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Targeting GLP-1 receptors to reduce nicotine use disorder: Preclinical and clinical evidence

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Abstract

Nicotine use disorder (NUD) remains a leading cause of preventable death in the U.S. Unfortunately, current FDA-approved pharmacotherapies for smoking cessation have limited efficacy and are associated with high rates of relapse. One major barrier to long-term smoking abstinence is body weight gain during withdrawal. Nicotine withdrawal-induced body weight gain can also lead to development of chronic disease states like obesity and type II diabetes mellitus. Therefore, it is critical to identify novel pharmacotherapies for NUD that decrease relapse and nicotine withdrawal symptoms including body weight gain. Recent studies demonstrate that glucagon-like peptide-1 receptor (GLP-1R) agonists attenuate voluntary nicotine taking and seeking and prevent withdrawal-induced hyperphagia and body weight gain. Emerging evidence also suggests that GLP-1R agonists improve cognitive deficits, as well as depressive- and anxiety-like behaviors, which contribute to smoking relapse during withdrawal. While further studies are necessary to fully characterize the effects of GLP-1R agonists on NUD and understand the mechanisms by which GLP-1R agonists decrease nicotine withdrawal-mediated behaviors, the current literature supports GLP-1R-based approaches to treating NUD.

Keywords

Smoking; Relapse; Self-administration; Withdrawal; Hyperphagia; Semaglutide

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1. Introduction

Nicotine consumption, whether through tobacco smoking or electronic nicotine delivery systems (i.e., e-cigarettes), remains a global health concern [1]. In 2021, approximately 46 million (18.7 %) U.S. adults reported using nicotine products (11.5 % of U.S. adults reported smoking traditional cigarettes, while 4.5 % reported using e-cigarettes) [2]. The rising popularity of e-cigarettes has led to an increase in youth nicotine product use with 2.55 million middle and high school students reporting e-cigarette use in 2022 [3]. Of these students, four in ten reported frequent use, and one in four reported daily use of e-cigarettes. Furthermore, 76 % of middle and high school students who consume e-cigarettes reported using another nicotine product, and adolescents who use e-cigarettes are 3.5 times more likely to initiate traditional cigarette smoking than adolescents who don't use e-cigarettes [4–6]. Smoking cessation at any age significantly increases life expectancy [7]. Approximately 68 % of adult cigarette smokers want to quit smoking, while 65.3 % of adolescent tobacco users seriously consider quitting all tobacco products [8,9]. Despite the well-known negative effects of nicotine and the large proportion of smokers that desire to quit smoking, fewer than one in ten smokers who attempt to quit are successful [8,10]. Moreover, 67.4 % of current e-cigarette users have tried unsuccessfully to quit vaping, in large part due to craving and withdrawal symptoms similar to traditional cigarette smokers [11,12]. Thus, given the health risks of vaping and the increased risk of tobacco smoking in a growing population of e-cigarette users, it is more important than ever to develop more effective treatments for nicotine use disorder (NUD).

Concerns about weight gain are a major barrier to achieving long-term smoking abstinence for both men and women [13–15]. Smoking cessation increases consumption of highly palatable foods, and 80–90 % of smokers who quit gain weight [16–21]. Most smokers who quit gain an average of 5–15 pounds in the first few months of abstinence, while some smokers (~14 %) gain more than 20 pounds [19]. Nicotine withdrawal-induced body weight gain contributes to an increased risk of type II diabetes mellitus (T2DM) and hypertension and can prevent cessation-induced improvements in lung function [19,22–24]. These health hazards are amplified by the high comorbidity of smoking with metabolic and cardiovascular diseases [15,25,26]. Therefore, it is critical to consider nicotine withdrawal-induced body weight gain as a potential health risk during smoking cessation.

FDA-approved treatments for NUD, including nicotine replacement therapy (NRT), varenicline, and bupropion, decrease smoking relapse. However, their long-term efficacy is modest, and these treatments delay, but do not prevent, body weight gain during smoking abstinence [15,19, 27–29]. Therefore, it is crucial to identify novel pharmacotherapies that promote long-term abstinence while minimizing withdrawal-induced hyperphagia and body weight gain [15,19]. Glucagon-like peptide 1 receptor (GLP-1R) agonists are FDA-approved for treating T2DM and obesity [30–32]. Mounting evidence indicates that GLP-1R agonists reduce the rewarding and reinforcing effects of licit and illicit drugs including nicotine [33–37]. Importantly, recent studies showed that GLP-1R agonist monotherapy attenuated nicotine withdrawal-induced hyperphagia and body weight gain in male and female rats [38]. GLP-1R agonists also decreased voluntary nicotine taking and seeking in rodent models [38,39], and may improve other nicotine withdrawal-related phenotypes including

cognitive deficits and mood disorders [40–42]. Together, these results suggest that GLP-1R agonists could be re-purposed for treating NUD, either as a monotherapy or as an adjunct therapy in combination with other NUD treatments. Here, we review the preclinical and clinical evidence supporting GLP-1R agonists as novel NUD pharmacotherapies.

2. GLP-1 and GLP-1Rs

GLP-1 is an incretin hormone and neuropeptide produced peripherally in L cells of the small intestine and centrally in the nucleus tractus solitarius (NTS) of the caudal brainstem [43–45]. GLP-1Rs are G-protein coupled receptors expressed pre- and post-synaptically throughout the brain, including nuclei within the mesolimbic dopamine system [46–48]. GLP-1Rs are predominantly G_s-coupled and activate cells via increased cAMP signaling [49]. However, GLP-1R activation also recruits β-arrestin to increase ERK1/2 signaling [50,51]. Differential activation of these downstream pathways, or biased agonism, likely occurs due to differences in ligand binding to extracellular loops on the GLP-1R [51–53]. The relative contributions of intracellular calcium, cAMP signaling, and ERK1/2 signaling to the cellular and behavioral effects of GLP-1R agonists are not clear [54]. Since GLP-1R agonists like liraglutide, semaglutide, dulaglutide and exenatide activate both cAMP and β-arrestin pathways, future studies should consider the potential of biased agonism when developing and testing novel GLP-1R agonists [55].

3. GLP-1R agonists

Given the role of endogenous GLP-1 in regulating food intake and glucose homeostasis, GLP-1R agonists have been developed to treat T2DM and obesity [30–32,56]. Endogenous GLP-1 has a very short half-life in human plasma of only 1–2 min due to rapid degradation by the enzyme dipeptidyl peptidase IV (DPP-IV) [47]. This pharmacokinetic profile limits the therapeutic potential of GLP-1. Serendipitously, Exendin-4 (trade name Byetta) was isolated from the venom of the lizard *Heloderma suspectum* (Gila monster) and found to function as an agonist of the GLP-1R [57]. Exendin-4 is 53 % homologous to human GLP-1, and resistant to DPP-IV degradation due to a serine-alanine amino acid substitution on the N-terminus [47,58]. As such, Exendin-4 has a half-life of ~2.5 h in humans and, therefore, requires twice daily dosing as a subcutaneous injection. However, it is also available in an extended-release formulation (trade name Bydureon) that is administered once weekly [59]. Subsequently, second-generation GLP-1R agonists with improved pharmacokinetics were developed. For example, the GLP-1R agonist liraglutide (trade names Victoza and Saxenda) was created by modifying the endogenous GLP-1 peptide sequence (97 % homologous) – specifically, inserting an aminoisobutyric acid into amino acid 8 of the N-terminus to increase resistance to DPP-IV degradation [60–62]. Liraglutide also has an added spacer and C-16 fatty monoacid side chain to enhance albumin binding and decrease renal clearance. These modifications impart a half-life of ~13 h which is amenable to once daily subcutaneous injection [58]. Other second-generation GLP-1R agonists incorporate different strategies, like conjugation with the Fc fragment of IgG to create dulaglutide (trade name Trulicity; 90 % homologous to GLP-1). Dulaglutide has a half-life of ~90 h and therefore is dosed once weekly [63–65]. More recently, the third generation GLP-1R agonist semaglutide (trade names Ozempic, Wegovy, and Rybelsus) was developed. Semaglutide

is 94 % homologous to human GLP-1, but with three modifications - 2 amino acid substitutions: one at position 8 (alanine to α-aminoisobutyric acid) and one at position 34 (lysine to arginine), and acylation of the lysine residue in position 26 with a spacer and C-18 fatty diacid chain - that increase its half-life to ~165–184 h making it amenable for once-weekly injection [66–68]. The fatty diacid and spacer modifications impart stronger binding to albumin, while the amino acid substitution at position 8 renders semaglutide more resistant to DPP-IV degradation [68]. Semaglutide is the first GLP-1R agonist available in a daily oral tablet formulation (trade name Rybelsus) [31]. Semaglutide also has greater free drug plasma concentrations and stronger affinity for the GLP-1R than older generation GLP-1R agonists, which may explain its greater magnitude of effect on weight loss (two and three times greater than liraglutide and exenatide, respectively) [69,70]. Given this increased efficacy, GLP-1R agonists have surged in popularity in recent years as treatments for T2DM and obesity. Newer generation drugs function as dual incretin receptor agonists. For example, tirzepatide (recently FDA-approved to treat T2DM, trade name Mounjaro, and chronic weight management, trade name Zepbound) is an analogue of gastric inhibitory polypeptide (GIP) that functions as a dual agonist of GIP receptors and GLP-1Rs. Tirzepatide produces a greater reduction in body weight compared to semaglutide, demonstrating that dual agonist “twincretin” approaches may provide even more efficacious pharmacotherapies for T2DM and obesity in the future [71–73].

