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Mini-Review

Treatment of Hypothalamic Obesity With GLP-1 Analogs

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Abstract

Introduction: Congenital and acquired damage to hypothalamic nuclei or neuronal circuits controlling satiety and energy expenditure results in hypothalamic obesity (HO). To date, successful weight loss and satiety has only been achieved in a limited number of affected patients across multiple drug trials. Glucagon-like peptide-1 (GLP-1) acts via central pathways that are independent from the hypothalamus to induce satiety. GLP-1 receptor agonists (GLP-1RAs) may provide an alternative approach to treating HO.

Methods: We performed a comprehensive search in Medline, Google Scholar, and clinical trials registries (ClinicalTrials.gov; clinicaltrialsregister.eur). This nonsystematic literature review was conducted to identify scientific papers published from January 2005 to February 2024 using the Pubmed and Embase databases. Key words used were GLP-1, GLP-1RA, hypothalamic obesity, suprasellar tumor, and craniopharyngioma.

Results: Our search identified 7 case studies, 5 case series, and 2 published clinical trials relating to the use of GLP-1RAs in HO. All case studies demonstrated weight loss and improved metabolic function. In contrast, results from case series were variable, with some showing no weight loss and others demonstrating moderate to significant weight loss and improved metabolic parameters. In the ECHO clinical trial, nearly half the subjects randomized to weekly exenatide showed reduced body mass index (BMI). Paradoxically, BMI reduction was greater in patients with more extensive hypothalamic injuries.

Conclusion: GLP-1RAs potentially offer a new approach to treating HO. There is a need to stratify patients who are more likely to respond. Further randomized controlled trials are required to determine their efficacy either in isolation or combined with other therapies.

Key Words: GLP-1, GLP-1 receptor agonist, hypothalamic obesity, suprasellar tumor, and craniopharyngioma

The hypothalamus is critical and central to the regulation of appetite and energy expenditure. It communicates with other central regulatory pathways that control appetite, food seeking and reward behavior, and metabolism. Damage to hypothalamic nuclei and the associated regulatory pathways leads to the development of hypothalamic obesity (HO) and metabolic dysfunction that has been historically resistant to drug intervention. Through our greater understanding of these critical pathways, new drugs are emerging that may activate hypothalamic and extra-hypothalamic receptors to promote weight loss and satiety, restoration of energy regulation, and improvement of cardiometabolic risk factors. Information about the mechanisms of hypothalamic energy regulation and satiety has on the most part come from rodent studies or from studying monogenic variants in humans. However, hypothalamic damage or disrupted hypothalamic development in humans results in hyperphagia and reduced energy expenditure, implying that the hypothalamus is likely to play a similar role in the physiology of human satiety and energy regulation. Nuclei in the mediobasal hypothalamus respond to signals from peripheral energy stores to adjust energy consumption to maintain a normal ratio of lean body to adipose mass. The arcuate nucleus (ARC) is located near the floor of the third ventricle and the median eminence with a fenestrated epithelium that facilitates hypothalamic sensing of peripheral metabolites and hormones [1, 2] including insulin, serotonin, leptin, and nutrients such as glucose and free fatty acids [3-5]. When these peptides attach to their respective receptors in the ARC, they activate anorexigenic proopiomelanocortin (POMC) neurons and stimulate POMC processing resulting in α-melanocyte-stimulating hormone (α-MSH) release [6, 7] leading to satiety, primarily via α-MSH-mediated activation of melanocortin 3 and 4 receptors [8-10]. This can also lead to stimulation of the sympathetic nervous system and downregulation of parasympathetic tone via the vagus nerve through the dorsal motor nucleus of the vagus. This results in increased energy expenditure and a net catabolic effect [11]. Orexigenic neurons also located in the ARC express the gene encoding agouti-related peptide (AgRP) and neuropeptide Y (NPY), which reside near the blood brain barrier-lacking median eminence. Increase in leptin leads to decreased activity of AgRP neurons [12]; conversely, ghrelin potently activates AgRP neurons [13], resulting in an orexigenic effect acting via the GH secretagogue receptor, which is highly expressed in the hypothalamic ARC [14]. Ghrelin decreases hypothalamic α-MSH levels and downregulates melanocortin

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signaling, thereby inhibiting the appetite suppressive effect of α-MSH [15]. NPY-expressing neurons in the ARC also inhibit sympathetic activation of brown adipose tissue through Y1 receptor-mediated signal regulation in the paraventricular nucleus (PVN), thus reducing thermogenesis and energy expenditure [16] by downregulation of sympathetic outflow from the locus coeruleus. Our understanding of the central pathways governing satiety and energy regulation in the hypothalamus and other areas in the brain has opened new avenues for the development of novel drugs to treat HO secondary to congenital or acquired hypothalamic disruption.

Congenital and Acquired Causes of HO

Patients with HO develop significant metabolic sequelae and excess future mortality risk related to cardiometabolic disease [17-19]. Dysfunctional leptin-melanocortin and gut hormone signaling lead to low sympathetic tone, fatigue with excess daytime sleepiness, and low physical activity, all contributing to decreased energy expenditure [20-27]. These mechanisms also variably produce hyperphagia, stemming from disturbed meal termination, decreased satiety, and increased food reward and craving, culminating in increased energy intake [28-31]. Furthermore, a paradoxical increase in parasympathetic tone may increase energy storage related to chronic hyperinsulinemia [32]. Monogenic forms of early-onset obesity can result from the disruption in peptide signaling primarily in the leptin-melanocortin pathway; pathogenic variants in leptin (*LEP*), leptin receptor (*LEPR*), *POMC*, prohormone convertase 1 (*PCSK1*), melanocortin 3 and 4 receptors (*MC3R* and *MC4R*), and *SH2B1* all lead to dysregulated energy homeostasis and hyperphagia secondary to defective hypothalamic signaling [33, 34]. Early-onset obesity seen in some patients with pseudohypoparathyroidism is thought to be due to disruption in hypothalamic leptin-melanocortin pathways, due to reduced Gsα signaling at the melanocortin receptors attenuating the effect of leptin on satiety [35, 36]. HO can also be caused by single gene mutations resulting in disruption of hypothalamic development. *SIM1, BDNF*, and *NTRK2* are necessary for the development of the hypothalamus, and mutations in any of these can lead to hyperphagia and severe obesity [37-42]. A recent study using targeted exome sequencing also found rare gene variants associated with hypothalamic development including *ADCY3, MYT1L, ISL1, LRP2*, and *GRPR* patients with severe early-onset obesity [43]. Structural hypothalamic changes are also seen in syndromes that incorporate hyperphagia and reduced energy expenditure. For example, patients with Prader-Will syndrome (PWS) have a smaller hypothalamic PVN volume and reduction in PVN cell number [34, 44]. Patients with Bardet-Biedl syndrome show increased levels of leptin and leptin resistance, secondary to changes in leptin receptor trafficking secondary to ciliary dysfunction [45, 46]. Mouse studies show alteration in POMC neurons and leptin signaling in the hypothalamus in Bardet-Biedl syndrome, suggesting that hypothalamic dysregulation is in part responsible for reduced energy expenditure and early-onset obesity [47].

