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GLP-1 receptor agonists: A novel pharmacotherapy for binge eating (Binge eating disorder and bulimia nervosa)? A systematic review

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ABSTRACT

Objective: Systematically review evidence on using GLP-1RAs for reducing BEB in BED and BN.
Methods: Comprehensive literature search (PubMed and Google Scholar) conducted for studies evaluating GLP-1Ras for BEB. Extracted data on study characteristics, efficacy, and safety.
Results: Studies show that GLP-1RAs (liraglutide and dulaglutide) reduce BE frequency and comorbidities in addition to favorable psychiatric side effect profile compared to current options. However, large-scale, blinded placebo-controlled trials are lacking.
Conclusion: Early findings suggest promising effects of GLP-1RAs on BEB. However, rigorous clinical trials are needed to firmly establish efficacy, dosing, safety, and comparative effectiveness before considering GLP-1RAs a viable novel approach.

Introduction

Binge eating involves consuming an abnormally large amount of food in a short period of time, accompanied by a feeling of loss of control. This is a core symptom of both Binge Eating Disorder (BED) and bulimia nervosa (BN), two important public health issues, with BED having an estimated lifetime prevalence worldwide of 1.9 % and BN approximately 1 %.

The first-line treatment for BED typically includes both psychological and pharmacological interventions. Psychological treatments, primarily cognitive-behavioral therapy (CBT), focus on addressing the underlying emotional and behavioral aspects of the disorder. Pharmacological treatments often involve the use of selective serotonin reuptake inhibitors (SSRIs) which are believed to help reduce the frequency of binge-eating episodes and associated psychological symptoms however they do not have the desired effect on weight loss. Topiramate, an antiepileptic drug, has been shown in randomized placebo-controlled trials to enhance the effectiveness of CBT in severe cases BED, reducing both the frequency of binge eating and body weight [1]. However, its use is sometimes limited due to side effects like headaches, paresthesia, amenorrhea, and sedation [2]. Lisdexamfetamine (LDX), a central nervous system stimulant that enhances the release of norepinephrine and dopamine, which are associated with attention and focus, and have an appetite-suppressing effect. LDX was shown to be effective in reducing binge eating behaviors and associated symptoms, as well as aiding in weight reduction in BED patients. While generally safe, LDX's potential side effects, such as increased heart rate and blood pressure, necessitate careful monitoring [3]. The current understanding of pharmacotherapy

Abbreviations: BE, binge eating; BEB, binge eating behaviors; BED, BED; BN, bulimia nervosa; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GLP-1, glucagon-like peptide-1; AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; GLP-1RA, glucagon-like peptide 1 receptor agonist; NPY, neuropeptide Y; POMC, proopiomelanocortin; 5-HT, serotonin; mPFC, medial prefrontal cortex.

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in BED, however, remains limited due to gaps and methodological limitations in the literature [4]. BED and BN are associated with reduced quality of life, increased healthcare utilization, functional impairment, obesity, and related conditions like diabetes, as well as psychiatric comorbidities [5]. BN also has elevated mortality risk.

Although BED and BN are disabling conditions, the limited treatment options highlight the need for identifying new pharmacological approaches such as glucagon-like peptide-1 receptor agonists (GLP-1RAs). Glucagon-like peptide-1 (GLP-1) is a hormone and neuropeptide produced in the intestine and brainstem that inhibits appetite. It does this by activating GLP-1 receptors, which reduces food intake, body weight, and stimulates insulin secretion in a glucose-dependent manner [6]. GLP-1 receptor activation regulates both normal feeding behavior and reward-driven feeding. Specific brain regions mediating the appetite-reducing effects of GLP-1 signaling include hypothalamic and hindbrain areas involved in feeding control, reward pathways like the ventral hippocampus, and forebrain regions like the medial prefrontal cortex (mPFC). GLP-1RAs are currently used for treating type 2 diabetes and obesity due to their effects on appetite, food intake, and weight loss. Because GLP-1RAs reduce eating and promote weight loss through these central and peripheral mechanisms, they may also have potential for reducing binge eating episodes in disorders like BN and BED [7].

