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Opinion

Do we need to Screen for Depression and Hedonistic Value of Food Before Initiating GLP–1 Agonist Treatment?

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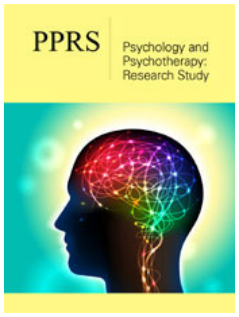

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Opinion

The glucagon-like peptide-1 receptor agonists (GLP-1-RAs) medications become more and more widely prescribed for weight loss and treatment of diabetes, by lowering the blood glucose levels [1]. They control appetite, food intake and reduce cravings at brain levels. Despite their demonstrated tolerability, efficacy and safety profiles across multiple studies, there had been some reports of possibly related psychiatric side effects. Concerns had been raised about possible link between some of these medications and suicidality (suicide thoughts, self-injurious behaviours). There had been even direct recommendations published back in 2024 for discontinuation of these medications, should new onset of depression occur [2]. These reports and concerns had been examined by European Medicines Agency (EMA) and Food and Drug Administration Adverse Event Reporting System (FAERS). As of January 2026, FDA [3] requested the removal of the Suicidal behaviours and ideation Warning from GLP-1RA medications. So, is there any link between depressive symptoms and GLP-1RA medications?

GLP-1 RAs impact the dopamine signalling in the ventral tegmental area during anticipatory (reward seeking) and consummatory (reward collecting) phases of reward processing. The Ventral Tegmental Area (VTA) integrates the signals between prefrontal cortex via neocortical pathway, and ventral striatum via mesolimbic pathway (nucleus accumbent). The food intake, the sense of hunger are reduced by modulation on hypothalamus, Nucleus Tractus Solitarius (NTS) and lateral septum. Current understanding is that this happens due to activating of a pathway from peripherally administered GLP-1 RAs to NTS. The GLP-1 secreting neurons (preproglucagon-PPG neurons) are located in the nucleus caudatus at NTS and some smaller populations at medulla oblongata. Their axons reach GABA neurons at VTA, which in their turn decrease dopamine activity of VTA [4].

Anhedonia seems to be a complex, transdiagnostic, clinically observable syndrome involving dysregulation of multiple neurotransmitters, not only dopamine, but also GABA, serotonin, noradrenaline, across different brain regions, including reward circuit, ventral striatum, nucleus accumbent; ventral, medial prefrontal cortex, amygdala, hypothalamus. While the intricacies of these interactions are still being exploration, the clinical presentation of anhedonia remains more obvious, measurable by variety of clinical scales. Anhedonia is noted in up to 70% of patients with diagnosed depressive disorder. Its objective occurrence is regarded as worsening of the depressive syndrome, with potential increased risk of escalation towards suicide ideations, suicide behaviours. Anhedonia is assessed as part of depressive disorder by clinical scales for depression diagnostics, screening and follow up, such as The Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM -D), Beck Depression Inventory (BDI), and Patient Health Questionnaire 9 (PHQ), with the latter being the most widely used one [5]. There are other scales that assess for anhedonia

independently of a specific psychiatric condition, such as Snaith-Hamilton Pleasure Scale (SHAPS), Temporal Experience of Pleasure Scale (TEPS), Dimensional Anhedonia Rating Scale (DARS). Food and appetite in general are always part of these assessments.

We commonly inquire about appetite in the context of depressive disorders, or eating disorders in order to assess the biological impact of decreased food intake, or sometimes overeating, to make decisions about severity of the condition, the response to medications, side effects and non-medication interventions. We assess to a lesser degree the psychological meaning and hedonistic value of food in psychiatric practice. There are several scales that provide such information, as Hedonic Scale Method, Power of food scale, Visual Analog Scale.

The impact of food itself on our brain and mental health is a subject of different research and clinical domain–Nutritional Psychiatry and Psychology. We are aware of food's short- and long-term effects on the brain reward system. They are mediated by neurotransmitters-dopamine, cannabinoids, endorphins, serotonin, and neuropeptides such as orexin, leptin, ghrelin. Different dietary choices can affect the up and down regulation of dopamine receptors and the reward system response. It had been hypothesized that ultra - processes, high calorie, "unhealthy" food lead to rapid increase of dopaminergic stimulation, cravings and habit formation, in order to "compensate" for the decrease in dopaminergic receptor production.

Food has two prong influence on our brain: 1) biochemical, nutritional effect on cellular, hormonal level and 2) psychological value affecting the mood, thought process, stress management, behaviours and motivation.

GLP-1 RA medications increase the sensation of satiety, utilization of blood glucose, thus decreasing the biological need for food [6]. However, the psychological value, the well-established route of emotional satisfaction, sources of reward remain unaddressed. If there are no other alternatives that could derive pleasure for the individual, anhedonia could settle in.

The readjustment of the dopaminergic reward system might take months, depending on the age, physical health before initiation of the medication and titration rate of the medication. Anhedonia can occur at any point during the titration of GLP 1 RA medication. There are reports that these medications actively decrease cravings also for alcohol and other substances. We could speculate that the anhedonia experienced in the early remission of substance dependence might be similar to the one reported during treatment with GLP-1 RAs, i.e. the change of food intake. Anhedonia could last for months, potentially triggering a full-blown depressive episode. The question is how to predict the occurrence, duration and severity of the anhedonia before initiating GLP-1Ras medications.

Of course there are a lot of confounding factors, multiple variables, obvious need for more data and longitudinal observation to devise any specific clinical advice. However, one could speculate that the higher the hedonistic value of food before treatment, the higher the risk of anhedonia after reaching the optimal dose of these medications. We could consider some additional protective factors (no prior personal history of depression, or anhedonia by itself, no prior substance abuse, no family history of depressive disorders, wider alternative sources of pleasure, motivation, aspirations and self-esteem, physical activity, etc) and risk factors (prior personal history of depression, anxiety disorders, eating disorders, psychiatric family history, dearth of alternative sources for self-affirmation).

In conclusion, the risk of anhedonia during treatment with GLP-1RAs is real, but less pronounced compared to some previous estimations. It might be worth incorporating assessment of this risk before starting treatment and during titration of these medications' doses. We can certainly use tools for assessment of the hedonistic value of food and discuss the need for finding alternative sources of reward system stimulation. This presentation is just a food for thought. It doesn't posit any other author's statements than the confirmation of the well-established need for integration of psychiatric, psychological and nutritionists' tools for assessment and treatment of obesity, diabetes, mood disorders. The overall hope remains that via the GLP-1 RA medications we could decouple the food from the hedonistic hunger, control the seeking behaviours and establish healthier relationship with food [3-6].

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