Review

Glucagon-Like Peptide-1 Receptor Agonists: A New Frontier in Treating Alcohol Use Disorder

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Review

Glucagon-like Peptide-1 Receptor Agonists: A New Frontier in Treating Alcohol Use Disorder

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Abstract: Background/Objectives: Glucagon-like peptide-1 receptor agonists (GLP-1RAs), which were originally developed for managing type 2 diabetes by enhancing insulin secretion and reducing appetite, have emerged as promising candidates in alcohol use disorder (AUD). These medications offer a dual mechanism of action that aligns with the multifaceted nature of addiction by targeting both peripheral metabolic and central reward pathways. This Review focused on the current clinical trials and real-world evidence regarding the effects of GLP-1RAs as novel therapeutics for AUD. We also discussed early but encouraging results from clinical trials in AUD, observational and real-world evidence, safety profile and psychiatric considerations, and future directions leading beyond GLP-1RAs. **Methods:** A comprehensive literature search was conducted across major databases (PubMed, Medline, Google Scholar, and Web of Science). Studies were included if they examined the relationship between GLP-1RA and AUD. **Results:** Out of 1,080 records identified, seven studies met the inclusion criteria. Findings from recent clinical trials, large-scale observational studies, and real-world evidence suggest that GLP-1RAs may significantly reduce alcohol consumption, cravings, and alcohol-related hospitalizations. Their central effect on reward processing, coupled with a generally favorable safety profile, supports their potential therapeutic role beyond metabolic disorders. **Conclusions:** Emerging evidence positions GLP-1RAs as a promising new pharmacologic approach for managing AUD. Ongoing and future research should prioritize larger, longer-duration randomized controlled trials that include diverse populations, with specific attention to treatment motivation, co-occurring psychiatric conditions, and long-term outcomes.

Keywords: GLP-1; GLP-1RA; AUD; Addiction; Substance Use Disorder

1. Introduction

As of 2024, glucagon-like peptide-1 receptor agonists (GLP-1RAs) rank among the top-selling drugs globally and are gaining recognition as potential therapeutic agents for alcohol use disorder (AUD), with growing interest in their roles in modulating alcohol consumption and alcohol craving (**Table 1**).

Table 1. Top ten drugs by sales globally in 2024.

Rank	Drug Name Manufacturer	Sales US$ (Billions)	Indication(s)	Pharmacological class
1	Keytruda (Pembrolizumab) Merck	29.5	Various cancers	Anti-PD1 monoclonal antibody
2	Ozempic (Semaglutide) Novo Nordisk	16.1	Type 2 diabetes and weight loss	GLP-1RA
3	Dupixent (Dupilumab) Sanofi/Regeneron	13.5	Severe atopic dermatitis, asthma, and other condition	Anti-IL4/IL13 monoclonal antibody

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4	Eliquis (Apixaban) BMS/Pfizer	13.3	Anticoagulation	Factor Xa inhibitor
5	Biktarvy (Bictegravir/emtricitabine/tenofovir alafenamide) Gilead	12.6	Infectious Diseases (HIV)	HIV treatment
6	Darzalex (Daratumumab) J&J	12	Multiple myeloma	Anti-CD38 monoclonal antibody
7	Opdivo (Nivolumab) BMS/Ono Pharma	11.3	Various cancers	Anti-PD1 monoclonal antibody
8	Comirnaty (Tozinameran) Pfizer/BioNTech	10.8	Infectious Diseases (COVID19)	SARS-COVID19 vaccine
9	Gardasil (Gardasil 9) Merck/CSL	10	Infectious Diseases (HPV)	HPV vaccine
10	Skyrizi (Risankizumab-rzaa) AbbVie	9.9	Various autoimmune disorders	Anti-IL23 monoclonal antibody

AUD is the most common substance use disorder (SUD) worldwide [1]. Current Food and Drug Administration (FDA)-approved pharmacotherapy for AUD includes disulfiram, acamprosate and naltrexone. However, approximately 50% of patients do not experience optimal outcomes, underscoring the urgent need for more effective anti-craving treatments [2,3].

