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# The emerging role of glucagon-like peptide-1 in binge eating

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## Abstract

Binge eating is a central component of two clinical eating disorders, binge eating disorder and bulimia nervosa, but the large treatment gap highlights the need to identify other strategies to decrease binge eating. Novel pharmacotherapies may be one such approach. Glucagon-like peptide-1 (GLP-1) is an intestinal and brain-derived neuroendocrine signal with a critical role in promoting glycemic control through its incretin effect. Additionally, the energy balance effects of GLP-1 are well-established; activation of the GLP-1 receptor (GLP-1R) reduces food intake and body weight. Aligned with these beneficial metabolic effects, there are GLP-1R agonists that are currently used for the treatment of diabetes and obesity. A growing body of literature suggests that GLP-1 may also play an important role in binge eating. Dysregulation of the endogenous GLP-1 system is associated with binge eating in non-human animal models, and GLP-1R agonists may be a promising approach to suppress the overconsumption that occurs during binge eating. Here, we briefly discuss the role of GLP-1 in normal energy intake and reward, and then review the emerging evidence suggesting that disruptions to GLP-1 signaling are associated with binge eating. We also consider the potential utility of GLP-1-based pharmacotherapies for reducing binge eating behavior.

### Keywords

liraglutide; semaglutide; estrogen; binge eating disorder; bulimia nervosa

## 1. What is binge eating?

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), binge eating is characterized by the following: 1) eating an objectively larger amount of food in a discrete time period than most people would under similar circumstances; and 2) a feeling of loss of control over eating (American Psychiatric Association, 2013). Binge eating is a central component of two clinical eating disorders – bulimia nervosa (BN) and binge eating disorder (BED). Of note, BED was first included as a standalone eating disorder diagnosis in the current version of the DSM (i.e., DSM-5)

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(American Psychiatric Association, 2013). This was critical as it strengthens efforts to deliver evidence-based care and increases access of care. The primary distinguishing feature between BN and BED is the use of recurrent inappropriate compensatory behaviors (e.g., vomiting, use of laxative/diuretics/diet pills, excessive exercise) in those with BN only. Binge eating is also a core component of subclinical (i.e., low frequency and/or of limited duration) BN and BED, which fall into the Other Specific Feeding or Eating Disorder category (American Psychiatric Association, 2013).

Although altered feeding behavior is only one facet of disordered eating in humans, finding strategies to normalize intake is a critical aspect of treating BN and BED. Currently, there are several evidence-based psychological treatments for BN and BED, including cognitive-behavioral therapy (Murphy et al., 2010), interpersonal psychology (Wilfley et al., 2002), and behavioral weight loss (Wilson et al., 2010). In addition to psychotherapy, binge eating can be treated with pharmacotherapy. Lisdexamfetamine (often sold under the brand name Vyvanse) is the only FDA-approved pharmacotherapy for BED (McElroy et al., 2015) and, although it decreases binge eating episodes, side effects are often reported (Bello and Yeomans, 2018). For BN, the only FDA-approved pharmacotherapy is fluoxetine, a drug originally used for treatment of depression. It is effective at reducing both binge eating and vomiting episodes, but undesirable side effects are common (Bello and Yeomans, 2018). Topiramate, an antiepileptic drug, is sometimes used off-label for BED (McElroy et al., 2003) and, while effective, it also has many side effects as well as interactions with other common drugs like oral contraceptives (McElroy et al., 2003). Moreover, although evidence-based treatments exist for eating disorders, there is a huge treatment gap with only 20% of individuals with eating disorders receiving any treatment (Kazdin et al., 2017). Rates of treatment are estimated to be slightly higher for BED, but they are still low; it is estimated that only about one quarter of those with current BED are receiving treatment and less than half receive treatment at any point (Westerberg and Waitz, 2013). Thus, there is a need for other treatment types and modalities, such as new pharmacotherapy options that cause fewer side effects, to decrease the act of binge eating.

