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GLP-1 Therapeutics and Their Emerging Role in Alcohol and Substance Use Disorders: An Endocrinology Primer

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Abstract

Alcohol and other substance use disorders (ASUDs) are complex, multifaceted, but treatable medical conditions with widespread medical, psychological, and societal consequences. However, treatment options remain limited, therefore the discovery and development of new treatments for ASUDs is critical. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), currently approved for the treatment of type 2 diabetes mellitus, obesity, and obstructive sleep apnea, have recently emerged as potential new pharmacotherapies for ASUDs. Following an overview of the epidemiology, biology, consequences, and treatments of ASUDs, this review provides a summary of the emerging role of GLP-1RAs in the treatment of ASUDs by elucidating their interactions with various neurobiological pathways involved in addiction. We also highlight existing gaps in research, future directions, and broader implications related to the potential use of GLP-1RAs for addiction treatment.

Key Words: alcohol, alcohol use disorder, substance use disorder, addiction, GLP-1, GLP-1Ras

Abbreviations: ASUD, alcohol and other substance use disorder; AUD, alcohol use disorder; BMI, body mass index; CNS, central nervous system; DPP-4, dipeptidyl peptidase-4; DSM-5, Diagnostic and Statistical Manual of Mental Disorders version 5; EX-4, exendin-4; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; NAc, nucleus accumbens; NRT, nicotine replacement therapy; NTS, nucleus tractus solitarius; OUD, opioid use disorder; PFC, prefrontal cortex; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; TUD, tobacco use disorder; VTA, ventral tegmental area.

Alcohol and other substance use disorders (ASUDs) represent chronic but treatable medical conditions that lead to several medical, psychological, and socioeconomic consequences. ASUDs are characterized by a constellation of symptoms and pattern of use in individuals who continue taking substances despite negative consequences [1]. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), ASUDs are diagnosed based on 11 criteria (with the severity increasing as more criteria are met) that can be grouped into 4 categories: physical dependence, risky use, social problems, and impaired control [1]. Diagnosis of ASUD requires at least 2 of the 11 symptoms listed on the criteria. In parallel, the International Classification of Diseases, 11th Revision, broadly defines "disorders due to substance use or addictive behaviors" as mental and behavioral disorders that stem from the use of certain psychoactive substances, medications, or any "repetitive rewarding and reinforcing" behaviors [2]. In this review, the term ASUD is used broadly to encompass alcohol use disorder (AUD) along with other substance use disorders.

The term "addiction" is often used synonymously with ASUD, especially in moderate to severe cases, but a subtle difference exists because the former refers to a nondiagnostic term that is used widely, including in clinical practice and research settings, whereas the latter is a diagnostic term that is defined by the previously mentioned criteria. Although the brain disease model of addiction is still somewhat controversial [3], there is science-based evidence supporting this model; this definition does not negate that similar to several other chronic diseases (eg, diabetes, obesity, hypertension), environmental factors, including psychosocial factors (eg, social support, network), play a pivotal role in the development and persistence of addiction [4].

The neurobiology of addiction is complex and involves mechanisms related to binge/intoxication, withdrawal/negative effect, and preoccupation/anticipation. Multiple

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neurotransmitters and neuromodulators are involved (eg, dopamine, opioid peptides, γ-aminobutyric acid [GABA], glutamate, serotonin, acetylcholine, and endocannabinoids) [5]. According to the 3-stage cycle of addiction, during the binge stage, there is an increase in dopamine and glutamine neurotransmission that promotes impulsive drug-seeking behavior and habit formation [5]. This effect is diminished by the withdrawal stage, which facilitates release of corticotropin-releasing factor and dynorphin, activating the stress system, including hubs like the amygdala [5]. On the other hand, excessive drug intake reduces executive function through dysregulated glutamatergic, GABAergic, and dopaminergic networks in the prefrontal cortex (PFC), which results in compulsive drug use [5]. The preoccupation/anticipation stage that follows increased sensitivity to substance-related cues alongside overactive stress and diminished reward processing, amplifies compulsive substance-seeking behavior [5]. For more comprehensive reviews of the neurobiology of addiction, see eg [5, 6].

Epidemiology of ASUD

According to the 2023 National Survey on Drug Use and Health, approximately 46.3 million adults aged 18 years and older and around 2.2 million adolescents aged 12 to 17 years have ASUDs [7]. In this survey, the three most common substances of misuse following alcohol, are cannabis, prescription psychotherapeutics, and opioids. There is a higher prevalence among adult males and an opposite trend observed in adolescents with a higher prevalence among females. It is also worth noting that there was an increase in the ASUD prevalence among female adolescents and a decrease among male adolescents from 2022 to 2023 [7].