GLP-1RAs have emerged as promising candidates in addiction medicine due to recent clinical and real-world evidence demonstrating their potential as a novel and effective therapy for AUD [4–6]. GLP-1RAs were originally developed for managing type 2 diabetes by enhancing insulin secretion and reducing appetite [7]. Several studies suggest that semaglutide may have a potential benefit for patients with AUD in real-world populations [4,8]. Also, a recent clinical trial showed that exenatide, which crosses the blood-brain barrier [9] significantly reduced heavy drinking days and total alcohol intake in a subgroup of obese patients, as determined by body mass index (BMI) > 30 kg/m2 [4]. GLP-1RAs have shown promising effects on the brain's reward system, particularly in regulating dopamine signaling, which plays a critical role in addictive behaviors. However, the precise mechanism remains to be elucidated [10].

GLP-1 is a 30-amino acid peptide produced by the cleavage of proglucagon. It is synthesized in the intestinal mucosal L-cells, pancreatic islet α-cells, and neurons in the nucleus of the solitary tract [11]. Dipeptidyl peptidase IV (DPP-4) catalyzes the enzymatic degradation of GLP-1, which results in the loss of its biological efficacy [11]. GLP-1 binds to GLP-1 receptor (GLP-1R), a core member of the G protein-coupled receptor (GPCR) family, which in turn regulates blood glucose levels and lipid metabolism. GLP-1 is also synthesized in the brain and plays a pivotal role in neuroprotection through the activation of GLP-1 receptor signaling pathways [12]. It augments learning and memory processes in the hippocampus, facilitates neurogenesis, diminishes inflammation and apoptosis, modulates reward behavior, and decreases food consumption. Its pharmacokinetics have been improved to enhance the peptide's half-life, enhancing exposure and time of action. GLP-1 agonists are currently in clinical use for the treatment of type-2 diabetes, obesity, and clinical evaluation for the treatment of neurodegenerative diseases. Due to its very short plasma half-life (1.5–5 minutes), GLP-1 has limited therapeutic utility [13]. To overcome its pharmacokinetic limitations, longer-acting GLP-1RAs have been developed that are resistant to DPP-4 degradation and renal clearance.

Several GLP-1RAs have been approved by the United States FDA for the treatment of type 2 diabetes or weight management (**Table 2**). Because of the poor bioavailability of peptide drugs, most GLP-1 RAs are administered as subcutaneous injections on a daily or weekly basis. Notably, the half-lives of GLP-1RAs and analogs vary depending on the specific formulation and individual differences. Additionally, Tirzepatide is a first-in-class dual incretin receptor agonist that targets both the GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) receptors, which are four-amino acid peptides produced by the K cells of the duodenum and jejunum. Triple agonists (glucagon, GIP, and GLP-1 receptors), like retatrutide, have not yet been evaluated in the context of AUD. This

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Review focused on the current clinical trials and real-world evidence with regard to the effects of GLP-1RAs as novel therapeutics for AUD. We also discussed early but encouraging results from clinical trials in AUD, observational and real-world evidence, safety profile and psychiatric considerations, and future directions leading beyond GLP-1RAs.

Table 2. FDA-Approved GLP-1RAs.

GLP-1RA	Half life	Molecular formula	Approval year	Indication
Exenatide	2-4 hours	$C_{149}H_{234}N_{40}O_{47}S$	2005	Type 2 diabetes
Liraglutide	12-13 hours	$C_{172}H_{265}N_{43}O_{51}$	2010	Type 2 diabetes
Albiglutide	4-7 days	$C_{148}H_{224}N_{40}O_{45}$	2014	Type 2 diabetes
Dulaglutide	5-6 days	$C_{2646}H_{4044}N_{704}O_{836}S_{18}$	2014	Type 2 diabetes
Semaglutide	~7 days	$C_{187}H_{291}N_{45}O_{59}$	2017	Type 2 diabetes
Tirzepatide*	12-13 hours	$C_{225}H_{348}N_{48}O_{68}$	2022	Type 2 diabetes

*Tirzepatide is a dual GIP and GLP-1 receptor agonist.

