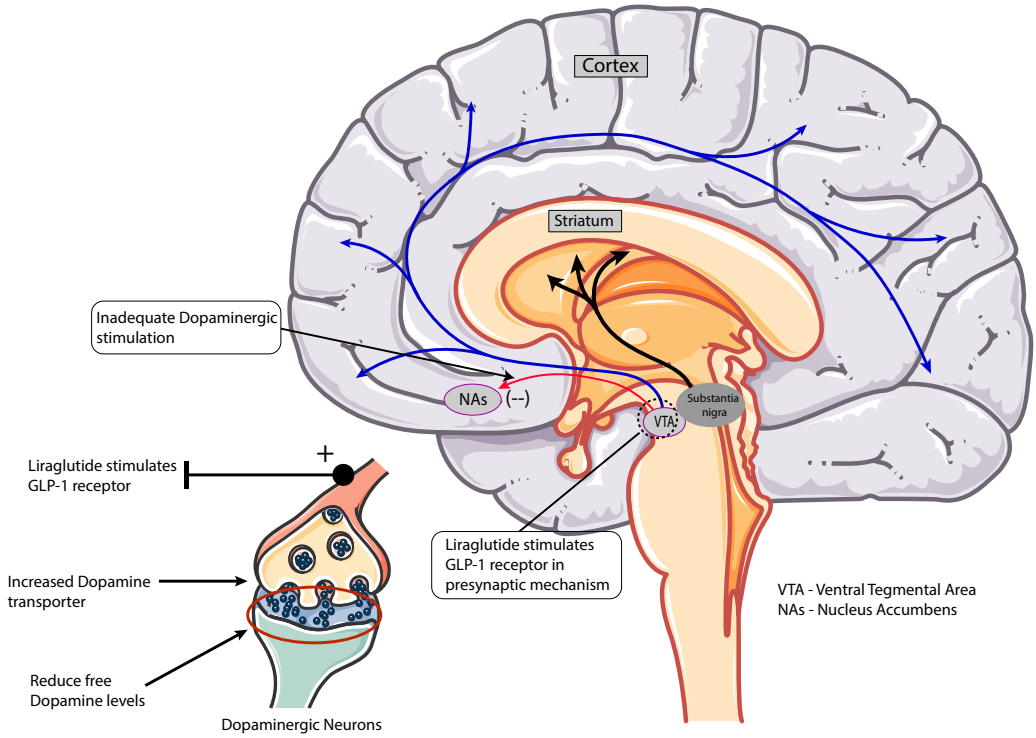

Figure 2. Possible mechanism of liraglutide-mediated depression. When GLP-1 activates its receptor, it causes dopaminergic neurons in the ventral tegmental area (VTA) to be more active and and increases the number of cleaners (dopamine transporters) on these cells, which remove dopamine. This can make usual activities less enjoyable, a feeling called anhedonia, and can also lead to signs of depression.

potential risk of depressive disorders, these medications ought to be administered with caution and under strict supervision [29].

It is to be noted that other anti-obesity medications are also reported to have depressogenic effects. For instance, semaglutide and tirzepatide have been associated with similar adverse effects [19]. Additionally, various anti-obesity drugs including tesofensine, phentermine, ecopipam, rimonabant, lorcaserin, and others have been withdrawn due to associated mental health concerns [30, 31]. Mood changes appear to be due to the imbalance in neurotransmitters within the central nervous system, as many of these medications mediate their anti-obesity action on most neurotransmitters [30, 31].

To sum up, this case report provides valuable insights into the complex interplay between liraglutide, obesity, and depression, ultimately informing treatment decisions, optimizing patient care, and improving the overall understanding of the risks and benefits of liraglutide in the management of obesity.

Conclusions

The use of liraglutide in the treatment of adult obesity may be linked to depression. It is imperative to explore these emerging concerns and better understand the risk-benefit profile of liraglutide in individuals with obesity.

Ethical Statement

This research was conducted in accordance with ethical standards outlined in the Helsinki Declaration and adhered to ethical guidelines.

Informed Consent

Written and verbal informed patient consent was obtained for this case report.

Data Availability

This report presents the clinical details and management of an individual clinical episode; data sharing not applicable.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

The authors declared no financial support.

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