Specific to AUD, 28.1 million adults aged 18 years and older and 757 000 adolescents aged 12 to 17 years had AUD in 2023 [7]. These are alarming statistics, especially given the increase of approximately 4000 cases from the prior year [7]. The World Health Organization reported that in 2019, an estimated 400 million people were diagnosed with AUD globally and 2.6 million deaths were attributed to alcohol consumption [8].

The negative consequences of ASUDs impact individual, family, community, and societal health at large. For example, alcohol has been shown to be the most harmful drug, considering consequences that extend beyond the individual (eg, related car accidents, gun and domestic violence) [9]. An observational study that investigated the prevalence of emergency department visits and hospitalizations of adults with ASUDs showed that rising addiction rates negatively impacts both safety net and non-safety net hospital settings [10]. The rise in hospitalization rates in both types of hospitals suggests a wider public health crisis because of the rise in ASUD rates.

Despite the high prevalence and consequences of ASUDs, less than one quarter of people with ASUD received treatment in 2023 [7], with less than 2% receiving pharmacotherapy for AUD [11]. From a clinical perspective, patients seeking care from endocrinologists or other clinicians may not recognize that their symptoms stem from an underlying ASUD [12]. Therefore, it is important for clinicians from all specialties to understand the harmful effects of ASUDs and be familiar with evidence-based treatment options.

A particularly concerning medical problem relates to ASUD in adolescents, given that consequences of early substance use results in poor long-term health outcomes [8]. This age group is highly susceptible to ASUD. One study showed the risk of initiation of drug use peaks around age 18 years for cannabis and alcohol and age 20 years for cocaine [13]. A growing body of literature indicates that any level of alcohol consumption can have negative impacts on the body [8]. Given the highly alarming data, it is crucial that education efforts be implemented to inform parents and children from a young age about the negative short- and long-term consequences of alcohol and substance misuse.

Addiction and Obesity

The World Health Organization reported that 890 million adults and 160 million children and adolescents aged 5 to 19 were obese in 2022 globally [14]. Obesity is a chronic disease defined by a body mass index (BMI) ≥ 30 kg/m^2 [2, 14] mainly resulting from imbalanced energy intake and expenditure, influenced by various psychosocial, genetic, and environmental factors [14]. For example, the growing access to hyperpalatable and ultraprocessed food plays an important role in the cyclical hedonistic relationship between consumption of energy-dense food and development of obesity [15].

Although controversial, there is growing evidence showing that some forms of obesity may have phenotypic characteristics that resemble addiction, including neurocircuitry mechanisms. Pathways implicated in addiction also contribute to pathological overeating and obesity [16]. Several studies indicate that key brain regions implicated in addiction (eg, the ventral tegmental area [VTA], nucleus accumbens [NAc], the PFC, and the amygdala) also contribute to overeating and obesity [17]. A functional magnetic resonance imaging study compared people with obesity to healthy controls and found increased functional coupling of the bilateral VTA with regions of the ventral visual pathway that are specialized for perceiving food cues (the left and right ventral occipitotemporal cortex, including the fusiform and the lingual gyri), as well as decreased functional coupling of the bilateral VTA with the PFC (specifically the left inferior frontal gyrus), typically engaged in cognitive control [18]. This hypoconnectivity was inversely associated with food craving. These findings likely reflect a stronger cue-reward association that favors food craving in people with obesity and dysregulated cognitive control of food craving and behavior by the PFC. Elements of compulsive eating mirror ASUDs in that they both present with episodes of habitual overuse to help alleviate negative emotions despite the potential harmful consequences [16]. At the intersection of obesity and addiction lies binge eating disorder, whose DSM-5 criteria include uncontrolled eating larger amounts of food than most people would in a discrete period [19]. Investigating the shared neurobiological and behavioral mechanisms underlying ASUDs and obesity may lead to the development of novel and more effective treatment strategies.

Neuroimaging evidence show that energy-dense palatable food can stimulate areas of the brain that are impacted by addictive substances [20, 21]. Positron emission tomography imaging studies have repeatedly shown similarities between changes in the dopamine receptor signaling in people with addiction and in those with obesity [20, 21]. Furthermore, metabolic biomarkers of clinical relevance in obesity medicine such as triglycerides have been linked to increased risk of AUD [22] and binge drinking [23].