2. Methods

A comprehensive literature search was conducted for this Review using the following academic databases: PubMed, Medline, Google Scholar, and Web of Science. The search was limited to English-language articles, with no restrictions on ethnicity or geographical location. Keywords used included: 'GLP-1RA' and 'AUD', 'alcohol use disorder', 'human study', 'novel treatment', 'GLP-1', 'GLP-1 and GIP', 'clinical trial', and 'real world data'. Studies were excluded if they were off-topic or not published in English. We then carefully reviewed the remaining articles to assess their relevance. Specifically, our inclusion criteria encompassed both clinical trials and observational studies that examined the effects of GLP-1RAs in the context of AUD. In addition, we searched ClinicalTrials.gov, EudraCT, and relevant conference abstracts to identify additional eligible studies and ongoing trials.

3. Results

A total of 1,080 results were retrieved. Following a thorough screening process, seven studies, including three double-blind placebo control studies and four observational studies, were deemed relevant and subsequently included in this Review (**Table 3**). These selected human clinical studies assess the effectiveness of GLP-1RAs in the human population, focusing on their associations with alcohol use, brain activity, alcohol cravings, and cognitive function. Beyond clinical trials, this Review also incorporates real-world data analyses and large-scale observational studies (**Table 3**).

Table 3. Summary of Clinical Trials and Real-world Data for GLP-1 Receptor Agonists (GLP-1RAs) in Alcohol Use Disorder (AUD).

Study	Study Design	Participants	Treatment	Control	Outcome Measures	Key Findings
Klausen et al., 2022	DBRCT Single-site 26 weeks treatment + 6-month follow-up N:127	Treatment-seeking heavy drinkers with AUD	Exenatide 2 mg SC weekly + CBT (N:65)	Placebo injection + CBT (N:62)	Number of heavy drinking days, as determined by TLFB. .fMRI alcohol cue reactivity. iii.SPECT-DAT .Alcohol craving, as determined by PACS.	i.No significant reduction in heavy drinking days overall. ii.In obese subgroup (BMI > 30), reduced heavy drinking days and monthly alcohol intake. ii.Reduced fMRI alcohol cue reactivity in key reward areas.

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						iv.Reduced SPECT-DAT availability in striatum at Week 26. v.No significant change in craving despite imaging findings.
Probst et al., 2023	DBRCT Single-site 12 weeks treatment + 6-month follow-up N:151	Patients in smoking cessation trial with comorbid AUD	Dulaglutide 1.5 mg SC weekly + varenicline + counseling (N:76)	Placebo injection + varenicline + counseling (N:75)	Alcohol consumption (questionnaire analogous to TLFB).	i.Participants receiving dulaglutide drank 29% less than participants receiving placebo. .Changes in alcohol use were not correlated with smoking status at week 12.
Hendershot et al., 2025	DBRCT Single-site 9 weeks treatment + 1week follow-up N:48	Non-treatment-seeking individuals with AUD	Semaglutide 0.25 mg escalating to 1.0 mg SC weekly (N:24)	Placebo injection (N:24)	.Grams of alcohol consumed (lab setting). ii.Peak breath alcohol concentration (BAC). iii.Alcohol consumption (TLFB). *v*.Weekly alcohol craving (PACS).	i.Medium to large effect size for alcohol reduction. ii.Decreased drinks per drinking day and craving. ii.Treatment of semaglutide reduced heavy drinking.
Wium-Andersen et al., 2022	Denmark Nationwide Retrospective Cohort Study 2009 – 2018 Median 4.1 years follow-up N: 87676	New users of GLP-1RAs or DPP-4 inhibitors	All GLP-1RAs (N:38454)	DPP4 inhibitors (DPP-4i) (N:49222)	The association between use of GLP-1 receptor agonists and the risk of subsequent alcohol-related events in Danish adults. The alcohol-related events measured by the following: (1) Hospital contacts with a main diagnosis of AUD in the Danish National Patient Registry, (2) registered treatments for alcoholism in the National Registry of Alcohol Treatment or (3) purchase of the benzodiazepine chlordiazepoxide, which is used for alcohol withdrawal syndrome or purchase of a	i.GLP-1 receptor agonist use was associated with a lower risk of a subsequent alcohol-related event compared with DPP-4i use both within the 90 days after initiation, and 1 year of follow-up. .However, the self-controlled design—which efficiently accounts for unmeasured between person confounding, demonstrates that the initiation of GLP-1 receptor agonist treatment was also associated with a lower risk of an alcohol-related event compared with the non-treatment period but only during the first 3 months after treatment. ii.Overall, this study did not support GLP-1 RAs as an effective alternative to the existing treatment of AUD.