BED is characterized by impaired satiety signaling, whereas GLP-1 promotes feelings of fullness and satiety. BED may also increase sensitivity and motivation for food rewards. In contrast, GLP-1RAs act in brain reward regions, which may reduce anticipatory and consummatory food reward.

Research indicates GLP-1RAs have a favorable psychiatric side effect profile compared to current medical treatments for BED and BN. For example, the BED drug LDX and BN drug fluoxetine can worsen bipolar symptoms. Topiramate and Zonisamide used for BED and BN can increase suicidal thoughts. However, GLP-1RAs have not shown these risks [8]. A pooled analysis of clinical trials found low rates of depression, anxiety, and suicidal ideation in Liraglutide (a GLP-1 agonist) vs placebo groups. Since BED and BN have high comorbidity with depressive, bipolar and other mental disorders, as well as increased suicidal behavior, the safety profile of GLP-1RAs gives them a key advantage over existing pharmacotherapy options for treating BED.

Treatment for BED largely targets the behavioral, psychological, and physical outcomes related to the disorder. According to several *meta*-analyses and reviews, psychotherapies, specifically cognitive behavior therapy-based approaches, are widely considered the most effective intervention for BED [9]. However, other methods of treatment, including weight loss and pharmacological treatments are proven effective in treating certain BED outcomes in specific populations [10]. This brings us to the main goal of our study, a systematic review emphasizing the use of GLP-1RA in patients with eating disorders.

It has been hypothesized that GLP-1RAs will reduce binge eating in BED and BN. Support includes preclinical binge eating models showing efficacy of GLP-1 and analogues, evidence of altered GLP-1 levels in BED/BN, preliminary human data with abnormal eating. Due to the favorable psychiatric profile, it has also been hypothesized that GLP-1RAs will be safe BED/BN treatments even with comorbid conditions like bipolar disorder.

Methodology

A comprehensive literature search was conducted using PubMed and Google Scholar databases to identify studies on the use of GLP-1 receptor agonists in eating disorders like BED and BN. The following keywords were used: “glucagon-like peptide-1 receptor agonist”, “GLP-1 receptor agonist”, “liraglutide”, “exenatide”, “lixisenatide”, “semaglutide”, “dulaglutide”, “eating disorder”, “BED”, “bulimia nervosa”, “binge eating”, “purging”.

Abstracts were screened for relevance and full text articles assessed for studies specifically evaluating GLP-1 receptor agonists for binge/purge behaviors in eating disorder populations.

Data extracted from the selected studies included: study design, sample size, participant demographics, diagnostic criteria, intervention details, comparator, duration of treatment, outcome measures, key efficacy and safety results, and limitations. The compiled data was analyzed to summarize the current evidence on the therapeutic potential and risks of using GLP-1 receptor agonists to treat BED and BN.

Discussion

The potential of GLP-1 receptor agonists (GLP-1RAs) in addressing binge eating behaviours in BED and bulimia nervosa represents a promising avenue for pharmacotherapy.

The prevalence of binge eating, impacting approximately 8 % of respondents with 3 % experiencing recurrent episodes, underscores the urgency for effective treatments. Episodes often began in the morning or early evening, with about 40 % reporting less than 4 h of fasting beforehand. Women had a significantly higher prevalence of binge eating compared to men (10 % vs 6 %). Binge eating was more common in younger respondents aged 20–29 (11 %) and decreased with older age [11].

Compounded by the health risks associated with eating disorders, including a significant correlation with obesity and metabolic comorbidities, the need for interventions that go beyond symptom management to address underlying physiological mechanisms is clear. Eating disorders are independently associated with increased risk of physical comorbidities including diabetes, hypertension, headaches, back/neck pain, and other types of chronic pain. A study showed that people with BED are 3–6 times more likely to be obese than individuals without BED. Similarly, in another study, the lifetime obesity prevalence was close to 90 % in BED patients [12]. Studies have also shown that binge eating was linked to increased likelihood (odds) of having hypertension (OR: 1.14, 95 % CI: 0.99, 1.37) and hypertriglyceridemia (OR: 1.21, 95 % CI: 1.06, 1.37) after adjusting for all confounding factors [13]. After controlling for various factors, Binge Eating Disorder (BED) status in severely obese adults was associated with higher odds of having high triglycerides (OR = 1.28, 95 % CI: 1.002–1.63) among other medical comorbidities. This association emphasizes the potential metabolic impact of BED beyond weight-related outcomes, highlighting the importance of addressing BED in the management of metabolic health [14].