There are important differences to consider with respect to the efficacy and therapeutic responses of GLP-1R agonists [74]. GLP-1R agonists can be categorized as short-acting or long-acting based on their half-lives and formulations [63]. These categories have diverging therapeutic effects [63,75]. Short-acting GLP-1R agonists (e.g., exenatide) lower blood glucose levels via glucose-stimulated insulin secretion from pancreatic beta cells, reduced glucagon release, and inhibition of gastric emptying [63,76]. In contrast, long-acting GLP-1R agonists (e.g., dulaglutide, extended-release exenatide, and liraglutide) have stronger efficacy to decrease fasting blood glucose levels through not only stimulation of insulin secretion and reduction of glucagon levels, but also a greater suppression of food intake [63]. Furthermore, meta-analyses of randomized controlled trials demonstrated differences in clinical outcomes based on GLP-1R agonist formulation [77]. Once-weekly GLP-1Rs, like extended-release exenatide and dulaglutide, were more effective in controlling glycaemia, but equally effective in decreasing body weight compared to twice daily exenatide in participants with T2DM [77]. Liraglutide was more effective in both decreasing body weight and controlling glycemia compared to twice daily exenatide. Analyses including the third generation GLP-1R agonist semaglutide supported the finding that long-acting GLP-1R agonists have the greatest effect on weight loss [78]. This study also demonstrated that semaglutide was the most effective GLP-1R agonist to reduce blood glucose levels. GI-related adverse effects (e.g., nausea, diarrhea, vomiting and dyspepsia) are the most common adverse effects associated with GLP-1R agonists [79]. GI adverse effects are often dose-dependent and can be improved by slower titration regimens [79]. Importantly, once-weekly GLP-1R agonists decreased the incidence of minor hypoglycemia compared to twice daily exenatide and did not increase the incidence of adverse effects [77].

Given that the therapeutic effects of GLP-1R agonists are due, at least in part, to activation of neuronal GLP-1Rs [80,81], one must also consider CNS distribution and central

effects when comparing GLP-1R agonists. Interestingly, semaglutide and liraglutide have different brain penetrance, central distribution, and transcriptomic changes after systemic administration, indicating that GLP-1R agonists have distinct interactions with the central nervous system [60,82]. Systemically administered, fluorescently labeled liraglutide and semaglutide both bound to proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) positive neurons in the arcuate nucleus of the hypothalamus [82]. However, semaglutide showed higher fluorescent signal intensity in the lateral septal nucleus, septofimbrial nucleus, medial mammillary nucleus, and more extensive lateral distribution in the arcuate nucleus, while liraglutide showed higher binding in the vascular organ of the lamina terminalis, supraoptic nucleus, subfornical organ and paraventricular nucleus of the hypothalamus [82]. Semaglutide, but not liraglutide, penetrated the posterior region of the arcuate nucleus, a nucleus known to regulate food intake through its projections to the parabrachial nucleus [82,83]. Semaglutide and liraglutide produced unique brain region-specific transcriptomic changes following systemic administration [82]. For example, semaglutide penetrated more effectively into the arcuate nucleus and lateral septal nucleus, and produced greater differential expression of genes in these nuclei including genes regulating metabolic pathways, ribosomes, and oxidative phosphorylation [82]. These differences in brain penetrance and distribution may be important factors underlying the differences in efficacy between GLP-1R agonists. It is important to note that the extent of GLP-1R agonist penetrance across the blood brain barrier and the necessity of central GLP-1R activation for the therapeutic effects of GLP-1R agonists is under some debate, and may depend on the agonist studied or experimental timeframe [81,84]. GLP-1R agonists may use specialized mechanisms to access circum-ventricular organs as well as more distal brain regions through the blood-cerebrospinal fluid barrier [85]. Interestingly, administration of GLP-1R agonists is associated with activation of neurons in the brain that do not express GLP-1Rs [86], further underscoring the complexity of the mechanisms underlying the efficacy of GLP-1R agonists. Understanding the central mechanisms underlying the effects of GLP-1R agonists will inform the development of more targeted and effective treatments tailored for specific patient needs [63].

In Section 4 below, we will discuss preclinical and clinical findings related to GLP-1R agonists and nicotine-mediated behaviors. In Section 5, we will review preclinical and clinical studies related to GLP-1R agonists and nicotine withdrawal phenotypes. Ongoing clinical trials investigating the efficacy of GLP-1R agonists to treat NUD will be discussed in Section 6.

4. GLP-1R agonists and nicotine-mediated behaviors

4.1. GLP-1R agonists and nicotine reinforcement

Recent preclinical studies indicated that GLP-1R agonists decreased the rewarding and reinforcing effects of nicotine in rodents (Table 1). Systemic administration of Exendin-4 (2.4 μg/kg, i.p.) attenuated the expression of nicotine-induced conditioned place preference (CPP) in male mice, suggesting that GLP-1R agonists reduce the rewarding effects of nicotine [87]. Consistent with these effects, systemic administration of Exendin-4 (10 μg/kg, i.p.) or the DPP-IV inhibitor sitagliptin (10 mg/kg, i.p.) attenuated nicotine self-

administration in male mice [39]. A recent study found that systemic administration of liraglutide (25 μg/kg, i.p) attenuated nicotine self-administration in male and female rats [38]. This study was the first to demonstrate a suppressive effect of a GLP-1R agonist on nicotine self-administration in females, which is particularly encouraging given that women often have greater difficulty quitting smoking and show poorer outcomes with NRT [88,89]. Together, these preclinical studies suggest that GLP-1R agonists attenuate the reinforcing efficacy of nicotine.

The neural mechanisms underlying the suppressive effects of GLP-1R agonists on nicotine taking are likely to be complex and involve neural circuits that mediate reward and aversion. Nicotine activated neurons in the interpeduncular nucleus (IPN) and constitutive GLP-1R knockout blocked these effects, suggesting that GLP-1R activation plays a role in the response of IPN neurons to nicotine [39]. The medial habenula (MHb) projects almost exclusively to the IPN, and this circuit regulates the aversive effects of higher doses of nicotine [90–94]. Based on this anatomy, GLP-1R activation in MHb->IPN circuits may increase the aversive effects of nicotine to limit nicotine taking. GLP-1Rs are expressed on MHb afferents in the IPN, and pharmacological activation of these receptors attenuated nicotine self-administration [39]. These results indicate that Exendin-4 activates presynaptic GLP-1Rs on MHb terminals in the IPN to decrease nicotine taking. Consistent with these effects, knockdown of GLP-1Rs in the MHb or pharmacological inhibition of GLP-1Rs in the IPN increased nicotine taking [39]. Interestingly, GLP-1R knockdown in the MHb increased nicotine self-administration only on the descending limb of the dose-response curve [39], further supporting the hypothesis that GLP-1R activation in the MHb augments the aversive effects of higher unit doses of nicotine to decrease drug taking. While it is clear that activation of GLP-1Rs in the IPN decreased nicotine taking [39], future studies are needed to confirm whether activation of GLP-1Rs in the MHb->IPN circuit increases the aversive effects of nicotine, decreases the reinforcing efficacy of nicotine, or both.

GLP-1Rs are expressed throughout the brain, including the mesolimbic dopamine system [48]. Given that GLP-1R agonists decreased nicotine-evoked dopamine release in the NAc, it is possible and likely that GLP-1R agonism attenuates nicotine taking via effects on striatal dopamine signaling [87,95]. This hypothesis is supported by studies showing that activation of GLP-1Rs in the NAc or VTA was sufficient to reduce voluntary cocaine taking [96–98]. Moreover, central GLP-1R activation reduced cocaine-evoked phasic dopamine signaling [99]. These findings suggest that GLP-1R agonists reduce nicotine taking, in part, by attenuating nicotine-evoked activation of the mesoaccumbens pathway. However, this question has not been investigated directly in rodents self-administering nicotine. Future work should determine the functional significance of NAc and VTA GLP-1Rs in nicotine taking to determine the relative contributions of the mesolimbic reward system versus MHb->IPN aversion circuits in the behavioral responses to GLP-1R agonists. Since systemically administered GLP-1R agonists activate neurons throughout the brain [100], it is likely that GLP-1R agonists influence activity of circuits involved in reward and aversion to reduce nicotine taking. Given that the patterns of distribution of GLP-1R agonists differ across the CNS, it is important to consider that individual GLP-1R agonists may differentially engage different neural circuits which may influence their efficacy in reducing nicotine taking and seeking [82].

