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Potential Role of Glucagon-like Peptide-1 (GLP-1) Receptor Agonist in the Treatment of Bulimia Nervosa

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Bulimia nervosa (BN) is a severe eating disorder characterized by recurrent episodes of binge eating followed by compensatory behaviors such as self-induced vomiting, misuse of laxatives, fasting, or excessive exercise. Current treatment strategies, including cognitive-behavioral therapy (CBT) and pharmacotherapy, have limitations, with many patients not responding adequately and experiencing high relapse rates. GLP-1 receptor agonists, initially developed for type 2 diabetes mellitus (T2DM) and chronic weight management, have shown potential in regulating appetite and modifying behavior, suggesting a possible role in treating BN.
Objective: This review aims to assess the current evidence regarding the efficacy and safety of GLP-1 receptor agonists, particularly Semaglutide, in the treatment of bulimia nervosa.
Methods: A comprehensive literature search was conducted using PubMed and Google Scholar, focusing on articles published between 2014 and 2024. Studies included were clinical trials, case reports, and reviews addressing the use of GLP-1 receptor agonists in BN. The search terms included "Bulimia Nervosa," "Semaglutide," "GLP-1 receptor agonists," and related terms. After screening and removing duplicates, five relevant articles were included in the qualitative synthesis.
Results: The included studies demonstrated that GLP-1 receptor agonists, such as Semaglutide, liraglutide, and dulaglutide, effectively reduced binge eating episodes and body weight in patients with BN. In a notable case report, a patient with long-standing BN experienced complete resolution of symptoms within two weeks of starting liraglutide, sustained over five years. Retrospective cohort and open-label studies also showed significant reductions in binge eating severity with GLP-1 receptor agonists compared to other anti-obesity medications. Additionally, preclinical studies suggested these agents' potential in modulating appetite and reward pathways in the brain.
Conclusion: The evidence indicates that GLP-1 receptor agonists may be a promising alternative pharmacotherapy for bulimia nervosa, addressing both appetite regulation and behavioral aspects of the disorder. However, the current paucity of large-scale, randomized controlled trials necessitates further research to confirm these findings and establish the efficacy, safety, and optimal dosing of GLP-1 receptor agonists in the treatment of BN. The favorable psychiatric side effect profile and potential for improved patient adherence highlight the need for continued exploration of these agents in clinical practice.

Keywords: Bulimia nervosa; GLP-1 receptor agonists; semaglutide; liraglutide; dulaglutide; eating disorders.

1. INTRODUCTION

Bulimia nervosa (BN) is a severe eating disorder characterized by recurrent episodes of binge eating followed by compensatory behaviors such as self-induced vomiting, misuse of laxatives, fasting, or excessive exercise [1]. Binge eating episodes are typically marked by a loss of control over eating and the consumption of an unusually large quantity of food within a short time. This behavior is often associated with intense feelings of guilt and shame. It is estimated to affect approximately 1-2% of women and 0.1-0.5% of men worldwide, with a higher prevalence among young adults [2]. The disorder is often comorbid with other psychiatric conditions, including depression, anxiety disorders, and substance abuse, complicating diagnosis and treatment.

Current treatment strategies for BN include psychotherapy and pharmacotherapy. Cognitive-behavioral therapy (CBT) is considered the gold standard, achieving remission in up to 50% of cases [3]. Pharmacological interventions include selective serotonin reuptake inhibitors (SSRIs), with fluoxetine being the only FDA-approved medication for BN. However, treatment limitations remain, as many patients do not respond adequately to medications or psychotherapy alone. Relapse rates are also high, and adverse effects can limit the tolerability and adherence to pharmacological treatments [4]. Thus, exploring alternative pharmacotherapies, such as Glucagon-Like Peptide-1 (GLP-1) receptor agonist is important to improve BN outcomes.

Medications such as Liraglutide, Dulaglutide, Semaglutide (marketed under the trade name Ozempic or Wegovy), are glucagon-like peptide-1 (GLP-1) receptor agonist, initially developed for the treatment of type 2 diabetes mellitus (T2DM). Semaglutide is currently FDA-approved for managing T2DM and chronic weight

management in adults with obesity (BMI ≥30) or overweight (BMI ≥27) with comorbid conditions [5]. Pharmacologically, these medications are synthetic analogues of the endogenous incretin hormone GLP-1, with up to 94% similarity (e.g. Semaglutide) to native GLP-1. It exerts its effects by binding to and activating GLP-1 receptors, resulting in glucose-dependent insulin secretion, inhibition of glucagon secretion, and delayed gastric emptying [6]. These actions contribute to improved glycemic control and weight loss.