Exploring the role of GLP-1 in appetite control, Barrera et al conducted a pivotal study employing two approaches to diminish GLP-1 activity in the brains of rats: RNA interference to decrease the synthesis of GLP-1 and the administration of a GLP-1 receptor antagonist. These interventions led to increased food consumption, significant fat accumulation, and the development of glucose intolerance in the subjects [15]. Interestingly, research has revealed hormonal disparities linked to bulimia nervosa, as per Sabine Naessén et al. women with BN had much lower levels of the hormones GLP-1 when fasting and after eating, compared to healthy women in the control group suggesting a potential endocrine dysfunction contributing to the pathophysiology of this eating disorder [16].

GLP-1RAs are promising for treating obesity due to their effects on appetite and food intake. Research shows GLP-1RAs work via combined peripheral and central effects to modulate gut signals, brain appetite circuits, food preferences and cravings [17]. GLP-1 is released from intestinal L cells when nutrients are detected, when bound to its receptor, GLP-1 boosts cAMP levels, which helps trigger the release of insulin. In addition to promoting insulin secretion, GLP-1 has other effects in the body: it slows down gastric emptying and reduces the amount of glucagon released [18].

The efficacy of GLP-1RAs is further supported by their impact on hunger and satiety regulation in the hypothalamus [19]. Animal research has illuminated GLP-1RA’s impact on modulating appetite and binge eating behaviors through serotonin (5-HT) pathways. Interactions

between 5-HT and GLP-1 in the hindbrain and its role in regulating feeding behavior were examined in rats. Results showed that the hypophagic effects of hindbrain 5-HT are dependent on central GLP-1R signalling [20,21]. This central 5-HT-GLP-1 interaction was further shown to enhance proopiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neuron activity, boosting satiety signals, and concomitantly suppress neuropeptide Y/agouti-related peptide (NPY/AgRP) neuron activity, which diminishes hunger [22]. (Fig. A) Activation of POMC neurons by GLP-1 and 5-HT, particularly through the 5-HT2C receptor, leads to the release of α-MSH, an endogenous agonist for MC4R. When α-MSH binds to MC4R neurons in the paraventricular nucleus (PVN) of the hypothalamus, it induces a signalling cascade that ultimately results in decreased appetite. This pathway is a critical component of the neuroendocrine regulation of energy homeostasis, highlighting the complex interplay between neurotransmitters and hormonal signals in the control of food intake [22]. These agents indirectly influence the CA1 region of the ventral hippocampus, thereby modulating hunger and satiety, as well as emotional responses to food, which are implicated in BEDs (BED) [23]. This effect is thought to occur via connections between CA1 and the mPFC [24,25]. The mPFC plays a critical role in emotional regulation, decision-making, and self-control. By enhancing the function of the mPFC, individuals may improve their ability to regulate emotions and impulses, potentially reducing the likelihood of engaging in binge eating behaviors [26]. (Fig. B).

This study shows that central 5-HT-GLP-1 interaction is relevant for physiological control of food intake and can reveal that GLP1 agonism is part of the final effect of SSRIs which gets us back to our hypothesis of using GLP1-RA as a treatment for BED.

Despite the promising data, GLP-1RAs are not without their side effects. Overall, GLP-1RAs are well tolerated in non-diabetic patients with obesity, with few treatment discontinuations due to side effects in trials. The most common side effects are mild to moderate gastrointestinal issues like nausea, vomiting and diarrhea. Nausea affected up to 48 % of patients initially but decreased over time. Vomiting and diarrhea also peaked early in treatment but then declined. Although unpleasant, these GI effects are rarely severe and tend to resolve [27]. Since GLP-1RAs are used to treat diabetes, there may be concerns about increased hypoglycemia risk in non-diabetic obese patients. However, GLP-1 action is glucose-dependent, only lowering glucose if it is elevated. Studies confirm this - GLP-1RAs cause minimal hypoglycemia in obesity without diabetes, which would also be safe for patients with eating disorders. Therefore, concerns about hypoglycemia and gastrointestinal side effects should not prevent GLP-1RA treatment initiation or continuation for most patients, given the generally manageable safety and tolerability profile demonstrated in studies [28].