4.2. GLP-1R agonists and extinction of nicotine-taking behavior

While there is not an extensive literature exploring the effects of GLP-1R agonism on extinction of drug taking, a recent study showed that repeated liraglutide administration during abstinence decreased the number of days required to extinguish nicotine self-administration [38]. In these tests, liraglutide was administered 10 min before each extinction training session [38]. These results are consistent with previous studies which showed that systemic administration of Exendin-4 facilitated extinction of cocaine-induced CPP and decreased subsequent cocaine priming-induced reinstatement of CPP in mice [101]. These findings suggest that the combination of GLP-1R agonist treatment and daily extinction training may facilitate extinction learning-related plasticity [38]. GLP-1Rs are expressed in nuclei known to mediate extinction of drug-taking behavior including the NAc shell and hypothalamic subregions, further supporting a potential role of central GLP-1Rs in extinction learning [48,102]. GLP-1R activation increased glutamate signaling and AMPA receptor trafficking in drug-naïve rats [103–106]. Since enhanced glutamate signaling and upregulation of AMPA receptors facilitated extinction and decreased drug seeking [107, 108], GLP-1R agonists may enhance glutamate-mediated synaptic plasticity and facilitate extinction learning to reduce nicotine seeking during abstinence. To identify the mechanisms underlying the effects of GLP-1R agonists on extinction learning, future studies should investigate whether activation of GLP-1Rs in nuclei like the NAc shell and hypothalamus facilitate extinction of nicotine-taking behavior and decrease nicotine reinstatement. Studies should also investigate whether systemic GLP-1R activation increases glutamate signaling in the NAc shell and hypothalamus of nicotine-experienced rats and, if so, whether this increase is necessary for the effects of liraglutide on extinction rates during nicotine abstinence [38]. These experiments would expand our understanding of the role of central GLP-1Rs in extinction learning and the potential mechanisms underlying the suppressive effects of GLP-1R agonists on nicotine-seeking behaviors.

4.3. GLP-1R agonists and the reinstatement of nicotine-seeking behavior

In addition to reducing voluntary nicotine taking, novel treatments for NUD should also prevent smoking relapse and promote long-term abstinence. Smoking relapse is modeled in laboratory animals using the nicotine self-administration/extinction/reinstatement paradigm. This model has good predictive validity as an *in vivo* medication screen for NUD pharmacotherapies [109–111]. For example, the FDA-approved smoking cessation pharmacotherapy varenicline attenuated both the reinstatement of nicotine-seeking behavior in rats and smoking relapse in humans [111–113]. With regard to GLP-1R agonists, a recent study showed that repeated liraglutide administration during abstinence attenuated drug seeking elicited by a priming injection of nicotine and re-exposure to conditioned light cues (i.e., lights that were previously paired with nicotine infusions during the self-administration phase of the experiment) [38]. These results suggest that GLP-1R agonist monotherapy may be effective in preventing smoking relapse. Given that GLP-1R agonists decreased neural responses to reward-related cues in humans [114,115], it will be important to determine if GLP-1R agonists reduce the incentive salience of nicotine cues, the reinforcing efficacy of nicotine, or both during withdrawal.

Little is known about the neural mechanisms underlying the efficacy of GLP-1R agonists to attenuate the reinstatement of nicotine-seeking behavior. GLP-1R agonists attenuated nicotine-evoked dopamine release in the NAc and phasic dopamine responses to food predictive cues [87,95,116]. Therefore, it is possible that GLP-1R agonists decrease nicotine- and/or cue-induced phasic dopamine signaling to attenuate the reinstatement of nicotine-seeking behavior. This hypothesis is supported by studies demonstrating that pharmacological inhibition of dopamine receptors decreased nicotine- and cue-induced reinstatement [110,117]. Future studies should measure dopamine levels during nicotine reinstatement tests in animals pretreated with a GLP-1R agonist to determine if the efficacy of GLP-1R agonists to reduce nicotine seeking is associated with reduced NAc dopamine signaling. In addition, there is some evidence that nicotine seeking is associated with changes in glutamate transmission in the NAc [110]. Cue-induced nicotine seeking was associated with increased extracellular glutamate, spine head diameter, and AMPA/NMDA ratios in the NAc, suggesting that glutamatergic plasticity may be necessary for cue-induced nicotine seeking [110,118]. Therefore, pharmacotherapies that increase glutamatergic plasticity and transmission in the NAc during withdrawal may attenuate the reinstatement of nicotine seeking [110]. Given that GLP-1R activation increased glutamate signaling and AMPA receptor trafficking in drug-naïve rats [103–106], future studies should investigate whether increased glutamatergic signaling underlies the efficacy of GLP-1R agonists to prevent the reinstatement of nicotine-seeking behavior. Changes in hippocampal long term-potentiation (LTP) may also promote nicotine seeking [110]. Chronic nicotine self-administration induced hippocampal LTP [119], which may facilitate learned associations between nicotine and environmental cues [110]. Nicotine-induced hippocampal LTP was associated with decreased activity of GABAergic interneurons [120] and GLP-1R agonism enhanced GABA release in the hippocampus [121]. Therefore, it is provocative to think that GLP-1R agonism may activate inhibitory hippocampal circuits to prevent LTP and decrease the incentive salience of nicotine-associated cues during withdrawal. Future studies should investigate changes in hippocampal GABA signaling and LTP during nicotine reinstatement tests in rats treated with a GLP-1R agonist. Altogether, these studies would expand our understanding of the potential mechanisms underlying the effects of GLP-1R agonists on reward-related cues.

4.4. Adverse effects of GLP-1R agonists in preclinical models of NUD

The translational potential of GLP-1R agonists for NUD may be limited by their propensity to elicit nausea and vomiting [122]. While these adverse effects can limit patient compliance, they are often transient and mainly occur during treatment initiation and/or after dose increases [74,123,124]. The incidence of adverse effects can be minimized by using an escalation protocol to induce tolerance before introducing higher doses [74]. To screen for these potential adverse effects, preclinical studies measure pica, a model of nausea-like behavior in which rats consume a non-nutritive substance, such as kaolin clay, in response to an emetic agent [125]. The behaviorally relevant dose of liraglutide (25 μg/kg) that reduced nicotine taking and seeking did not produce pica in male and female nicotine-experienced rats [38]. This liraglutide dose is lower than doses shown to suppress locomotor activity and produce malaise-like effects in drug-naïve rats, indicating a behaviorally selective effect on nicotine taking and seeking [38,126, 127]. Consistent with these findings, doses of

Exendin-4 that reduced nicotine taking had no effect on food self-administration [39]. Thus, preclinical studies show that GLP-1R agonists reduced voluntary drug taking and seeking at doses that are well-tolerated in nicotine-experienced rats.

4.5. Limitations of current preclinical studies of GLP-1R agonists in models of NUD

While emerging preclinical studies support re-purposing GLP-1R agonists for treating NUD, there are several limitations to consider when analyzing the current literature. To date, no studies have investigated how GLP-1R agonist pretreatment shifts the nicotine self-administration dose-response curve. These studies are critical towards understanding how GLP-1R agonists alter the reinforcing efficacy of nicotine. Moreover, previous nicotine self-administration and reinstatement studies only examined the efficacy of one dose of a GLP-1R agonist (25 μg/kg liraglutide or 10 μg/kg Ex-4) [38,39]. More comprehensive dose-response curves for each GLP-1R agonist are needed to fully understand the behavioral and physiological effects of GLP-1R agonists in nicotine-experienced rodents. Another significant limitation of the current literature is the lack of a reference compound (i.e., FDA-approved NUD medications including varenicline). Future studies should aim to compare the efficacy of GLP-1R agonists directly to an established NUD treatment to clarify their effect size and potential as a monotherapy. Finally, future studies should also compare the efficacy of GLP-1R agonist monotherapy to a combinatorial treatment (i.e., GLP-1R agonist + varenicline or GLP-1R agonist + NRT) to identify the most efficacious pharmacotherapeutic approach to treating NUD.

4.6. Clinical studies of GLP-1R agonists and NUD

Findings from preclinical studies of GLP-1R agonists and nicotine taking/seeking have recently been translated into clinical trials. One double-blind, randomized, placebo-controlled trial investigated the effects of extended-release exenatide (2 mg weekly, s.c.) on nicotine abstinence, craving, withdrawal, and post-cessation body weight gain [128]. This study measured outcomes after six weeks of treatment in overweight and/or prediabetic participants. In addition to exenatide or placebo, all participants received daily 21 mg NRT patches and brief weekly smoking cessation counseling (10–20 min weekly). The study enrolled 84 participants (41 in the exenatide + NRT group and 41 in the placebo + NRT group). Participants who received exenatide + NRT had increased seven-day point prevalence abstinence (defined as self-report of no smoking in the past seven days and expired CO level ≤5 ppm) compared to participants who received placebo + NRT at week six. Specifically, after six weeks of treatment 46.3 % of participants receiving exenatide + NRT were abstinent compared to 26.8 % of participants treated with placebo + NRT. Participants in the exenatide + NRT group also had decreased craving for cigarettes. During smoking abstinence, exenatide + NRT decreased withdrawal symptoms compared to placebo + NRT. However, there were no effects of exenatide + NRT on withdrawal symptoms in participants that did not reach abstinence. As discussed in more detail in Section 5.2.2 below, exenatide + NRT also reduced post-cessation body weight gain after six weeks of treatment [128]. While these results were an encouraging demonstration of the efficacy of GLP-1R agonists to decrease smoking and cigarette craving in the clinic, a different trial found no differences in smoking abstinence or craving in participants treated with dulaglutide + varenicline versus placebo + varenicline [129]. In this study, 255 daily

smokers (mean body weight = 176.6 lbs) were treated with 0.75 mg dulaglutide (n = 127) or placebo (n = 128) for one week. Participants were then treated with 1.5 mg dulaglutide or placebo for the next 11 weeks (for a total of 12 weeks of dulaglutide treatment). All participants also received behavioral counseling and varenicline pharmacotherapy. After 12 weeks of treatment, there were no effects of dulaglutide + varenicline on abstinence – defined by self-reported seven days smoking abstinence and expired CO level ≤10 ppm – compared to placebo + varenicline. There were also no effects of dulaglutide + varenicline on craving for smoking. However, dulaglutide + varenicline was effective in decreasing post-cessation body weight gain and improving glucose metabolism compared to placebo + varenicline. A questionnaire measuring withdrawal symptoms was not utilized in this study.