Acquired HO arises after an injury to the hypothalamus due to various causes such as brain tumors, surgery, trauma, inflammation, or radiation. Intracranial tumors including craniopharyngiomas, germinomas, gliomas, hamartomas, and pituitary adenomas can lead to hypothalamic injury either directly or as a complication of their treatment. Hypothalamic obesity occurs in up to 50% of patients who have a craniopharyngioma (CP) [48-50], and up to 20% of patients with CP are obese at diagnosis [50, 51]. Higher preoperative BMI, radical tumor resection, larger preoperative tumor size, hypothalamic tumor invasion, adamantinomatous subtype, and familial predisposition to obesity are cited as factors that increase the risk of HO [49, 52, 53]. HO is further compounded by the associated comorbidities that include endocrine dysfunction with multiple pituitary hormone deficiencies, sleep disturbance, visual dysfunction, and neurological sequalae due to the intimate colocation of the hypothalamus with other structures such as the pituitary gland, optic chiasm, and cavernous sinus [54]. Pre- and perioperative glucocorticoids in high doses also potentially increase the risk for excessive weight gain. Even with appropriate hormonal replacement, damage to the hypothalamus disrupts integration of peripheral hormonal signals and central neuropeptides, finally resulting in excessive food intake and weight gain [20]. A number of obesity drug interventions either singularly or in combination have been trialed (or are being trialed) in patients with congenital and acquired HO, with response rates varying in patients.

Despite multiple trials of pharmacological interventions, HO remains relatively refractory to most interventions. A number of agents have been previously trialed including diazoxide [55], metformin in combination with fenofibrate (a peroxisome proliferator-activated receptors alpha activator) [56]; central nervous system stimulants such as dextroamphetamine [57, 58], caffeine, and ephedrine [59]; sibutramine [60, 61]; T3 monotherapy [62, 63]; and oxytocin [64, 65] with either no or a limited number of subjects responding to treatment. Other trials of novel therapeutics are ongoing. Tesomet is an investigational fixed-dose combination therapy of tesofensine (a triple monoamine reuptake inhibitor) and metoprolol (a beta-1 selective blocker). Early studies have demonstrated a significant reduction in body weight, waist circumference, and blood glucose in adults with HO [66]. Synthetic melanocortin receptor agonists have also shown some promise in the treatment of genetic and acquired HO. Setmelanotide, an MC4R agonist, is Food and Drug Administration (FDA) approved for the treatment of monogenic obesity related to POMC deficiency, LEPR, and MC4R deficiency [67-69]. The FDA has now recommended a prospective, randomized, blinded trial of setmelanotide for acquired HO over a 12-month treatment period (https://clinicaltrials.gov/ct2/show/NCT05774756) following early phase 2 trial indications that this drug may be clinically effective in weight reduction [70, 71]. An alternative approach to appetite regulation in patients with established HO is to target areas of the brain that control satiety that may not be directly impacted by hypothalamic damage. To this end, glucagon-like peptide-1 receptor agonists (GLP-1RAs) hold more potential in achieving successful outcomes in HO patients

The Central Action of GLP-1

Glucagon-like peptide-1 (GLP-1) is a 31-amino-acid-long incretin hormone produced and secreted by intestinal enteroendocrine L-cells [72]. Upon nutrient intake, gut GLP-1 is released in a biphasic pattern with an "early phase" release after 10 to 15 minutes followed by a longer "second phase" secretion after 30 to 60 minutes. Fasting plasma concentrations of biologically active GLP-1 range from 0 to 15 pmol/L

and increase 2- to 3-fold upon food consumption [73]. As the majority of L-cells are located in the distal ileum and colon, the early phase release is likely to be explained by intramural autonomous neural signaling, gut peptides, or neurotransmitters [74, 75], although the small population of L-cells located in the proximal jejunum may be sufficient to account for the early phase secretion through direct contact with luminal nutrients [76]. Peripherally, GLP-1 potentiates glucose-dependent insulin release, upregulates insulin gene expression, enhances ß-cell proliferation, inhibits ß-cell apoptosis, and suppresses hepatic glucose output by suppressing glucagon secretion [77]. Centrally, GLP-1 functions as a satiety hormone, promoting reduced food intake and meal termination (see overview Fig. 1). However, once GLP-1 is released into the bloodstream, it is rapidly degraded by the enzyme dipeptidyl-peptidase-4, limiting the amount of L-cell-derived GLP-1 reaching the systemic circulation and thus the brain. This suggests a paracrine rather than an endocrine mode of action of intestinal GLP-1 on the brain [81, 82]. Upon gastric distention, GLP-1 signals are relayed via vagal nerves to the ventromedial nucleus tractus solitarius (NTS) in the brainstem. Two brain nuclei receive gastrointestinal vagal inputs via the NTS: the PVN and the parabrachial nucleus that in turn promote satiety. In mice, evidence points to chemogenetic stimulation of Glp1r+ vagal afferents to induce a transient inhibition of AgRP neuron activity in the arcuate nucleus to directly promote satiety [82]. Additional evidence suggests that GLP-1 may directly act on areas of the brain without the blood brain barrier. In mice, injection of 125I-labeled GLP-1 into the aorta can be located in subfornical organ and the area postrema, which in turn connects with the NTS to promote satiety [83]. However, the concentration of GLP-1 required to directly activate the area postrema exceeds levels normally found in the systemic circulation, questioning whether this is a physiological mechanism. However, it may be a plausible mechanism for GLP-1RA activation if levels of GLP-1RAs far exceed endogenous GLP-1 production [84].