The pharmacological class of GLP-1 receptor agonists encompasses various generic formulations, characterized by differential pharmacokinetics and therapeutic outcomes.

Starting with Liraglutide (Victoza), a GLP-1 analog with a fatty acid added to extend its half-life, requiring once-daily injection [29]. In one study, focused mainly on Liraglutide and its effect on weight, metabolism, and neuroprotection, it was shown that Liraglutide can cross the blood–brain barrier and may have positive impacts on neuron growth and protection [30]. A randomized, prospective, controlled trial conducted at a tertiary medical institution assigned 44 obese individuals who binge eat to either an intervention group or a control group for 12 weeks (about 3 months). The intervention group received 1.8 mg of liraglutide daily along with diet and exercise guidance, while the control group only received diet and exercise guidance. They assessed binge eating severity (BES) (The Binge Eating Scale (BES) has been shown to be an effective tool for identifying individuals who engage in binge eating and for monitoring the efficacy of treatments for binge eating) ghrelin levels, and other anthropometric measures at the start of the study, week 1, week 6, and week 12. They obtained baseline measurements for these outcomes plus final measurements at the end of the 12-week study period [31]. Based on BES scores, individuals scoring below 18 would be categorized as non-binge. Liraglutide had larger decreases in binge eating behavior, as measured by the BES [20 (IQR 18–27) to 11 (IQR 7–16), $p < 0.001$]) compared to patients who did not get liraglutide. Also, patients taking liraglutide lost more weight over the study than those not treated with it [32].

To emphasize the effect of GLP1-R agonist on the brain and its efficacy in patients with hyperphagia and eating disorder, a case report examined the effects of the Liraglutide for treating behavioral disturbances in a 20-year-old male with autism spectrum disorder, intellectual disability, and severe food obsessions with compulsive overeating. Prior treatment with antipsychotics had led to weight gain and worsening of food-related behaviors in this patient. After starting Liraglutide, the patient experienced significant reductions in food obsessions, overeating, aggression, and other repetitive behaviors. Over 36 weeks (about 8 and a half months) of Liraglutide 2.4 mg/day, the patient lost 12–13 % of body weight, with no adverse side effects reported. The authors hypothesize Liraglutide may have improved satiety signaling and reward circuits involved in obsessive behaviors.[33] To confirm previous findings that liraglutide can be used as a treatment even in patients with psychiatric conditions; [24] a cohort study evaluated 100 patients with obesity treated with Liraglutide for weight loss over 6 months. Liraglutide was found to be significantly effective, with 27 %, 45 %, and 57 % of patients achieving $\geq$ 5 % weight loss at 1, 3, and 6 months respectively. Efficacy was similar regardless of BED or psychiatric comorbidities. Early weight loss response at 1 month strongly predicted longer-term weight loss at 3 and 6 months. Even lower Liraglutide doses remained effective for weight reduction. [34] Furthermore, the patients' psychiatric profiles did not influence the therapeutic response to liraglutide showing its safe use in patients with psychiatric conditions.

Semaglutide (Ozempic), on the other hand, is a long-acting GLP-1 analog similar to Liraglutide but with greater receptor binding, taken weekly. Studies on Semaglutide showed improved overeating control, reduced food cravings, and lowered preference for high-fat, high-calorie foods. Also, Semaglutide therapy led to a notably larger decrease in Binge Eating Scale (BES) scores in comparison to LDX and topiramate, which are frequently utilized anti-obesity drugs for managing BED.[35] When compared to Liraglutide, Semaglutide metabolizes slower than Liraglutide, resulting in higher Semaglutide plasma levels that may contribute to greater anti-obesity effects. Semaglutide also has the advantage of weekly dosing compared to daily Liraglutide, which may improve adherence and quality of life [36,37].