Of note, medications used to treat people with ASUD often affect appetite and weight. Naltrexone is Food and Drug

Administration (FDA) approved for the treatment of AUD and opioid use disorder (OUD) and is also used as an antiobesity medication in the extended-release form when combined with bupropion [24]. Topiramate is used for weight loss and is also used off-label and endorsed by the American Psychiatric Association as a second-line treatment for AUD [25].

In summary, there is evidence from basic neuroscience, human neuroimaging, and clinical research and practice indicating mechanistic and phenotypic overlaps between ASUDs and obesity. That said, it is important to note that although both ASUDs and obesity are chronic conditions influenced by complex gene-environment interactions, there are distinct differences between the two. For example, a recent study found a significant polygenic overlap between AUD and BMI; however, the shared genetic variants associated with AUD and BMI had opposing effects [26].

Medical Consequences From Alcohol and Other Substance Use Disorders

Alcohol has a widespread and negative effect on a variety of organ systems and is associated with myriad chronic medical conditions. A few examples include alcohol-associated liver disease, chronic pancreatitis, hypertension, cardiomyopathy, diabetes, cancer, Korsakoff syndrome, dementia, and depression [27]. Similarly, opioids have significant acute (eg, respiratory depression) and chronic (eg, constipation, other gastrointestinal effects) medical consequences [28]. Stimulants like cocaine and methamphetamine generally activate the sympathetic nervous system, leading to significant cardiovascular complications including increased risk of atherosclerosis, arrhythmias, and myocardial infarction [28]. Therefore, ASUDs can be seen as multisystem medical disorders that may lead to severe, acute, chronic, and "acute on chronic" (eg, acute pancreatitis on top of chronic pancreatitis) complications.

Stigma

An important factor to consider in ASUD and obesity is the influence of stigma in the effectiveness and quality of prevention and treatment [29]. Cultural biases and negative stereotypes contribute to stigma, which undermine patients' emotional well-being and often the care received. Stigma can either be an implicit attitude or an explicit form of expression reflecting overt negative beliefs, of which the latter is more commonly observed when it comes to individuals with ASUD and/or obesity [30]. There can also be self-stigma or internalized stigma, triggered by negative experiences, which can lead to reluctance to seek adequate care and treatment. Identifying the causes of stigma and educating the public about the associated consequences may help equip communities with more effective social skills to combat these pervasive and harmful attitudes and ultimately improve prevention and treatment endeavors [31, 32].

Current Treatments for ASUDs

There is a range of treatments for ASUDs, including behavioral treatments (eg, brief interventions, contingency management, motivational interviewing, motivational enhancement therapy, cognitive behavioral therapy), as well as pharmacological treatments. The number of approved medications is limited, however, and their penetrance in clinical practice is dramatically low. This underutilization is due to a variety of barriers at the patient, clinician, and organizational levels. Among these factors, stigma (see previous section) plays a significant role in the reasons why people with ASUDs are undertreated. Consequently, current treatments for ASUD fall short of addressing public health needs [11].

Disulfiram, a longstanding medication approved to treat AUD works by causing an irreversible pharmacological blockade of the enzymatic process that metabolizes acetaldehyde (produced by the partial oxidation of alcohol via the alcohol dehydrogenase) to acetate [33]. Acetaldehyde accumulation leads to discomforting symptoms, such as flushing, nausea, vomiting, headache, and tachycardia. As a deterrent, disulfiram has demonstrated maximal effectiveness when strong support systems are in place for patients who are already abstinent and are highly motivated to maintain abstinence [33]. Acamprosate, whose mechanism of action involves modulating the glutamate system, is also approved to treat AUD. It helps prevent relapse in abstinent people, although it is also used for people who want to reduce alcohol drinking [33, 34]. Finally, naltrexone (oral and intramuscular) and nalmefene are opioid antagonists that are approved for AUD treatment with the latter approved in Europe only and on an "as-needed" basis for AUD (of note, nalmefene, as well as naloxone, are approved in the United States for opioid overdose) [33, 34]. Naltrexone promotes reduction in heavy drinking rather than total abstinence, whereas acamprosate's effects are stronger in preventing return to drink in already abstinent people [33]. Meta-analyses show that both naltrexone and acamprosate are effective medications for AUD [35]. Other medications that are often used off-label to treat AUD include gabapentin, topiramate, baclofen, varenicline [36 , 37], and several other medications and targets are under investigation [38].