Upon food consumption, GLP-1 is also released centrally [82]. To understand the gastrointestinal control of the centrally mediated effects of GLP-1, the peripheral and central release of GLP-1 should be considered as 2 distinct systems. In addition to the paracrine action of GLP-1 on vagal afferents (see earlier discussion), recent evidence from rodent models suggests that central GLP-1 release may also be controlled by GLP-1 action on the gut. Centrally, GLP-1 acts as a neuropeptide by which neuronally produced GLP-1 is transported to the axon terminals and is stored in synaptic vesicles until its eventual release into the synaptic cleft or, in the case of extrasynaptic release, into the brain parenchyma [85]. Preproglucagon neurons projecting from the NTS carry GLP-1 to other areas of the brain that induce satiety including critical areas of the hypothalamus. Orexigenic and anorexigenic neurons in the hypothalamic ARC possess GLP-1R so that GLP-1 binding promotes satiety through upregulation and downregulation of POMC and NPY/AgRP, respectively [86, 87]. Direct activation of preproglucagon neurons occurs following gastrointestinal distension, but, paradoxically, this was not through peripheral GLP-1 gut activation but via input from oxytocin receptor-expressing vagal neurons. This implies that gut GLP-1 centrally mediated satiety is potentially regulated by a system that is independent of its paracrine mechanism [88]. The rationale for 2 independently functioning systems to control satiety remains unexplained. However, given the presence of GLP-1R in the ARC and the direct contact of the ARC with the circulation, it is plausible that GLP1-RAs could have a direct effect on the hypothalamus, on the proviso that GLP-1RA levels exceed physiological levels of GLP-1. A recent study in mice has demonstrated that liraglutide is shuttled to target cells in the mediobasal hypothalamus by tanycytes containing GLP-1 receptors, to exert its effect on food intake, body weight and fat mass, and fatty acid oxidation [89]. In addition, GLP-1RAs may modulate activity in appetite- and reward-related brain areas, such as the insula, amygdala, orbitofrontal cortex, and putamen [78, 90].

GLP-1RAs

GLP-1RAs are novel and encouraging therapies for HO as their mechanism of action includes targets outside of the damaged hypothalamus. In addition, GLP-1RAs may change the balance of sympathetic/parasympathetic tone [91-93], potentially counteracting the autonomic imbalance seen in HO [28]. In rodents, the GLP-1RA semaglutide modulates food preference, reduces food intake, and causes weight loss without decreasing energy expenditure [94]. Importantly, in humans GLP-1RAs, such as semaglutide in the setting of type 2 diabetes (T2D) treatment, reduce the risk of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke [95]. Moreover, improvement in cardiometabolic factors in HO is fundamental in reducing the risk of early mortality. In 2021, efficacy and safety data in 3 randomized controlled trials (RCTs) using semaglutide 2.4 mg in people with common obesity (STEP Trials) were published. Across these trials, mean placebo-subtracted weight loss averaged 12.3%, and more than half of the patients lost ≥15% of their baseline weight after 56 to 68 weeks of treatment [96-98]. Moreover, the degree of brain activation in response to food cues has also been associated with the relative degree of satiety or nausea in individuals receiving GLP-1RAs [78].

There are multiple GLP-1RAs available. Liraglutide is now FDA approved for the treatment of T2D in patients as young as 10 years [99]. Recently semaglutide was approved for the treatment of obesity in adolescents 12 years and older, with a 17% decrease in BMI with semaglutide compared with placebo after 68 weeks of intervention [100]. High-dose liraglutide (subcutaneous injection of 3 mg once per day) is also approved for weight loss treatment in adults and was shown to be effective in adolescents with obesity [101]. Semaglutide is a similarly derived GLP-1RA agent with the advantage of weekly administration and was more effective than liraglutide in a head-to-head trial (−16.3% vs −7.8% change in body weight) [102]. An oral form of semaglutide is available; however, comparable weight loss effects were only seen at doses 2.8 times the highest approved dose [103]. Due to the less effective gastric absorption rate of oral semaglutide [104], the "high-dose" oral preparation results in similar blood levels compared to the lower subcutaneous doses. Analyzing changes of body composition, several studies documented reduction of body fat mass while preserving lean body mass in response to GLP-1RA treatment for obesity. In a clinical trial conducted by Wilding et al [96] in adults with overweight or obesity, semaglutide 2.4 mg injections once weekly led to significant reductions in both fat mass (−8.36 kg vs −1.37 kg placebo-treated controls) and lean mass (−5.26 kg vs −1.83 kg in the control group). However, the proportion of lean body mass relative to total body mass increased,

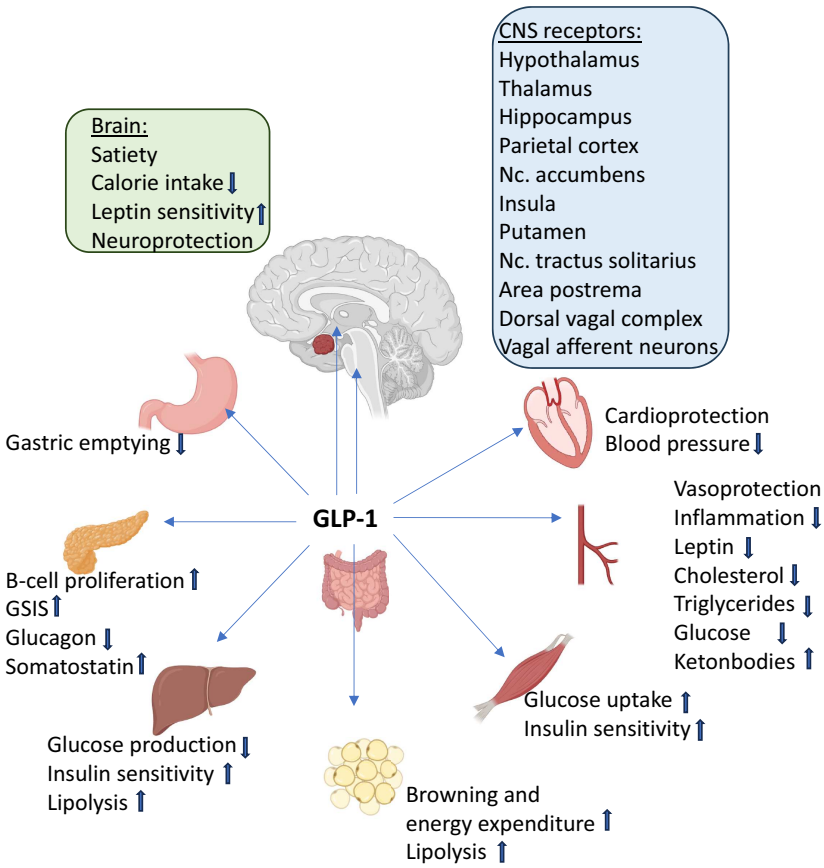

Figure 1. Physiological effects of GLP-1 (based on 72, 77-80). GLP-1 receptors are expressed in different areas of the brain, including areas that are related to the reward system (nucleus accumbens, insula, putamen), and hindbrain. Even if mediobasal hypothalamic structures such as the arcuate nucleus and paraventricular nucleus are damaged by a hypothalamic tumor or its treatment, GLP-1 and GLP-1RAs can interact with peripheral or brain and hindbrain receptors outside of hypothalamic structures. A tumor is shown in the hypothalamic location. (Figure created with BioRender.com.)