GLP-1 receptor agonist potential relevance to BN stems from its dual impact on appetite regulation and behavior modification. The drug acts on the central nervous system (CNS), specifically targeting areas involved in appetite regulation, such as the hypothalamus and brainstem. By activating GLP-1 receptors in these regions, these medications enhance satiety signals and reduce hunger [7]. In addition, it influences reward pathways in the mesolimbic system, potentially reducing the reinforcing effects of food and altering binge-eating behaviors [8].

In clinical trials for obesity management, the GLP-1 receptor agonist- Semaglutide significantly reduced body weight by up to 15% in patients, primarily through its appetite-suppressing effects [9]. Its influence on eating behavior, particularly in reducing caloric intake and controlling cravings, suggests a potential role in treating eating disorders such as BN.

Given the pharmacological profile of GLP-1 receptor agonists and its potential to modulate appetite and reward mechanisms, it represents a promising alternative for BN treatment. This review aims to assess the current evidence regarding the potential efficacy and safety of GLP-1 receptor agonists in BN treatment and identify gaps in the literature that warrant further investigation.

2. METHODOLOGY

Inclusion Criteria:

- Articles published in English
- Studies focusing on pharmacological treatment of BN
- Research articles, clinical trials, case reports, and systematic reviews related to Semaglutide or other GLP-1 receptor agonists

Exclusion Criteria:

- Articles published before 2014
- Non-English publication
- Studies not related to BN or GLP-1 receptor agonists

To identify relevant articles addressing the effect of GLP-1 receptor agonists on the treatment of BN, we utilized a structured search strategy using Medical Subject Headings (MeSH) terms and keywords. Our search was conducted across two databases, PubMed and Google Scholar, to capture a comprehensive set of articles.

Using this Mesh Term on PubMed Search, “(("Bulimia Nervosa" [Title/Abstract] OR "Eating Disorder"[Title / Abstract] OR "Binge Eating"[Title / Abstract]) AND ("Semaglutide" [Title/Abstract] OR "Ozempic" [Title/Abstract] OR "GLP-1 receptor agonists" [Title/Abstract] OR "Glucagon-like peptide-1 receptor agonists" [Title/Abstract])) AND (("Treatment" [Title/Abstract] OR "Pharmacotherapy" [Title/Abstract] OR "Medication" [Title/Abstract] OR "Drug therapy" [Title/Abstract]))”, we initially found 7 articles. After applying a publication date filter (2014-2024), the same 7 articles remained. After reviewing titles and abstracts, 3 articles were deemed relevant to our study objectives. Due to the limited number of available articles, no exclusion criteria based on article type were applied.

Using this Mesh Term on Google Scholar Search, “("Semaglutide" OR "Ozempic" OR "GLP-1 receptor agonists" AND "Bulimia Nervosa")”, Publication Date Range 2014-2024, initial search found 298 articles. After screening for information relevant to our study objective by reading the topics and abstracts, 5 articles were deemed relevant.

Finally, we screened all 8 articles for duplicates (3 articles from PubMed and 5 articles from Google Scholar) and removed 3 duplicate articles. Hence, we were left with 5 relevant articles for our study.