FDA-approved medications for OUD include methadone, buprenorphine, and naltrexone. These medications help reduce cravings and reduce the risk of relapse [39]. Naltrexone (intramuscular formulation) is approved for those who are not actively using opioids to prevent relapse [34]. Methadone is a full mu-opioid receptor agonist and is associated with better retention in treatment with dosing slowly increased over time [39]. Compared to methadone, buprenorphine may offer some advantages, which in part explains its expanding use for OUD treatment. It has fewer side effects and has been shown to help improve depressive symptoms commonly observed in people with OUD [39]. Buprenorphine is administered in a formulation with naloxone because the latter efficiently blocks the addictive effects of buprenorphine to prevent misuse [39].

Approved pharmacological treatments for tobacco use disorder include nicotine replacement therapies (NRTs), varenicline, and bupropion [34]. NRTs are used as patches, gums, lozenges, or sprays [40]. Varenicline is a partial agonist of the nicotinic cholinergic receptors that modulates reward processing and reduces nicotine craving [40]. Bupropion is a tetracyclic antidepressant that helps reduce dopamine uptake and works best when combined with NRT and counseling [40].

There are currently no medications approved for the treatment of cannabis or stimulant use disorders [34]. It should also be noted that in addition to medications, behavioral interventions play a critical role in management of ASUD, as stated previously, and a combination of behavioral and pharmacological treatment often yields better outcomes than single modality treatments [41].

Current Treatments for Obesity

Lifestyle changes that reduce caloric consumption and increase physical activity can significantly improve one's overall health [29]. Although several weight loss programs involving lifestyle interventions exist, their success rates remain limited, with about one half of people regaining the weight they lost within 2 years [42]. Medications for weight loss may enhance the effect of behavioral therapies and other weight loss programs. FDA-approved drugs for the treatment of obesity include phentermine, phentermine-topiramate, bupropion-naltrexone, liraglutide, semaglutide, and tirzepatide. Their mode of action includes regulating homeostatic hunger controlled mainly by the brainstem and hypothalamus, hedonic feeding via corticolimbic structures, and functions in the periphery such as delaying gastric emptying [43].

Bariatric surgery is also an effective treatment for obesity; these include adjustable gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass [29]. It is important to highlight that bariatric surgery, especially Roux-en-Y gastric bypass, has shown to increase the incidence of alcohol use and hence the potential to develop AUD [44]. As such, screening for AUD risk should be integrated into the preoperative and postoperative care for patients considering these procedures. Tailored pharmacological and surgical treatments should be combined with evidence-based lifestyle and behavioral modifications for weight loss to help patients maintain and sustain a healthy lifestyle.

GLP-1 Therapies

Glucagon-like peptide-1 (GLP-1) is an insulinotropic incretin hormone released from the L cells present in the intestines, pancreatic α cells, taste buds, and the hindbrain nucleus tractus solitarius (NTS) [45]. The action of GLP-1 is mediated by the GLP-1 receptor (GLP-1R), a G-protein coupled receptor widely distributed throughout the body, including pancreatic islets, kidneys, gastrointestinal tract, pituitary gland, thyroid gland, and various parts of the peripheral and central nervous systems [46]. GLP-1, alongside the glucose-dependent insulinotropic polypeptide hormone, is responsible for most of the insulin release after consuming a meal. Incretin hormones produce the so called "anti-diabetogenic" effects such as inhibition of gastric emptying and suppressing glucagon secretion [47]. GLP-1R agonists (GLP-1RAs), unlike the endogenous GLP-1, are engineered to resist degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) resulting in longer half-lives and sustained pharmacological activity to exert therapeutic effects [48]. Figure 1 provides an overview of the physiology and roles of GLP-1 and GLP-1RAs. The introduction of GLP-1RAs has revolutionized the treatment of metabolic disorders like type 2 diabetes mellitus (T2DM) and more recently obesity, with even more labels recentyl approved and more potential indications on the horizon.