Abbreviations: GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonists; GSIS, glucose-stimulated insulin secretion.

indicating a positive change of the body composition. Similar changes in body composition were noted in patients with T2D in response to injected [105, 106] or oral semaglutide [107, 108]. Even if there were reductions in total lean body mass [96, 107, 108], the overall observed reduction in weight was primarily attributed to the loss of fat mass, while the lean body mass percentage was preserved or increased. While these clinical studies documented only moderate and heterogeneous effects of GLP-1RAs on lean body mass, rodent studies have demonstrated a reduction of visceral adipose tissue and upregulation of browning-related genes in subcutaneous white adipose tissue, which can lead to a stimulation of energy expenditure by upregulated thermogenesis [79, 109, 110]. However, studies in humans do not show consistent results of GLP-1RAs on energy expenditure, as some studies do not demonstrate changes [111, 112], while other studies show increased [113-115] or decreased energy expenditure post-GLP-1RA therapy [80, 116]. With regards to GLP-1RA side effects, gastrointestinal adverse effects are frequent, particularly at the start of treatment, and potentially lead to cessation of therapy [117, 118]. Hospitalization for acute pancreatitis has also been reported [119]. GLP-1RAs such as liraglutide can cause dose-dependent and treatment duration-dependent thyroid C-cell tumors in rodent models at much higher dose exposures than those used in humans [120]. Therefore, even if the relevance for humans of such tumors has not been determined, GLP-1RAs are contraindicated in patients with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

Clinical Research on GLP-1RA Treatment in Acquired HO

A nonsystematic literature review was conducted. Our initial search of "Hypothalamic obesity and GLP-1" identified 312 potentially eligible records with "Hypothalamic obesity and GLP-1 and humans" producing 185 results. "Hypothalamic obesity and GLP-1 and intervention and human" revealed 54 results, and "Hypothalamic obesity and GLP-1 and craniopharyngioma" yielded an additional 6 results. Ten studies are recorded in the ClinicalTrials.gov database for the terms of "hypothalamic obesity" and "GLP-1" or "craniopharyngioma," and 7 of them are related to GLP-1RA intervention (NCT06217848, NCT02664441, NCT02718950, NCT02860923, NCT01783717, NCT01061775, NCT01484873). NCT02664441 and NCT01484873 have published results in journals, and NCT06217848 is currently recruiting (drug: Saxenda, location: Seoul). The clinicaltrialsregister.eur revealed 2 additional studies: EudraCT Numbers: 2014-000871-17 (exenatide; location: Lund, Sweden) and 2020-004115-27 (exenatide; location: Barcelona, Spain); the latter 2 are ongoing. Results are summarized in Table 1.

Case Reports

Seven reports of single patients with HO who were treated with a GLP-1RA have been published to date. The first paper from Simmons et al [121] reported the case of a young man who underwent chemoradiotherapy for treatment for a hypothalamic germ cell tumor diagnosed at age 17 years. Postoperative laboratory results were consistent with panhypopituitarism. He developed HO and at 20 years of age also T2D with an hemoglobin A1c (HbA1c) of 9.6%. At the age of 21 years, he was started on exenatide at a dose of 5 µg subcutaneously twice daily, which resulted in a weight reduction of 6.3 kg (−5.7%) and a reduction of HbA1c levels to less than 6% over a 6-month period. After 2.5 years of treatment, his body weight dropped by 29 kg, translating to a BMI reduction from 37.1 to 29.1 kg/m^2. However, significant weight gain occurred shortly after exenatide was discontinued. In the same year, Thondam et al [122] published on a female patient who developed GH deficiency and severe HO following surgery for a hypothalamic tumor (no further diagnosis) at the age of 7 years. At the age of 28 years, she had developed T2D, which was treated with insulin, metformin, and gliclazide. At the age of 42 years, she was started on exenatide and lost 10 kg (−7.3%) during 4 months of treatment. Subsequently, she was able to maintain the reduced body weight while on GLP-1RA treatment (exenatide and later liraglutide) for more than 4 years. Castro-Dufourny et al [123] reported a female patient who developed postoperative panhypopituitarism and HO after surgical intervention and radiation for a CP. She also developed T2D. At the age of 30 years, she was treated with various diabetes drugs. When weekly dulaglutide injections were added, her body weight dropped from 88 to 77.7 kg (−11.7%), with a change of BMI from 34 to 30 kg/m^2 after 2 months of treatment. Similarly, Ashraf et al [124] published on a female patient who had developed panhypopituitarism and HO due to excessive hunger and lack of satiety immediately following resection of a CP at the age of 8 years. She was initially treated with T3 and dextroamphetamine in addition to lifestyle modification with limited efficacy. Treatment with liraglutide was started at age 21 years. Her body weight dropped from 88.9 to 79.8 kg (−10.3%) with a change in BMI from 35.3 to 31.8 kg/m^2 after 6 months of treatment. She subsequently maintained her weight reduction over the following 27 months with continued liraglutide use. Soon after starting the treatment, she started to recognize satiety after meals, and her health improved, both physically and emotionally. No adverse effects of the medication were noted. Bretault et al [125] reported on a patient with craniopharyngioma who developed postoperative panhypopituitarism significant reduction of body weight in response to daily liraglutide 3 mg in a 23-year-old male with HO following CP surgery 14 years before. He underwent bariatric surgery at age 19 years of age. After initial weight loss he regained weight over a 4-year period. When treated with liraglutide 3 mg per day subsequently, he lost 29 kg (16%) after 8 months of therapy with a concomitant improvement in triglycerides. A robust reduction in BMI was also observed in a case report from Sciacovelli et al [126], who described an 18-year-old male who developed panhypopituitarism and HO after surgical intervention of a CP. Two years after surgery, semaglutide 2.4 mg was given weekly, which resulted in a weight loss of more than 30 kg (−25%) and BMI reduction from 46.9 to 35.1 kg/m^2 after 6 months of treatment. The patient also had improvement of insulin resistance, low-density lipoprotein, triglycerides, transaminases, and HbA1c. In the most recent case report, Chartoumpekis et al [127] described a 45-year-old female patient who developed central adrenal insufficiency, HO, and T2D after surgery of an adamantinomatous CP. On commencing semaglutide 0.25 mg, her body weight was 96 kg (BMI = 34 kg/m^2). Semaglutide was increased to 0.5 mg for the second month and to 1 mg afterward. After 12 months on semaglutide, she has lost 10 kg (−10.4%), arriving at a body weight of 86 kg (BMI = 30.5 kg/m^2).