There are several potential reasons for the differential effects observed in these two studies. In Lengsfeld et al. [129], seven-day abstinence rates were much higher than anticipated (63 % with dulaglutide + varenicline and 65 % with placebo + varenicline). Increased abstinence rates may have been due to frequent contact with study staff and feedback on carbon monoxide measurements used to measure nicotine exposure [129]. In contrast, Yammine et al. [128] found that 46.3 % of liraglutide + NRT-treated participants were abstinent for at least seven days following six weeks of treatment, compared to 26.8 % of vehicle + NRT-treated participants. These results suggest that high quit rates may have concealed any potential effects of dulaglutide on nicotine abstinence [129]. There are other key differences that should be considered when comparing these studies. Yammine et al. [128] utilized NRT as an adjunct therapy instead of varenicline, and only participants with prediabetes or that were overweight were included. Furthermore, the study population was predominantly older, black, and male. In contrast, Lengsfeld et al. [129] did not specify that participants must have prediabetes or be overweight, and their study group was predominantly younger, female, and white. Differences in GLP-1R agonists should also be considered when comparing these results, as pharmacokinetic and pharmacodynamic profiles differ between GLP-1R agonists (as discussed above) and may therefore affect therapeutic outcomes [63, 75].

4.7. Adverse effects of GLP-1R agonists in clinical studies of NUD

Adverse effects in Yammine et al. [128] were reported in four (9.5 %) participants in the exenatide + NRT group and one (2.3 %) participant in the placebo + NRT group. There was no significant difference in the percentage of adverse effects between treatment groups. In the exenatide + NRT group, adverse effects were injection site nodules that were mild in severity, resolved within two weeks, and did not result in treatment discontinuation. There were no reports of hypoglycemia, nausea, vomiting, dyspepsia, diarrhea, constipation, or tachycardia in either group. In contrast, Lengsfeld et al. [129] found higher rates of adverse effects during GLP-1R agonist treatment. GI distress was the most notable adverse effect (90 % of participants treated with dulaglutide + varenicline and 81 % of participants treated with placebo + varenicline reported GI distress at any time during treatment). Dulaglutide + varenicline-treated participants had more severe GI symptoms that required treatment (e.g., proton-pump inhibitors, antiemetics) more often. Specifically, 28 (22 %) participants in the dulaglutide + varenicline-treated group required treatment versus 14 (11 %) in the placebo + varenicline group. Participants in the dulaglutide + varenicline group were 2.5 times as

likely as the placebo group to experience nausea. However, few participants withdrew due to adverse effects (dulaglutide + varenicline, $n = 10$; placebo + varenicline, $n = 6$). Differences in adverse effects between the studies by Lengsfeld et al. [129] and Yammine et al. [128] could be due to co-treatment with varenicline vs. NRT and/or differences in participant demographics as discussed above. Importantly, a recent meta-analysis of GLP-1R agonist treatment in overweight or obese patients without diabetes found no differences in adverse GI effects between participants treated with semaglutide and placebo [130]. However, exenatide and liraglutide both produced adverse GI effects greater than placebo [130]. These results suggest that newer generation GLP-1R agonists may have more favorable adverse effect profiles. Future research should compare the frequency and severity of adverse effects across studies with different adjunct treatments, patient populations, and GLP-1R agonists to identify treatment protocols that minimize the incidence of adverse effects and maximize patient compliance and treatment efficacy.

5. GLP-1R agonists and nicotine withdrawal symptoms

5.1. Nicotine withdrawal symptoms

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes seven main symptoms of nicotine withdrawal: irritability/anger/frustration, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, and insomnia. For simplicity, these symptoms can be categorized as affective, somatic, or cognitive [131]. Affective symptoms include anxiety, anhedonia, depression, dysphoria, hyperalgesia, and irritability. Somatic symptoms include tremors, bradycardia, gastrointestinal discomfort, and increased appetite. Cognitive symptoms include difficulty concentrating and impaired memory [132]. Concerns about experiencing withdrawal symptoms are associated with decreased intention to quit [133] and increased smoking relapse [134]. Indeed, higher negative affect, craving, and composite withdrawal symptoms increase the likelihood of subsequent smoking relapse [135]. Furthermore, there is a cyclical relationship between withdrawal symptoms and relapse (i.e., relapse to smoking leads to subsequent increases in withdrawal symptoms such as negative affect), [135]. This cycle makes it even more important to address withdrawal symptoms in order to sustain long-term smoking abstinence. Nicotine withdrawal symptoms can be measured in rodent models of NUD after abrupt cessation of nicotine exposure or administration of a nicotinic acetylcholine receptor antagonist to precipitate withdrawal [136,137]. As in humans, withdrawal symptoms are alleviated by nicotine administration (e.g., NRT) or administration of a pharmacotherapy such as varenicline or bupropion [138]. Therefore, rodent models can be used to identify the neural substrates underlying nicotine withdrawal phenotypes and test the efficacy of potential treatments to ameliorate nicotine withdrawal symptoms.

5.2. GLP-1R agonists and nicotine withdrawal-induced hyperphagia and body weight gain

Nicotine consumption directly influences appetite and body weight. Adult smokers weigh less than non-smokers and are less likely to be overweight or obese [139]. Smokers tend to gain weight after quitting, and nicotine withdrawal-induced body weight gain is highly variable [18,139]. Smoking cessation is associated with an average weight gain of seven to 19 pounds within eight years of quitting [140,141]. In contrast, participants who continue

to smoke gain, on average, 4–5 pounds of body weight [140]. As many as 13 % of those who quit smoking gain at least 23 pounds [18]. Body weight gain is greatest in the first two months of abstinence, but body weight can continue to increase for six months or more thereafter [15,142,143]. Concerns about post-cessation body weight gain are a major barrier to achieving long-term smoking abstinence for both men and women [13–15,144]. Furthermore, nicotine withdrawal-induced body weight gain contributes to an increased risk of T2DM and hypertension [15,19,22,24]. Given the prevalence of nicotine withdrawal-induced body weight gain and its role as a major barrier to maintaining long-term smoking abstinence, it is critical to develop pharmacotherapies for NUD that prevent or reduce body weight gain during withdrawal, particularly in patient populations at a higher risk of excessive body weight gain. In this section, we will review preclinical and clinical evidence supporting GLP-1R agonists as potential treatments for nicotine withdrawal-induced body weight gain.

5.2.1. Preclinical studies of GLP-1R agonists and nicotine withdrawal-induced hyperphagia and body weight gain—Nicotine withdrawal is associated with increased consumption of high sugar and high fat food [21,145]. Therefore, novel medications that reduce nicotine withdrawal-induced hyperphagia and body weight gain should reduce consumption of highly palatable food. Two recent pre-clinical studies that support re-purposing GLP-1R agonists as treatments for nicotine withdrawal-induced body weight gain utilized high fat diet (HFD) in their models. In the first study, male mice maintained on HFD were implanted with subcutaneous osmotic minipumps that released nicotine at a rate of 15 mg/kg/day [146]. After 14 days of exposure, the minipumps were surgically removed and replaced with new minipumps containing nicotine, vehicle, or Exendin-4 (2.5 or 5.0 μg/kg/day). Body weight and energy consumption were measured for 14 days after minipump replacement. Nicotine-vehicle (N–V) mice gained significantly more weight than nicotine-nicotine (N–N) mice, with the highest incremental change in body weight during the first three days after minipump replacement. N–V mice continued to consume more food than N–N mice for one week after minipump replacement. In one experiment that utilized a pair-fed design, N–V mice were maintained on a HFD amount equal to that consumed by N–N mice. Pair-fed N–V mice did not demonstrate body weight gain after nicotine cessation, indicating that increased food intake is critical for nicotine withdrawal-induced body weight gain [146]. Chronic exposure to both doses of Exendin-4 during nicotine withdrawal significantly decreased both food intake and body weight gain compared to N–V rats [146]. Together, these preclinical findings suggest that GLP-1R agonists may attenuate nicotine withdrawal-induced hyperphagia and body weight gain in humans with NUD.

