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Feasibility of GLP-1 Receptor Agonists as an Adjuvant Treatment for Substance Use Disorder

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Abstract

Substance use disorder (SUD) is a pervasive and escalating global public health issue. While current pharmacotherapies for SUD directly act on the disease state and aid in symptom management, only few treat the underlying craving in substance abuse. When coupled with low rates of seeking treatment in chronic drug users, this lack has resulted in unsuccessful efforts to mitigate SUD. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), a class of drug known for glycemic control and aiding in weight loss, have shown promise in preclinical studies to target underlying “wanting” or incentive salience in drug addiction. This review aims to examine preclinical literature and randomized controlled trials (RCTs) to determine the feasibility of GLP-1RAs in reducing craving and compulsive behavior. Findings of this review suggest that the feasibility of this class of drug is potentially contingent on dosing and duration of treatment, specificity, metabolism, and the treatment philosophies of drugs moving forward. Future directions for this topic include larger and longer clinical RCTs – which are currently in progress – evaluation of the efficacy of GLP-1RAs in different metabolic dispositions, exploration of the combination with conventional treatments as a potential adjuvant, and expanded neuroimaging to assess mechanisms.

Keywords: GLP-1 receptor agonist, substance use disorder, drug craving, reward circuitry, addiction

Introduction

Substance use disorder (SUD) is a manifestation of behavioral addiction that is an extreme and cyclic form of substance use characterized by periods of craving, intoxication, and withdrawal that repeats and worsens as the disease becomes more entrenched in the neurobiology of the patient (Le Moal and Koob 2007; Imperio et al. 2024). SUD is an umbrella term in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) that encompasses 10 classes of drugs: alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, anxiolytics or hypnotics, stimulants, tobacco, and other or unknown substances (American Psychiatric Association 2022). According to the American Psychiatric Association, the diagnostic criterion of SUD is lack of control over substance use, social impairment, risky use of substance, and pharmacological tolerance and dependence (American Psychiatric Association 2022). The proliferation of SUD represents an escalating and pervasive public health issue in many jurisdictions, exhibiting a global prevalence rate of 2.2% (Castaldelli-Maia and Bhugra 2022), with upwards of 35 million suffering from non-alcohol SUDs, and 283 million people from alcohol use disorder (AUD) alone (World Health Organization 2018). On a societal level, SUD as a public health issue has presented itself in localized epidemics such as the ongoing opioid crisis in the United States and the ever-increasing burden of alcohol use disorder across industrialized and developing regions (World Health Organization 2024).

Treatment of SUD is complicated due to the heterogeneity in the presentation of SUD across patients (Carroll 2021); this is especially seen in cases where polysubstance use is a core feature of a patient's presentation of SUD. For the same reason, treatment philosophies differ: abstinence-based treatments such as the 12-step program are more suited for forms such as AUD,

while harm reduction are more suited for forms such as opioid use disorder (OUD) (Volkow and Blanco 2023). The commonality of debilitating symptoms, such as the plain reason that addicted individuals are not ready to quit, has caused notably low rates of treatment among SUD patients (Paquette et al. 2022; Volkow and Blanco 2023). Additional factors such as practical barriers and premature termination of treatment in those who do seek it contribute to low rates of remission altogether (Paquette et al. 2022).

Despite these difficulties, SUD is treated through both pharmacotherapies and psychotherapies with the goal of rehabilitation and self-management (Sellman 2010). The complementary methods of psycho- and pharmacotherapies aim to address SUD from both behavioral and physiological standpoints. Pharmacologic treatments aim to modulate the neurobiological mechanisms that underlie behavioral control, often by compensating for existing neuroadaptations. Pharmacotherapies achieve this end through different strategies such as the targeting of receptor active or allosteric sites, the prevention of neurotransmitter reuptake, the inhibition of enzymes, or the neuromodulation of whole neuronal systems (Mateu-Mollá et al. 2025). Thus, many current pharmacotherapies manage symptoms and treat the disease state. Despite their relative efficacy in meeting that end – especially in patients who suffer from more severe forms of SUD – conventional treatments do not address the underlying craving for the drug of abuse. Cravings for a drug are a hallmark of SUD and an important biological mechanism in addiction, yet there are not many drugs that treat craving. This craving component of SUD is associated with the mesocorticolimbic system, which comprises of networks of brain structures responsible for behavior and reward (Robinson and Berridge 1993).

Existing literature supports a parallelism between substance use disorder and obesity through a shared mechanism in the mesocorticolimbic system (Martinelli et al. 2024). In this

parallelism, hyperpalatable foods activate the same neural pathways as SUD and modulate important neuroendocrine signals (Martinelli et al. 2024). It is consequently thought that glucagon-like peptide-1 receptor agonist (GLP-1RA) drugs have a therapeutic potential to treat underlying cravings in SUD (Klausen et al. 2021). Known for their high efficacy in glycemic control, GLP-1RAs are popular and increasingly prescribed for the goal of weight loss, especially in Western countries. GLP-1RAs mimic an incretin hormone called glucagon-like peptide-1 (GLP-1), which is a type of metabolic hormone that decreases blood glucose levels. GLP-1 is thus secreted in response to nutrient digestion by enteroendocrine L-cells in the colon and ileum, and in neurons of an area in the brain's medulla called the solitary nucleus (NTS, for Latin *nucleus tractus solitarii*) (Abdulrazeq et al. 2024; Marquez-Meneses et al. 2025). GLP-1RAs work to activate GLP-1 receptors (GLP-1Rs). GLP-1Rs are a type of G protein-coupled receptor present in the axon terminals of vagal afferents – nerves that carry signals from organs to the brain – in the gastrointestinal system (Hayes and Schmidt 2016). These receptors are also generally populated within the central nervous system (CNS). GLP-1Rs in the CNS populate various areas of the brain responsible for hunger, satiety, metabolism, autonomic regulation, and reward (Marquez-Meneses et al. 2025). GLP-1RAs are designed to be resistant to degradation by dipeptidyl peptidase-4 (DPP-4), an enzyme that breaks down endogenous GLP-1. Their resistance to DPP-4 allows GLP-1 signaling to be prolonged and amplified. Activation of GLP-1 receptors within the mesocorticolimbic system has shown to decrease the rewarding effects of food and drug consumption (Marquez-Meneses et al. 2025). Translational research through preclinical models has suggested that GLP-1 receptor agonists can aid in the treatment of psychiatric disorders that are contingent on reward circuit dysfunction.