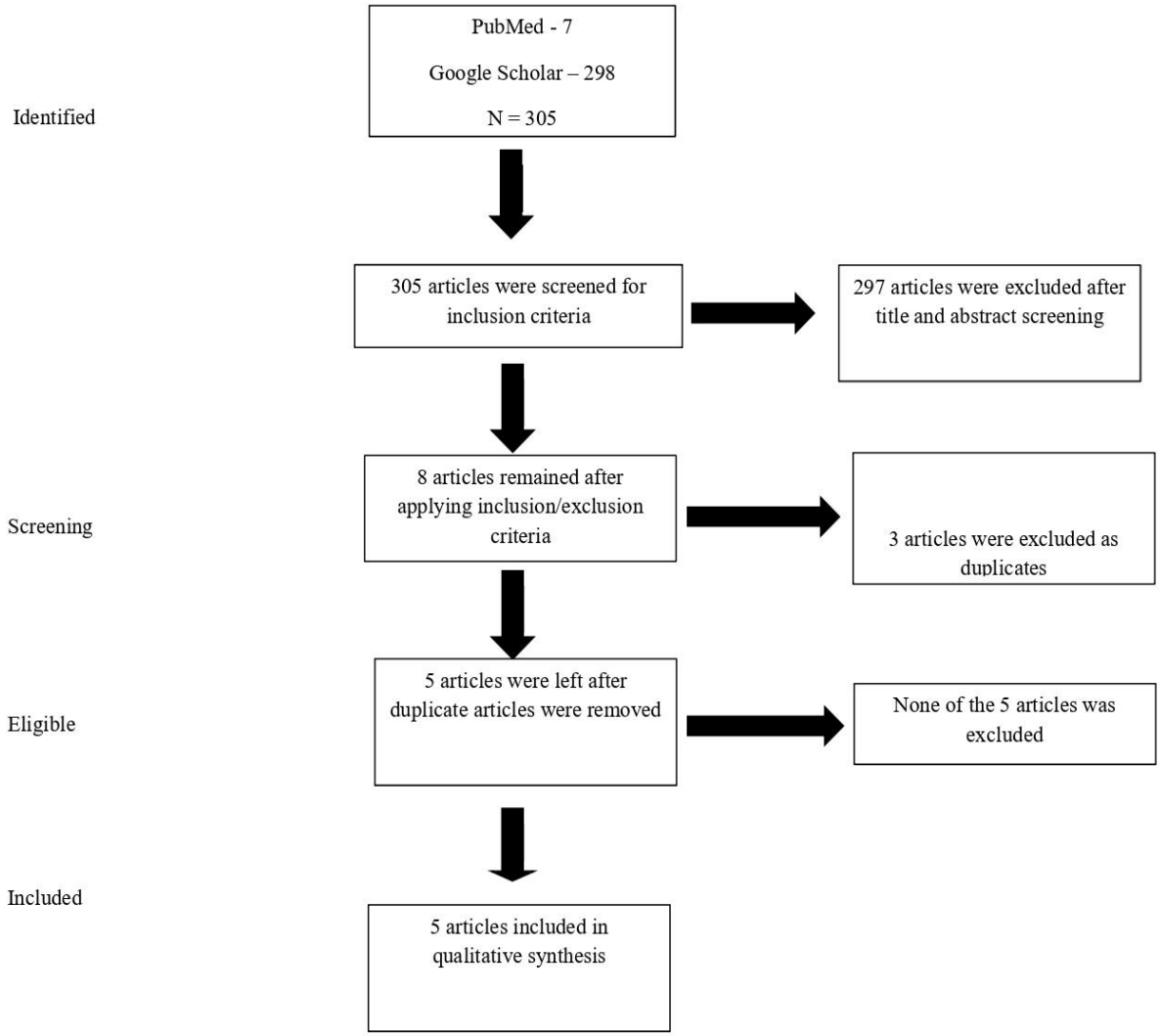
A standardized data extraction to collect information on study design, participant characteristics, interventions, and outcomes was completed as shown in Table 1.

Table 1. Overview of studies examining the potential role of GLP-1 receptor agonists in the treatment of bulimia nervosa and binge eating disorder

Study	Study Design	Sample size	Population Characteristics	Intervention	Comparator	Outcome Measures	Results	Conclusion
Perez-Cheron [10]	Case report	1	26-year-old female with PCOS, bulimia nervosa, and depression; unresponsive to antidepressants	Liraglutide + metformin	None	Resolution of Bulimia symptoms; depression	Resolution of bulimia symptoms within 2 weeks of starting liraglutide; maintained for 5 years	Combination of metformin and liraglutide effectively controlled hunger and bulimia in this patient
Richards et al. [11]	Retrospective cohort	98	Adults with moderate to severe BED	Semaglutide	Lisdexamfetamine or topiramate	BES scores; weight loss	Semaglutide group showed greater reductions in BES scores compared to comparator groups	Therapeutic effects of semaglutide in BED warrant further investigation
McElroy et al. [12]	Literature review	-	NA	GLP-1 receptor agonists	NA	Evidence from preclinical models, clinical trials	GLP-1 receptor agonists appear to reduce binge eating behavior and promote weight loss	GLP-1 receptor agonists could have efficacy in BED and BN; further studies needed
Andrea Da Porto et al. [13]	Open label, prospective controlled study	60	Type 2 diabetic patients with BED	Dulaglutide	Gliclazide	BES score; body weight; BMI; percentage fat mass; HBA1c	Greater reduction in BES, body weight, BMI, percentage fat mass and HbA1c in patients treated with dulaglutide compared with patients on gliclazide	GLP1-RAs (Dulaglutide) decreases binge eating behavior in patients with Type 2 DM and co-existing BED