One potential limitation of this study is that continuous nicotine exposure via osmotic minipumps does not model the pattern of nicotine intake in human smokers, who voluntarily consume nicotine throughout the day. To more accurately model nicotine consumption patterns in humans, a recent study allowed male and female rats to self-administer nicotine (0.03 mg/kg/inf) during twice daily two-hour operant sessions over the course of 22 days [38]. Each rat that was allowed to respond for contingent infusions of nicotine was paired with a yoked rat that received infusions of saline. While lever pressing for the yoked

saline rats had no scheduled consequences, these rats received the same number and temporal pattern of infusions as self-administered by their paired nicotine-experimental rat. Liraglutide (25 μg/kg, i.p.) or vehicle was administered daily beginning on the last day of self-administration and continued throughout 10 days of subsequent abstinence. All rats had ad libitum access to HFD during the self-administration and abstinence phases. Male and female rats experiencing nicotine withdrawal (nicotine-experimental group) consumed more HFD and gained more body weight than yoked-saline controls. Importantly, both hyperphagia and body weight were significantly reduced in nicotine-experienced rats treated with liraglutide compared to nicotine-experienced rats treated with vehicle. This study was the first to demonstrate that GLP-1R agonist monotherapy is sufficient to decrease hyperphagia and body weight gain during nicotine withdrawal.

Together, the studies by Takeda et al. [146] and Herman et al. [38] provide strong support for re-purposing GLP-1R agonists to reduce or prevent nicotine withdrawal-induced hyperphagia and body weight gain. Notably, both studies utilized HFD instead of normal chow. There is some evidence that nicotine withdrawal-induced hyperphagia may not occur in rodents given access to bland or normal chow [38, 146–150]. Therefore, it is important to consider chow palatability as a potential factor modulating nicotine withdrawal-induced hyperphagia. Nonetheless, by demonstrating that GLP-1R agonists attenuate consumption of highly palatable food during nicotine withdrawal, these studies address an important question of high clinical relevance.

5.2.2. Clinical studies of GLP-1R agonists and nicotine withdrawal-induced hyperphagia and body weight gain—Consistent with the aforementioned preclinical studies, recent clinical trials showed that GLP-1R agonists reduced nicotine withdrawal-induced hyperphagia and body weight gain (Table 2). In one pilot, randomized, controlled trial (described above in Section 4.6), prediabetic and/or overweight smokers received once-weekly placebo ($n = 41$) or extended-release exenatide (2 mg, s.c.) ($n = 41$), along with NRT (21 mg patches) and brief smoking cessation counseling (10–20 min weekly) [128]. After six weeks of treatment, body weight was 5.6 pounds lower for the exenatide + NRT-treated group compared to placebo + NRT-treated controls. Participants treated with exenatide + NRT lost an average of 0.3 % of their baseline body weight over the course of treatment, while participants treated with placebo + NRT gained an average of 1.4 % of their baseline body weight. In a second study (described above in Section 4.6), treatment-seeking smokers were recruited for a randomized, double-blind, placebo-controlled, parallel group trial [129]. All participants were treated with the partial nicotinic receptor agonist varenicline along with subcutaneous injections of either dulaglutide ($n = 127$) (0.75 mg/0.5 ml in week 1, 1.5 mg/0.5 ml in week 2–12) or vehicle ($n = 128$). Participants also underwent behavioral counseling. Dulaglutide + varenicline treatment decreased withdrawal-induced body weight gain compared to placebo + varenicline after 12 weeks of treatment. Specifically, participants treated with dulaglutide + varenicline lost an average of 1.3 % of their baseline body weight, while participants treated with placebo + varenicline gained an average of 2.3 % of their baseline body weight. Additionally, dulaglutide + varenicline treatment decreased median HbA1c levels - an average of blood sugar level over the past 90 days and an indicator of prediabetes or T2DM - compared to placebo + varenicline. HbA1c

decreased from 5.3 to 5.1 for participants treated with dulaglutide + varenicline. In contrast, mean HbA1c remained the same before and after treatment (5.4) in participants treated with placebo + varenicline [151]. New onset prediabetes (HbA1c between 5.7 % and 6.4 %) was more frequent in participants treated with placebo + varenicline than participants treated with dulaglutide + varenicline during smoking abstinence. Therefore, GLP-1R agonists may help to prevent or delay the development of diabetes in abstinent smokers. A 12-month follow-up of this study found that the beneficial effects of dulaglutide + varenicline treatment on body weight and HbA1c compared to varenicline alone gradually subsided after treatment discontinuation [152], emphasizing the importance of continued GLP-1R agonist treatment to maintain positive effects on body weight and blood glucose. These findings are consistent with previous studies demonstrating weight regain after cessation of GLP-1R treatment [153,154].

As discussed above, Yammine et al. [128] found no significant difference in the percentage of adverse effects between treatment groups. Adverse effects in the exenatide + NRT group were mild and transient. Moreover, there was no hypoglycemia, nausea, vomiting, dyspepsia, diarrhea, constipation, or tachycardia in either group. However, Lengsfeld et al. [129] found that participants treated with dulaglutide + varenicline had more severe GI symptoms that required treatment and were 2.5 times more likely to experience nausea than placebo + varenicline-treated participants. Nonetheless, few participants withdrew due to adverse effects (dulaglutide $n = 10$; placebo $n = 6$). Differences in the incidence of adverse effects may be due to co-treatment with varenecline versus NRT and/or differences in the study populations (i.e., younger, mostly female, Caucasian population in Lengsfeld et al. [129] versus older, predominantly African American, prediabetic or overweight male population in Yammine et al. [128]). Overall, these findings support further clinical trials of GLP-1R agonists in treatment-seeking smokers. Interestingly, preclinical studies showed that co-administration of liraglutide and nicotine had greater efficacy to decrease fat mass and body weight compared to either treatment alone (albeit in diet-induced obese mice that are not experiencing nicotine withdrawal), supporting a GLP-1R/NRT combinatorial approach to achieve the greatest effects on body weight [95]. Future clinical trials should identify efficacy and adverse effect profiles for potential GLP-1R agonist co-treatments to maximize patient compliance and reduction of body weight gain during nicotine withdrawal.

5.2.3. GLP-1R agonists and nicotine withdrawal-induced hyperphagia and body weight gain: neural mechanisms—Nicotine withdrawal-induced body weight gain involves both behavioral and metabolic changes [142]. Increased energy intake is a major factor contributing to nicotine withdrawal-induced body weight gain. Subjects who quit smoking increased their mean daily calorie consumption by 227 kcal, which explained 69 % of body weight gain observed at three months [17]. While clinical studies cannot identify the specific changes in feeding architecture that lead to increased caloric intake, pre-clinical studies showed that the effects of nicotine withdrawal on meal patterns were complex and included dynamic changes in meal size, meal number, and inter-meal interval [147,155–157]. Overall, withdrawal-induced hyperphagia could be, in part, due to a reversal of the appetite suppressant effects of nicotine [15]. However, nicotine withdrawal leads to increased motivation for/consumption of highly palatable foods in humans and rodents,

suggesting that alterations in homeostatic feeding do not fully explain withdrawal-induced hyperphagia [15,20,21,145,158,159]. Furthermore, the effects of nicotine cessation on food intake are variable between studies. Hyperphagia did not occur in several studies measuring intake of normal or bland chow in male and female rats during nicotine abstinence [38,147–150]. However, hyperphagia was observed in studies that utilized a high fat diet or food restriction [38,146,160]. While route/dose of nicotine exposure and study design are undoubtedly a factor in the effects of nicotine withdrawal on hyperphagia, these findings suggest that nicotine withdrawal has a complicated reward value-enhancing effect on food that may be unmasked in the presence of high palatability or food scarcity [161,162].

The rewarding effects of nicotine and food are mediated by the mesolimbic dopamine reward system [163], and nicotine withdrawal alters dopamine signaling in the striatum [164,165]. GLP-1R agonists suppressed phasic dopamine responses to food-related cues [116], and pharmacological inhibition of dopamine receptors in the NAc prevented cue-induced reinstatement to sucrose seeking in drug-naïve rats [166]. Therefore, it is possible that GLP-1R agonists reduce central dopamine signaling in response to food-related cues during nicotine withdrawal, which may, in part, underlie its efficacy to reduce withdrawal-induced hyperphagia. Measuring the effects of GLP-1R agonists on VTA dopamine neuron responses to food cues during nicotine withdrawal could verify this potential mechanism. In addition to central dopamine signaling, preclinical studies showed that corticotropin-releasing factor (CRF) and hypothalamic CART regulated the effects of nicotine withdrawal on body weight [167,168]. Since GLP-1R agonists act directly on POMC/CART neurons in the arcuate nucleus of the hypothalamus to reduce food intake [169] and GLP-1-expressing neurons directly target paraventricular nucleus CRF neurons [170], these circuits should also be considered as potential targets by which GLP-1R agonists reduce nicotine withdrawal-induced hyperphagia and body weight gain. Nicotine withdrawal-induced body weight gain is not explained completely by increased caloric intake [171]. While a reduction in food intake is responsible for the majority of weight loss during GLP-1R agonist treatment, GLP-1R agonists also increase metabolism and energy expenditure through central pathways [79]. Therefore, it is likely that GLP-1R agonists also increase metabolism to prevent nicotine withdrawal-induced body weight gain. Given the complexity of the neural circuits underlying the effects of nicotine and nicotine withdrawal on food intake, GLP-1R agonists likely act on multiple systems to attenuate nicotine withdrawal-induced hyperphagia and body weight gain [15,142]. Further studies are also necessary to clarify whether GLP-1R agonists prevent or reverse the neural mechanisms underlying the effects of nicotine withdrawal on food intake and body weight gain or engage separate mechanisms that oppose the effects of nicotine withdrawal on these phenotypes. While the neural mechanisms underlying the efficacy of GLP-1R agonists remain unclear, the preclinical and clinical evidence discussed here support GLP-1R-based approaches to treating nicotine withdrawal-induced hyperphagia and weight gain.

