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Glucagon-like Peptide 1 Receptor Agonists and Obesity Associated with Eating Disorders

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Key words

Obesity
GLP-1RA
Eating disorder
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Binge-eating disorder
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Treatment

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective medications for managing obesity and related metabolic complications. However, their use presents specific challenges when obesity is coexisting with eating disorders. In such cases, the appetite-suppressing effects of GLP-1RAs could potentially exacerbate behaviors like dietary restriction and dietary restraint, two behavioral patterns that help sustain eating disorder psychopathology, thus complicating treatment for these disorders. Because of these concerns, it is essential for clinicians to screen for eating disorders before prescribing GLP-1RAs in individuals with overweight or obesity. Their use is currently contraindicated for patients with atypical anorexia nervosa, bulimia nervosa, or subthreshold bulimia nervosa, as GLP-1RAs could worsen the restrictive eating behaviors common in these conditions. Although some emerging research suggests that GLP-1RAs might reduce binge-eating episodes, there is not yet enough evidence to support their use specifically for treating binge-eating disorder (BED) and its associated psychopathology. According to new recommendations from cognitive behavior therapy for BED, GLP-1RAs may be cautiously considered in patients with clinical obesity who do not overvalue shape and weight, have no history of anorexia nervosa or bulimia nervosa, and who have already made progress in adopting regular eating patterns and reducing binge-eating episodes.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of drugs initially approved for the treatment of type 2 diabetes. They enhance glycemic control by stimulating insulin secretion and suppressing glucagon production in response to energy intake (Neumiller, 2015). Beyond their blood sugar-lowering effects, certain medications—such as liraglutide, semaglutide, and tirzepatide—have demonstrated significant effectiveness in promoting weight management, and they have been approved by the Food and Drug Administration (FDA) for long-term obesity treatment.

In individuals with obesity or overweight and weight-related comorbidities (excluding diabetes), liraglutide at a daily dose of 3.0 mg and semaglutide at a once-weekly dose of 2.4 mg—both GLP-1RAs—have demonstrated significant weight reduction. Liraglutide achieved an 8% weight loss over 56 weeks (Pi-Sunyer et al., 2015), while semaglutide resulted in a 15% reduction over two years (Wharton et al., 2023). Both medications primarily work by modulating hunger and satiety centers in the brain and delaying gastric emptying, thereby reducing energy intake (Ard et al., 2021). Tirzepatide, a dual glucagon-like peptide-1 (GIP) and GLP-1RAs, administered once weekly at a 15 mg dose, resulted in an average weight loss of 20.9% over 72 weeks (Jastreboff et al., 2022), driven by its synergistic effects on appetite regulation, energy intake reduction, and fat mass decrease (Heise et al., 2023).

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Semaglutide at 2.4 mg has also been associated with a 20% reduction in the risk of heart attack or stroke in non-diabetic patients with obesity or overweight with existing cardiovascular conditions (Lincoff et al., 2023). Additionally, it has been shown to enhance symptoms, improve physical fitness, and lower inflammation and body weight in patients with obesity and heart failure with preserved ejection fraction (Kosiborod et al., 2023). Emerging research suggests that GLP-1RAs may also be beneficial in treating conditions like obstructive sleep apnea (Malhotra et al., 2024), osteoarthritis (Bliddal et al., 2024), metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis with liver fibrosis (MASH) (Loomba et al., 2024), polycystic ovary syndrome (PCOS) (Szczesnowicz et al., 2023), Alzheimer's disease (Liang et al., 2024), Parkinson's disease (Kalinderi et al., 2024), and addiction (Klausen et al., 2022).

Despite these promising clinical outcomes, challenges remain in the use of new weight-loss medications. Common concerns include side effects, the weight potential regain upon discontinuation, high costs, and their possible impact on eating disorders (Dalle Grave, 2024b). These factors highlight the need for careful consideration and monitoring when prescribing these medications, especially in individuals at risk of eating disorders (Bartel et al., 2024).

This article aims to review the potential negative impact of GLP-1RAs on eating disorder psychopathology and treatment. It also explores when and how these medications may be incorporated into cognitive behavioral therapy (CBT) for binge-eating disorder (BED) associated with obesity.