Study	Study Design	Sample size	Population Characteristics	Intervention	Comparator	Outcome Measures	Results	Conclusion
Laurence Aoun et al. [14]	Systematic review	-	NA	GLP-1 receptor agonists	NA	Frequency of binge eating; Presence of co-occurring conditions; Psychiatric side effect profile.	Reduced frequency of binge eating and co-occurring conditions. Beneficial psychiatric side effect features	Possible favorable effects of GLP-1RAs were depicted by early findings, however, more in-depth clinical trials are necessary for conclusive confirmation of the dosing, efficacy, safety and comparative effectiveness.

Footnote: PCOS: Polycystic Ovary Syndrome; BED: Binge Eating Disorder; BN: Bulimia Nervosa; GLP-1: Glucagon-Like Peptide-1; BES: Binge Eating Scale; TFEQ-R18: Three-Factor Eating Questionnaire-R18



Flow chart 1. Prisma

3. RESULTS

According to the case report by Perez-Cheron of a 26-year-old woman with polycystic ovary syndrome (PCOS), reactive hypoglycemia, bulimia nervosa, and depression who experienced a complete resolution of her bulimic behavior and depression within 2 weeks of starting liraglutide in combination with metformin. The patient had long-standing bulimia nervosa for 15 years, unresponsive to conventional psychotherapy and antidepressants. She reported a prolonged sensation of satiety after meals and complete resolution of bulimic behavior within 2 weeks of starting liraglutide 1.2 mg daily in addition to her ongoing metformin therapy. The remission of bulimia nervosa and depression was sustained for 5 years on the combination of liraglutide (increased to 1.8 mg daily) and metformin. Stopping either liraglutide or metformin separately resulted in recurrence of hunger and weight gain within 1-2 weeks, suggesting the combination was effective for controlling her hunger, bulimia, and weight. The author hypothesizes that bulimia nervosa, in some cases, may represent a metabolic disorder rather than a purely psychiatric disorder, possibly related to GLP-1 deficiency or resistance, insulin resistance, and abnormalities in appetite-regulating hormones. The case suggests that GLP-1 receptor agonists like liraglutide, either alone or in combination with metformin, may be an effective medical therapy for bulimia nervosa, potentially addressing an underlying metabolic component [10].

In a retrospective cohort study by Richards et al. that examined the effects of the GLP-1 agonist

semaglutide on binge eating disorder symptoms. A total of 98 patients were included, with 48 identified as having moderate to severe BED based on Binge Eating Scale (BES) scores >16. Patients were divided into three groups: those receiving semaglutide only (n=19 for moderate/severe BED), those receiving semaglutide combined with other anti-obesity medications (lisdexamfetamine or topiramate) (n=13), and those receiving only other anti-obesity medications (OAOM) (n=16). The primary outcome was change in BES score from baseline to follow-up. For the moderate/severe BED subsample (n=48): One-way ANCOVA showed a significant effect of treatment type on BES score change ($F(2,42)=8.02$, $p<0.01$), Tukey's post-hoc tests revealed the semaglutide only group had a significantly greater reduction in BES scores compared to the OAOM group ($p<0.01$), and mean BES reductions were 14 points for semaglutide only, 12.9 for semaglutide+OAOM, and 5.9 for OAOM only. Analysis of the full sample (N=98) showed similar results, with a significant treatment effect ($F(2,92)=10.1$, $p<0.001$) and greater BES reductions in the semaglutide groups versus OAOM ($p<0.001$ for both). The authors concluded that the therapeutic effects of semaglutide for binge eating disorder warrant further study, as it may be a promising treatment option, potentially more effective than commonly used anti-obesity medications like lisdexamfetamine and topiramate [11].