Case Series

Despite primarily positive outcomes in case reports in the use of GLP-1RA in HO, results from case series are variable. In a case series of 9 patients with hypopituitarism and HO due to hypothalamic tumors having undergone surgical interventions (6 CP, 1 hamartoma, 1 germinoma, 1 pilocytic astrocytoma) and injuries published by Zoicas et al [128], treatment with GLP-1RAs induced substantial weight loss in 8 patients (−13.1 ± 5.1 kg) with a mean weight reduction of 10.9% (range −8% to −14%). Eight patients were treated with exenatide 5 µg once or twice a day, and 1 patient was treated with liraglutide 0.6 mg once per day. Under a treatment duration of 24.3 ± 18.9 months (range 6 to 51), metabolic parameters also improved [homeostatic model assessment of insulin resistance −3.2 ± 3.5 (range −9.1 to 0.8); HbA1c values −1.3 ± 1.4% (range −4.5 to 0.0); and triglyceride levels reduced from 430 ± 180 to 324 ± 162 mg/dL, $P < 0.05$] in 8 patients, while 1 subject treated with exenatide (11%) discontinued treatment after 2 weeks of treatment because of intolerable nausea and vomiting. In 2 men with HO, hypopituitarism, and hyperphagia due to traumatic brain injuryand hypothalamic lesions, Ando et al [129] reported improvements of obesity with liraglutide 0.3 to 0.9 mg per day leading to a weight reduction of 3.2% and 13.8% after 6 months and a reduction of HbA1c by 1.5% and 1.6%, respectively. Both male patients reported a reduction in hyperphagia. In a 52-week open-label pilot study, Lomenick et al [130] tested the effects of exenatide twice daily on body weight in 10 adults with HO (6 CP, 4 other hypothalamic tumors). These patients had variable degrees of hypopituitarism and hormonal replacements including central hypothyroidism, hypogonadism, GH deficiency, diabetes insipidus, and adrenal insufficiency. Eight participants completed the study. Among those, change in weight with exenatide therapy was not significant (−1.4 ± 4.3 kg, $P = .40$); however, 6 completers lost weight (−6.2 to −0.2 kg). In this study, calorie intake was recorded by food recall and free buffet meal at baseline and 50 to 52 weeks of intervention. Participants who completed the study reported significantly lower intake on food recall during treatment compared with baseline (7837.8 ± 2796.6 vs 6258.4 ± 1970.7 kJ, $P = .027$), but there was no change in intake during buffet meals. A French study tested the efficacy and safety of once-weekly semaglutide in 6 children with CP and morbid obesity. After a mean duration of semaglutide treatment of 7.3 ± 5.8 months using a mean last dose of 1.1 ± 0.2 mg/week, the mean excess weight loss was −28 ± 28% (0 to −70%) while the BMI z-score decreased by −0.41 [131]. Finally, in a more recent retrospective analysis of cases, van Schaik et al [132] analyzed the effects of weekly exenatide 2 mg in 5 adolescents aged 13 to 18 years with acquired HO following treatment of

Table 1. GLP-1 receptor analogs for treatment of HO

References	Subjects, tumor, drug, and design	Additional information	Outcomes
Case reports			
Simmons et al 2012 [121]	21-year-old male, hypothalamic germ cell tumor, exenatide 5 μg subcutaneously twice daily	Chemoradiotherapy, hypothalamic germ cell tumor diagnosed at age 17 y. Developed HO, panhypopituitarism, and T2D.	After 2.5 years, HbA1c changed from 9.6% to less than 6%, reduction of body weight from 111 to 82 kg (−26%), and reduction of BMI from 37.1 to 29.1 kg/m^2. Weight re-gain after stopping exenatide.
Thondam et al 2012 [122]	28-year-old female, hypothalamic tumor, exenatide, followed by liraglutide (doses not stated in report)	Hypothalamic tumor at the age of 7 years, multiple medications as adult for treatment of T2D.	Reduction of body weight from 148 to 138 kg (−7.3%) and reduction of HbA1c from 7.8% to 6.1% during first 4 months of treatment with exenatide; after that some weight regain and HbA1c increase, reductions of both when exenatide was switched to liraglutide.
Castro-Dufourny et al 2017 [123]	30-year-old woman, CP, dulaglutide 1.5 mg once weekly	Panhypopituitarism, T2D.	Reduction in body weight from 88 to 77.7 kg (−12%), and BMI from 34 to 30 kg/m^2 after 2 months of treatment.
Ashraf et al 2018 [124]	21-year-old woman, CP, liraglutide daily 3 mg daily	Panhypopituitarism. Was also on dextroamphetamine.	Reduction of body weight from 89 to 80 kg (−10%), and BMI from 35.3 to 31.8 kg/m^2 after 6 months of treatment.
Bretault et al 2020 [125]	23-year-old male, CP, liraglutide 3 mg daily	Panhypopituitarism, gastric bypass at 19 y of age but regained all his weight following surgery.	Reduction of body weight from 179 to 150 kg (−16%) after 6 months of treatment.
Sciacovelli et al 2023 [126]	18-year-old male, CP, semaglutide 2 mg weekly	Panhypopituitarism.	Reduction of body weight from 123 to 92 kg (−25%) and BMI from 46.9 to 35.1 kg/m^2 after 6 months of treatment. HOMA-IR dropped from 5.1 to 0.93.
Chartoumpekis et al [127]	45-year-old female, CP, semaglutide 1 mg weekly	Hypopituitarism, T2D.	After 12 months on semaglutide reduction of body weight from 96 to 86 kg (−10.4%), and BMI from 34 to 30.5 kg/m^2.
Case series			
Zoicas et al 2013 [128]	9 hypothalamic tumors (6 CP, 1 hamartoma, 1 germinoma, 1 pilocytic astrocytoma), open label intervention with exenatide 5 μg subcutaneously once or twice daily in 8 cases and 0.6 mg liraglutide in 1 case.	Partial (n = 2) or pan (n = 7) hypopituitarism; 8 subjects with T2D.	Under treatment duration of 24.3 ± 18.9 months (range 6 to 51), weight loss in 8 patients from 120.6 ± 21.7 to 107.5 ± 18.4 kg (−13.1 ± 5.1 kg; mean −10.9%, range 8-14%). Metabolic parameters also improved [HOMA-IR −3.2 ± 3.5 (range −9.1 to 0.8]; HbA1c values −1.3 ± 1.4% (range −4.5 to 0.0); and triglyceride levels reduced from 430 ± 180 to 324 ± 162 mg/dL, $P < .05$) in 8 patients.
Ando et al 2014 [129]	Two males, 38 and 71 years old, with traumatic brain injuries; treatment with liraglutide 0.3 mg daily.	HO and hyperphagia due to traumatic brain injury in 1 and cerebral aneurysm and meningitis in the other	Weight reduction of 3.2% and 13.8% after 6 months and reduction of HbA1c by 1.5% and 1.6%, respectively.
Lomenick et al 2016 [130]	10 adults, 18 to 40 years old, with HO (138.3 ± 41.5 kg; 6 CP, 4 other hypothalamic tumors), 52-week open-label pilot study with exenatide 10 μg twice daily.	Assessment of food intake by 24-hour dietitian-led food recall, activity by accelerometer, and total energy expenditure (method not mentioned) in 7-8 subjects who completed the study.	Weight loss −1.4 ± 4.3 kg (95% CI −2.2 to 4.9, $P = .40$, n = 8) with peak weight loss at week 22 (−3.0 kg ± 5.8, range −13.2-3.8 kg). Two patients who withdrew gained 1.7 and 2.5 kg over the 1-year postenrollment. Significant reduction of calorie intake but no changes in energy expenditure or activity.
Joudren et al, 2021 [131]	Retrospective study included 6 children, (1 girl, 5 boys)—mean age 15 ± 3.1 years; all had CP and severe obesity (BMI Z-score > 3 or rapid increase in BMI despite appropriate hormone replacement and lifestyle intervention)	Subjects received subcutaneous semaglutide once a week, with a starting dose of 0.25 mg/week, monthly increased to 0.5 mg, then 1 mg/week, maintained at 1 mg/week for 6 months and then increased to the maximally tolerated dose (not exceeding 2 mg).	After a mean duration of semaglutide treatment of 7.3 ± 5.8 months using a mean last dose of 1.1 ± 0.2 mg/week, the mean excess weight loss was 28 ± 28% (0-70%) while the BMI z-score decreased by −0.41.