GLP-1RAs and ASUDs: What We Know

In addition to controlling glucose homeostasis and inhibitory effects on gastrointestinal motility, GLP-1 has key functions in the central nervous system (CNS). Among many pleiotropic effects, GLP-1 reduces apoptosis, restores neuronal growth, and promotes neurogenesis [49]. GLP-1R activation within the CNS regulates homeostatic feeding by modulating appetite and satiety. The "feeding center" hypothalamus has been well studied in relation to GLP-1's effects on feeding [50]. The anorectic effects of GLP-1 appear to be mediated largely by the hypothalamic arcuate nucleus, which contains anorexigenic pro-opiomelanocortin and orexigenic neuropeptide Y/Agouti-related peptide (AgRP) neurons [51]. GLP-1 binding to the GLP-1R promotes satiety by up and down regulating pro-opiomelanocortin and neuropeptide Y/Agouti-related peptide, respectively. Beyond homeostatic regulation, current evidence also supports the role of GLP-1 in hedonic feeding, which is driven by palatability rather than physiological need [52], and involves neurobiological pathways related to mesolimbic dopamine transmission and mechanisms related to reward processing [53]. GLP-1Rs are widely expressed in areas of the mesolimbic reward pathway (eg, VTA) that receive direct projections from the NTS [49]. GLP-1 exerts its effect on VTA and striatal dopamine levels by regulating hedonic hunger [54]. Activation of GLP-1Rs in these regions reduces consumption of palatable food and drug seeking and consummatory behaviors [53]. Next, we provide a summary of the growing literature on the promise of GLP-1 therapies for ASUDs. For a more comprehensive review, please see [55].

The effects of GLP-1RAs on alcohol use have been studied extensively. Preclinical studies in rodents and nonhuman primates show that exendin-4 (EX-4), and other GLP-1RAs (eg, dulaglutide, liraglutide, semaglutide) reduce alcohol intake and other alcohol-related outcomes in different rodent models and paradigms [55]. For example, a study showed that EX-4 suppressed alcohol-induced locomotion, accumbal dopamine release, voluntary alcohol consumption, and seeking behavior in mice [56]. Liraglutide, a longer acting GLP-1RAs, has also shown promising results in terms of reductions in alcohol intake, self-administration, and alcohol preference in rats [57, 58]. More recent studies have examined semaglutide and showed a dose-dependent reduction in alcohol intake in both dependent and non-dependent male and female mice and rats [59, 60]. Exenatide, liraglutide, and semaglutide have also shown to reduce alcohol consumption in non-human primates [61, 62], further supporting the potential of GLP-1RAs in treating AUD.

There have also been anecdotal human reports of reduced alcohol use posted on social media by patients using GLP-1RAs for other indications [63-65]. Furthermore, pharmacoepidemiological studies have examined electronic health records to explore associations between GLP-1RAs prescriptions and alcohol-related outcomes. A national cohort study conducted in Denmark showed a reduction in risk of alcohol-related events in those receiving GLP-1RAs [66]. Cohort studies have also shown promising results with GLP-1RAs in terms of alcohol intoxication, hospitalization, and AUD incidence/recurrence [67-69]. A recent pharmacoepidemiological study found that receipt of GLP-1RAs was associated with reduced Alcohol Use Disorder Identification Test Consumption scores, whereas DPP-4 inhibitors, another class of antidiabetic medications that increase endogenous GLP-1 levels (see Figure 1), had no effect of alcohol intake [70]. The latter observation was back-translated in a mouse model of alcohol binge-like drinking and in a rat model of alcohol dependence; in both cases, unlike GLP-1RAs, DPP-4 inhibitors did not reduce alcohol intake [70].

Only two randomized controlled trials (RCTs) with GLP-1RAs in the context of alcohol use have been published so far. The earlier RCT showed no significant effect of exenatide on alcohol consumption in people with AUD, although a