In preclinical studies, four main categories of SUD were widely investigated: alcohol, nicotine, psychostimulants (such as cocaine), and opioids. In these preclinical rodent models, many methodologies were used; but typically, individual experiments fell under the categories of site-specific microinjections, behavioral observations, and various neurochemical and molecular assays (Marquez-Meneses et al. 2025). The goal of preclinical modeling is to produce translational results that could confirm mechanistic theories about GLP-1R involvement in the reward system, and the efficacy of GLP-1RAs in modulating behavior and craving. Through a vast array of approaches, researchers found that across most substances, GLP-1RA efficacy seemed to be predicated on dosing and the specific GLP-1RA used in the model (Marquez-Meneses et al. 2025). Altogether, preclinical models show a therapeutic potential of GLP-1RAs for substance use disorder that confirms the viability of human clinical trials and further explorations of the different facets of GLP-1RAs on SUD. This review aims to explore published preclinical studies, emerging human clinical trials, and developing literature on the feasibility of GLP-1RAs as a treatment for SUD in order to reduce cravings and/or compulsive behaviors as a result of serious and prolonged substance use. Despite a scant body of human data and evidence, the administration of GLP-1 receptor agonists has high promise to reduce compulsive behaviors, with a clinical efficacy that is especially moderated by dosing and duration, specificity of drug, metabolism, and treatment philosophy.

Description

The following section surveys the overall literature relevant to understanding the topic of GLP-1RAs as a potential adjuvant in treating SUD. Establishing the foundations and current trial results will provide important context for the feasibility of this type of medication in treating SUD. This section will describe the hypothesized mechanistic basis for using GLP-1RAs in both

theory and preclinical studies, examine promising clinical trial results in alcohol and cocaine, then inspect variable clinical trial results in cocaine and opioids.

Neurobiology of Addiction and Preclinical Findings

To understand the underlying biology of drug addiction, it is important to look at theories of addiction and how they shape current insights into the mechanisms of addiction and SUD.

Early in addiction research, two camps of theories emerged that aimed to provide an explanation for the development and progression of addiction. The physical dependence theory of addiction is a negative reinforcement model that posits that the cycle of substance abuse is driven by the need to relieve physical withdrawal symptoms (Pinel and Barnes 2022). This theory was mainly shaped by studies on alcohol and opioid use, leading to a popular conclusion that withdrawal was a primary driver in addiction overall (Robinson and Berridge 2025). Physical dependence theories were later criticized, as evidenced in later animal models observing physical dependence as a contributing factor of addiction development rather than a direct cause (Robinson and Berridge 1993), and in the lack of physical dependence in drugs such as nicotine or cocaine (Lyvers 1998). The other camp of explanations for how addiction occurs in the brain are the positive-incentive theories. Positive-incentive theories postulate that addicted individuals use drugs to experience the drug's hedonic effects. Like its counterpart, positive-incentive theories were later criticized, particularly by neuroscientists Terry E. Robinson and Kent C. Berridge (1993), who argued that positive reinforcement solely is insufficient to explain addiction due to observations in chronic drug users that report decreased "highs" but consistent cravings.

To address the limitations of both positive and negative reinforcement theories of addiction, Robinson and Berridge proposed the incentive-sensitization theory. They postulated that repeated drug use causes neuroadaptations, namely the increase of positive-incentive value –

or anticipated pleasure – in drugs (Robinson and Berridge 1993). According to this theory, sensitization would be most apparent in those who are addiction-prone (Pinel and Barnes 2022). Furthermore, this theory stated that the basis for addiction is in the “wanting,” also known as the incentive salience or anticipated pleasure of the drug. In the initial taking of a drug, both components of “wanting” and hedonic “liking” are equal. Over time, a discrepancy grows and the two components dissociate, as the anticipated pleasure becomes stronger while the “liking” component diminishes, as shown in Figure 1 (Robinson and Berridge 1993). Robinson and Berridge (1993) further identified that dopamine (DA) is the neurotransmitter for reward and craving rather than for pleasure. DA as a neurotransmitter for pleasure was the conventional thinking in earlier theories. Robinson and Berridge’s work helped to define the current understanding of addiction.

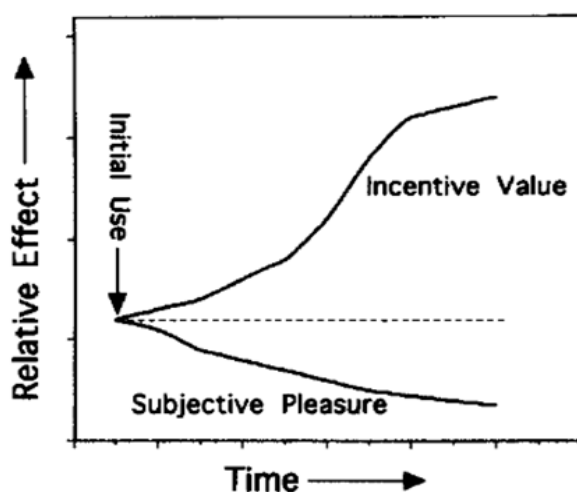


Figure 1. A diagram illustrating the dissociation and discrepancy of “wanting” (incentive value) and “liking” (subjective pleasure over time). In addiction, tolerance is formed, and the hedonic effects of a drug diminish over time. Conversely, craving or incentive value increases due to the sensitization of dopamine structures from repeated drug use. (Robinson and Berridge 1993, Figure 3)

It is now understood that these neuroadaptations affect various neurotransmitter systems due to repeated and increased DA stimulation (Volkow et al. 2019) within neurons of the overall mesocorticolimbic system of the brain. The mesocorticolimbic system consists of two

component pathways: the mesocortical pathway and the mesolimbic pathway. Both neural pathways originate from the ventral tegmental area of the midbrain and project to either the prefrontal cortex (PFC) to regulate cognitive functions such as behavior and executive functions, or the nucleus accumbens (NAcc) to regulate pleasure and incentive salience.

In preclinical models, researchers found that varying SUDs are modulated by slightly different mechanisms within the mesocorticolimbic system. When treated with GLP-1RAs, behavioral results varied, especially with different specific receptor agonists. Findings in rodents addicted to alcohol showed that consumption and behaviors caused by alcohol were generally attenuated, and dopamine signaling was reduced upon treatment with a GLP-1RA (Egecioglu et al. 2013; Vallöf et al. 2019; Aranäs et al. 2023). The work of Vallöf et al. (2019) in particular showed that the activation of GLP-1Rs in the NTS through microdialysis of exendin-4 (Ex4) – a natural peptide that activates GLP-1 receptors while resistant to DPP-4 – diminished outward behavior in rodents such as alcohol-induced locomotion, conditioned place preference, and consumption of ethanol. GLP-1 signaling caused by Ex4 also reduced DA release from the NAcc (Vallöf et al. 2019).