Eating disorders associated with overweight and obesity

Eating disorders are prevalent among individuals with a body mass index (BMI) in the range of overweight or obesity, with BED being the most common. Among those seeking obesity treatment, 1.4% to 9% meet DSM criteria for BED (Allison et al., 2007; Gorin et al., 2008; Ricca et al., 2000). In the same population, the presence of recurrent binge-eating episodes has been reported with a percentage ranging from 9% to 29% (Allison et al., 2007; Gorin et al., 2008; Ricca et al., 2000). In addition, among those with a BMI ≥ 50.0 seeking bariatric surgery, up to 50% experience recurrent binge-eating episodes (Vinai et al., 2015). Many individuals seeking obesity treatment also exhibit BED of low frequency and/or limited duration (Dalle Grave, 2023). Other eating disorders frequently associated with overweight and obesity are atypical anorexia nervosa, bulimia nervosa, and bulimia nervosa of low frequency and/or limited duration.

Table 1 presents the prevalence and diagnostic distribution of eating disorders assessed with the Eating Disorder Examination interview (Calugi et al., 2015) among 2,810 consecutive patients who sought obesity treatment at the Department of Eating and Weight Disorders, Villa Garda Hospital.

Table 1. Prevalence and diagnosis of eating disorders diagnosed in consecutively seeking treatment patients with obesity*.

Diagnosis of nutrition and eating disorder	n	%
Binge-eating disorder	184	6.5
Binge-eating disorder with low frequency and/or limited duration	83	3
Bulimia nervosa	23	0.8
Bulimia nervosa of low frequency and/or limited duration	57	2
Absence of eating disorder	2462	87.6
Total	**2810**	**100**

* The diagnosis was made with the Eating Disorder Examination interview (Calugi et al., 2015). From Dalle Grave, R. (2023). Obesity and eating disorders: an interactive and complex coexistence. IJEDO, 5. doi:10.32044/ijedo.2023.04. Reprinted with the permission of Positive Press.

Assessing the presence of eating disorders in patients seeking treatment for obesity

The high prevalence of eating disorders among patients seeking treatment for obesity highlights the need for thorough screening in this population. Clinicians should ask patients if they have experienced episodes of overeating with a loss of control over eating within the past 4 weeks. It is important to clarify that 'overeating' refers to consuming what most people consider an unusually large amount of food in in a discrete period of time (e.g., within any 2-hour

period), while 'loss of control over eating' implies an inability to stop eating or control what or how much is consumed. If patients report such episodes, the clinician should further inquire about the average frequency of these episodes over the past 3 months.

To confirm a diagnosis of BED, clinicians can ask whether these episodes involved eating significantly more than usual, eating until uncomfortably full, eating even when not physically hungry, or eating alone due to embarrassment about the amount of food consumed. Patients should also be asked if they felt self-disgust, depression, or guilt after these episodes. Additionally, for an accurate diagnosis of BED, clinicians must rule out bulimia nervosa, ensuring patients do not regularly engage in inappropriate compensatory behaviors, such as self-induced vomiting and laxative or diuretic misuse, as seen in bulimia nervosa.

Screening should also assess weight suppression (the difference between a patient's maximum and current weight) and consider whether, following weight loss, patients experienced an intense fear of weight gain or symptoms of starvation (e.g., low body temperature, reduced heart rate, preoccupation with thoughts of food, irritability, decreased sexual desire, or social isolation). These features may suggest atypical anorexia nervosa.

The Eating Disorder Examination Questionnaire (EDE-Q) (Calugi et al., 2017) is also recommended for screening, as it assesses cognitive aspects—such as the overvaluation of shape and weight, where individuals judge themselves predominantly or even exclusively in term on their shape, weight, and control over them—and behavioral symptoms, including binge eating, self-induced vomiting, laxative/diuretic misuse, excessive exercise, and dietary restraint. This assessment tool evaluates these aspects of eating disorder psychopathology over the previous 28 days, providing valuable insights into the patient's recent expressions of eating disorder psychopathology.

All patients suspected of having an eating disorder should be referred to a specialist for a comprehensive assessment of eating disorder psychopathology before initiating obesity treatment.