The glucagon-like peptide-1 (GLP-1) system has become an area of intense research focus due to its ability to reduce food intake and body weight in humans and non-human animals (Grill, 2020). Indeed, agonists and co-agonists targeting the GLP-1 receptor (GLP-1R) are currently leading strategies for pharmacological treatment of obesity and produce significant and sustained weight loss (Wang et al., 2023, Baggio and Drucker, 2021). GLP-1R agonism continues to be investigated as a component of next-generation dual- and tri-agonists for obesity to improve weight loss efficacy (Baggio and Drucker, 2021, Knerr et al., 2022). In addition to the utility of GLP-1-based pharmacotherapies for treating obesity, the GLP-1 system may also be a promising target for treating BED and BN (McElroy et al., 2018, Richards et al., 2023). Here, we briefly discuss the role of GLP-1 in normal energy balance control. We then review evidence implicating GLP-1-based therapy as a potential strategy to treat BED, including data from animal models for BED as well as a small but growing body of literature evaluating the effects of GLP-1R agonists on binge eating in humans. We also consider some major gaps in the literature, in particular the lack of clarity surrounding sex differences in the GLP-1 system and how GLP-1 may interact with estrogens to affect

feeding. Finally, we highlight some key questions that remain in terms of the possible utility of targeting GLP-1 to ameliorate binge eating.

## 2. Glucagon-like peptide-1

### 2.1 What is GLP-1?

GLP-1, formed as a cleavage product from a larger precursor called preproglucagon, is produced peripherally in the ileum of the small intestine as well as centrally in the nucleus tractus solitarius (NTS) (Holst, 2007, Daniels and Mietlicki-Baase, 2019). GLP-1R activation improves glycemic control and reduces food intake and body weight, leading to a focus on the development of GLP-1-targeting pharmaceutical agents and current usage of long-acting GLP-1R agonists in the treatment of diabetes and obesity (Elmaleh-Sachs et al., 2023, Anderson et al., 2020). Particularly relevant to the consideration of GLP-1 signaling in binge eating is the fact that GLP-1R activation has potent suppressive effects on palatable food intake and food reward. Binge eating in humans frequently includes the intake of energy-dense, highly palatable foods that are considered rewarding (Moraes et al., 2023, Allison and Timmerman, 2007). GLP-1R agonist administration in humans is associated with reduced food cravings and improved satiety (Friedrichsen et al., 2021), both of which may help to reduce binge eating. GLP-1R signaling in the NTS, as well as mesolimbic reward system nuclei including the ventral tegmental area and nucleus accumbens, reduces motivation to work for a palatable food in rodent models (Alhadeff et al., 2017, Colvin et al., 2020, Dickson et al., 2012), providing basic science evidence for potential sites of action for these agonists.

GLP-1R agonists have also been examined for their ability to reduce intake of drugs of abuse. In rodent studies, GLP-1R agonists have been shown to decrease self-administration of and motivation for substances including alcohol (Sorensen et al., 2016, Vallof et al., 2016, Colvin et al., 2020, Vallof et al., 2019), cocaine (Schmidt et al., 2016, Hernandez et al., 2018, Hernandez et al., 2019b, Graham et al., 2013, Sorensen et al., 2015), and heroin (Douton et al., 2022b, Douton et al., 2022a). Data from human studies are limited in these areas, and in particular there is a paucity of high-quality randomized controlled trials evaluating the effects of more recent GLP-1R agonists like semaglutide (Leggio et al., 2023, Klausen et al., 2022). Nevertheless, the findings from non-human animal studies imply that there may also be broader motivational consequences of GLP-1R activation beyond effects on feeding, and it is possible that GLP-1 may affect compulsive behaviors more generally. Compulsive behavior is one feature of addictive behaviors (Koob and Volkow, 2016, Gori et al., 2023). There is evidence that binge eating is associated with alterations in some domains of compulsivity [e.g., enhanced reward- and punishment-related compulsivity; (Waltmann et al., 2021)], and there may be parallels between compulsive eating and drug taking (Serafine et al., 2021), highlighting the possibility that GLP-1-based drugs effective to suppress intake of food and drugs may do so in part by reducing compulsive behavior – an effect that would also be relevant to addressing binge eating.