5.3. GLP-1R agonists and nicotine withdrawal-induced cognitive deficits

Nicotine withdrawal is associated with decreased verbal and working memory in abstinent smokers [172,173], and cognitive impairments during abstinence predicted more rapid relapse to nicotine use [174]. Higher-order cognitive function is associated with the ability

to exert “self-control” (i.e., motivate behaviors based on expected rewards and penalties) [175,176]. Therefore, in addition to withdrawal-induced cognitive deficits promoting relapse via negative reinforcement [135], dysregulation of higher-order cognitive systems may directly increase relapse vulnerability by weakening circuits that are necessary for maintaining abstinence [177]. Thus, enhancing cognitive function has emerged as a novel approach to treating NUD [177–179]. Acetylcho-linesterase inhibitors – drugs like galantamine and donepezil that improve cognitive deficits by increasing cholinergic signaling in the brain [180] – improved cognitive performance during nicotine withdrawal in mice [181] and prevented the reinstatement of nicotine-seeking behavior in rats [182,183]. Consistent with these results, galantamine decreased smoking rates in treatment-seeking smokers [184]. FDA-approved NUD medications like varenicline and bupropion also improve cognitive function during nicotine abstinence [174,185,186] and decrease relapse to smoking [187,188]. These studies indicate that pharmacotherapies aimed at enhancing cognitive performance during withdrawal may promote long-term smoking abstinence.

Emerging evidence suggests that GLP-1R agonists improve cognitive function. In preclinical studies, GLP-1R agonists increased learning and memory in drug-naïve animals as well as in animal models of T2DM, neurodegenerative disease, and neuropathic pain [42,189–196]. While clinical studies investigating the impact of GLP-1R agonists on cognitive function showed mixed results, several studies found that GLP-1R agonists improved cognitive performance in participants with prediabetes or T2DM [197–201]. These studies support the efficacy of GLP-1R agonists to maintain and improve cognitive function across several disease states. However, no studies have investigated whether GLP-1R agonist treatment improves cognitive function during withdrawal following nicotine self-administration. Nicotine withdrawal increases markers of inflammation, and treatment with the nonsteroidal anti-inflammatory drug indomethican prevented nicotine withdrawal-induced deficits in novel object recognition in mice [202]. GLP-1R agonists also have neuroprotective/anti-inflammatory effects while improving cognitive performance in models of T2DM and dementia [190,191]. Together, these studies suggest that GLP-1R agonists may improve cognitive deficits during nicotine withdrawal, in part, by decreasing neuroinflammation. Importantly, individuals with T2DM are at higher risk of developing cognitive impairments [203]. Given that cognitive impairments are associated with higher risk of smoking relapse [177], GLP-1R agonists may be particularly effective at preventing withdrawal-induced cognitive impairments and decreasing smoking relapse in this patient population. Future studies should investigate whether GLP-1R agonists decrease neuroinflammation and improve cognitive function during nicotine withdrawal in the presence and absence of metabolic disease.

5.4. GLP-1R agonists and nicotine withdrawal-induced affective symptoms

Withdrawal from nicotine produces negative affective symptoms, including anxiety and depression [204]. Anxiety-like behaviors are assessed in rodents with a battery of behavioral tests including conditioned place aversion, open field test (OFT), elevated plus maze (EPM), and light-dark box, while depressive-like behaviors are assessed with the forced swim test (FST), and tail suspension test (TST), among others [131,205–211]. Nicotine withdrawal

increases anxiety- and depressive-like behaviors in these assays, supporting their validity to screen potential treatments for nicotine withdrawal phenotypes [205, 207,209,212].

While no studies have directly investigated the efficacy of GLP-1R agonists to prevent nicotine withdrawal-induced affective symptoms, GLP-1R agonists decreased anxiety- and depressive-like behaviors in drug-naïve animals. For example, repeated liraglutide administration decreased immobility in the FST, a measure of behavioral despair, in mice with and without chronic unpredictable stress experience [195]. In another study utilizing a model of corticosterone-induced depressive--like behaviors, repeated liraglutide decreased immobility in the TST and FST and increased time spent in the center of an open field [40]. However, liraglutide did not affect anxiety-like behavior in the EPM. These results suggest that GLP-1R agonists may have antidepressant-like effects, but their anxiolytic-like effects are unclear. It is important to note that while repeated liraglutide had no effects in corticosterone-naïve mice, the DPP-IV inhibitor sitagliptin decreased immobility time in both the FST and TST [196]. Therefore, liraglutide may only affect immobility time in animals already experiencing stress or exhibiting depressive-like behaviors. These studies only investigated the effects of liraglutide on depressive- and anxiety-like behaviors in male rodents. A recent study extended these findings to female rats and found that repeated liraglutide prevented ovariectomy-induced despair and anxiety-like behavior as measured by FST, OFT, and EPM [213]. Together, these findings support the efficacy of liraglutide to decrease depressive- and anxiety-like behaviors in both male and female rodents. Repeated dulaglutide treatment improved chronic social defeat stress-induced anxiety- and depressive-like behaviors and improved biomarkers of inflammation, identifying a potential mechanism underlying the effects of GLP-1R agonists on anxiety- and depressive-like behaviors [214]. Interestingly, repeated Exendin-4 attenuated lipopolysaccharide-induced depressive-like behavior but did not affect markers of inflammation [215]. These results suggest that GLP-1R agonists may act via separate mechanisms to alleviate depressive-like symptoms depending on the agonist and/or paradigm studied, which is supported by previous studies demonstrating differences in the neuroprotective effects of GLP-1R agonists [216]. In sum, preclinical studies demonstrated antidepressant-like and anxiolytic-like effects of GLP-1R agonists in drug-naïve animals. Therefore, future studies should investigate whether GLP-1R agonists decrease affective symptoms like anxiety and depression during nicotine withdrawal.

GLP-1R agonists act on neural circuits implicated in the pathophysiology of depression. Depression is associated with neuroinflammation, deficits in neuroplasticity, and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [217–219]. In preclinical studies of anxiety- and depressive-like behaviors, inflammatory biomarkers, hippocampal LTP, adult neurogenesis, and levels of the stress hormone adrenocorticotropic hormone were all normalized by GLP-1R agonist treatment [40,41,214]. Therefore, these central mechanisms may mediate the effects of GLP-1R agonists on nicotine withdrawal symptoms. Future studies should investigate the effects of GLP-1R agonists on neuroplasticity, neuroinflammation, and stress systems during NUD and their relationship to depression- and anxiety-like behaviors.

HPA axis dysregulation is not only associated with the development of depression but also with the affective symptoms of nicotine withdrawal. Smokers have elevated cortisol levels compared to non-smokers [220,221] and nicotine withdrawal leads to a rebound decrease in cortisol/corticosterone levels in both human smokers and animal models [222,223]. Somewhat counterintuitively, lower cortisol levels during nicotine withdrawal were associated with increased craving, self-reported withdrawal symptoms, and subjective stress [222,224]. Furthermore, nicotine withdrawal decreased cortisol/corticosterone levels in response to acute stressors [223,225,226]. These findings indicate that reduced HPA axis function during withdrawal may be related to smoking cessation-induced stress and depression [222,223]. Therefore, treatments that normalize HPA axis function during nicotine withdrawal may help to prevent depressive-like behaviors. Importantly, GLP-1R agonists increased HPA axis function/corticosterone release in healthy and streptozotocin-induced-diabetic rats and increased cortisol release in drug-naïve humans (both T2DM participants and healthy controls), suggesting that GLP-1R agonists could help to ameliorate HPA axis dysregulation during nicotine withdrawal [227,228]. Future studies should investigate whether GLP-1R agonists reverse the effects of nicotine withdrawal on HPA axis function and determine whether changes in HPA axis activity during withdrawal are correlated with self-report scale measurements of nicotine craving, withdrawal, and stress during GLP-1R agonist treatment.