Dulaglutide (Trulicity), another GLP-1RA given weekly. An open-label pilot study examined the effects of the GLP-1RA Dulaglutide in patients with type 2 DM and BED. Sixty diabetics on metformin were randomized to add either Dulaglutide 1.5 mg/week or Gliclazide (a sulfonylurea) 60 mg/day for 12 weeks. Dulaglutide treatment led to significantly greater reductions compared to gliclazide in binge eating frequency, body weight, BMI, body fat percentage, and HbA1c. The reduction in binge eating was independently associated with decreases in both body weight and HbA1c with Dulaglutide. This was the first study testing GLP-1RA in diabetic patients with BED. The results support the hypothesis that GLP-1 signaling may be involved in binge eating, and that GLP-1RAs could be an effective treatment for BED [38].

Other GLP1-RAs: Lixisenatide (Adlyxin) another short-acting GLP-1RA for daily injections, structurally based on exendin-4. Exenatide (Byetta, Bydureon) which was the first - it is a synthetic version of the hormone exendin-4 found in Gila monster saliva and it is a long-acting once-weekly injection. Finally, Byetta a short-acting injectable GLP1-RA taken twice daily [39].

Comparative studies of GLP-1 receptor agonists for weight loss are scarce. (Fig. C) However, it has been shown that Exenatide twice daily dosage outperforms Lixisenatide and is just as effective as liraglutide 1.8 mg, Exenatide weekly doage, and dulaglutide 1.5 mg. Meanwhile, liraglutide 1.8 mg has demonstrated superiority in weight loss results over albiglutide, Exenatide weekly dosage, and dulaglutide 1.5 mg [40].

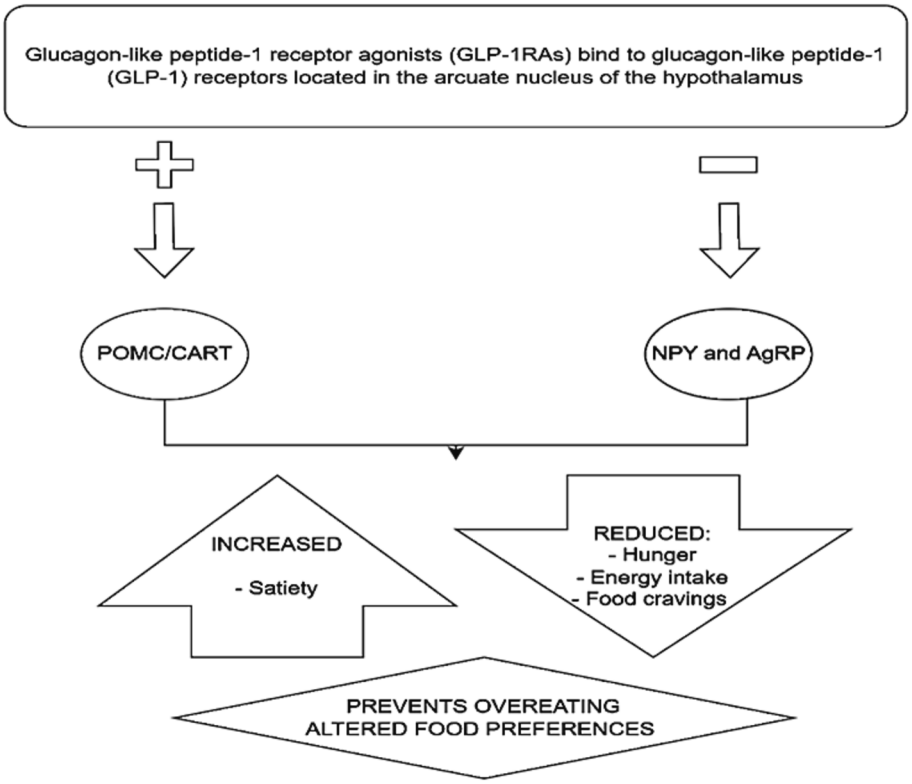

Fig. A. This schematic illustrates the action of GLP-1 on CNS AgRP: Agouti-related peptide, CART: cocaine- and amphetamine-regulated transcript, GLP-1RA: glucagon-like peptide 1 receptor agonist, NPY: neuropeptide Y, POMC: proopiomelanocortin.