(*continued*)

Table 1. Continued

References	Subjects, tumor, drug, and design	Additional information	Outcomes
van Schaik et al [132]	Retrospective analysis of 5 adolescents 13 to 18 years old, suprasellar tumors (4 CP, 1 suprasellar germinoma), exenatide 2 mg weekly	HO secondary to a suprasellar tumor with hypopituitarism.	No change in BMI SDS 3.39 ± 1.44 at start, BMI SDS 3.39 ± 1.48 at the end of 1-y intervention of 5 subjects. Among those, 1 experienced weight loss after 1 year (−5.4 kg; BMI SDS change from 3.49 to 3.17). Mild side effects, such as pain at injection site or nausea in all subjects. Two of the 5 patients stopped treatment upon their own request after 8 and 11 months, respectively.
Clinical trials			
ECHO trial (NCT02664441), Roth et al 2021 [133] Shoemaker et al 2022 [30] Perez et al 2020 [134]	10- to 25-year-old patients with HO due to treatment of a hypothalamic tumor [42 were randomly assigned to 36-week treatment with weekly exenatide 2 mg (n = 23) or placebo (n = 19)]; 18-week open label extension where all participants received weekly exenatide; 41 patients started treatment (38 with CP, 1 with mixed germ cell tumor, 1 with germinoma, and 1 with ganglioglioma).	Subjects were 5 y (SD 2.0) postdiagnosis. Measures of energy balance included intake studies using a free buffet meal and dietary intake using validated 24 hours dietary recall (ASA24), as well as assessment of physical activity by actimetry and free-living total energy expenditure by gold-standard doubly labeled water method. The degree of hypothalamic damage was assessed using a hypothalamic lesion score [138].	In reponse to weekly exenatide, BMI increased by 1.7% (95% CI −0.1 to 3.5%) compared to 3.5% (95% CI 1.7 to 5.9%) among subjects randomized to placebo, a treatment difference of −1.7% (95% CI −4.1 to 0.6%; $P = .4$). Percent body fat was unchanged after weekly exenatide but increased after placebo ($P = .008$). In the intention-to-treat analysis, the estimated treatment difference for total body fat was −3.1 ± 1.4 kg, 95% CI −5.7 to −0.4 kg, $P = .02$). Exenatide also significantly decreased waist circumference ($P = .004$). After 36 weeks, exenatide significantly decreased energy intake during a free buffet meal compared to placebo, [−1800 kJ (−430 kcal), 95% CI −3 184 to −418 kJ, $P = .02$ compared to placebo]. There were no significant differences in physical activity between groups; weekly exenatide treatment was associated with a decrease in TEE [−695 kJ/day (−166 kcal/day), 95% CI −1 130 to −264 kJ/day, $P < .01$]. The treatment effect was still significant after further adjustment for change in body composition [−372 kJ/day (−89 kcal/day), 95% CI −699 to −42 kJ/day, $P = .04$] or change in leptin [−695 kJ/day (−166 kcal/day), 95% CI −1130 to −264 kJ/day, $P < .01$]. This decrease in TEE occurred despite an increase in lean mass and fat mass (1.7 vs 1.3 kg lean mass, $P = .88$ and 1.5 vs 4.6 kg fat mass, $P = .04$, weekly exenatide vs placebo). Participants assigned to exenatide reported slightly higher rates of adverse events (21/23, 91%) compared with placebo (15/18, 83%) ($P = .64$). The most frequently reported adverse events were mild to moderate gastrointestinal symptoms.