In a literature review by McElroy et.al, they reported that preclinical studies in animal models have demonstrated that both GLP-1 and GLP-1 receptor agonists suppress binge-like eating behaviors. For instance, systemic administration of GLP-1 was shown to reduce hedonically mediated sucrose overconsumption in mice, a model of binge-like behavior. One of the studies they reviewed found no difference in GLP-1 levels between obese BED patients and obese non-BED patients. In a randomized study of 44 obese, non-diabetic patients with subclinical binge eating behavior receiving the GLP-1 agonist liraglutide exhibited significantly greater reductions in binge eating severity and body weight compared to the control group. Additionally, in women with polycystic ovary syndrome (a condition associated with binge eating), liraglutide treatment was associated with clinically significant decreases in uncontrolled eating scores. While the evidence is preliminary and requires further investigation through well-designed, randomized, placebo-controlled clinical trials, the authors hypothesize that GLP-1 receptor agonists may safely and effectively reduce binge eating behavior in individuals with BED and BN, including those with comorbid psychiatric disorders, due to their favorable psychiatric adverse event profile [12].

In a 12-week open-label, prospective controlled trial on 60 type 2 diabetic outpatients with binge eating disorder by Andrea Da Porto et al, patients were randomized to receive either dulaglutide 1.5 mg/week (n=30) or gliclazide 60 mg/day (n=30), in addition to metformin. After 12 weeks, patients treated with dulaglutide had significantly greater reductions compared to gliclazide in: Binge eating scale (BES) score (reduction of 12.067 vs 0.467, $p<0.0001$; Body weight (reduction of 4.767 kg vs 0.073 kg, $p<0.0001$); BMI (reduction of 1.653 vs 0.040, $p<0.0001$); Percentage body fat mass (reduction of 1.850% vs 0.197%, $p<0.0001$) and HbA1c (reduction of 1.073% vs 0.753%, $p=0.009$). Multivariate regression analysis showed that the reduction in BES score was independently associated with reductions in body weight ($p<0.0001$) and HbA1c ($p=0.033$). The authors concluded that dulaglutide treatment effectively reduces binge eating behavior in type 2 diabetic patients with binge eating disorder, along with improvements in anthropometric and metabolic parameters [13].

In a recent 2024 systematic review article by Laurence Aoun et al. which focused mainly on the potential use of glucagon-like peptide-1 receptor agonists for treating binge eating behaviors in binge eating disorder and their relevance for bulimia nervosa. The article hypothesized that glucagon-like peptide-1 receptor agonists may be a promising novel pharmacotherapy for BN due to their effects on reducing binge eating episodes by targeting satiety signaling and food reward pathways in the brain. One of the studies they reviewed found that women with BN had much lower levels of the hormone GLP-1 when fasting and after eating compared to healthy controls, suggesting a potential hormonal dysregulation contributing to the disorder's pathophysiology. They concluded that GLP-1 receptor agonists could be a potentially promising pharmacological approach for bulimia nervosa, by targeting the core binge eating behavior [14].

Table 2. Comparison between the different types of GLP-1RAs used in the selected studies

S/N	GLP-1RA	Metabolism	Plasma levels	Dosing	Efficacy	Side Effects	Other information
1	Liraglutide (Victoza)	Faster than Semaglutide	Lower	Once daily injection	Has better weight loss potential than albiglutide and exenatide weekly injection.	superior Weight loss results	Can cross blood-brain barrier and might play a role in neuroprotection
2	Semaglutide	Slower	Higher than Liraglutide	Once Weekly (long acting)	Better control of hyperphagia, less food cravings, lowered preference for fat-rich and calorie-dense meals Remarkable reduction in BES scores	Anti-obesity effects	Better adherence and improved quality of life
3	Dulaglutide (Trulicity)	-	-	Once weekly	Reduced binge eating frequency,	weight loss, reduced body fat percentage and HbA1C	
4	Lixisenatide (Adlyxin)	-	-	Daily injections	Weaker weight loss effects than exenatide twice daily injections		
5	Exenatide (Byetta, Bydureon)	-	-	-Weekly injections -Twice daily injections (Byetta)	-Better Weight Loss induction than lixisenatide		

4. DISCUSSION

Our review highlights the significant gender disparity in the prevalence of BN, with women being more affected than men, as reported by Laurence et al [14]. This finding aligns with existing literature on eating disorders, which consistently shows a higher prevalence in females. Additionally, the age distribution indicates that young adults, particularly those aged 20-29, are more susceptible to BN compared to older age groups [14]. This demographic trend suggests the need for targeted interventions in young women, who appear to be at the highest risk of developing bulimia nervosa and similar conditions.