Depression is also associated with dysregulation of the gut-brain axis and energy homeostasis [41,229–231]. Smoking cessation alters gut microbiota composition and diversity [232], and nicotine disrupts mitochondrial function [233]. Therefore, disruption of the gut-brain axis and energy homeostasis may underlie, in part, the affective symptoms of nicotine withdrawal. GLP-1R agonists modulated gut microbiota composition and diversity and improved mitochondrial biogenesis and function [41,234–236]. Therefore, GLP-1R agonists may alter the microbiome and mitochondrial function to prevent depression-like behaviors during nicotine withdrawal. Future studies should measure the effects of GLP-1R agonists on mitochondrial function and the microbiome during nicotine withdrawal to identify whether GLP-1R agonists improve withdrawal-induced deficits in these systems. Given the high comorbidity of both depression and smoking with metabolic diseases like T2DM, it is critical to understand how altered function of the gut-brain axis and dysregulated energy homeostasis contribute to depressive-like symptoms during nicotine withdrawal [15,237,238]. Although further research is needed, the current literature suggests that GLP-1R agonists could be targeted towards this patient population to improve nicotine withdrawal-induced depression.

While there are no published clinical trials investigating the effects of GLP-1R agonists on depression or anxiety, there are several retrospective observational studies that measured these outcomes. One population-based, longitudinal study identified a decreased risk of depression and anxiety in participants with T2DM treated with GLP-1R agonists [239]. Significant effects were observed in female, but not male participants. These effects were also specific to dulaglutide, with no effects observed in subjects treated with liraglutide or exenatide. Risk of anxiety was decreased more than risk of depression. Another recent clinical study found that low doses of GLP-1R agonists and DPP-IV inhibitors were associated with a lower risk of depression in T2DM participants [240]. Furthermore, a

meta-analysis demonstrated that GLP-1R agonists reduced depression severity scores, with a stronger effect in diabetic participants [241]. However, one analysis of participants with T2DM found no effects of GLP-1R agonists or DPP-IV inhibitors on risk of a new diagnosis of depression or episodes of self-harm [242]. Furthermore, a retrospective population-based study found no effects of GLP-1R agonists on depression [243]. Importantly, a recent retrospective study found that GLP-1R agonists decreased suicidal ideation compared to non-GLP-1R agonist anti-obesity or anti-diabetes medications across large cohorts of patients with overweight/obesity or T2DM [244]. These effects were consistent across sex, age, and ethnicity stratification. Overall, while there are promising results demonstrating potential antidepressant and anxiolytic effects of GLP-1R agonists, the lack of controlled studies and mixed results make it impossible to draw firm conclusions about the efficacy of these drugs to decrease mood disorders [245]. Furthermore, no studies have investigated whether GLP-1R agonists decrease depression and anxiety in participants with NUD. Future randomized, blinded, placebo-controlled trials investigating the therapeutic benefit of GLP-1R agonists in participants with NUD should include affective symptoms of withdrawal as primary outcomes to better understand their overall effects on anxiety and depression in abstinent smokers.

5.5. GLP-1R agonists and cardiovascular disease

Smoking is a major risk factor for atherosclerotic cardiovascular disease [246]. While quitting smoking decreases the incidence of cardiovascular disease [247], decreasing tobacco consumption can actually increase cardiovascular disease risk factors like blood pressure, high-density lipoprotein cholesterol, body weight, and waist-to-hip ratio [248]. Furthermore, heavy smokers (≥ 20 pack-years) continue to have an elevated risk of cardiovascular disease 10–15 years after smoking cessation [249]. Unfortunately, nicotine withdrawal-induced body weight gain can prevent the beneficial effects of quitting on markers of cardiovascular health [250] and elevate the short-term risk of T2DM [251]. This is particularly concerning given the elevated risk of cardiovascular disease in individuals with T2DM [252]. GLP-1R agonists including liraglutide and semaglutide had positive effects on cardiovascular outcomes in participants with T2DM [60]. Specifically, participants with T2DM treated with liraglutide had a 13 % reduction in major adverse cardiovascular events compared to placebo [253]. This reduction was likely due to decreased atherosclerosis, as changes in HbA1c, body weight, and blood pressure were not significant enough to mediate the effect [60,253]. Another clinical study found a 26 % reduction in major adverse cardiovascular events in participants with T2DM treated with semaglutide compared to placebo [254]. Semaglutide also improved cardiometabolic risk factors including waist circumference, systolic/diastolic blood pressure, fasting plasma glucose, and lipids in individuals with overweight/obesity without T2DM [255]. While the mechanism(s) underlying these effects is unclear, GLP-1R agonists may reduce atherosclerosis via decreasing inflammation [256]. Together, these findings demonstrate improved cardiovascular outcomes after GLP-1R agonist treatment and suggest that GLP-1R agonists may exert cardioprotective effects during nicotine withdrawal. However, it is important to note that these studies were all conducted with participants that were overweight/obese or had T2DM, so the cardioprotective efficacy of GLP-1R agonists may differ in participants without metabolic diseases. Nonetheless, these results demonstrate

reduced cardiovascular risk in a highly clinically relevant population. Future studies should investigate the effects of GLP-1R agonists on cardiovascular risk for participants with and without metabolic disease. These results could identify a novel benefit of GLP-1R agonist treatment that may be critical for individuals at risk of negative cardiovascular outcomes during nicotine withdrawal.

6. Ongoing clinical trials and areas for future study

Overall, pilot clinical studies validate preclinical reports and suggest that GLP-1R agonists attenuate nicotine withdrawal-induced body weight gain [128,129]. While the evidence is not as strong, these studies also suggest that GLP-1R agonists may reduce nicotine craving and smoking relapse. However, studies published to date are limited in number and have relatively small sample sizes that limit the conclusions that can be drawn from their results. More robust findings from larger studies are necessary to fully understand the clinical potential of GLP-1R agonists to treat NUD. There are recently completed and ongoing clinical trials that will improve our current understanding of GLP-1R agonists as potential NUD pharmacotherapies (Table 2). One recently completed double-blind, parallel arm study measured the effects of 32 weeks of liraglutide treatment (escalating doses of 0.6–3.0 mg, s.c.) on smoking abstinence, calorie consumption, and body weight change in overweight and obese smokers (ClinicalTrials.gov ID NCT03712098). Participants also underwent eight sessions of smoking cessation behavioral counseling. By measuring calorie consumption during liraglutide treatment and nicotine withdrawal, this study will determine if reduced caloric intake is the primary mechanism by which GLP-1R agonists reduce body weight gain during withdrawal. Another study is currently recruiting participants to investigate the effects of nine weeks of escalating weekly doses of semaglutide (0.25–1.0 mg, s.c.) on smoking behaviors (ClinicalTrials.gov ID NCT05530577). Specifically, this study will investigate changes in resistance to smoking relapse after overnight abstinence and tobacco smoking after eight weeks of treatment. Changes in cigarette craving during exposure to smoking-related conditioned cues and subjective responses to cigarette smoking will also be measured. Finally, this study will assess changes in daily cigarettes smoked, body weight, and HbA1c levels from baseline to the study endpoint at week 10. No clinical trial has measured the efficacy of GLP-1R agonist monotherapy alone to treat NUD. Therefore, this study will provide our first insights into the efficacy of GLP-1R agonist monotherapy for NUD. Yammine et al. are also following up on their pilot trial in a randomized, double-blind, placebo-controlled study that is currently recruiting study participants (2021). This study will determine the effects of 14 weeks of exenatide (2 mg) on nicotine withdrawal-induced body weight gain in overweight and/or prediabetic participants (ClinicalTrials.gov ID NCT05610800). Participants will also receive smoking cessation counseling and de-escalating doses of NRT during the active treatment phase. Abstinence rates and body weight change will be assessed at 14 weeks and 26 weeks after treatment initiation. Neural responses to visual stimuli will also be measured to identify the effects of GLP-1R agonism on neural correlates of craving [257]. Overall, this study will provide more information about the neural mechanisms underlying the effects of GLP-1R agonists on smoking relapse. It will also determine the efficacy of GLP-1R agonists to reduce withdrawal-induced body weight gain and increase abstinence in a larger sample population.

More recently, Yammine et al. registered a study (not yet recruiting) investigating the effects of semaglutide (0.24–2.4 mg, s.c.) on post-smoking cessation weight management (ClinicalTrials.gov ID NCT06173778). In addition to semaglutide, participants will also receive smoking cessation counseling and de-escalating doses of NRT. This study will expand our understanding of the efficacy of newer generations of GLP-1R agonists for preventing nicotine withdrawal-induced weight gain.