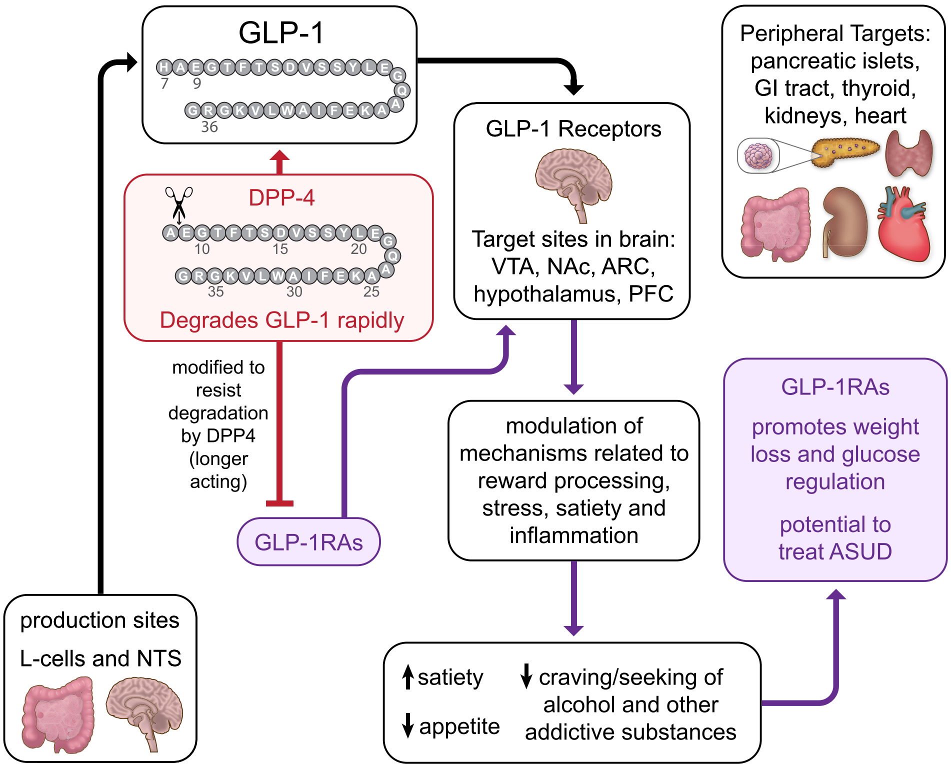

Figure 1. Overview of the effects of GLP-1 and GLP-1RAs. GLP-1 is mainly produced by the L cells in the intestines and the NTS in the brain. Endogenous GLP-1 is rapidly degraded by the enzyme DPP-4. GLP-1RAs are engineered to resist degradation by DPP-4, resulting in longer lasting and more potent effects of the drug. Peripheral targets include the pancreatic islets, gastrointestinal tract, thyroid, kidneys, and the heart, among others. GLP-1Rs are widely distributed in brain regions involved in reward processing, stress, satiety, and appetite regulation such as the VTA, NAc, ARC, PFC, and the hypothalamus. GLP-1-induced appetite suppression is not only mediated by interactions with GLP-1R in the hypothalamus, but also via the vagus nerve and the dorsal vagal/NTS complex. Activation of the GLP-1Rs expressed in these peripheral and central organs and tissues modulate various physiological pathways, thus promoting glucose regulation and weight loss. Furthermore, GLP-1RAs have the potential for treating ASUDs, as discussed in this review.

Abbreviations: ARC, arcuate nucleus; ASUDs, alcohol and other substance use disorders; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; PFC, prefrontal cortex; VTA, ventral tegmental area.

secondary analysis indicated reduced alcohol intake in the subgroup with AUD and comorbid obesity [71]. In addition, exenatide lowered dopamine transporter availability (observed via single-photon emission computed tomography) and reduced reactivity to alcohol cues in the ventral striatum and septal area, as observed via functional magnetic resonance imaging [71]. A more recent RCT showed that low-dose semaglutide reduced laboratory alcohol self-administration, as well as drinks per drinking days and craving, in people with AUD [72]. In a subgroup analysis, semaglutide also reduced number of cigarettes smoked per day in the subgroup of people with AUD who were also smokers.

In terms of opioid addiction, several GLP-1RAs have been shown to reduce self-administration and reinstatement of drug-seeking behavior for heroin, fentanyl, and oxycodone in rodent models [73-76]. Some studies, however, have produced negative results. For example, EX-4 had no effect on abuse-related effects of morphine and remifentanil in mice [77]. Although no RCTs have been published to date on the topic, pharmacoepidemiological data support the potential benefits of GLP-1RAs for people with OUD. Specifically, two separate analyses using electronic health records show that prescription of GLP-1RAs is associated with lower rates of opioid overdose [69, 78].