GLP-1RAs and their impact on eating disorder psychopathology

GLP-1RAs are not approved for treating eating disorder psychopathology. Although extensive misuse is not yet well-documented, these medications—like other weight-loss drugs such as stimulants, topiramate, and orlistat—may contribute to the development or worsening of eating disorder psychopathology (Bartel et al., 2024). Warnings and calls to action have also been issued regarding the misuse of GLP-1RAs among children and adolescents (Cooper et al., 2023).

GLP-1RAs, which increase satiety and reduce hunger and increasing satiety could exacerbate dietary restriction (i.e., physiological undereating) and dietary restraint (i.e., the cognitive effort to reduce food intake) by encouraging the adoption of extreme and rigid dietary rules (see Figure 1). Such behaviors may include skipping meals, eating minimal portions, and avoiding numerous foods. According to the transdiagnostic theory of eating disorders, dietary restriction and restraint are key behavioral expressions and maintaining mechanisms of eating disorders psychopathology (Fairburn et al., 2003). Additionally, side effects such as nausea, vomiting, and diarrhea—common with GLP-1RAs—could further decrease appetite and reinforce dietary restriction and dietary restraint.

The appetite-modulating effects of GLP-1RAs may clash with key treatment strategies for eating disorders, particularly those focused on establishing regular eating patterns and addressing dietary restriction and restraint (Dalle Grave & Calugi, 2020). However, emerging evidence suggests that GLP-1RAs could be beneficial for specific eating disorder symptoms in individuals with obesity who do not have diabetes, potentially reducing binge eating, dietary disinhibition, overall eating disorder psychopathology, and concerns about body shape (Chao et al., 2019).

In light of the above data, the following section will outline clinical recommendations for using GLP-1RAs to treat patients with specific eating disorder diagnoses and a BMI in the range of overweight or obesity. These recommendations aim to optimize treatment outcomes while addressing potential risks and challenges unique to this population.

Atypical anorexia nervosa

Patients with atypical anorexia nervosa, a subtype of other specified feeding and eating disorder (OSFED), meet all criteria for anorexia nervosa except that, despite significant weight loss, their weight remains within or above the normal range (American Psychiatric Association, 2013).

Weight loss and the use of GLP-1RAs are contraindications in individuals with atypical anorexia nervosa, even for those with a BMI in the overweight or obese range. As shown in Figure 2, GLP-1RAs potentially increase focus on weight loss as a measure of self-worth, accentua-