### 2.2 Sex differences in GLP-1-mediated energy balance control

BED and BN are more common in women, with a 3.5:2 and 3:1, respectively, female to male lifetime prevalence ratio (Hudson et al., 2007). This underscores the possibility of sex differences in mechanisms underlying binge eating. Many studies of GLP-1 signaling to date have examined effects only in male subjects, but a growing body of research is beginning to address the physiological and behavioral implications of GLP-1 signaling in females and whether sex differences exist in GLP-1-relevant outcomes (Rentzeperi et al., 2022). Sex differences in the food-directed motivational and reward-related consequences of GLP-1R activation appear to be at least partially dependent on the site of action and route of administration (Lopez-Ferreras et al., 2019, Lopez-Ferreras et al., 2018, Richard et al., 2016). Although the mechanisms underlying these sex differences are still being determined, the phase of the estrous cycle in rodents [and possibly also the menstrual cycle in humans; see (Rogan and Black, 2023) for review] can greatly impact feeding behaviors (Asarian and Geary, 2013) as well as motivation for food (Richard et al., 2017), and estrous phase may underlie at least some of the sex differences in GLP-1 (Huang and Raybould, 2020, Asarian and Geary, 2013). For example, the ability of site-specific pharmacological GLP-1R activation to alter operant behavior varies over the estrous cycle in some (Lopez-Ferreras et al., 2018), although not all (Lopez-Ferreras et al., 2019) brain nuclei.

Removing ovarian-derived estrogens can influence endogenous GLP-1 production, evidenced by the finding that ovariectomized mice had lower intestinal synthesis of GLP-1, an effect that was reversed by providing estradiol (Handgraaf et al., 2018). This implies that estrogens may impact the GLP-1-mediated outcomes like feeding. In fact, estrogens enhance the hypophagic effects of GLP-1R activation in female rodents (Maske et al., 2017, Asarian et al., 2012). Given this cooperative interaction of GLP-1 and estrogens to suppress feeding, other studies have shown that a GLP-1/estrogen conjugateis more effective than either hormone alone to reduce body weight and improve glycemic control in rodents (Finan et al., 2012, Tiano et al., 2015, Vogel et al., 2016). It has been proposed that targeting GLP-1 along with estrogen signaling could be a novel strategy for improving obesity treatment (Baretic, 2022), and this concept may also be relevant for ameliorating binge eating (Cao et al., 2014).

## 3. GLP-1 and binge eating

To understand whether GLP-1-based pharmacotherapies may provide benefits in treatment of BED, it is critical to understand the neurobiology of BED and of binge eating behavior. Imaging work in humans has provided some insight into neural changes that may underlie binge eating, which include altered signaling and function in brain areas mediating reward processing (Haynos et al., 2021, Vrieze and Leenaerts, 2023, Wang et al., 2011) and those that express GLP-1R (Merchenthaler et al., 1999). To further characterize the mechanistic underpinnings of binge eating, non-human animal models are especially useful. In this section, we consider how binge eating is modeled in rodents and how this has been used to understand the relationship between GLP-1 and binge eating behavior.

### 3.1 Binge-like eating and GLP-1: animal studies

Animal models cannot fully recapitulate the complexity of human eating disorders, particularly psychological aspects of these disorders [e.g., (Berner et al., 2020)]. However, food overconsumption can be modeled, facilitating examination of neurobiological changes that occur in the context of binge eating. To acknowledge this limitation, we refer to this behavior in non-human animals as “binge-like” eating.

Rats and mice are the most common species used for investigating the neurobiology of binge-like eating. The general model used to induce the overconsumption associated with binge eating involves intermittent access to palatable food (i.e., intermittent access model); intake in these animals is compared to that of controls with less restricted palatable food access (Corwin, 2011, Corwin and Wojnicki, 2006, Mukherjee et al., 2020, Mukherjee et al., 2022, Hildebrandt et al., 2023b, Hildebrandt et al., 2023a). This manipulation drives binge-like eating in the experimental group. This is a robust phenomenon that occurs in both sexes (Dimitriou et al., 2000, Wojnicki et al., 2013) and under different schedules of restriction and access (Corwin, 2004). Notably, this general model produces binge-like eating of different types of highly palatable foods including fats (e.g., vegetable shortening) (Dimitriou et al., 2000, Wojnicki et al., 2013), sucrose solutions (Wojnicki et al., 2007), and high-fat/high-sugar combinations (Wong et al., 2009), suggesting that the particular type of food may be less important to driving binge-like feeding than is the aspect of intermittency in food access. This is a noteworthy detail that may enhance translational relevance because foods eaten during a binge episode in humans can vary in macronutrient content but are generally highly palatable (Moraes et al., 2023, Allison and Timmerman, 2007). Variations of the intermittent access model have been used to assess the neurobiological underpinnings of binge-like feeding and to probe how manipulating endogenous feeding-related signals and/or administering exogenous pharmacologic treatments affects overconsumption. This strategy has been fruitful, revealing the role of multiple signaling pathways in binge-like eating including dopamine, GABA, and endogenous opioids (Corwin et al., 2016, Wong et al., 2009, Sun et al., 2021, Hardaway et al., 2016, Bello et al., 2011).