With regard to nicotine, preclinical data show that GLP-1RAs reduce nicotine self-administration, reinstatement of nicotine seeking, and other nicotine-related outcomes in rodents [56, 79, 80]. One study using pharmacological manipulations, as well as chemogenic/optogenetic stimulations, found a significant role of GLP-1 neurons in the habenula and its projections to promote nicotine avoidance [80]. A study that analyzed social media posts showed that around 23% of posts about nicotine reported a cessation in use in conjunction with GLP-1RAs [63]. A retrospective pharmacoepidemiological study analyzed electronic health records from people with comorbid T2DM and tobacco use disorder found that semaglutide, compared with other antidiabetic medications, was associated with improved smoking-related outcomes, including lower rates of medical encounters, smoking cessation prescriptions, and counseling [81]. The first RCT in the nicotine field tested exenatide as an adjunct to nicotine patch. Compared to placebo, exenatide promoted smoking abstinence, reduced nicotine craving and withdrawal, and attenuated postcessation weight gain [82]. A secondary analysis from this study found stronger effects of exenatide in heavy smokers, those normal blood glucose levels and/or weight, no/minimal depressive symptoms, and a specific nicotinic acetylcholine receptor genotype [83]. Another RCT tested dulaglutide as an adjunct to varenicline. Although dulaglutide did not promote smoking abstinence in this study [84], it did reduce alcohol intake [85]. Secondary analyses from this study found that dulaglutide attenuated postcessation weight gain in the short-term (3 months of active treatment) [84], but not in the long term (12 months posttreatment) [86].

In terms of stimulants, several preclinical studies have shown that EX-4 reduces cocaine seeking behavior, reinstatement, and other related outcomes [87-90]. Other studies have also found that GLP-1RAs reduce amphetamine use and amphetamine-induced hyperlocomotion in rodents [91-94]. Clinical research on the potential link between GLP-1 and stimulants remains limited. An experimental study showed that serum concentrations of GLP-1 reduced after intravenous cocaine administration in cocaine users [95]. The only study to date, to our knowledge, that examined a GLP-1RA in people with cocaine use disorder found no effect of exenatide on cocaine self-administration or subjective effects, albeit this study was limited by the fact that only a single dose of exenatide was administered [96].

The endocannabinoid system plays an important role in regulating body weight and an inverse relationship between cannabis use and BMI in humans has been reported (for review, see [97]). The link between the endocannabinoid system and body weight regulation was the foundation for the development of the cannabinoid CB1 receptor inverse agonist rimonabant as an effective medication in promoting weight loss in people with obesity. However, soon after its approval, rimonabant was removed from the market because of severe psychiatric side effects. As a consequence, more recent efforts have focused on the development of second- and third-generation CB1 receptor antagonists that are peripherally restricted and still produce the metabolic benefits of rimonabant in rodent models of obesity and diabetes without the central psychiatric side effects (for review, see [98]). Despite the breadth of knowledge on the role of the endocannabinoid system in appetite, body weight, and obesity, there is a paucity of preclinical or human studies on the link between cannabis use and GLP-1. A human laboratory study that involved oral, smoked, and vaporized cannabis administration found reduced peripheral GLP-1 under cannabis compared to placebo [99]. An analysis of social media posts from people on GLP-1RAs showed mixed results in terms of cannabis use. Most posts, however, discussed the opposite effects of GLP-1RAs and cannabis on appetite and nausea [63]. A pharmacoepidemiological study found that semaglutide, compared to other non-GLP-1RA antiobesity and anti-T2DM medications, was associated with lower risks of incident and recurrent cannabis use disorder diagnosis [100].

In summary, preclinical studies have consistently demonstrated the potential of GLP-1RAs in reducing the consumption and rewarding properties of various substances, including alcohol, opioids, nicotine, and psychostimulants. Effects of GLP-1RAs appear to be mediated through the modulation of reward pathways, stress regulation, and cognitive function in the CNS, as well as a host of functions in the periphery. Although clinical studies remain limited for most substances, early results showing reductions in cravings, substance use, and other related outcomes are encouraging.

GLP-1RAs and ASUDs: Gaps and Future Directions

Despite promising evidence that supports the potential of GLP-1RAs in ASUD treatment, additional research is needed. On the basic science side, more studies are needed to unveil the mechanisms underlying GLP-1RAs in relation to addictive behaviors and substance use. On the clinical side, RCTs are critically needed to investigate the safety and efficacy of GLP-1RAs in patients with ASUDs [101, 102]. Based on the existing evidence, and pending further clinical and translational research, GLP-1RAs have the potential to help people with polysubstance use, as well as those with medical comorbidities—phenotypes that are more the norm than exception in addiction medicine.

As the use of GLP-1RAs continues to rise, a thorough evaluation of their safety profile is essential. GLP-1RAs have certain side effects, mostly involving the gastrointestinal system, including nausea (the most frequently reported side effect), diarrhea, constipation, dyspepsia, and vomiting [103]. It is also important to consider that long-term use of GLP-1R agonists may have adverse effects on muscle mass, composition, and function, and that many patients with ASUDs already have nutritional problems and/or sarcopenia [104].