(*continued*)

Table 1. Continued

References	Subjects, tumor, drug, and design	Additional information	Outcomes
CRANIOEXE randomized placebo-controlled trial (NCT02860923). Gatta-Cherifi B et al [135]	Randomized, double-blind superiority trial; 41 adults with craniopharyngioma-related obesity (BMI > 30 kg/m2). After a 4-week run-in period with a lifestyle intervention, participants were randomized (1:1) to receive exenatide 5 µg × 2/day for 4 weeks increased to 10 µg × 2/day for the following 22 weeks or placebo injected subcutaneously twice a day.	The lifestyle intervention (hypocaloric diet and regular physical activity) was maintained during the 26-week follow-up.	At week 26, weight decreased from baseline by a mean of −3.8 (SD 4.3) kg for exenatide and −1.6 (SD 3.8) kg for placebo. Adjusted mean treatment difference was −3.1 kg (95% CI −7.0 to 0.7, $P = .11$) in favor of exenatide. The estimated treatment difference from baseline to week 26 was −2.3 (95% CI −4.5 to −0.2) for reduction of hunger score, −1.2 (95% CI −3.2 to +0.8) for reduction of disinhibition score and −8.1 cm (95% CI −21.1 to 4.9) reduction in waist circumference in favor of exenatide. Adverse events occurred in 19 (95%) participants in the exenatide group vs 14 (70%) in the placebo group. Conclusion: Exenatide was not demonstrated to be superior to placebo when combined with intensive lifestyle interventions.

Abbreviations: BMI, body mass index; CI, confidence interval; CP, craniopharyngioma; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HO, hypothalamic obesity; HOMA-IR, homeostatic model assessment of insulin resistance; SDS, SD score; T2D, type 2 diabetes; TEE, total energy expenditure.

suprasellar tumors (4 CP, 1 suprasellar germinoma). After 1 year of exenatide treatment, BMI SD score and absolute weight had not changed significantly compared to the period without treatment. Only 1 patient experienced weight loss after 1 year (−5.4 kg; BMI SD score change from 3.49 to 3.17). All patients experienced mild side effects, such as pain at the injection site or nausea. Two of the 5 patients stopped treatment upon their own request after 8 and 11 months, respectively.

Clinical Trials

Only 2 clinical trials relating to GLP-1RAs have been published to date, with 1 of these published as a conference abstract. The exenatide ECHO RCT, which started in 2015, was a randomized, multicenter, double-blind, parallel-group, placebo-controlled phase III clinical trial that enrolled 10- to 25-year-old individuals with HO [133] with variable degrees of hypopituitarism who received hormonal replacements accordingly (central hypothyroidism, hypogonadism, GH deficiency, diabetes insipidus, and adrenal insufficiency). A total of 42 participants were randomly assigned to once-weekly GLP-1RA exenatide (n = 23) or placebo (n = 19), and 41 subjects received at least 1 dose of the randomized treatment. Subjects were 5 years (SD 2.0) postdiagnosis and had developed HO (mean BMI 37.3, SD 7.1). Over a 36-week treatment with weekly exenatide 2 mg, BMI increased by 1.7% [95% confidence interval (CI) −0.1 to 3.5%] compared to 3.5% (95% CI 1.7 to 5.9%) among subjects randomized to placebo, a treatment difference of −1.7% (95% CI −4.1 to 0.6%; $P = .4$), which was not statistically significant but in favor of exenatide treatment. Percent body fat was unchanged after weekly exenatide but increased after placebo ($P = .008$). In the intention-to-treat analysis, the estimated treatment difference for total body fat was −3.1 ± 1.4 kg (95% CI −5.7 to −0.4 kg, $P = .02$). Exenatide also significantly decreased waist circumference ($P = .004$).

In this RCT, measures of energy balance were also assessed and included intake studies using a free buffet meal and dietary intake using validated 24-hour dietary recall (ASA24), as well as assessment of physical activity by actimetry and free-living total energy expenditure by the gold-standard doubly labeled water method [30, 136, 137]. After 36 weeks, exenatide significantly decreased energy intake during a free buffet meal compared to placebo [−1800 kJ (−430 kcal), 95% CI −3184 to −418 kJ, $P = .02$ compared to placebo] change from baseline to 36 weeks. While there were no significant differences in physical activity between groups, weekly exenatide treatment was associated with a decrease in total energy expenditure (TEE) assessed by double water methodology [−695 kJ/day (−166 kcal/day), 95% CI −1130 to −264 kJ/day, $P < .01$, adjusted for baseline TEE]. The treatment effect was still significant after further adjustment for change in body composition [−372 kJ/day (−89 kcal/day), 95% CI −699 to −42 kJ/day, $P = .04$] or change in leptin [−695 kJ/day (−166 kcal/day), 95% CI −1130 to −264 kJ/day, $P < .01$]. This decrease in TEE occurred despite an increase in lean mass and fat mass (1.7 vs 1.3 kg lean mass, $P = .88$ and 1.5 vs 4.6 kg fat mass, $P = .04$, weekly exenatide vs placebo). Exenatide treatment was associated with a decrease in TEE, which was not explained by treatment group differences in physical activity. In addition, in this study the degree of hypothalamic damage was assessed using a hypothalamic lesion

score [134, 138]. There was no association between baseline BMI and hypothalamic lesion score values at baseline. However, patients with more extensive hypothalamic damage showed a greater reduction in percent body fat at 36 weeks following exenatide treatment compared to patients with less severe hypothalamic injuries [134]. Specifically, treated subjects with magnetic resonance imaging evidence of bilateral mammillary body (MB) injury and more severe MB damage subscores had a better response to GLP-1RA intervention compared to subjects with intact MBs. While exenatide-treated subjects had a greater reduction in body fat, no association between ΔBMI% and imaging measures of hypothalamic damage was found. Participants assigned to exenatide reported slightly higher rates of adverse events (21/23, 91%) compared with placebo (15/18, 83%) ($P = .64$). The most reported adverse events were mild to moderate gastrointestinal symptoms—abdominal pain (exenatide 39%, placebo 17%), nausea (exenatide 30%, placebo 22%), vomiting (exenatide 17%, placebo 22%) and diarrhea (exenatide 30%, placebo 17%). Cholelithiasis was reported in 1 patient treated with exenatide. Injection site reactions were also relatively common (exenatide 39%, placebo 22%). One patient on exenatide was withdrawn from the study due to a severe and increasing sensitivity reaction including significant hives on her thighs. Additional adverse events reported included constipation, dizziness, and headaches. A more recent randomized placebo-controlled clinical trial named CRANIOEXE (NCT02860923), which commenced in 2017 and completed more than 5 years ago, randomized 41 patients with CP-related obesity on intensive lifestyle intervention to exenatide twice daily (n = 20) or placebo. The adjusted mean treatment difference for weight between the exenatide and placebo arm was −3.1 kg (95% CI −7.0 to 0.7) in favor of exenatide [135]. In another single-arm study, exenatide twice daily was tested in HO starting in 2012 (NCT01783717). The status of this trial is unknown.