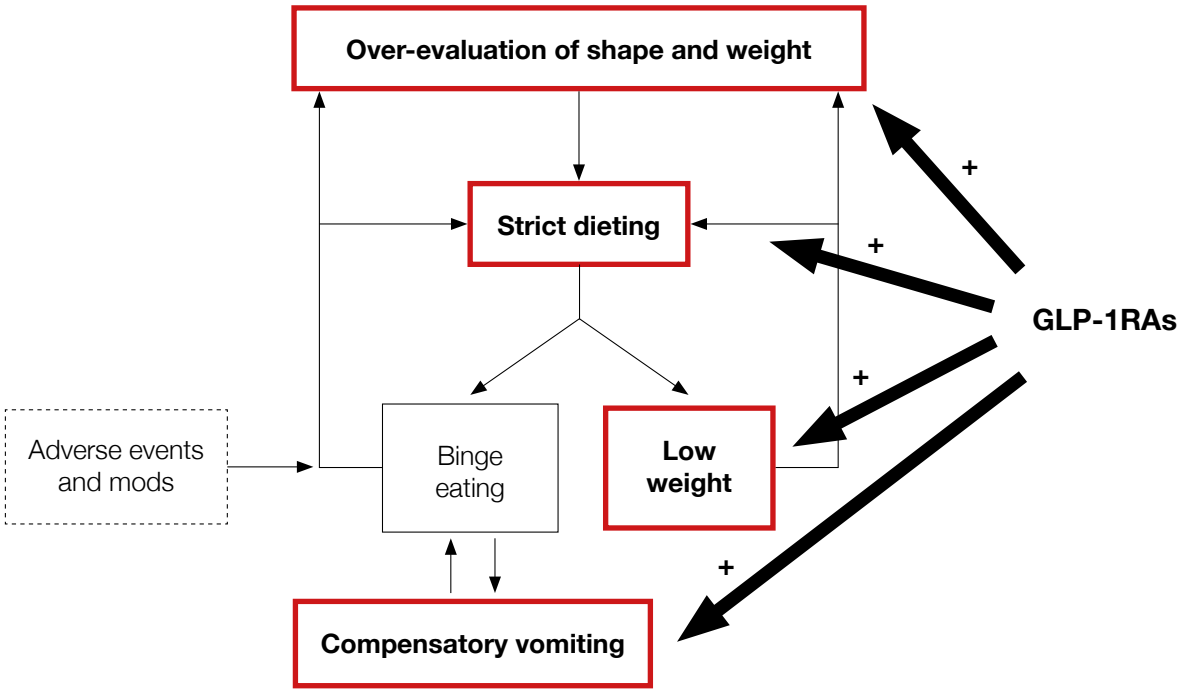

Figure 1. Potential mechanisms by which GLP-1RAs contribute to eating disorder psychopathology

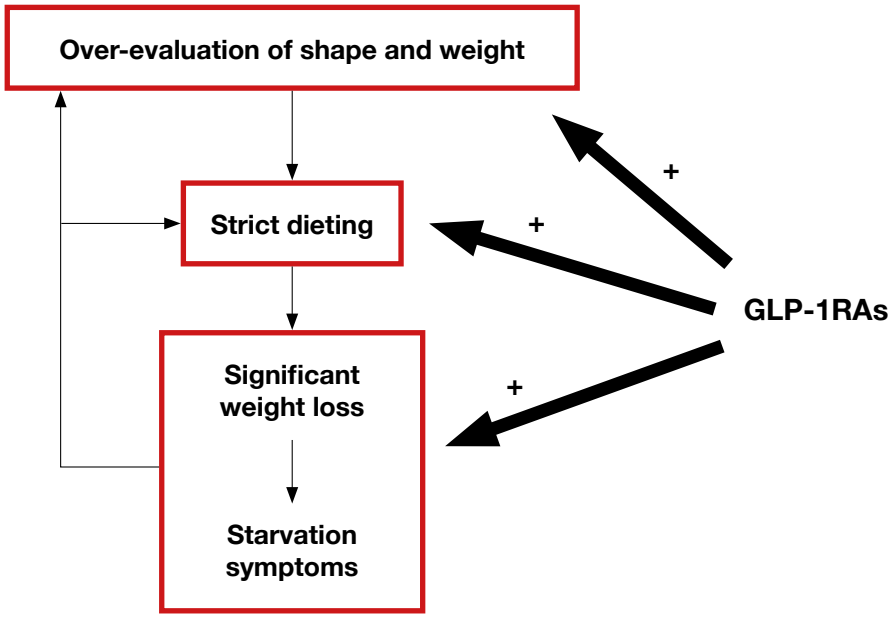

Figure 2. Potential adverse effects of GLP-1RAs in atypical anorexia nervosa

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ting overvaluation of shape and weight, which is the core psychopathology of eating disorders. They also intensify dietary restriction and restraint and exacerbate symptoms associated with starvation (e.g., irritability, preoccupation with food, fatigue, and social indifference), reinforcing the primary maintaining mechanisms of this eating disorder.

Bulimia nervosa and bulimia nervosa of low frequency and/ or limited duration

Patients with bulimia nervosa experience recurrent episodes of binge eating, characterized by consuming a large quantity of food in a brief period while feeling a loss of control over eating. These episodes are typically followed by inappropriate compensatory behaviors intended to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise (American Psychiatric Association, 2013). For a diagnosis of bulimia nervosa, binge-eating episodes and compensatory behaviors must occur, on average, at least once a week for three months. When all criteria for bulimia nervosa are met except that binge eating and compensatory behaviors happen less frequently or for a shorter duration, the diagnosis is a subtype of OSFED known as bulimia nervosa of low frequency and/or limited duration.

Some patients with bulimia nervosa fall within the overweight or obese BMI range (Dalle Grave, 2023; Masheb & White, 2012), and a subset of these patients report significant weight loss and symptoms of starvation (Bodell & Keel, 2015).

Weight loss and GLP-1RAs are contraindications for patients with bulimia nervosa, as well as for those with low-frequency and/or limited-duration bulimia nervosa. As illustrated in Figure 3, GLP-1RAs potentially exacerbate the overvaluation of shape and weight and promote strict dieting—a primary mechanism that maintains binge-eating episodes (Fairburn et al., 2003). In turn, binge-eating episodes reinforce the overvaluation of shape and weight and the strict dieting behaviors.