Our findings strongly support the efficacy of GLP-1 receptor agonists (GLP-1RAs) in treating BN and BEDs. Patients with eating disorders have been noticed to have reduced GLP-1 levels which causes increased gastric emptying and a surge in appetite. Since GLP agonists have been found to be effective in promoting satiety and reducing gastric emptying times [10], it is not surprising that this medication class is a promising first-line option for the treatment of bulimia nervosa and similar disorders. This is buttressed by the reduction in binge eating behaviors, resolution of bulimic symptoms, and lowering of Binge Eating Scale (BES) scores, observed in studies by McElroy and Perez-Chevron, which underline the potential of GLP-1RAs as a viable treatment option [10,12]. This efficacy was consistent across different GLP-1RAs, including Semaglutide, dulaglutide, and liraglutide, indicating a class effect rather than a drug-specific phenomenon.

When compared with other medications commonly used for BN and BEDs, such as Lisdexamfetamine, topiramate, and gliclazide, GLP-1RAs demonstrated superior effectiveness. Studies by Richard's et al. and Andrea Da Porto et al. showed greater reductions in BES scores among subjects treated with GLP-1RAs compared to those receiving other treatments [11,13]. This superior efficacy highlights the potential of GLP-1RAs to become a preferred pharmacological option for managing BN and BEDs.

The adverse effects associated with GLP-1RAs, including nausea, vomiting, diarrhea, and hypoglycemia in non-diabetic individuals, are relatively mild compared to those of other treatment options like SSRIs and anticonvulsants. Laurence et al. noted that these side effects are more tolerable, which is crucial for patient adherence and quality of life [14]. Furthermore, our review found no reports of treatment discontinuation due to adverse effects, contrasting with higher dropout rates seen with other medications such as topiramate [15].

The interaction between GLP-1RAs and serotonin pathways raises the possibility of combination therapy with SSRIs. Given the effectiveness of SSRIs in treating BN and the additional benefits of GLP-1RAs, a combined approach may offer enhanced therapeutic outcomes. Future research should explore this potential, particularly in randomized controlled trials, to determine the efficacy and safety of such combination therapies. However, GLP-1RAs offer practical advantages over current treatments, such as fluoxetine, which requires daily administration. The weekly injection regimen of semaglutide, dulaglutide, and exenatide may improve patient compliance and treatment adherence. Additionally, the ability of GLP-1RAs to manage comorbid conditions like diabetes is particularly beneficial for patients with BN and BEDs, as it reduces the medication burden and simplifies treatment regimens. Furthermore, GLP-1RAs have a demonstrated short treatment-to-resolution timeline as reported by Perez-Cheron et al's study where the patient had a total disappearance of her bulimic symptoms within two weeks of starting Liraglutide [10]. This will further improve adherence to treatment for better and more sustained outcomes.

5. CONCLUSION

Our review underscores the promising role of GLP-1RAs in the treatment of BN and BEDs. The consistent efficacy, favorable side effect profile, and practical advantages of GLP-1RAs make them a compelling option for further investigation and potential adoption as a first-line treatment. However, the current paucity of data necessitates more extensive research to validate these findings and establish GLP-1RAs as a standard treatment for BN and BEDs.

6. LIMITATIONS AND FUTURE RESEARCH

The primary limitations of our review include the lack of randomized controlled trials and the small sample sizes of the studies reviewed. These factors limit the generalizability of our findings

and highlight the need for more robust research. Future studies should focus on large-scale RCTs to confirm the efficacy and safety of GLP-1RAs in treating BN and BEDs. Additionally, research on BN patients without comorbid diabetes is essential to eliminate potential confounding effects and provide clearer insights into the specific benefits of GLP-1RAs.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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