Mental Health Effects of Tirzepatide:

A Report of 2 Patients

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Glucagon-like peptide-1 (GLP-1) receptor agonists are known to exert beneficial effects on inflammation, insulin resistance, glycemic control, body weight, and lipid metabolism.[1] There is mounting evidence that these drugs may also have positive mental health effects. Exenatide, liraglutide, and semaglutide have been shown to improve depressive symptoms, reduce the incidence of anxiety, and decrease binge-eating symptoms.[2–6]

The next generation of GLP-1 receptor agonists has a dual action mechanism, targeting both GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptors, and shows greater efficacy for weight loss.[7] In a 72-week study, tirzepatide, a GLP-1/GIP receptor agonist, was more effective at achieving weight loss (20% reduction in body weight) when compared to studies of conventional GLP-1 receptor agonists (15% reduction in body weight).[7] However, the mental health effects of GLP-1/GIP receptor agonists have not been described. The cases herein, to our knowledge, are the first to demonstrate potential mental health benefits of tirzepatide, a GLP-1/GIP receptor agonist.

Patient 1

The patient is a 36-year-old college-educated woman with a psychiatric history of major depressive disorder, generalized anxiety disorder, and binge-eating disorder and a medical history of asthma, eczema, and seasonal allergies. Symptoms of each psychiatric disorder are described in Figure 1. This patient demonstrated improvement in psychiatric symptoms with start and titration of tirzepatide and worsening in psychiatric symptoms with taper and discontinuation of tirzepatide (see Figure 1). Of note, this patient endorsed a psychological benefit of tirzepatide, which she felt was unrelated to weight loss.

Patient 2

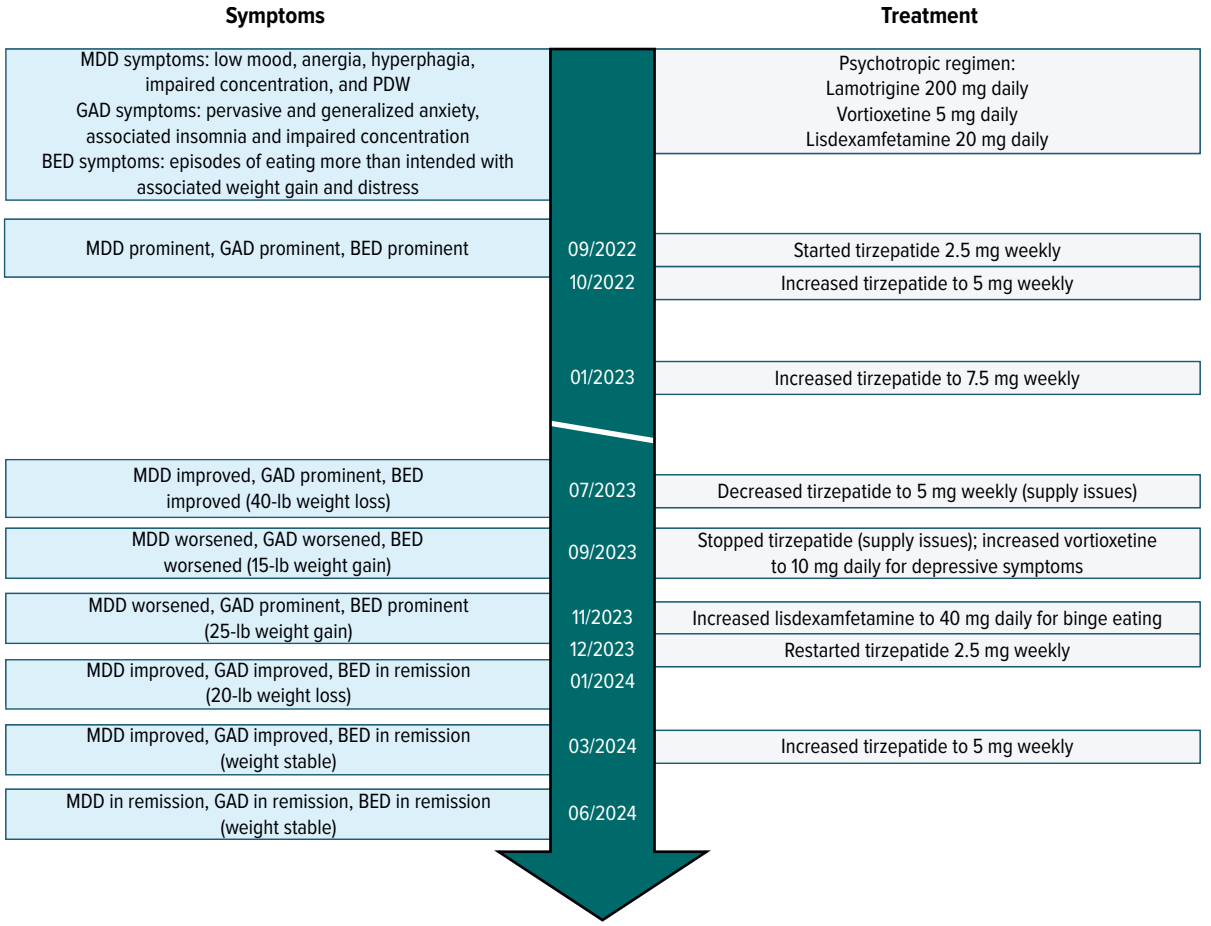
The patient is a 44-year-old woman with a history of major depressive disorder, attention-deficit/hyperactivity disorder, generalized anxiety disorder, and obesity. She was on chronic treatment with vortioxetine, dextroamphetamine/amphetamine salts, bupropion, and buspirone upon initiation of tirzepatide 2.5 mg weekly. At the time, she reported ongoing depressive symptoms. Her Patient Health Questionnaire-9 (PHQ-9)[8] score was 14, and weight was 248 lb. There was initially no change in mood and minimal change in weight. At 8 weeks, the tirzepatide dose was increased to 5 mg, leading to rapid improvement in mood within a few days. Sleep also improved along with an increased sense of happiness. After 5 months, she had lost nearly 50 lb, and her PHQ-9 score was 1 (with no change in antidepressant treatment). She reported feeling happy and motivated and more engaged with others. Tirzepatide was subsequently increased to 7.5 mg, leading to additional improvements: the patient reported increased confidence, felt "in the best mood" with a "spring in [her] step," and had no more negative self-talk. The following month, her tirzepatide dose was lowered to 5 mg due to insurance restrictions. Her mood was subsequently reported as "not as good" but still happy. Of note, she had previously undergone gastric bypass surgery 5 years earlier. Despite a 100-lb weight loss, her depression at the time significantly worsened, leading to entry into a partial hospital program and switching of her antidepressant medications.