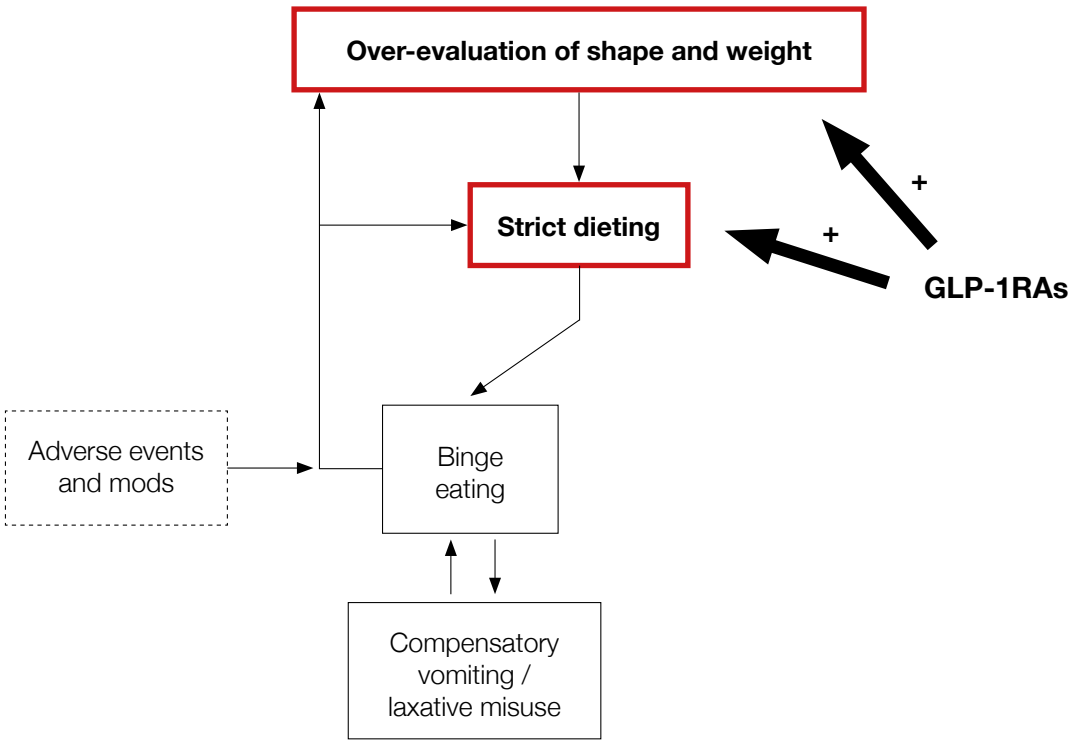

Figure 3. Potential adverse effects of GLP-1RAs in bulimia nervosa and bulimia nervosa of low frequency and/or limited duration

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BED and BED of low frequency and/or limited duration

Binge-eating episodes are the main feature of BED. These are not associated with the recurrent use of inappropriate compensatory behaviors seen in bulimia nervosa. There is marked distress regarding binge eating and, usually, accompanying shame and self-criticism. The binge eating is required to occur, on average, at least once a week for 3 months (American Psychiatric Association, 2013). When all criteria for binge-eating disorder are met except that binge eating occurs less frequently or for a shorter duration, the diagnosis is a subtype of OSFED known as BED of low frequency and/or limited duration. Binge eating, not followed by recurrent use of inappropriate compensatory behaviors, often results in weight gain, and for this reason, some individuals make several attempts to lose weight.

Some studies have shown a reduction in binge eating in patients with obesity without diabetes who were treated with GLP-1RAs (Chao et al., 2023; Robert et al., 2015). However, there is currently no available data assessing the efficacy of these medications specifically for the treatment of BED. Findings from the only randomized controlled trial involving liraglutide in this population were compromised due to incorrect participant randomization (Allison et al., 2023). As a result, GLP-1RAs should not be prescribed for treating BED. Furthermore, research has revealed that dietary restraint is not a monolithic concept. Evidence suggests that flexible dietary restraint, as opposed to rigid approaches, can support effective binge-eating control and weight management in patients with BED. This flexibility is associated with both the cessation of binge eating and improved weight-loss outcomes. (Blomquist & Grilo, 2011; Hagan et al., 2017).