Findings for nicotine and psychostimulants were similar to alcohol, with an added mechanism in habenular projections, outside of the typical mesocorticolimbic structures (Marquez-Meneses et al. 2025). The habenula is a microstructure that acts as a converging point for neurons, especially outward to the mesocorticolimbic system. A study involving cocaine – a psychostimulant – and GLP-1R knockout mice (laboratory mice with specific genes inactivated for testing), implicated the lateral septum as a contributor to cocaine-induced behaviors, as knockout mice without GLP-1Rs expressed in the lateral septum displayed increased sensitization of cocaine-induced locomotor activity and increased conditioned place preference

(Harasta et al. 2015). In nicotine, specific studies such as those conducted by Tuesta et al. (2017) identified a distinct pathway of nicotine avoidance beginning with the NTS, to the medial habenula (MHb) – a distinct region within the habenula – and ending with the interpeduncular nucleus (IPN) – a group of neurons in the midbrain that send inhibitory signals implicated in nicotine avoidance. MHb and IPN structures are both linked to aversive behavior (Marquez-Meneses et al. 2025). GLP-1 signaling activates GLP-1 receptors expressed along these neurons and triggers avoidance due to a cascade of excitatory signals from the binding of GLP-1Rs (Tuesta et al. 2017). This suggests a secondary robust mechanism for attenuating compulsive behaviors in regard to nicotine, leading to the conjecture that GLP-1RAs could be very beneficial in treating tobacco use disorder (TUD).

While the GABAergic system was implicated in alcohol and nicotine, opioids differed from the rest of drug categories, as the orexin system (Douton et al. 2022) and the hypothalamic-pituitary-adrenal (HPA) axis (Łupina et al. 2020) were connected to GLP-1RA targeting, instead of the GABA system. The orexin system is a key modulator in stress and anxiety, and increases of orexin are associated with drug craving in OUD (Raymond et al. 2025). The HPA axis is known primarily as a neuroendocrine system that regulates stress. In OUD, the HPA axis is dysregulated, with dependence on opioids yielding a decreased function and lower levels of cortisol, while withdrawal results in high cortisol and adrenocorticotrophic hormone levels, contributing to stress and anxiety experienced during withdrawal (Zhang et al. 2008). Opioid models also differed to the previous forms of SUD in that results were extremely variable. For example, in Łupina et al. (2020), linagliptin, a DPP-4 inhibitor with a similar mechanism of action to GLP-1RAs, was studied in morphine-dependent rats. The results of this study found that behaviors indicating withdrawal were attenuated, and there was lower activity in the HPA

axis, suggesting efficacy in treating withdrawal (Łupina et al. 2020). By contrast, another study examined Ex4 in morphine-treated mice and found that it was weak in preventing morphine tolerance and reducing the reinforcing effects of morphine (Bornebusch et al. 2019). These variable results may be a product of different methodologies, but it is unclear why the outcomes of studies are inconsistent in OUD compared to other forms of SUD such as AUD.

Promising Clinical Trial Results in Alcohol and Nicotine

In the search for GLP-1RA viability as a treatment for SUD, numerous clinical trials have already been conducted. They are considered Phase 1 clinical trials, indicating that these clinical trials are nascent in the research timeline. This has resulted in a key caveat, as pilot studies have smaller sample sizes and a tendency toward shorter treatment durations. This can be a cause for concern, as this is a strong limitation on their scope. However, they provide a solid basis and reference for further study of GLP-1RAs. Phase 2 clinical trials larger in participant size and in scope are currently in progress. Alcohol and nicotine have been the primary focus of research based on what is published, as there is a plethora of existing trials that describe findings in AUD and TUD. This is due in part to strong preclinical evidence for the attenuation of addiction in alcohol and nicotine, contrasted to other drugs in substance abuse. In this section, two small-sample randomized controlled trials (RCTs) will be examined in detail, for alcohol and nicotine respectively.

An RCT by Klausen et al. (2021) investigated the behavioral outcomes when AUD patients were treated with exenatide, a GLP-1RA with a proven dosing schedule for patients with type 2 diabetes. Exenatide penetrates the blood-brain barrier (BBB), where it can enter the CNS and exert its effects more readily (Klausen et al. 2022). Over a 26-week period, researchers measured heavy drinking days using self-report calendars, and used functional MRIs (fMRIs) to

measure dopamine transporter (DAT) availability – an indicator of dopaminergic activity – and alcohol cue reactivity in the brain (Klausen et al. 2022). Patients were also divided into two groups with body mass indices (BMIs) less than and more than 30 to measure the relationship between metabolism and treatment outcomes.

There were no significant differences in the number of heavy drinking days between treatment and placebo groups. However, further analyses based on BMI suggested that the subset of patients that were considered obese ($BMI > 30$, $n = 30$) saw tangible results, as exenatide-treated obese patients had a marked reduction in heavy drinking days and alcohol intake compared to obese patients on placebo. This led to the authors' conclusion that the participants in this study gained the same incretin benefits as a typical individual who is taking a GLP-1RA for glycemic purposes. The results for this particular metric are outlined in Figure 2. Less alcohol cue reactivity at week 26 was observed in exenatide-treated patients compared to the placebo-treated group as well. Neuroimaging shows that this is most apparent on the ventral striatum, which contains the NAcc and is highly involved in reward processing. Furthermore, Klausen et al. (2022) found that exenatide patients showed lower DAT availability toward the end of the study compared to their baseline, and to placebo at both timestamps (see Figure 3). Specifically, lower DAT availability was noted in the ventral striatum among exenatide-treated patients (Klausen et al. 2022). Lower DAT availability was also noted in the caudate nucleus or putamen, which compose the dorsal side of the striatum. It is important to highlight that at baseline as depicted in Figure 3, AUD patients trended toward a lower DAT availability compared to healthy controls. This is due in part to a hypodopaminergic state that can occur during a protracted period of abstinence (Hirth et al. 2016). Lower expression of dopamine receptors

occurs in this state, possibly due to neuroadaptations caused by frequent substance use and hardwired by the addiction cycle.