**3.1.1 Pharmacological GLP-1R activation and binge-like eating—**Interest in the GLP-1 system as a potential mediator of binge eating is a relatively new area of investigation, and a handful of studies to date have begun to explore this relationship. Some work has sought to understand the effects of pharmacological manipulation of GLP-1R activity on binge-like feeding, and demonstrated that systemic administration of GLP-1 reduced intake of a sucrose solution in mice given intermittent access to this palatable fluid (Yamaguchi et al., 2017). Given the role of opioid signaling in binge-like eating (Novelle and Dieguez, 2018), a recent study examined how GLP-1R signaling may alter overeating produced by mu opioid receptor activation (Pierce-Messick and Pratt, 2020). Acute administration of the mu opioid receptor agonist DAMGO directly to the nucleus accumbens, a key nucleus within the mesolimbic reward system, produced overeating of a high-fat/high-sugar diet in rats, and this effect was attenuated by co-administration of the GLP-1R agonist Ex4. Moreover, this study also revealed that the GLP-1R antagonist exendin-9 enhanced DAMGO-induced overeating, suggesting the physiological relevance of mesolimbic GLP-1R for influencing binge feeding. In addition, one study using a GLP-1/

estrogen conjugate showed increased efficacy of the conjugate in reducing binge-like eating in ovariectomized mice compared to the suppression of this behavior produced by GLP-1 alone (Cao et al., 2014), highlighting the possible utility of combining GLP-1 with estrogens for enhanced mitigation of binge eating symptoms.

**3.1.2 Influence of binge-like eating on the endogenous GLP-1 system—**Other lines of investigation have probed how binge-like feeding influences the endogenous GLP-1 system, with changes observed on both the ligand and receptor sides of the equation. Studies in this area are limited but have generated some intriguing data implicating the GLP-1 system as a physiological mediator of binge-like feeding. One elegant series of experiments in female rats used intermittent access to a high-sugar diet to evaluate compulsive eating, or habitual, stimulus-driven feeding behavior (Spierling et al., 2020), which can be seen in the context of BED and binge eating (Moore et al., 2017, Davis, 2013). As part of a battery of behavioral and physiological outcomes, circulating GLP-1 was measured and found to be part of a feeding hormone profile associated with higher compulsive-like feeding (Spierling et al., 2020). In accordance with these findings, a study of binge-like feeding in male rats found that animals with limited intermittent access to fat over a ~2 month period had elevated plasma GLP-1 compared to counterparts with daily access to this palatable food (Mukherjee et al., 2020). In schedule-fed rats, a pre-meal increase in circulating GLP-1 has been observed (Vahl et al., 2010). As GLP-1 increases fasting gastric volume (Andrews et al., 2007), it is possible that a food-anticipatory increase in systemic GLP-1 prepares the individual for an upcoming large meal, such as that which might occur during scheduled access to palatable food. However, other studies have detected no differences in systemic GLP-1 in female rats with prior binge-like eating compared to relevant controls (Mukherjee et al., 2022), so the particular conditions eliciting cephalic secretion of GLP-1 are not entirely clear. It is possible that these divergent effects on circulating GLP-1 levels among experiments are related to nuances of the paradigm used to induce binge-like feeding, as these three studies all used different timings of palatable food access to produce overconsumption.

It is also important to consider how binge-like eating impacts the central GLP-1 system, which can act separately from peripheral GLP-1 (Brierley et al., 2021). Two studies have investigated how binge-like eating affects GLP-1 production in the hindbrain by examining mRNA expression of preproglucagon, the precursor to GLP-1, in the nucleus of the solitary tract (NTS). Interestingly, NTS preproglucagon expression was suppressed in male (Mukherjee et al., 2020), but not female (Mukherjee et al., 2022), rats who had previously engaged in binge-like feeding. Again, due to differences in the palatable food access schedules, it is unresolved whether the differential hindbrain PPG suppression produced by binge-like eating in males versus females is a true sex difference or whether this effect is driven by methodological details. Nevertheless, the differential directions of effect that binge-like eating has on circulating versus NTS GLP-1, at least in males, highlights the importance of assessing impacts on the GLP-1 system at multiple levels. Furthermore, the suppression in hindbrain GLP-1 after binge-like eating in males is particularly intriguing because central GLP-1R activation is relevant for the control of food intake, suggesting the possibility that hindbrain GLP-1-mediated signaling required to suppress feeding is