Also, while psychotherapy (such as cognitive behavioral therapy) is generally seen as more effective than pharmacological treatment, medication may require less time or be less costly than therapy. Thus, it would be reasonable to use medication as the initial treatment for patients who would rather take medication than do psychotherapy, as well as for patients who are unable to access psychotherapy. If medication is chosen as the treatment, SSRIs is known to be the type of drug to use [41].

Summarizing the above, GLP-1 in the brain plays an important role in appetite and glucose regulation, and reduced GLP-1 is associated with disordered eating behaviors like bingeing and purging. Targeting the GLP-1 system may therefore be a therapeutic approach for obesity and eating disorders.

Future research directions

Limitations of the studies above include small sample sizes, short durations of the studies, and a lack of head-to-head comparisons. We have very few animal studies, and these fail to study behavioral therapy in rodents with eating disorders nor compare them to pharmacological treatments. Additionally, there is a lack of animal studies that compare different GLP1-RAs as opposed to the general effects of the GLP1 molecule itself.

While early research indicates potential for GLP1-RAs as a promising therapy for benefiting metabolic regulation and possibly cognitive function in mood disorders, more rigorous, large-scale clinical trials are needed to firmly establish its efficacy and safety in these contexts. Ideal future studies should be high-quality, blinded, and placebo-controlled to account for bias and placebo effects. They should also clarify optimal dosing, treatment duration, patient responder subgroups, side effect monitoring requirements, and how GLP1-RAs compares to existing options.

Conclusion

In summary, BED and BN are characterized by recurrent episodes of uncontrolled overeating and represent major public health concerns. However, treatment options remain limited. Early research suggests GLP1-RAs may provide a novel pharmacological approach by targeting satiety signaling and food reward pathways involved in binge eating. Small pilot studies and case reports indicate promising reductions in binge eating frequency, body weight, and comorbidities with GLP-1RA like liraglutide and dulaglutide. Importantly, these agents demonstrate a favorable psychiatric side effect profile compared to existing options. It is important to note that while cognitive behavioral therapy-based approaches are widely considered the most effective long-term intervention for binge eating behaviors, GLP1-RAs can support the treatment process by improving compliance and satisfaction.

However, large-scale, rigorous, blinded placebo-controlled trials are critically needed to firmly establish the efficacy, safety, optimal dosing, and comparative effectiveness of GLP-1RAs for BED and BN. Well-designed head-to-head studies of different agents in this class would also be beneficial. While preliminary findings are encouraging, the viability of GLP-1RAs as a much-needed new therapeutic direction cannot be confirmed without additional high-quality clinical research in patients with BED. Nevertheless, these agents remain an exciting prospect that warrants further investigation. Carefully conducted studies will clarify whether the early promise of GLP-1RAs as a novel pharmacological approach for reducing binge eating is being realized. This research was conducted without the support of external funding or grants.

CRediT authorship contribution statement

Laurence Aoun: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration. **Shaza Almardini:** Writing – review & editing, Writing – original draft, Visualization,