Trials of GLP-1RAs in the Treatment of Prader-Willi Syndrome

The effects of GLP-1RAs on weight and glycemic control in PWS have been reviewed in a systematic review conducted by Ng et al [139]. In brief, 10 studies were reviewed on GLP-1RA use in 23 PWS patients aged 13 to 37 years trialing exenatide (n = 14) or liraglutide (n = 9) over a duration of 14 weeks to 4 years. Sixteen of the patients with PWS had T2D. Ten patients experienced improvement in body mass index, ranging from 1.5 to 16.0 kg/m^2. Improvement in HbA1c (0.3-7.5%) was seen in 19 patients. Five studies that measured appetite or satiety showed improvement in satiety levels. There were no reported serious side effects using either GLP-1RA.

Discussion

To date, HO has been a particularly challenging condition to treat. Several pharmacological therapies used to treat nutritional obesity and metabolic dysfunction, or those that have targeted pathways disrupted due to pathogenic variants (eg, setmelanotide in POMC deficiency), have been trialed in patients with HO, with variable success limited to a small number of patients [54]. This is likely to be due to the extent and location of the hypothalamic damage and the neuronal pathways associated with energy regulation and metabolism. Given that GLP-1 regulates satiety, energy expenditure, and metabolism via neuronal pathways that are independent of the hypothalamus, GLP-1RAs may open up new opportunities either in isolation or in combination with other drugs to treat HO. Case studies have demonstrated the potential value of GLP-1RAs including exenatide, liraglutide, dulaglutide, and semaglutide in treating HO, demonstrating relatively rapid and sustained weight loss and improvements in metabolic profile including HbA1c, lipids, liver function, and insulin sensitivity, with the potential to reduce future cardiometabolic risk factors and early mortality [121-127]. However, case studies are not controlled, and potential negative results from nonresponders obviously are often not published, which is a limitation in scientific rigor. In contrast, published case series have shown a variable impact of GLP1-RAs in HO, with some showing significant improvements in metabolic parameters, appetite, and weight and others showing no impact [128-132]. In the ECHO RCT [133], almost half of the subjects treated with weekly exenatide had a favorable treatment response with a reduction of BMI, while the other half did not respond to treatment, thus illustrating the need for an approach to address treatment nonresponse and to stratify patients with respect to predicted treatment response, using more potent GLP-1RAs and considering the use of GLP-1RAs in combination with other pharmacological approaches to treat HO. The significant reduction of body fat gain in drug- vs placebo-treated subjects occurred without reduction of muscle mass. This is remarkable, as the reduction of body fat in response to GLP-1RA treatment is often associated with a reduction of muscle mass as well [140]. Surprisingly, BMI reduction was greater in patients suffering from more extended hypothalamic injuries [134]. Patients with bilateral MB injury or small MB were more likely to also have posterior hypothalamus injury. MB damage and small MB could reflect secondary injury to other remote brain structures responsible for GLP-1RA response. This suggests that GLP-1RA treatment supplements a pathway that is deficient due to hypothalamic damage, while sensitivity to treatment is maintained. One possible explanation for this finding is that destruction of endogenous ligand sites of action in the hypothalamus heightens responsiveness and sensitivity of extra-hypothalamic sites of action to exogenous ligands. It further suggests that disruption of hypothalamic pathways involved in appetite and energy homeostasis may result in alterations in other pathways such as GLP-1-mediated signaling in the brainstem, which remain intact in HO patients. Gastrointestinal side effects during initiation of treatment are commonly reported with GLP-1RAs but are generally well tolerated with only a small proportion discontinuing therapy.

The mechanism by which GLP-1RAs induce reduction of body weight and hunger is believed to relate to multiple mechanisms by which GLP-1 regulates appetite and energy consumption and supports metabolic homeostasis via central neuronal pathways and through neuronal activation in the gastrointestinal tract [94, 141]. Areas including the hypothalamic ARC and the area postrema containing GLP-1RA but lacking a blood brain barrier may respond to direct stimulation from more potent GLP-1RAs. Newer GLP-1RA agents may offer advantages that address this unmet need. Specifically, the GLP-1RA semaglutide may have increased pharmacological activity for weight loss compared to exenatide [142, 143], and semaglutide was recently approved for

the treatment of obesity in adolescents 12 years and older, with a 17% decrease in BMI with semaglutide compared with placebo [100]. Recently, a phase 2 study of the novel oral GLP-1R orforglipron in adults demonstrated weight loss and improvement in cardiometabolic parameters. Although further data are needed, oral GLP-1RAs may present an alternative treatment for HO [144]. Further RCTs are required to test the efficacy and impact of GLP-1RAs in patients with HO. Given the complexity of the neuronal pathways involved in satiety and energy regulation, patients may benefit from trials of combination therapies of GLP-1RAs used in combination with other drugs previously trialed in patients with HO.

Conclusion

HO is a debilitating condition that has been relatively resistant to pharmacological therapies to date, with only small numbers showing a positive treatment response [54]. While the degree of change in BMI in published case reports, case series, and RCTs are inconclusive, GLP-1RAs may offer a new approach to HO treatment as the action of GLP-1 on appetite and energy regulation combines hypothalamic signaling and pathways that are independent of hypothalamic signaling. Even in patients with larger hypothalamic injury or lesions, GLP-1RAs appear to be efficient in reducing BMI, regulating appetite, and improving glycemic control. GLP-1RA treatment results in a reduction of total and visceral adipose tissue, while the effect on lean body mass is consistent with the preservation of lean body mass. The effects of energy expenditure are, however, controversial. Future RCTs are required to test the efficacy of different GLP-1RAs in HO, to determine viable approaches to stratifying patients according to predicted therapy response, and to trial injectable or oral GLP-1RAs in combination with other therapies used in congenital and acquired HO. However, there are limitations of the current published data. The definitions of hyperphagia and HO are not established by using standardized criteria. The outcome parameters were not always comparable (changes in BMI, BMI z-scores, body weight, vs % body fat, etc.). In particular, assessments of changes in caloric intake and dietary composition are challenging and were not included in most of the reported studies. These points should be considered in future research. In summary, the exploration of GLP-1RAs as a therapeutic modality for the treatment of HO offers some hope to patients with this challenging condition. However, future research and definitive clinical trials are essential to refine treatment strategies to improve patient outcomes.

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C.L.R. is on an advisory board for Rhythm Pharma; there is no conflict to disclose. P.D. has nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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