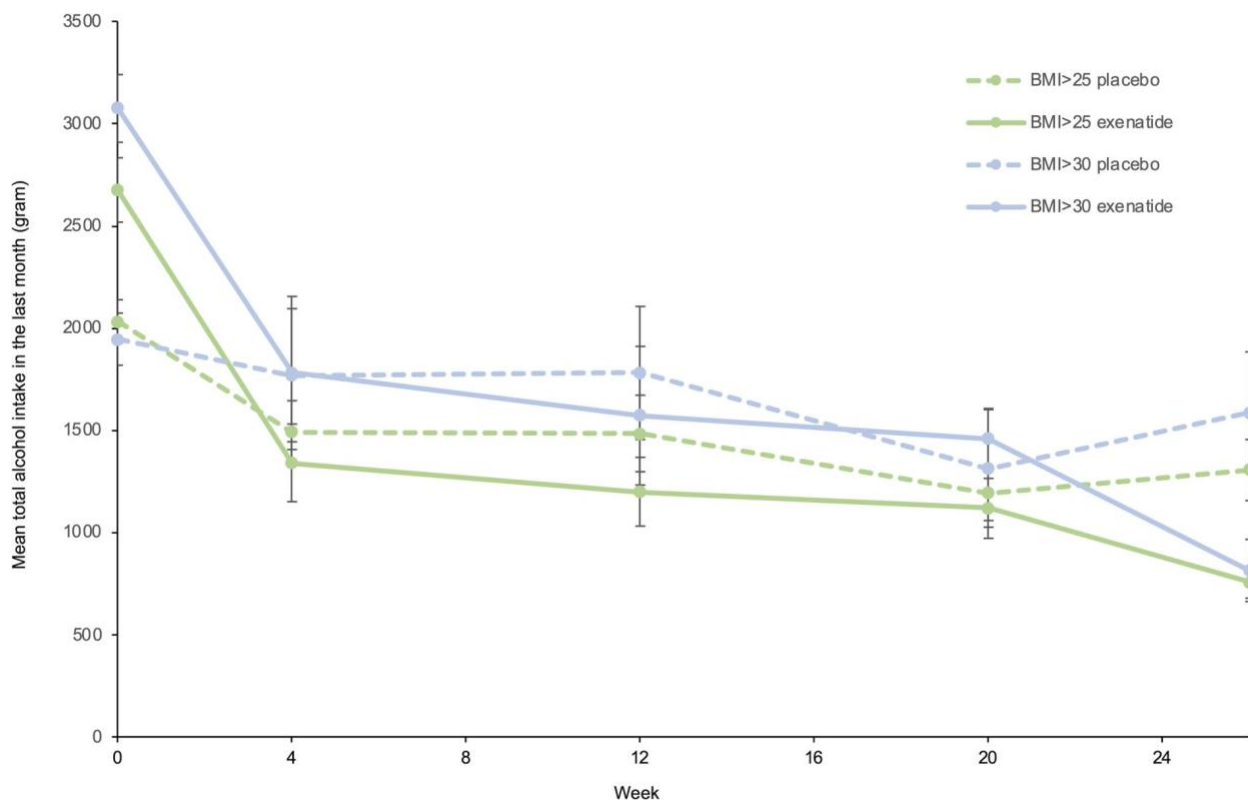


Figure 2. The mean percentage of heavy drinking days across patients treated with placebo and exenatide. The graph is further divided into patients with a BMI <30 ($n = 52$) and those with a BMI >30 ($n = 30$). Within the subset of patients with a BMI <30, the percentage of mean drinking days shows trendlines opposite to expectations with exenatide. In this subset, the percentage of drinking days increases in exenatide rather than decreases. Meanwhile, in the subset of patients with a BMI >30, there is a reduction in the percentage of heavy drinking days among exenatide-treated patients compared to placebo. (Klausen et al. 2022, Figure 5)