The findings mentioned above have led CBT for BED (Dalle Grave et al., 2024) to adopt a clinical stance on using GLP-1RAs for patients with BED who also have higher body weight.

When and how CBT for BED use GLP-1RAs

CBT for BED, as detailed in a manual (Dalle Grave et al., 2024), integrates strategies and procedures from both CBT-E for eating disorders (Dalle Grave & Calugi, 2020; Fairburn et al., 2003) and personalized CBT for obesity (Dalle Grave et al., 2018). Unlike treatments based on the 'disease model,' which addresses the patient's illness (e.g., BED), CBT for BED is based on the 'psychological model'. This approach targets, in a personalized and flexible way, the specific cognitive-behavioral processes that sustain binge-eating episodes, excessive and dysregulated eating, and, in some cases, clinical obesity. The treatment is delivered in three steps and is highly collaborative, adaptable, and tailored to individual needs.

In the context of CBT for BED, GLP-1RAs are considered an adjunctive approach for patients with coexisting higher weight when traditional behavioral and psychological interventions alone are insufficient to manage binge-eating behaviors and support weight management.

Step One - Starting Well aims to (i) enhance mutual understanding of the cognitive-behavioral mechanisms that sustain a patient's BED, (ii) reduce preoccupation with weight, (iii) decrease the frequency of binge-eating episodes, and (iv) promote the adoption of an active lifestyle. Notably, weight loss is not addressed during this stage, and attempts to lose weight are discouraged, as they may inadvertently trigger dysfunctional dieting behaviors. Such behaviors could hinder the effective implementation of the regular eating procedure, a fundamental strategy within CBT for managing binge-eating episodes. This treatment step spans four weeks, with two sessions held per week.

Review Session - Taking Stock is scheduled at the end of Step One. It is dedicated to (i) reviewing the progress made during the first four weeks, (ii) identifying any obstacles to treatment, (iii) revisiting the personal formulation, and (iv) planning the next steps in treatment.

Step Two - Addressing the Change focuses on helping patients address the specific mechanisms maintaining their manifestations of BED. The procedures introduced in Step One are continued, and the treatment is tailored using one or more modules shown in Figure 4. The duration of this step varies, depending on the number of modules to be implemented and the patient's pace of recovery. Step Two takes approximately 20 weeks for most patients, with weekly sessions during the first two months, followed by biweekly sessions. For patients who achieve early remission from their eating-disorder psychopathology and do not need weight loss, Step Two consists of only the *Setbacks and Mindsets and Maintenance Preparation* modules, which can be completed in three biweekly sessions.

The *Healthy Weight Loss* module is designed specifically for patients with clinical obesity (Rubino et al., 2023) who are motivated to pursue healthy and sustainable weight loss. It is also intended for those with non-clinical obesity who aim to improve overall health and reduce the risk of developing clinical obesity or other non-communicable diseases. Eligibility for this module requires that patients have established a regular eating pattern and significantly reduced binge-eating episodes during Step One. However,