dampened with a history of binge eating. Indeed, NTS GLP-1-producing neurons project directly to mesolimbic nuclei relevant for reward-relevant behaviors (Dossat et al., 2011, Alhadeff et al., 2012). GLP-1R activation in these afferent targets reduces the intake of and motivation for palatable foods (Alhadeff et al., 2012, Mietlicki-Baase et al., 2013, Mietlicki-Baase et al., 2014, Colvin et al., 2020) as well as other types of motivated behaviors like drug taking and seeking (Schmidt et al., 2016, Hernandez et al., 2019b). Altered mesolimbic neurotransmission is observed in rodent models for binge-like eating (Corwin et al., 2016, Valdivia et al., 2015) and in humans with BED (Haynos et al., 2021, Vrieze and Leenaerts, 2023), suggesting that mesolimbic GLP-1 signaling might be dysregulated in binge eating. A reduction in hindbrain GLP-1 expression in the context of binge-like feeding as demonstrated previously (Mukherjee et al., 2020) could reflect a mechanism by which binge-like palatable food intake is disinhibited via reduced GLP-1 output to mesolimbic or other central targets, but this remains to be explored in further studies.

Overall, the importance of investigating the impact of GLP-1 signaling on binge eating in both sexes is clear, but differences in methodologies have hampered direct comparisons in some previous work. It will be especially valuable in the future to more rigorously compare sex differences in GLP-1-related mechanisms in binge-like feeding. It may be particularly enlightening to examine interactions of GLP-1 and estrogens, given interactions between GLP-1 and estrogen signaling in the normal control of feeding discussed above.

## 3.2 Binge eating / BED and GLP-1: human studies

**3.2.1 Binge eating and GLP-1 levels—**A fundamental consideration in individuals with BED or BN is whether binge eating affects GLP-1 levels. However, the extant pre-clinical literature is mixed on the impact of binge eating on circulating GLP-1 levels. In one sample of individuals with obesity, those with BED had higher levels of fasting GLP-1 levels than those without BED (Caldas et al., 2022). In contrast, in another sample, GLP-1 levels in response to a meal were examined in a sample of women with obesity, with and without BED (Geliebter et al., 2008). Those results showed no differences in fasting or meal-related changes in GLP-1 between those with and without BED, potentially clarifying that binge eating might not alter GLP-1 levels beyond its impact on weight status, with similar findings in another study of adults with obesity and BED (Hernandez et al., 2019a). There are no pre-clinical data indicating that levels of GLP-1 are elevated in those with BN-spectrum disorders, and in fact the relationship between GLP-1 and binge eating may be in the opposite direction compared to those with BED. Presseller and colleagues (2021) examined the relationship between GLP-1 levels, global eating disorder pathology, and eating disorder behaviors in a sample of women with bulimic-spectrum eating disorders and found that GLP-1 was not associated with frequency of eating disorder behaviors but was negatively associated with global eating disorder pathology, concluding that GLP-1 may be related to cognitive ED symptoms but not ED behaviors. Another study measured pre- and postprandial GLP-1 levels after a standardized test meal in women with BN, purging disorder (PD), and non-eating disorder controls (Dossat et al., 2015). As expected, GLP-1 levels increased after the test meal consumption for everyone, but women with BN had lower GLP-1 both before and after eating the test meal. This study was innovative in that it helps elucidate a mechanism for the differences in GLP-1 levels (i.e., whether

it is due to bingeing or purging), and the results suggest that the GLP-1 difference is not related to the purging aspect of BN but may be related to binge eating. In another sample of women with BN and healthy controls, women with BN had both lower fasting and post-prandial GLP-1 levels than healthy controls (Naessen et al., 2011). Certainly, the aforementioned studies provide conflicting information on the relationship between GLP-1 levels and binge eating in humans, but differences in study population, eating disorder diagnosis, and protocol limit the ability to make direct comparisons among these reports. Importantly, given that binge eating is part of the diagnostic criteria for BED and BN, more work is needed to understand the differences underlying these pre-clinical findings. Future pre-clinical research is especially needed to systematically investigate differences in GLP-1 levels between those with varying weight statuses and eating disorder diagnoses.