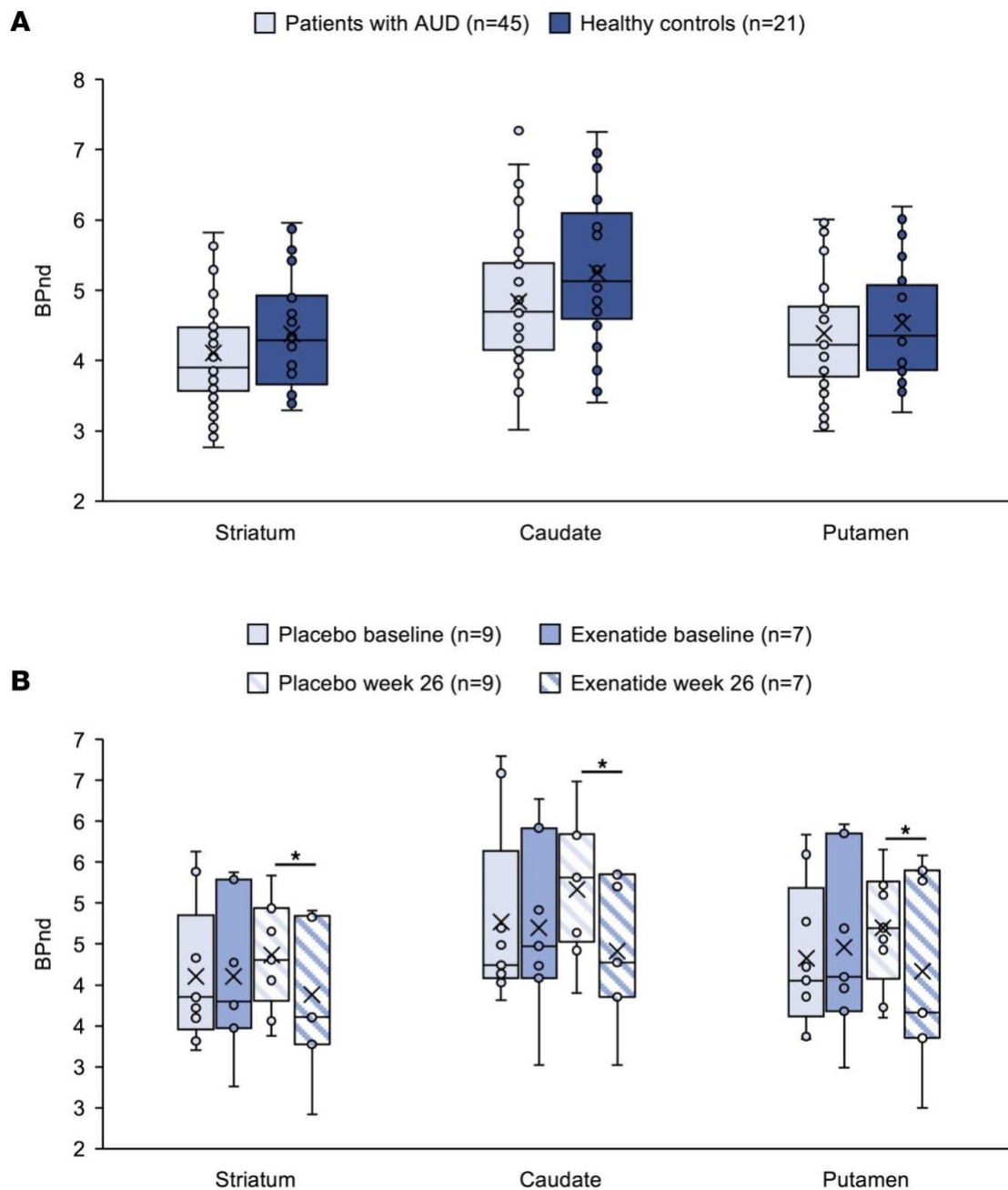


Figure 3. Box and whisker plot depicting differences in DAT availability between timestamps. Y-axis *BPnd* refers to the DAT specific binding ratio. **(A)** depicts baseline at the beginning of the 26-week study. Note the lower DAT availability overall in AUD patients due to hypodopaminergia. **(B)** depicts DAT availability at week 26 of the study. Comparison of exenatide patients at both timestamps shows a reduction in DAT availability. This data is line with the reduced alcohol cue reactivity exhibited by exenatide-treated patients. (Klausen et al. 2022, Figure 9)

An RCT conducted by Yammine et al. (2021) investigated the effects of exenatide in addition to nicotine replacement therapy (NRT) in treating symptoms of tobacco use disorder. NRT, widely known in forms such as nicotine patches, lozenges, gum, etc., is a first-line treatment for smoking cessation. However, NRT on its own is known to diminish over time (Yammine et al. 2021), prompting studies pairing GLP-1RAs with existing first-line treatments such as NRT. The researchers followed prediabetic or overweight smokers over a 6-week period, tracking through self-reports the metrics of total abstinence over 7-day periods, craving, withdrawal, and post-cessation body weight. It should be noted that post-cessation body weight is an important outcome to consider, as most quitters of smoking tend to gain weight (Yammine et al. 2021).

Yammine et al. (2021) discovered that the proportion of participants who were abstinent was higher in the exenatide group compared to the placebo group. Craving had marked reduction in non-abstaining exenatide participants, but not in abstaining exenatide participants. In withdrawal, abstaining exenatide participants had a marked decrease, but not in non-abstaining exenatide-treated individuals. It was noted that there was no differential change in withdrawal symptoms over time between overall groups (Yammine et al. 2021). In post-cessation body weight, the treatment group saw reduced body weight, as seen in Figure 4. The authors noted that the result of reduced body weight in post-cessation may be seen as a benefit to use GLP-1RAs, as this side effect is not noted in other nicotine use treatments.

Collectively, the findings from these clinical trials show the tangible benefits of GLP-1RAs in attenuating behaviors, particularly in alcohol and nicotine use cases. The study conducted by Klausen et al. (2022) was successful in demonstrating improvements in key endpoints despite an overall insignificance in heavy drinking reduction. Yammine et al. (2021)

was able to establish a positive trend in various endpoints that indicate behavioral attenuation. However, these studies show that treatment is not uniform, as evidenced by overall mixed behavioral outcomes within these trials. Nevertheless, these two studies suggest that certain variables such as metabolic phenotype, or usage as an adjuvant, enhance therapeutic success.

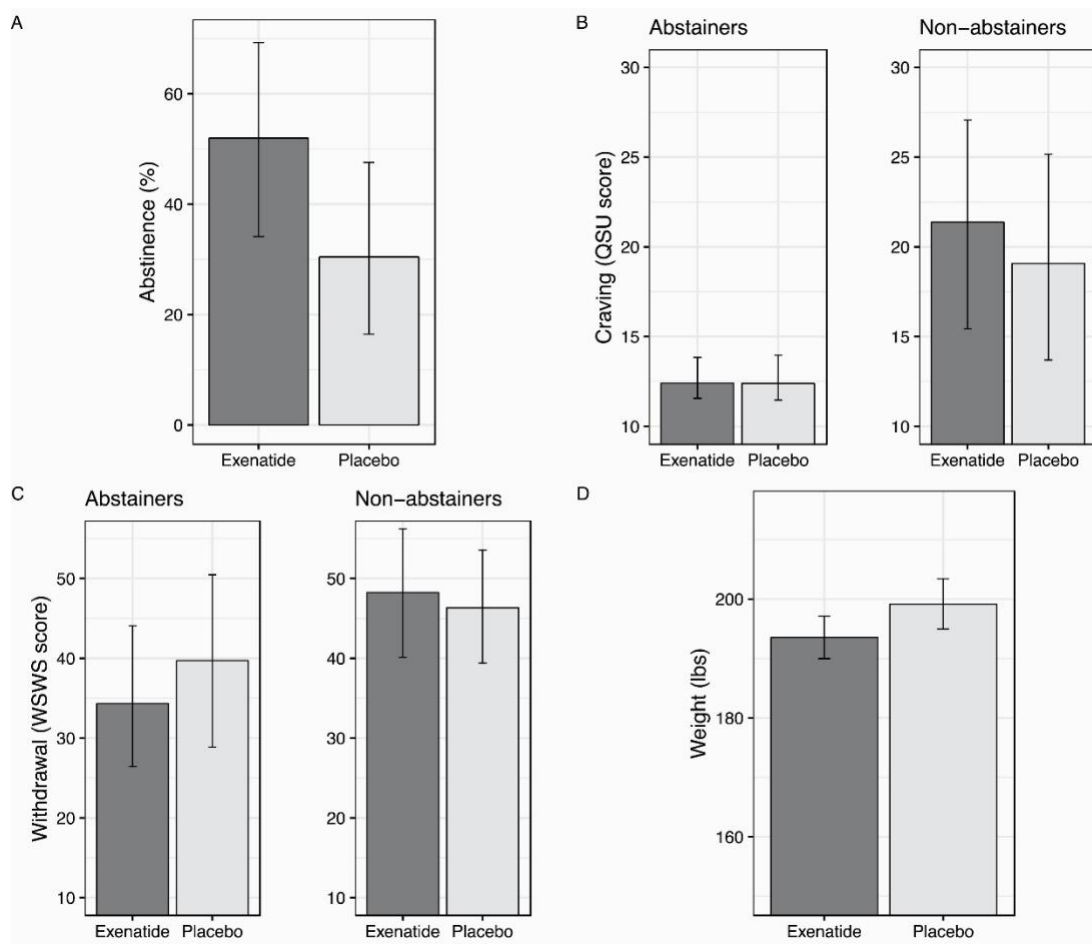


Figure 4. Bar graphs illustrating results in each of the four determined metrics. ($n = 82$, abstainers $n = 30$, non-abstainers $n = 39$). **(A)** illustrates the percentage of abstinent participants, based on the raw proportion of participants found to have experienced a 7-day period of abstinence. The exenatide group shows the largest abstinence proportion. **(B)** displays craving scores from the Questionnaire of Smoking Urges, divided into exenatide and placebo groups, and further divided into abstainers and non-abstainers. Note that the overall non-abstaining group has marked differences. **(C)** shows scores from the Wisconsin Scale of Withdrawal Symptoms questionnaire. Lower scores were reported for abstaining exenatide individuals, while the same is not apparent in non-abstainers. **(D)** illustrates post-cessation body weight, with a lower overall body weight shown in exenatide-treated participants. (Yammine et al. 2021, Figure 2)