Discussion

While there is mounting evidence for the mental health effects of GLP-1 agonists, these cases are the first, to our knowledge, to demonstrate a temporal correlation between administration of tirzepatide, a dual GLP-1/GIP agonist, and improvement in mental health symptoms. Research suggests that GLP-1 agonism may reduce inflammation, improve mitochondrial biogenesis, stimulate neurogenesis, exert neurotropic effects, and restore neuronal signaling[9] in the central nervous system. In this context, GLP-1 receptor agonists have been linked to improved mental health outcomes, including improvements in depression and anxiety (as measured by standardized scales such as the Hamilton Depression Rating Scale[10] and Beck Depression Inventory)[11] and improvements in quality of life (as measured by standardized scales such as the Psychological General Well-Being Index[12] and Global Assessment of Functioning).[10] Further, GLP-1 receptor agonists have been shown to reduce cumulative incidence of anxiety in patients with type I or II diabetes[3] and binge-eating symptoms in patients with binge-eating disorder.[4–6] It is notable that the positive mental health effects of GLP-1 receptor agonists appear to be independent of weight loss.[13]

While concerns about the mental health risks of GLP-1 receptor agonists have been raised, evidence is largely inconclusive. There is no cause-and-

Figure 1.
Symptoms and Treatment of Patient 1



Abbreviations: BED = binge-eating disorder, GAD = generalized anxiety disorder, MDD = major depressive disorder, PDW = passive death wish.

effect relationship between this class of drugs and suicidality[14–16] or increased incidence of psychiatric disorders.[15]

In the first case, a longitudinal assessment demonstrates clear worsening in symptoms with taper or discontinuation of tirzepatide and clear improvement in symptoms with initiation or titration of tirzepatide. The patient felt her mood improvements were independent of weight loss. Given that the patient's psychotropic regimen was not modified during this time, it is unlikely that changes to psychiatric symptoms are attributable to the psychotropic medications. Case 2 demonstrates a rapid improvement in mood with tirzepatide dose titration that preceded significant weight loss. Mood improvement also appeared to be dose dependent, ie, mood benefit lessened with lowering of tirzepatide dose. However, any conclusions drawn from these cases may be limited by inability to isolate the positive mental health effects of tirzepatide (as tirzepatide was administrated concurrently with psychotropic medications) and other unidentified factors that may have impacted mood. Further, positive feelings about real or potential weight loss with tirzepatide may have contributed to the observed improvement in psychiatric symptoms.

Conclusion

Mounting evidence suggests that GLP-1 receptor agonists exert beneficial effects on mental health, though little is known about dual GLP-1/GIP receptor agonists. To our knowledge, the cases herein are the first to demonstrate potential mental health benefits of this next-generation class of drugs, as demonstrated by the GLP-1/GIP receptor agonist tirzepatide. Both cases underscore the need for future research into potential psychotropic effects of this novel class of medications.

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