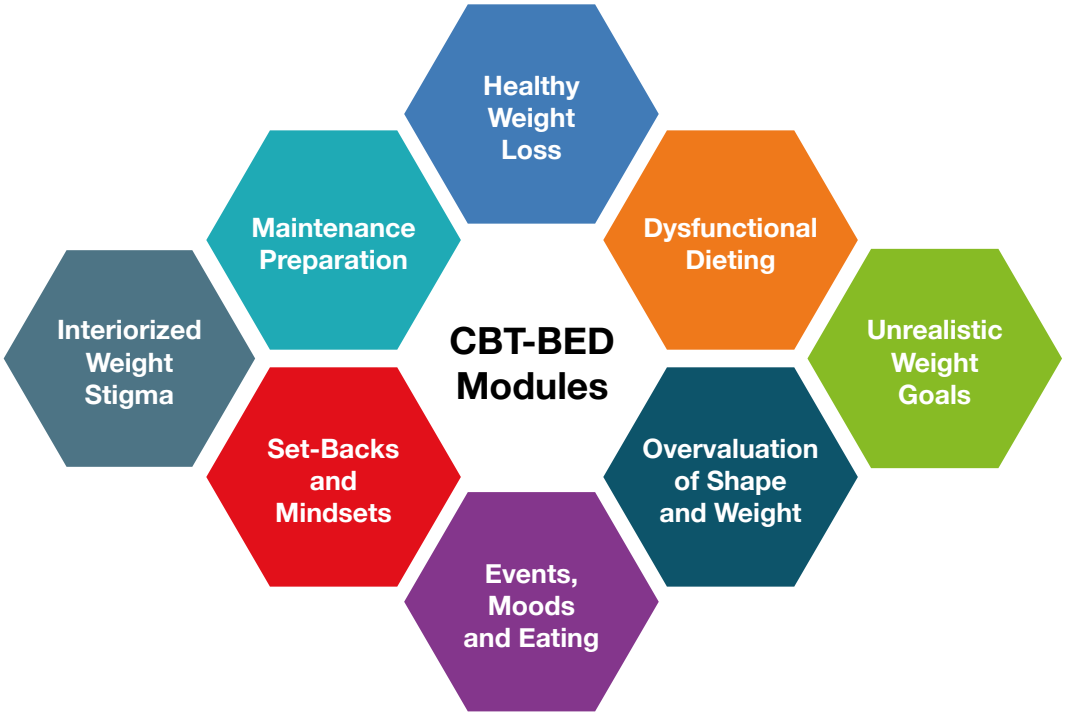

Figure 4. The modules of CBT for BED

it is not recommended for patients who: (i) have an overvaluation of shape and weight, (ii) a history of anorexia nervosa or bulimia nervosa, or (iii) are experiencing major depression or other severe, unstable mental health disorders.

If a patient opts to begin medication, it is essential to monitor and promptly address any emerging signs of exacerbation of eating disorder psychopathology (e.g., adoption of extreme and rigid dietary rules, skipping meals, self-inducing vomiting). They should also receive periodic evaluations from a physician experienced in managing obesity, GLP-1RAs, and the principles of CBT for BED. Additionally, patients should be encouraged to combine these medications with healthy lifestyle changes. Adopting balanced and flexible eating patterns and engaging in physical activity can offer added benefits, improving the patient's overall health and well-being beyond weight loss (Dalle Grave, 2024a).

Step Three - Preventing Relapse aims to prevent the recurrence of binge eating and to support maintaining a healthy weight. This step typically lasts 48 weeks, with one session every four weeks. However, for patients who chose not to pursue weight loss during Step Two, Step Three is condensed to three monthly sessions and focuses specifically on preventing binge-eating relapse.

Conclusions

GLP-1RAs are highly effective medications for treating obesity and its complications, and emerging research suggests they may also be promising for managing other medical conditions. Despite these encouraging outcomes, challenges remain regarding the use of new weight-loss medications due to their potential negative impact when overweight and obesity are associated with eating disorders. Specifically, GLP-1RAs increase satiety and reduce hunger, which could exacerbate dietary restriction and dietary restraint—key behavioral patterns that help sustain eating disorder psychopathology—and potentially hinder eating disorder treatment.

Clinicians treating obesity should screen for the presence of eating disorder psychopathology before prescribing GLP-1RAs, as these medications are contraindicated in cases of overweight or obesity associated with atypical anorexia nervosa, bulimia nervosa, and subthreshold bulimia nervosa. While there is emerging evidence that GLP-1RAs may help reduce binge-eating episodes, current data are insufficient to support their use for treating BED and its associated psychopathology.

However, as proposed in the new CBT for BED approach, these medications may be suitable for patients with

BED associated with clinical obesity without an overvaluation of shape and weight, without a history of anorexia nervosa or bulimia nervosa, and other severe, unstable mental disorders, who have successfully adopted a regular eating pattern and significantly reduced binge-eating episodes.

Future research will be needed to assess whether the new CBT for BED, which combines GLP-1RAs for a subset of patients, is more effective than existing psychological treatments for BED associated with obesity. Current psychological therapies are effective in reducing binge-eating episodes, but they typically do not lead to significant weight loss. For this new approach to be considered superior, it must demonstrate similar effectiveness in controlling binge eating and associated psychopathology while also achieving clinically meaningful and sustainable weight loss over time.

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