**3.2.1 The utility of GLP-1R agonists to reduce binge eating—**The use of GLP-1R agonists in treatment for binge eating is an emerging area of clinical research (Bartel et al., 2024). GLP-1R agonists have been routinely used for diabetes management due to their ability to lower HBA1c (Andreadis et al., 2018), and have been used more recently for weight loss as part of obesity care (Rubino et al., 2021). In terms of the investigation of how long-acting GLP-1R agonists impact binge eating, liraglutide has been the most well-researched, though there has only been one blinded randomized controlled trial (RCT). In this pilot RCT, liraglutide was tested against a placebo to treat BED in 27 adults with overweight/obesity (Allison et al., 2023). Both treatment groups experienced decreases in objective binge episodes, and while the liraglutide group experienced a greater reduction in binge frequency, the difference between groups did not achieve statistical significance. The liraglutide group did experience greater weight loss, indicating that liraglutide might be beneficial in those with concurrent BED and elevated weight status. However, these findings are limited by the low sample size and as such, more research is needed in fully-powered RCTs of patients with BED, and similar trials are needed to examine impact on binge eating in those with BN.

There have also been several open-label studies examining the impact of liraglutide on binge eating. In an open-label study examining the impact of adding liraglutide to behavioral weight loss treatment both with and without a portion-controlled low-calorie diet, there were global reductions in binge eating with those who were given liraglutide compared to those only receiving behavioral weight loss treatment, but differences between groups were not significant at follow-up. This study showed that liraglutide resulted in greater short-term improvements in global eating disorder psychopathology, but these results were attenuated in the long term (Chao et al., 2019). Another open-label, exploratory pilot study investigated the use of liraglutide in non-diabetic individuals with obesity and subclinical binge eating for 12 weeks (Robert et al., 2015) and found that individuals in both the liraglutide and control groups had decreases in Binge Eating Scale scores. While the size of the sample limited the ability to compare changes between the liraglutide and control groups, more individuals in the liraglutide group moved from binge eating to non-binge eating category based on Binge Eating Scale score cutoffs. Those in the liraglutide group also experienced significant weight loss and improvements in other biomarkers (e.g., total cholesterol, fasting glucose). Another GLP-1-targeting drug that has been studied is dulaglutide. In

another open-label trial, Da Porto and colleagues (2020) conducted an open-label trial to compare the impact of 12 weeks of either dulaglutide, a synthetic analogue of GLP-1, or gliclazide, a traditional anti-diabetic, on binge eating in adults with type 2 diabetes and BED. Those taking dulagutide experienced greater reductions in Binge Eating Scale scores along with greater reductions in body weight, fat mass, and BMI. Findings from an open-label retrospective chart review of adults with elevated Binge Eating Scale scores also provide some initial evidence that GLP-1 agonists might be more effective than existing pharmacotherapies at treating binge eating. In this study, the GLP-1R agonist semaglutide was more effective than two of the most prescribed medications for BED, lisdexamfetamine and topiramate, at reducing binge episodes (as indicated by scores on the Binge Eating Scale) in adults with (Richards et al., 2023). However, a RCT is needed to confirm and replicate these findings.

Taken together, emerging research provides some evidence that GLP-1R agonists might be effective at reducing binge eating in adults with subclinical or clinical BED compared to behavioral weight loss treatment or standard medications used to treat BED. However, several critical research gaps remain. First, most of the work has focused on adults with BED and obesity, and thus much more work is needed among those with clinical or subclinical BN and in populations without obesity. Second, most of the evidence comes from open-label trials and more evidence is needed from double-blinded RCTs. Moreover, given that most trials have relied on self-reported data like Binge Eating Scale scores, it will be important in future research to include more objective methods like utilizing clinical interviews to examine improvements in BN and BED diagnoses. Still, although we still lack clarity on the relationship between binge eating and GLP-1 levels in humans, the fact that numerous studies have found significant differences in GLP-1 in samples of people who binge eat versus controls implies that there might be a subset of individuals for whom GLP-1-based pharmacotherapy would be most effective; more precision medicine approaches are needed to identify who this would be.