Given that overweight and obese smokers are at greater risk for body weight gain during nicotine withdrawal [19], it is encouraging that exenatide decreased withdrawal-induced body weight gain in smokers with prediabetes and/or overweight [128,258]. However, future studies should also investigate the effects of GLP-1R agonists on hyperphagia and body weight gain in other subgroups including smokers with T2DM. This population is particularly important to study given their higher risk for worsening glycemic control during smoking cessation and that traditional pharmacotherapies for smoking cessation may be less effective for them [258–261]. Preclinical studies supporting GLP-1R agonist treatment of nicotine withdrawal-induced hyperphagia and body weight gain utilized a high fat diet [38,146]. The current clinical literature does not measure or manipulate food type in their analyses of GLP-1R efficacy. Therefore, future studies should also investigate whether GLP-1R agonists retain their efficacy to reduce nicotine withdrawal-induced hyperphagia and body weight gain when participants consume a healthy diet versus a western diet high in fats and sugars. It is also important to continue to investigate the effects of newer generation GLP-1R agonists like semaglutide on NUD and associated withdrawal symptoms, given that GLP-1R agonists have differences in pharmacodynamics, pharmacokinetics, and brain penetrance [63,75,82]. Future studies should also compare the efficacy of GLP-1R agonist monotherapy alone to combinatorial treatments with FDA-approved pharmacotherapies including NRT and varenicline. While one study found a general effect of GLP-1R agonist treatment on nicotine withdrawal symptoms as measured by the Wisconsin Scale of Withdrawal Symptoms, a 28 item questionnaire evaluating anger, anxiety, concentration, craving, hunger, sadness, and sleep, future studies should measure the effects of GLP-1R agonists on specific symptoms of withdrawal (e.g., separate measurements of somatic, cognitive, and affective symptoms) [128]. These measurements would allow precision treatment with GLP-1R agonists alone or in combination with other therapies to target the most relevant symptoms for each patient. Interestingly, there are several anecdotal reports of individuals who were taking semaglutide for weight loss that unexpectedly quit smoking due to cigarettes suddenly tasting “repulsive” or “disgusting” [262,263]. Given that GLP-1 is synthesized in taste buds, GLP-1Rs are expressed on taste bud afferent nerve fibers, and GLP-1 signaling affects taste perception [264–266], it is possible that, in addition to their central effects, GLP-1R agonists may act directly at taste buds to alter smoking behavior. Indeed, constitutive GLP-1R knockout decreased taste responses to sweeteners and may increase sour taste sensitivity, effects that could alter the flavor profile of tobacco smoke and reduce smoking behaviors [266]. Future studies should investigate changes in taste sensitivity during GLP-1R agonist treatment and the relationship between taste sensitivity and nicotine abstinence to further understand this potential mechanism.

7. Concluding remarks

A small but growing preclinical literature indicates that GLP-1R agonists attenuate voluntary nicotine taking- and seeking-behaviors as well as nicotine withdrawal-induced hyperphagia and body weight gain in rodents. Consistent with these findings, clinical studies indicate that GLP-1R agonists reduce nicotine withdrawal-induced hyperphagia and body weight gain, two major obstacles to quitting smoking and achieving long-term abstinence in male and female smokers. Despite these promising results, the effects of GLP-1R agonists on nicotine craving and abstinence in human smokers have been mixed. While emerging studies in drug-naïve animals suggests that GLP-1R agonists may improve cognitive deficits, depression, and/or anxiety, there are no studies directly measuring these effects in nicotine-exposed laboratory animals or human smokers. The neural mechanisms underlying the effects of GLP-1R agonists on nicotine-mediated behaviors are not clear, and likely involve neural circuits mediating reward and aversion. To determine the exact mechanisms underlying the efficacy of GLP-1R agonists, future studies should investigate the effects of GLP-1R agonists on nicotine-induced changes in neurotransmitter signaling and synaptic plasticity in nuclei regulating nicotine taking and seeking including the VTA, NAc, MHb, IPN, hypothalamus, and hippocampus. Future studies should also investigate the effects of GLP-1R agonist treatment on neuroinflammation and HPA axis function and their relationship to cognitive and affective symptoms during nicotine withdrawal. These experiments would clarify potential mechanisms underlying the efficacy of GLP-1R agonists to improve cognitive deficits and produce anxiolytic- and/or antidepressant-like responses during nicotine withdrawal. Finally, clinical studies establishing which GLP-1R agonists and treatment protocols (e.g., monotherapy versus combinatorial treatments) are most effective in promoting long-term smoking abstinence while minimizing adverse effects will enhance their potential as NUD pharmacotherapies. Understanding the specific patient populations and nicotine withdrawal symptoms that GLP-1R agonists most effectively treat may also facilitate their use as customized, efficacious treatments for NUD.

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Data availability

No data was used for the research described in the article.

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Table 1

Effects of GLP-1R agonists on nicotine-mediated behaviors and neurochemical responses.

Study	Sex/strain/species	Model	GLP-1R agonist pretreatment	Route of admin	Results
Egecioglu et al. [87]	Male NMRI mice	Nicotine-induced locomotor activation	Acute Exendin-4 (0 or 2.4 μg/kg)	i.p.	Attenuated nicotine-induced locomotor activation
	"	Nicotine-evoked dopamine release	Acute Exendin-4 (0 or 2.4 μg/kg)	i.p.	Attenuated nicotine-evoked dopamine release in the NAc
	"	Expression of nicotine CPP	Acute Exendin-4 (0 or 2.4 μg/kg)	i.p.	Blocked expression of CPP
	"	Expression of nicotine-induced locomotor sensitization	Acute Exendin-4 (0 or 2.4 μg/kg)	i.p.	Attenuated expression of locomotor sensitization
Tuesta et al. [39]	Male C57BL6/J mice	Nicotine IVSA (0.1 mg/kg/infusion)	Acute Exendin-4 (0 or 10 μg/kg) & sitagliptin (0 or 10 mg/kg)	i.p.	Attenuated nicotine self-administration
	Male Wistar rats	Nicotine IVSA (0.03 mg/kg infusion)	Acute Exendin-4 (0 or 0.1 μg/0.5 μl/hemisphere)	intra-IPN	Attenuated nicotine self-administration
	"	Change in ICSS threshold after nicotine IVSA	Acute Exendin-4 (0 or 0.1 μg/0.5 μl/hemisphere)	intra-IPN	Prevented nicotine-induced changes in ICSS thresholds
Herman et al. [38]	Male and female Sprague Dawley rats	Nicotine IVSA (0.03 mg/kg/infusion)	Acute liraglutide (0 or 25 μg/kg)	i.p.	Attenuated nicotine self-administration
	"	Extinction of nicotine taking	Repeated liraglutide (0 or 25 μg/kg)	i.p.	Decreased days to extinguish
	"	Drug + cue-induced reinstatement of nicotine seeking	Repeated liraglutide (0 or 25 μg/kg)	i.p.	Attenuated nicotine seeking during withdrawal
Falk et al. [95]	Male NMRI mice	Nicotine-evoked dopamine release	Acute Liraglutide (0 or 10 nmol/kg)	s.c.	Attenuated nicotine-evoked dopamine release in the NAc

i.p. = intraperitoneal; CPP = conditioned place preference; IVSA = intravenous self-administration; ICSS = intra-cranial self-stimulation; IPN = interpeduncular nucleus; s.c. = subcutaneous; NAc = nucleus accumbens.

Table 2

Clinical studies of GLP-1R agonists and nicotine use disorder.

Publication/ ClinicalTrials.gov ID	Clinical population	Outcome measures	GLP-1R agonist	Study length	Results/Study status
Lengsfeld et al. [129]	255 smokers 18–75 y/o with at least moderate nicotine dependence (*n* = 128 placebo + varenicline, *n* = 127 dulaglutide + varenicline)	Smoking abstinence Craving for smoking Body weight change HbA1c levels	Dulaglutide (1.5 mg weekly) or placebo in addition to smoking cessation counseling and oral varenicline (2 mg/daily)	12 weeks	No effect on abstinence or craving Reduced post-cessation body weight gain Decreased HbA1c levels
Yammine et al. [128]	84 treatment-seeking smokers 18–75 y/o with prediabetes and/or overweight (*n* = 41 placebo + NRT, *n* = 41 exenatide + NRT)	Smoking abstinence Craving for smoking Self-reported withdrawal Body weight change	Extended-release exenatide (2 mg weekly) or placebo in addition to smoking cessation counseling and NRT (21 mg/daily)	6 weeks	Increased abstinence Decreased craving Decreased withdrawal Reduced post-cessation body weight gain
NCT03712098	40 treatment-seeking smokers 18 y/o and older with overweight and obesity	Smoking abstinence Body weight change Calories per day	Liraglutide (escalating doses of 0.6–3.0 mg weekly) or placebo in addition to smoking cessation counseling	32 weeks	Study completed, results not yet published
NCT05530577	Treatment-seeking smokers 21–65 y/o with at least moderate nicotine dependence	Nicotine self-administration Reinstatement of nicotine seeking Daily cigarette smoking Craving for and subjective responses to smoking Body weight change HbA1c levels	Semaglutide (escalating doses of 0.25–1.0 mg weekly)	10 weeks	Currently recruiting
NCT05610800	Treatment-seeking smokers 18–75 y/o with prediabetes and/or overweight	Smoking abstinence Body weight change Neural responses to visual stimuli	Extended-release exenatide (2 mg weekly) or placebo in addition to smoking cessation counseling and NRT (de-escalating doses of 21–7 mg/daily)	14 weeks	Currently recruiting
NCT06173778	Treatment-seeking smokers 18–75 y/o with prediabetes and/or overweight	Body weight change Body fat mass change Waist circumference change	Semaglutide (escalating doses of 0.24–2.4 mg weekly) in addition to smoking cessation counseling and NRT (de-escalating doses of 21–7 mg/daily)	28 weeks	Not yet recruiting

y/o = years old; NRT = nicotine replacement therapy.