Variable Evidence in Cocaine and Opioid Use Disorders

Despite early clinical trial results being promising for alcohol and tobacco use disorders, results for other forms of SUD are more unclear. This is due to a lack of published preclinical evidence in other commonly abused drugs, such as that of opioids. In addition, much of the available experimental literature is based on Phase 1 clinical trials, restricting the range of many of these studies. This has resulted in the sole clinical trial in cocaine use being marred by the same limitations as RCTs in alcohol and nicotine, albeit to a much greater extent. Currently, there is no published work on opioid use disorder and the effects of GLP-1RAs on its treatment (Bruns et al. 2024). However, there is a completed clinical trial that examined the effects of liraglutide on OUD (Freet et al. 2024), for which a published protocol exists. Analogous translational evidence from preclinical studies on opioids is variable, with behavioral outcomes varying or even contradicting each other. It is important to note however that the completed trial by Freet et al. (2024) and ongoing Phase 2 clinical trials may rectify the limitations of these studies. In this section, one RCT for cocaine use and one retrospective cohort study for opioid use will be examined in detail.

An RCT pilot trial (Angarita et al. 2021) examined the effects of exenatide on cocaine self-administration and other metrics in 13 individuals with cocaine use disorder (CUD) that were in good health and without metabolic or related psychological conditions. This clinical trial measured the number of cocaine infusions observed in a controlled environment for self-administration, and the subjective effects such as the “wanting” and “high,” measured through self-ratings. Secondary outcomes such as GLP-1, insulin, and amylin levels were also measured through blood sampling. A single low 5-microgram (μg) dose of exenatide or placebo was administered to their respective groups three hours before cocaine self-administration sessions.

This low dose was noted to be clinically relevant, as it is a standard dose for anti-diabetic purposes (Angarita et al. 2021). Following ascending “safety eligibility” doses of cocaine administered by a nurse to avoid cardiovascular complications, voluntary infusions during the self-administration sessions were measured, capped at 18 doses in a single session.

Following the collection of data, which occurred from 2014 to 2018, it was found that a 5 µg exenatide dose did not significantly change self-administration of cocaine or subjective effects of CUD, as referenced in Figures 5 and 6. In the secondary outcomes, exenatide and cocaine independently reduced plasma levels of GLP-1 and insulin, while amylin was reduced solely by cocaine. The results of the primary outcomes suggest that a higher or chronic dose may be more effective in inducing behavioral changes. Additionally, the authors concluded that other GLP-1RAs should be examined for CUD as each treatment has different pharmacokinetics and characteristics (Angarita et al. 2021).

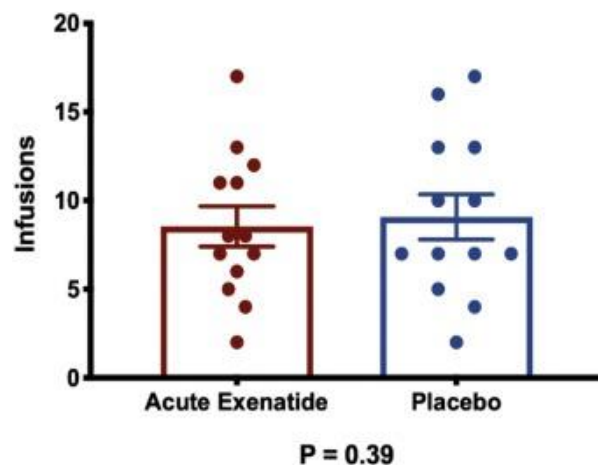


Figure 5. Bar-dot plot with error bars illustrating the behavioral outcomes between treatment groups. The number of infusions during self-administration were not significantly different across either group. (Angarita et al. 2021, Figure 3)

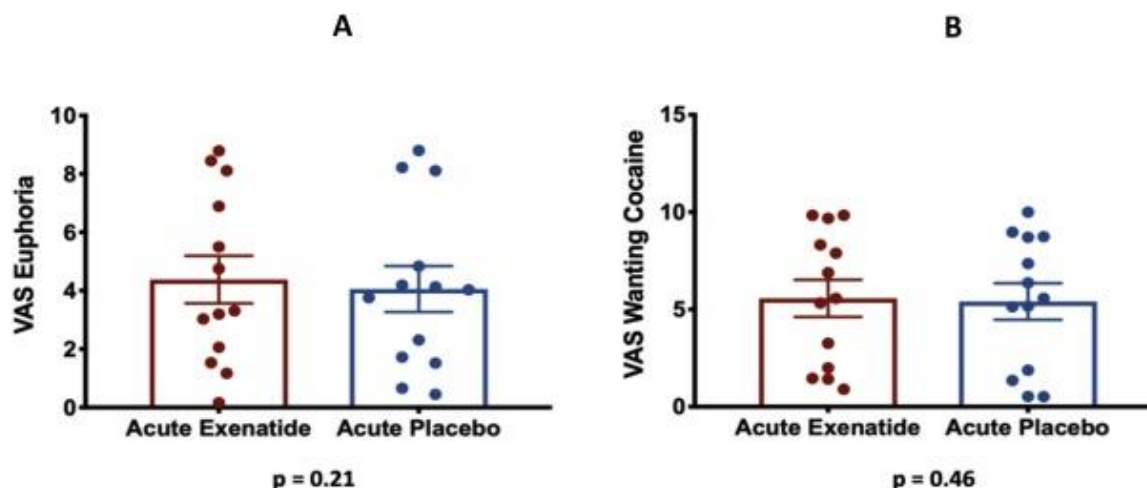


Figure 6. Bar-dot plots with error bars illustrating the subjective outcomes between treatment groups. The methodology for this paradigm was a computerized visual analogue scale (VAS) where participants self-rated their subjective euphoria, or “high,” and their craving, or “wanting.” (A) depicts the overall results for the euphoric effects after pre-treatment with exenatide or placebo. There was no significant difference between the treatment groups. (B) represents the overall results for wanting cocaine after pre-treatment with exenatide or placebo. There was also no significant difference between the two treatment groups. (Angarita et al. 2021, Figure 4)

Though there are currently no published RCTs on GLP-1RA effects on opioid use, observational studies are an important study type to consider when ascertaining correlations and relationships. Analyzing electronic health records (EHRs) is one methodology that is incredibly useful in producing observational evidence in this emerging topic of research. A retrospective cohort study (Qeadan et al. 2025) analyzed de-identified EHR records and separated AUD and OUD cohorts. Patients in each cohort were separated into those with or without a GLP-1RA prescription. It is crucial to highlight that those with a GLP-1RA prescription are highly likely to have related comorbidities such as type 2 diabetes and/or obesity. In this cohort study, permutations of these conditions among the patient population were stratified and examined in detail. The authors noted that the OUD cohort had a slightly higher proportion of female patients. Confounders were additionally adjusted during the analysis of data. The outcomes of interest from this study were incidence rates of opioid overdose and alcohol intoxication between GLP-1RA prescription groups.