## 4. Conclusions

Although psychological treatments for BED and BN exist, there is a need to identify additional interventions to reduce binge eating. The GLP-1 system is a viable target for pharmacotherapies aimed at reducing the occurrence of binge eating. Evidence suggests that central GLP-1 signaling is altered in rodent models with binge-like eating, and GLP-1R activation can suppress overeating and binge-like eating in non-human animals. Further, available data from human studies indicate that GLP-1R agonists may, at least in some cases, decrease binge eating behavior. Major findings of these studies discussed above are summarized in Table 1 (focused on endogenous changes to GLP-1 in the context of binge eating) and Table 2 (highlighting effects of pharmacological manipulations of GLP-1 signaling on binge eating). However, many gaps in our knowledge still remain. Investigations of the neurobiological changes to GLP-1 and its receptors produced by binge eating, as well as the potential therapeutic relevance of GLP-1-based pharmacotherapies to reduce binge eating, are still limited. Additionally, although studies over the past decade have established important sex differences in GLP-1 physiology and the effects of GLP-1R signaling on feeding behaviors, there are still many gaps in our understanding that need to

be addressed and that may be relevant to understanding and treating binge eating. Overall, clarification of the role of GLP-1 signaling in binge eating and the potential utility of targeting GLP-1Rs to reduce motivation and craving for palatable foods and to improve satiety, could be of great utility in thinking about strategies to reduce binge eating and potentially could improve treatment of eating disorders with a component of binge eating like BED and BN.

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**Table 1**

Summary of some key findings from studies on endogenous GLP-1 and binge-like eating in non-human animal models, as well as research examining how binge eating influences GLP-1 in humans.

| Non-Human Animal Studies | | | |
|---|---|---|---|
| **Author** | **Sex/Gender** | **Summary of Method** | **Key Findings** |
| Mukherjee et al., 2020 | Male rats | Rats were given access to vegetable shortening either 3x/week (binge-like eating group) or daily (control). | Rats with a history of binge-like eating showed reduced NTS preproglucagon mRNA expression, but increased plasma GLP-1. |
| Mukherjee et al., 2022 | Female rats | Rats were given access to vegetable shortening either every 4$^{th}$ day (binge-like eating group) or ad lilbitum (fat access control), or chow only. | No differences were found among groups for NTS or ileal preproglucagon mRNA or circulating GLP-1 in a terminal experiment. |
| Spierling et al., 2020 | Female rats | Rats had varying levels of access to a palatable, high-sucrose diet to model compulsive-like eating. | A subset of rats with intermittent access to palatable food were considered to have the highest compulsive-like eating (“Int-High”) and had an endocrine profile including elevated GLP-1 levels. |
| **Human Studies** | | | |
| **Author** | **Sex/Gender** | **Summary of Method** | **Key Findings** |
| Caldas et al., 2022 | Male and Female | In an observational study of adults with obesity, BED status was assessed using a clinical interview. A fasting blood draw was used to assess GLP-1 level. | Individuals with both BED and obesity had higher levels of fasting GLP-1 levels than those with just obesity. |
| Dossat et al., 2015 | Female | Participants were women with bulimia nervosa, purging disorder, and healthy controls. Participants fasted overnight and were given a standardized liquid test meal. Both fasting and postprandial blood were measured. | Women with bulimia nervosa had lower fasting and post-prandial GLP-1 levels compared to those with purging disorder and healthy controls, with no differences between women with purging disorder and healthy controls. |
| Geliebter et al., 2008 | Female | Plasma concentrations of gut peptides were measured in pre-menopausal women with obesity with and without BED. | There were no differences in fasting plasma GLP-1 levels between those with and without BED. |
| Hernandez et al., 2019a | Male and Female | Participants with obesity, with and without binge eating (defined as having either clinical BED or subthreshold BED) underwent two conditions, in counterbalanced order: 1) liquid meal; and 2) water condition. Blood samples were measured after both conditions. | While both time and condition had an influence on GLP-1 levels, there were no differences based on binge eating status. |
| Naessen et al., 2011 | Female | Women with BN and age- and BMI-matched healthy controls fasted overnight and then consumed a standardized meal. Both fasting and post-meal blood were drawn. | Women with BN had lower fasting GLP-1 levels than healthy controls. While GLP-1 levels increased following the meal similarly for both women with BN and healthy controls, the total GLP-1 response (assessed as AUC) was lower for women with BN. |
| Presseller et al., 2021 | Male and Female | Participants were treatment-seeking adults with bulimia nervosa-spectrum eating disorders. Fasting blood samples were used to assess levels GLP-1 and other hormones. The Eating Disorder Examination was used to assess binge episodes and eating disorder pathology. | GLP-1 levels were not associated with number of binge episodes, but were negatively associated with global eating disorder pathology, eating concern, and weight concern. |