Although these side effects typically present in a transient mild to moderate manner, they must be carefully evaluated if GLP-1RAs will be used in patients with ASUD, who often have complex medical comorbidities. As previously discussed, ASUDs carry their own complications and are associated with increased risk of multiorgan system complications. Alcohol is a major cause of pancreatitis, and GLP-1RA use also increases the risk of pancreatitis in some cases; however, the overall risks associated with alcohol use outweigh the comparatively low incidence of serious GLP-1RA-related adverse effects. Such considerations underscore the need to conduct a patient specific risk-benefit analysis to ensure that outcomes are in the best interest of the patients being treated.

There have been reports of rebound weight gain after stopping long-term GLP-1RA treatment. It has been speculated that stopping the GLP-1RA treatment can result in the loss of balance in appetite regulation, though the specific underlying mechanisms remain unclear [105]. Furthermore, most patients who start treatment with GLP-1RA for obesity discontinue treatment within 1 year because of side effects, high cost, or reaching a plateau in weight loss [106]. A similar trend could occur with the use of GLP-1RAs for ASUDs, although additional research is needed.

Although not conclusive, there have also been reports of depression in those who take GLP-1RAs, raising some concerns about potential increase in risks of self-harm and suicidality. However, the European Medicines Agency [107] and the FDA [108] have issued statements that current data do not support an association between the use of GLP-1RAs and increased suicidal ideation/behavior. A recent study applied the Bradford Hill criteria to investigate this potential association, while considering confounding variables; it showed that there was no evidence of a causal relationship between the FDA-approved GLP-1RAs and suicidality [109]. Yet, this is still a topic that requires further evaluation and monitoring.

Future research should also investigate the efficacy of combination therapies involving GLP-1RAs with existing FDA-approved treatments for ASUDs to better understand potential synergistic beneficial effects. Furthermore, future research should aim to develop personalized treatment protocols that optimize dosing and duration according to patient specific factors, such as severity of ASUD, comorbid conditions, and basal metabolic activity.

Several higher level factors must also be considered in the GLP-1RAs/addiction arena. First, the high cost of novel GLP-1RAs limits accessibility, especially for those from underserved communities. Second, we need to further investigate the tolerability, safety, and effectiveness of these drugs in people with ASUD [101]. Finally, it is important to keep in mind that we are still in the early stages of understanding the potential role of GLP-1RAs in addiction treatment and more and larger RCTs are needed. Case in point, several RCTs are currently ongoing or close to begin testing GLP-1RAs, dual and poly-agonists (eg, tirzepatide, pemvidutide, cagrilintide) in ASUDs. The number of these trials keep growing and include RCTs in patients with AUD (NCT05895643, NCT06015893, NCT05891587, NCT05892432, NCT06994338, NCT06987513), and in patients with AUD and comorbidities such as schizophrenia (NCT06939088), alcohol-associated liver disease (NCT 06546384; NCT06409130) and Human Immunodeficiency Virus infection (NCT07040592). Ongoing RCTs in other substance use disorders include studies in people with tobacco use disorder (NCT06924697, NCT06015893, NCT06986993, NCT06173778; U01DA064384), OUD (NCT04199728, NCT06639464, NCT06548490 and NCT06651177), and cocaine use disorder (NCT06252623), including an RCT in patients with cocaine use disorder and Human Immunodeficiency Virus infection (NCT06691243).

Conclusions

GLP-1RAs, traditionally prescribed for glycemic control in T2DM and weight management in obesity, are emerging as promising therapies for ASUDs. Preclinical and early clinical investigations suggest that GLP-1RAs modulate neurobiological pathways underlying addictive behaviors, thereby potentially reducing substance craving and use while simultaneously addressing comorbid conditions. Despite these encouraging findings, the long-term efficacy and safety of GLP-1RAs and their potential role in addiction medicine needs to be explored further.

Considering the rising global prevalence and burden of ASUDs, future research should prioritize large-scale RCTs and real-world studies that encompass diverse populations. Although basic research should continue to explore the mechanisms of GLP-1RAs in modulating addictive behaviors, human research is needed to examine the safety and efficacy of GLP-1RAs, optimize dosing strategies, and evaluate their utility as part of combination therapies with established pharmacological and behavioral interventions.

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Data Availability

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

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