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Psychiatric Side Effects Caused by Tirzepatide

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ABSTRACT

The work reveals the issue of neuropsychiatric (psychological) safety of GLP-1 receptor agonists of tirzapatide used for the treatment of type 2 diabetes mellitus, obesity and eating disorders. The complex advantages of tirzepatide in relation to metabolic and psychological health are highlighted, making it a safe and effective remedy for patients with severe obesity (BMI>30), including night eating syndrome. The profile of psychiatric side effects when taking tirzepatide is described. The emphasis is placed on the fact that a number of patients use these drugs as a form of corrective (cleansing) behavior. In this regard, when prescribing these drugs, comorbid mental disorders in the patient and early maladaptive patterns should be taken into account.

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Tirzepatide are injectable GLP-1RA drugs that act as GLP-1 receptor agonists. However, tirzepatide is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist that combines the effects of both incretin hormones in a single molecule. In various clinical studies, all three drugs have demonstrated a significant effect of weight loss in obese or overweight patients with concomitant somatic diseases, but little attention has been paid to the issue of side effects from mental health [1]. The most common side effects associated with liraglutide are mild to moderate nausea and diarrhea, which often lead to discontinuation of liraglutide. When taking tirzepatide and semaglutide, patients most often report side effects from the gastrointestinal tract, such as nausea, vomiting, diarrhea, irritable bowel syndrome, and abdominal pain. The frequency of occurrence varies from 6 to 22%. Common side effects of GLP-1 receptor agonists include nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, headache, and nasopharyngitis. Neuropsychiatric (psychological) safety issues have become the subject of close attention only in the last few years, given that many approved anti-obesity drugs are centrally acting appetite suppressants. Recall that rimonabant, the first selective antagonist of the central cannabinoid receptors (CB1), was not approved by the FDA due to concerns about psychiatric side effects, including episodes of depression, increased anxiety, and suicidal thoughts. Depression is a common mood disorder and a serious health problem that is often combined with other diseases, including metabolic disorders such as T2DM and obesity. Studies have shown that people suffering from obesity and type 2 diabetes are more likely to face mental health problems [2]. GLP-1RAs treatment may be useful for the treatment of depressive disorders. Some studies have shown that the administration of GLP-1RAs can directly have an antidepressant effect, but only in animal experiments [2]. Although semaglutide and liraglutide demonstrate antidepressant and anxiolytic effects in animal models, in daily clinical practice, when taking these drugs in patients with comorbid mental disorders that are not taken into account when prescribing drugs, we observe: increased anxiety, a feeling of lack of strength, thoughts of loss of control, feelings of uselessness, increased irritability, decreased enjoyment of life (patients note that life has become bland, “I do it, but I don’t feel it”). Patients note that they forget to eat, the taste of food has changed.

Taking these drugs is accompanied by an increase in negativism, pessimism, and the appearance of suicidal thoughts. The number of reported cases of suicide attempts and completed suicides while taking semaglutide, liraglutide, and tirzepatide is increasing. What kind of patients are we talking about? These are patients with emotional hunger, compulsive overeating (eating is a form of emotional regulation), recurrent depression, anxiety spectrum disorder, dysmorphophobia, obsessive-compulsive disorder, borderline personality disorder. A comparison of the three drugs revealed a greater number of fatal adverse effects associated with liraglutide (8 patients had a fatal outcome out of 147 ICSR cases) compared with semaglutide (one fatal outcome out of 210 ICSR cases) and none with tirzepatide (out of 15 ICSR cases). Deaths were mostly the result of completed suicide and were more common in men in the 18-64 age group. Half of the reported suicide cases occurred when taking semaglutide, followed by liraglutide, while only four cases occurred when taking tirzepatide [1]. It should be noted that in these cases, patients had comorbid mental disorders that were not taken into account when prescribing the GLP-1RAs class of drugs. Obese patients (BMI=30-39) taking tirzepatide showed significant weight loss, observed during the SURMOUNT study, which contributed to increased self-esteem, improved body image and physical functioning, which are key factors in reducing the risk of suicide in general [3]. Our results, combined with data from the SURMOUNT studies, suggest that the complex benefits of tirzepatide in relation to metabolic and psychological health make it a safe and effective remedy for patients with severe obesity, including night eating syndrome. I

will make a reservation that most often patients use these drugs as a form of corrective (cleansing) behavior, for example, "lose 2-3 kg", "lose excess fat", "get in shape", "dry out", "eat less", "be perfect for a partner otherwise he will leave, reject, find another". Often, these drugs are self-prescribed by patients not according to their indications. For example, our patient had a BMI of 25 before starting treatment, but there were no concomitant somatic diseases related to weight. Despite pre-existing anxiety and depression, the patient developed paranoia and visual hallucinations on an ultra-high dose of semaglutide, which disappeared after discontinuation of the drug. This suggests that patients can independently select and increase dosages due to dysfunctional beliefs ("the more the better"), which is accompanied by the development of a range of negative effects. We remember that people who struggle with obesity, and everyone who unsuccessfully tries to change their behavior, think that something is wrong with them. They internalize this prejudice. There is shame, a sense of guilt. And it really prevents them from continuing to try. Self-administration of semaglutide, liraglutide, and tirzepatide outside of cognitive behavioral therapy leads to negative effects. The patient does not develop a sense of mastery in managing his condition, a sense of self-efficacy (they control, not the drug, the food), he does not get rid of the so-called "food noise" or obsessive thoughts related to food (the patient notes that "I always worried: when am I going to eat? What am I going to eat? Will I be full? Will I get hungry again? It's always been something constant in the back of my mind.") However, there are caveats. In some patients, "food noise" may indicate poor nutrition in general and the presence of emotional hunger when food is used as a way of emotional regulation. As in the case of the famous Minnesota fasting experiment during World War II, during which men could not stop fantasizing, reading and talking about food when they were deprived of it [4]. The cure for "food noise" is not to drown it out with drugs, but to, let's say, respond to it literally with food, and not use it as a way of rewarding, working out emotions. Taking medications semaglutide, liraglutide, and tirzepatide often causes patients to feel that "I noticed that I was feeling depressed, like what is the meaning of life? It's not suicide, it's just a lack of pleasure." Indeed, although medications seem to dull many desires, such as excessive consumption of certain foods, booze, or games, they can also deplete the dopamine response to any pleasurable activity. These drugs can cause depression and suicidal thoughts in people with a genetic predisposition to low dopamine function [4]. In this regard, patients who take these drugs should be advised to report any changes in mood or behavior. An assessment of symptoms of depression and anxiety should be carried out every 10-14 days during admission (PHQ-9; GAD-7), suicidal tendencies (C-SSRS). The decision to start this drug therapy should be made individually, after weighing the risks and benefits, within the framework of cognitive behavioral therapy and under the supervision of the attending physician.

It is important to set clear treatment goals and take into account the patient's preferences and tolerance, as this may affect treatment adherence. Take into account the patient's sensitivity to side effects of the drug, health concerns, changes in body image and the risks of excessive use of the drug to achieve a rapid effect. To conduct an additional examination using the Young Schema Questionnaire (YSQ S3R), designed to determine the degree of formation of early maladaptive schemas (stable structures that include memories, emotions, thoughts and bodily sensations) in the form of "rigid standards", "punitivity", "failure", "distrust", "abandonment/ instability" and "emotional deprivation".

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