It was found that overall, there was a positive correlation between GLP-1RA prescription and the incidence rate of outcomes in both prescription groups within the cohorts. Of interest to this review is the OUD cohort, of which an overall incidence rate ratio (IRR) of 0.60 was reported (Qeadan et al. 2025). This indicates a 40% reduction in the incidence rate of opioid overdose compared to non-prescribed patients. When adjusting for comorbidities within the prescription group, an IRR of 0.62 was reported for the type 2 diabetes stratum alone, an IRR of 0.67 was noted for obesity stratum alone, and a 0.65 IRR reported for those with both type 2 diabetes and obesity (Qeadan et al. 2025). These ratios signify a 38%, 33%, and 35% reduction in incidence rates respectively. Despite the positive results from this retrospective cohort study, it by no means establishes causality.

Overall, in contrast to the more successful AUD and TUD trials, these studies for cocaine and opioid use cases publish mixed evidence for the efficacy of GLP-1RAs with these substance use disorders particularly. Angarita et al. (2021) notably yielded insignificant results, while the observational study Qeadan et al. (2025) is not as authoritative when basing considerations off of the hierarchy of evidence. Despite the overtly ambiguous outcomes, these studies highlight the importance of replicable studies, and how vital it is to explore manipulating numerous variables such as dosing length/regimen and metabolic phenotype in future studies to gain a wider understanding of how GLP-1RAs might help to manage and treat the subsequent behaviors exhibited by SUD.

Synthesis

To determine the clinical feasibility of GLP-1RAs in treating substance use disorder, it is imperative to synthesize research findings elaborated in the previous Description section. In this section, the following subsections will examine key determinants, such as the relationship

between dosage & duration with clinical outcomes, the potential role of metabolism in the effectiveness of GLP-1RA treatment, and treatment philosophies to consider in the emergence of a potential adjuvant such as GLP-1RAs.

Importance of Dosing and Duration of Treatment

The dosing of the medication and the length of treatment seems to be a critical determinant in therapeutic success. As demonstrated in these clinical trials, dosing was a recurring theme in research findings. Because current published clinical trials are mainly Phase 1 clinical trials – meaning that their primary objective is to test for safety – small and acute doses administered in a clinical setting were used across current publications. Authors of these various studies also remarked that many of these acute doses are clinically significant despite their size (see Angarita et al. 2021). It can be hypothesized that larger doses may elicit more evident results, positively or negatively. As mentioned earlier in the introduction, it can also be concluded through preclinical evidence that efficacy is predicated on varying doses (Marquez-Meneses et al. 2025), indicating the need for the investigation of an ideal dose that results in significant attenuation of behaviors, while prioritizing safety and minimization of side effects. Self-administration of the GLP-1RA medication in question is also a potential factor that can affect future results, as this is the widespread mode of usage among patients who use these medications to treat diabetes or lose weight. Later studies that employ a GLP-1RA self-administration methodology would be able to measure real-world patterns of medication usage, correlating to treatment success and the efficacy of GLP-1RAs in attenuating symptoms and behaviors associated with SUD. Ongoing clinical trials with larger participation and elaborate methods may have accounted for all of these factors mentioned.

A longer, more chronic duration of dosing may also be key to increasing attenuating effects of GLP-1RAs on “wanting.” Although the dosing and circumstances like the particular SUD were different, there is no comparison more evident than between the studies of Klausen et al. (2022) and Angarita et al. (2021). Both studies utilized exenatide in the treatment of their respective SUDs. The study conducted on individuals with CUD utilized an acute dosage approach, with a single cocaine self-administration phase characterizing the methodology of the study (Angarita et al. 2021). This study subsequently reported no significant reduction in cocaine self-administration. By contrast, the study conducted on individuals with AUD was a 26-week longitudinal trial that involved weekly doses in clinic (Klausen et al. 2022), mimicking a more chronic dosage. The behavioral results of this particular study were not significant despite the dosing regimen. However, the reduction of heavy drinking days and decreased DAT availability in treated individuals was a promising outcome from this study. This indicates that a chronic dosing regimen will be an important determinant in the success of clinical trials moving forward.

Metabolism as a Factor in Efficacy of Treatment by GLP-1RAs

One of the most successful RCTs mentioned in this review is an alcohol study conducted by Klausen et al. (2022). The findings themselves can be deemed disappointing, as there was little evidence in this study that pointed to significant behavioral outcomes between exenatide-treated patients and placebo patients. However, one factor of importance that was measured in this study was BMI. Higher BMI patients treated with exenatide saw marked reductions in heavy drinking days compared to their lower BMI exenatide-treated peers. The results from Klausen et al. (2022) suggest that metabolic phenotypes may also be a critical determinant of drug response. This may be unsurprising due to an established and well-known link between hyperpalatable foods and drugs sharing the same dopaminergic circuit (Hayes and Schmidt 2016). Those with a

BMI over 30 and SUD could possibly be primed for an effective subsequent incretin response to GLP-1RAs.

The evidence further compounds, as individuals with a BMI over 30 may have a compromised blood-brain barrier (BBB). Rodent models show downregulation of tight junction proteins in a high-fat diet (Rhea et al. 2017), suggesting decreased integrity of the BBB. The BBB is present in most areas of the brain, including that of the mesocorticolimbic system. The RCTs that utilized exenatide reasoned that it was able to cross the BBB. The subsequent results in these studies, specifically in regard to high-BMI patients, showed positive results in attenuation. There is a high possibility that the efficacy of specific GLP-1RAs in high-BMI patients can be explained through a more permeable BBB. A more permeable BBB allows deeper pharmacologic saturation; and with GLP-1RAs, would result in substantial reward suppression as it is more likely to reach structures such as the VTA and NAcc. Furthermore, the correlation between metabolic phenotype and efficacy is strengthened in the results of the retrospective cohort study involving an OUD cohort. With reduced incidence rates across all strata, this further implicates metabolism as a determinant in the success of GLP-1RA treatment.