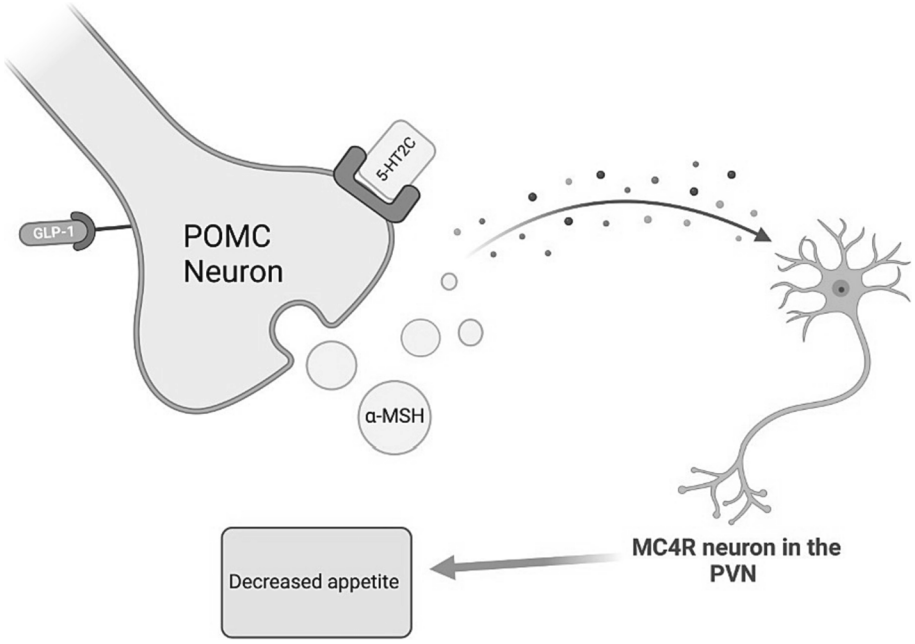

Fig. B. This schematic illustrates the interaction between POMC neurons, serotonin (5-HT), and melanocortin 4 receptors (MC4R) in the regulation of appetite. Activation of POMC neurons by GLP-1 and serotonin, particularly through the 5-HT2C receptor, leads to the release of α-MSH, an endogenous agonist for MC4R. When α-MSH binds to MC4R neurons in the paraventricular nucleus (PVN) of the hypothalamus, it induces a signaling cascade that ultimately results in decreased appetite. This pathway is a critical component of the neuroendocrine regulation of energy homeostasis, highlighting the complex interplay between neurotransmitters and hormonal signals in the control of food intake.

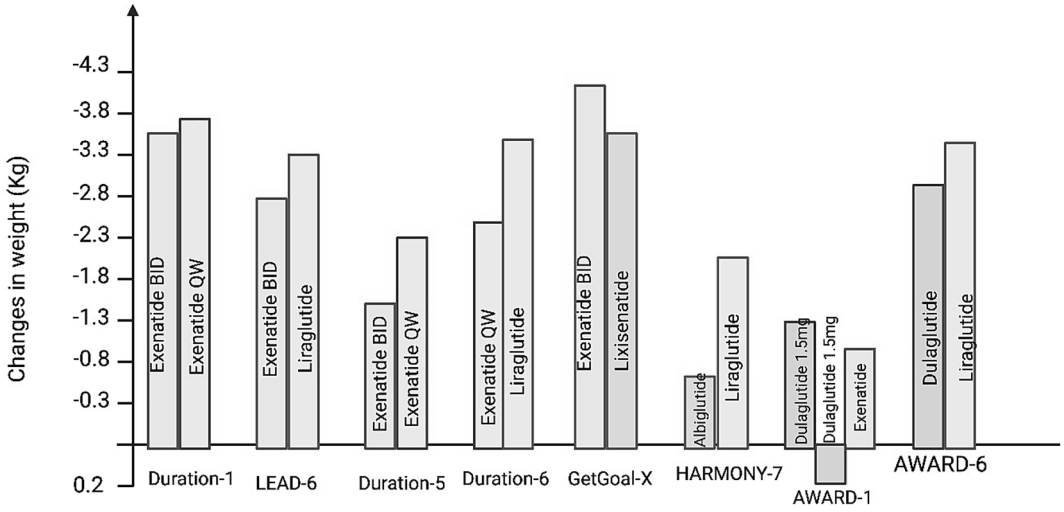

Fig. C. Adapted from dar, s. et al. (2015). 'the role of glp-1 receptor agonists as weight loss agents in patients with and without type 2 diabetes.' practical diabetes, 32(8), 297–300. copyright © 2015 john wiley & sons [40]. The above graph shows the changes in weight in kg among different study groups.

Validation, Supervision, Methodology. **Fares Saliba:** Writing – review & editing, Writing – original draft, Project administration, Methodology. **Fadi Haddadin:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources. **Omar Mourad:** Writing – original draft, Visualization, Investigation. **Jennifer Jdaidani:** Validation, Visualization, Writing – review & editing. **Zeina Morcos:** Writing – review & editing. **Ibrahim Al Saidi:** Writing – review & editing. **Elie Bou Sanayeh:** Writing – review & editing. **Saliba Saliba:** Writing – original draft. **Michel Almardini:** Writing – original draft. **Julie Zaidan:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendices

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