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**Table 2**

Summary of some key findings from research on how exogenous GLP-1R agonists affect binge-like eating in non-human animal models and binge eating in humans.

| Non-Human Animal Studies | | | |
|---|---|---|---|
| **Author** | **Sex/Gender** | **Summary of Method** | **Key Findings** |
| Cao et al., 2014 | Female mice | Ovariectomized mice were given intermittent access to high-fat diet to induce binge-like eating. Intake was measured after SC injection of vehicle, GLP-1, or a GLP-1/estrogen conjugate. | In wild-type mice, GLP-1 injection suppressed binge-like eating compared to saline injection. The GLP-1/estrogen conjugate was significantly more effective at reducing binge-like eating than was saline or GLP-1 alone. |
| Pierce-Messick and Pratt, 2020 | Male rats | Binge-like feeding was generated under conditions of limited access to a high-fat, high-sugar diet. Interactions of GLP-1 receptor signaling with μ-opioid receptor activation in the nucleus accumbens core were evaluated for outcomes on binge-like feeding. | Intra-accumbens injection of the GLP-1R agonist exendin-4 alone did not significantly impact binge-like feeding, but a trend for exendin-4 to suppress the increased binge-like feeding produced by direct accumbens injection of the μ-opioid receptor agonist DAMGO was observed.<br>Accumbal GLP-1R blockade with the pharmacological antagonist exendin-9 had no independent effect on binge-like eating, but enhanced DAMGO-induced binge-like feeding. |
| Yamaguchi et al., 2017 | Male mice | Mice were given limited access to sucrose solution to induce hedonic feeding. This model was used to test how IP injection of feeding-relevant hormones, including GLP-1, affected sucrose intake. | GLP-1 injection suppressed hedonic intake of sucrose in a limited access paradigm. |
| **Human Studies** | | | |
| **Author** | **Sex/Gender** | **Summary of Method** | **Key Findings** |
| Allison et al., 2023 | Male and Female | In this pilot RCT, participants with BMI ≥ 27 kg/m$^2$ and BED were given either liraglutide (3.0 mg/day) or placebo for 17 weeks. | While participants in both groups experienced reductions in weekly objective binge episodes, only the liraglutide group had clinically significant weight loss. |
| Chao et al., 2019 | Male and Female | In an open-label study, patients with obesity were randomized to behavioral weight loss (BWL) treatment, BWL + liraglutide, or BWL + liraglutide + low-calorie portion-controlled diet. | The BWL + liraglutide group had greater short-term improvements global eating disorder psychopathology than BWL alone, but results were attenuated in the long-term. The BWL + liraglutide + portion-controlled diet had greater short-term decreases in binge episodes than the BWL group, with no differences between groups in the long-term. |
| Da Porto et. al., 2020 | Male and Female | In this 12-week pilot open-label controlled study, participants with type 2 diabetes and BED were given either dulaglutide (synthetic GLP-1 analog) or gliclazide (traditional anti-diabetic). | Patients who were given dulaglutide had greater 12-week reductions in Binge Eating Scale scores, body weight, fat mass, and BMI. |
| Robert et al., 2015 | Male and Female | In this pilot trial, adults with binge eating (assessed as scores ≥ 18 on the Binge Eating Scale) and obesity were randomized to receive 12 weeks of either a diet + exercise intervention (control) or a diet + exercise + liraglutide. | While participants in both groups experienced reductions in Binge Eating Scale scores, a greater percentage of participants who received liraglutide moved into the non-binge eating category. Only those in the liraglutide group experienced improvements in body weight and BMI. |
| Richards et al., 2023 | Male and Female | An open-label retrospective chart review compared three groups of patients with binge eating (defined as Binge Eating Scale scores ≥ 16): 1) semaglutide only; 2) lisdexamphetamine or topiramate only; and 3) semaglutide and either lisdexamphetamine or topiramate. | Patients who took semaglutide, either by itself or in combination with either lisdexamphetamine or topiramate, had greater reductions in Binge Eating Scale scores than patients taking only lisdexamphetamine or topiramate. |