Treatment Philosophies to Consider in the Usage of GLP-1RAs

The unique mechanism of GLP-1RAs in treating addiction and the limited body of evidence for its efficacy alone suggests that its feasibility is most apparent as an adjuvant treatment paired with existing pharmacotherapies and psychotherapies. Its strength seems to lie in its mechanism within the dopaminergic circuit, which can be combined with conventional medications that treat the disease state.

With the potential integration of GLP-1RAs in the conventional treatment landscape for SUDs comes the necessity to reconcile various treatment philosophies. Although not rigidly

diametrically opposed to each other, the treatment philosophies of abstinence and harm reduction are distinct in their approaches. As mentioned earlier, this is seen in abstinence being more suited for SUDs such as AUD, and harm reduction being a philosophy more suited for OUD. As an adjuvant therapy, GLP-1RAs can help to reconcile these treatment philosophies into a pragmatic and gradual approach across many SUDs if future studies are successful in proving efficacy outside of AUD and TUD. GLP-1RAs may provide a crutch to suppress reward and cravings to allow combined pharmacotherapies to entrench and treat the disease state. There is potential for total cessation as a viable goal, combined with conventional pharmacologic treatments, but the current evidence suggests that it is more likely that GLP-1RAs are more useful in harm reduction. This is proven through a reduction of heavy drinking days in the Klausen et al. (2022) study and the potential for GLP-1RAs to modulate stress hormones as implicated in rodent models for OUD (Łupina et al. 2020).

Future Directions and Conclusion

This particular topic of research is an emerging one, with limited human RCTs unable to establish causality in GLP-1RA ability to attenuate compulsive behaviors in SUD. GLP-1RA clinical trials are certainly at their infancy, with the published studies being Phase 1 trials that pioneered safety protocols, methods, and outcomes of interest within this topic of research. It is known through a vast array of preclinical studies that there is a relationship between the endogenous GLP-1 system and addiction. To what extent this preclinical evidence is translatable to human research remains an important question, as findings are taken from rodent models. As mentioned earlier, ongoing RCTs and completed RCTs that have yet to be published may fill in large gaps in knowledge one study at a time.

It should be highlighted that much of the current preclinical evidence was conducted in trials involving male rodents. This is a massive limitation in the translatability of preclinical evidence to real-world outcomes, as there is a small sample of literature that addresses female rodents. It is plausible that some sex differences may exist, particularly in that of OUD. There are not many marked sex differences in the human brain, as 1% of total differences in brain structure is due to sex (Eliot et al. 2021). However, there is evidence suggesting that there are sex differences in the circuitry for stress, especially in orexin expression and the higher baselines and overall activity that characterizes stress in females (Goel et al. 2014). As previously mentioned, orexin and stress was highly implicated in preclinical mechanistic findings (Łupina et al. 2020; Douton et al. 2022). These facts may point to a possible increased reward suppression in female OUD patients by GLP-1RAs. Thus, future preclinical research must examine effects of GLP-1RAs in female rodents, as current findings cannot be considered generalizable to females.

Of special interest is the examination of polysubstance use in those with SUD. It is not atypical for individuals with SUD to exhibit polysubstance use, because of a characteristic heterogeneity in this disorder (Carroll 2021). There are currently no human RCTs that have examined GLP-1RA effects on SUD patients that compulsively take multiple types of substances. Polysubstance use in SUD presents an additional layer of complexity that can be a confounder in real-world treatment. In polysubstance use, there are numerous permutations of patterns of drug use that potentially affect the effectiveness of treatment, and this extends to novel pharmacotherapies such as GLP-1RAs.

Although some conclusions from the existing yet limited human research may postulate this, many current publications have not explored the idea of combined pharmacotherapies as a strategy for treatment, with most opting to explore the effects of GLP-1RAs alone. Angarita et al.

(2021) is an example of a published trial that explored combining NRT with a novel therapy in GLP-1RAs. Results were mixed, due in part to various confines from being a Phase 1 safety/pilot trial. However, it does show promise in the idea that GLP-1RAs could aid in the treatment of SUD with other existing therapies. Like many psychiatric disorders, SUD treatment is oriented toward polypharmacy – the usage of multiple medications – in addition to psychotherapy. GLP-1RAs should be considered as an adjuvant therapy because of the potential synergistic effects of combining pharmacotherapies in the treatment of SUD. This is an especially important paradigm to consider, as presentations of SUD with polysubstance use necessitates polypharmacy nonetheless. Combined pharmacotherapies may also yield more effective results in already-promising outcomes pertaining to metabolic phenotypes with a BMI over 30.

Human RCTs must also examine neuroactivity more closely. The behavioral outcomes yielded from published trials are confusing and unclear. However, more robust neuroimaging can help to bridge gaps and explain the discrepancies in behavioral outcomes. There are numerous methods for neuroimaging, but it might be ideal to use complementary methods that provide high spatial and temporal resolution in order to elucidate the impacts on the mesocorticolimbic system and related circuits. This can especially be useful when studying cue exposure in real-time. Neuroimaging can also serve as a vital tool to corroborate or disprove metabolism as a factor in treatment efficacy. Paired with subjective self-reporting, more frequent usage of neuroimaging across later stages of clinical trials will help to create a more definitive body of evidence for or against hypothesized mechanisms of GLP-1RAs on addiction and SUD.

The prospect of GLP-1RAs as a novel pharmacotherapy for the treatment of addiction represents a paradigm shift in treatment philosophies and in pharmacologic research. Conventional treatments are tailored to treat the disease state rather than an underlying

mechanism of addiction that has been hypothesized and tested for decades. This will potentially change depending on the success of GLP-1RA research. However, as of now, it is extremely difficult to ascertain a causal relationship between GLP-1RAs and optimal clinical outcomes in treating SUD. There is a small body of human evidence that is inconclusive at best due to the prevalence of current literature being pilot studies. These pilot studies do not definitively support GLP-1RAs as a totally viable treatment for substance use disorder. At this stage, it cannot be known how effective GLP-1RAs are, either alone or as an adjuvant treatment. Nevertheless, the existing literature provides a decent basis to draw provisional conclusions and perhaps hypothesize future outcomes in research. Although the heterogeneity in treatment effects and outcomes can be confusing at times, it can be elucidated that metabolic phenotype seems to be an extremely important factor dictating the success of GLP-1RAs currently. Future research must explore the various facets of GLP-1RA treatment and address massive gaps in published research in order to provide definitive conclusions for clinical practice.

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