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				medication against alcohol dependence.		
Qeadan et al., 2024	USA De-identified electronic health record data from the Oracle Cerner Real-World Data. Retrospective Cohort Study 2014 – 2022 Up to 2 years follow-up N:817309	Patients with AUD	GIP and/or GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, tirzepatide) (N:5621)	No GIP/GLP-1 RA prescription (N:811688)	Alcohol intoxication events.	.Treatments with GIP and/or GLP-1 RAs were associated with a 50% reduction in alcohol intoxication events.
Wang et al., 2024	USA De-identified patient electronic health records within the TriNetX Platform. Retrospective Cohort Study 2017 – 2022 Up to 3 years follow-up N:83825	Patients with obesity and/or T2DM	Semaglutide (N:45797)	Other anti-obesity and anti-diabetic medications: naltrexone and topiramate (N:38028)	Incident and recurrent AUD.	i.Semaglutide was associated with a significantly lower risk of incident AUD diagnosis, as compared to naltrexone or topiramate. i.Semaglutide was associated with lower risk of recurrent AUD diagnosis, as compared to non-GLP-1RA anti-obesity medications, i.e. naltrexone and topiramate. iv.
Lähteenvuo et al., 2025	Swedish nationwide electronic registries. Retrospective Cohort Study 2006 – 2023 Median 8.8 years follow-up N:227868	Patients with AUD	Semaglutide, Liraglutide, Exenatide, Dulaglutide (N:6276)	Other AUD medications (N:75454)	i.The primary outcome was AUD hospitalization. ii.Secondary outcomes were any substance use disorder (SUD)-related hospitalization, somatic hospitalization, and suicide attempt.	i.Semaglutide and liraglutide may be effective in the treatment of AUD. i.Semaglutide and liraglutide lower alcohol-related hospitalization. i.Semaglutide and liraglutide lower hospitalization due to somatic reasons v.Use of GLP-1RAs was not associated with suicide attempt.

Abbreviations: AUD: Alcohol Use Disorder; CBT: cognitive-behavioral therapy; DBRCT: Double Blind, Randomized, Placebo-Controlled Clinical Trial; DPP-4: Dipeptidyl peptidase-4; fMRI: Functional Magnetic Resonance Imaging; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1RA: Glucagon-like Peptide 1 Receptor Agonist; PACS: Penn Alcohol Craving Score; SC: subcutaneous; SPECT: Single-Photon Emission Computerized Tomography; T2DM: Type 2 Diabetes Mellitus; TLFB: Timeline Follow Back; USA: The United States of America.

3.1. Clinical Trials: Early but Promising Results

The therapeutic potential of GLP-1RAs in AUD was first suggested in a cross-sectional study investigating liraglutide in patients with type 2 diabetes, where reduced alcohol consumption was observed as a secondary finding [14]. In 2022, Klausen *et al.* published the first randomized clinical

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trial (RCT) to investigate the effects of GLP-1RAs on alcohol consumption, brain function, and alcohol craving in patients with AUD [15] (**Table 3**). Specifically, Klausen *et al.* evaluated the effects of exenatide in treatment-seeking individuals with AUD. Although exenatide did not significantly reduce heavy drinking days compared to placebo overall, a subgroup with BMI >30 kg/m² experienced notable reductions in both heavy drinking days and total alcohol intake over the past 30 days [15]. In addition, the neuroimaging study revealed that the exenatide group exhibited reduced alcohol cue reactivity in reward- and addiction-related brain regions, especially the ventral and dorsal striatum. Whole-brain fMRI analyses further demonstrated decreased activation in the left caudate, septal area, and right frontal cortex after 26 weeks of exenatide treatment. These findings suggest that exenatide may decrease the brain's reward response to alcohol-related cues. Moreover, single-photon emission computed tomography (SPECT) scans showed significantly lower dopamine transporter (DAT) availability in reward-processing areas among those receiving exenatide compared to placebo. However, no significant differences were observed in subjective alcohol craving or cognitive performance between groups [15].

Subsequently, Probst *et al.* conducted a randomized controlled trial to investigate the effects of dulaglutide on alcohol consumption during smoking cessation [16] (**Table 3**). The study reported a 29% reduction in alcohol use compared to placebo [16]. Importantly, these benefits occurred regardless of the smoking status, indicating that GLP-1RAs may have independent effects on alcohol use. It should be noted that this trial was initially designed to study the effect of dulaglutide on smoking cessation. Thus, the participants did not *per se* suffer from AUD, and the subgroup of heavy drinkers was too small to provide conclusive evidence [16].

More recently, Hendershot *et al.* published a phase 2 trial in 2025, evaluating semaglutide in non-treatment seeking patients [17]. This study found that low dose semaglutide significantly reduced alcohol craving, the number of drinks per drinking day, and heavy drinking episodes, with medium to large effect sizes. However, it did not impact the number of drinking days or average drinks per day. These mixed but encouraging results highlight the complexity of treating AUD and the need to tailor interventions to individual patterns of alcohol use and motivation for treatment [17]. Notably, participants in both Probst and Hendershot's studies were not seeking treatment for AUD [16,17]. Underscoring the potential utility of GLP-1RAs in broader, real-world clinical contexts. Given that the majority of individuals (~90%) with AUD do not seek formal treatment [18]. The efficacy of these medications in non-treatment-seeking populations suggests they may still provide benefits when prescribed for other conditions [19].

3.2. Real-World and Observational Evidence

Beyond clinical trials, observational studies using electronic health records and national registries have provided real-world evidence supporting the therapeutic potential of GLP-1RAs for AUD. Wium-Andersen *et al*. investigated whether GLP-1RA use was associated with a reduced risk of alcohol-related events using information on the entire Danish population from nationwide registers [2]⁰. Alcohol-related events were defined as (1) hospital contacts with a main diagnosis of alcohol use disorders (international classification of diseases [ICD]-10 code *DF10*) in the Danish National Patient Registry, (2) registered treatments for alcoholism in the National Registry of Alcohol Treatment or (3) purchase of the benzodiazepine chlordiazepoxide (ATC code *N05BA02*), which is used for alcohol withdrawal syndrome or purchase of a medication against alcohol dependence (ATC code *N07BB*), registered in the Danish National Prescription Registry. GLP-1 receptor agonist users (n= 38544) and users of dipeptidyl peptidase-4 (DDP-4) inhibitors (n= 49222) were included in the analysis. This study suggests that use of GLP-1 receptor agonists was associated with a lower risk of a subsequent alcohol-related event compared with use of DPP-4 inhibitors after adjustment for covariates. It should be noted that the initiation of GLP-1 receptor agonist treatment was also associated with a lower risk of an alcohol-related event compared with the non-treatment period, however, this was observed only during the first three months after treatment initiation. However,

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the study concluded that GLP-1RAs did not appear to be effective alternatives to current AUD treatments (**Table 3**) [2][0].

In the United States, Qeadan *et al.* analyzed data from over 817,000 individuals with a documented history of AUD from the Oracle Cerner Real-World Data. This study found that prescriptions for GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide) and gastric inhibitory polypeptide (GIP) receptor agonists (tirzepatide; dual agonist for GLP1 and GIP) were associated with a 50% reduction in alcohol intoxication events, compared to those without a prescription for GIP/GLP-1 RA. When stratified by type 2 diabetes, obesity, as well as type 2 diabetes and obesity, the rate of incident alcohol intoxication for those with a GIP/GLP-1 RA prescription was 49% lower, 42% lower, and 42% lower, respectively, as compared to those without GIP/GLP-1 RA prescriptions among subjects with AUD (**Table 3**) [21].

Wang *et al.* conducted a large retrospective cohort study using electronic health records from the TriNetX Platform. Of 83825 patients with obesity who had no prior diagnosis of AUD, 45797 subjects were first prescribed semaglutide, and 38028 subjects were non-GLP-1RA anti-obesity medications, including naltrexone or topiramate, during June 2021–December 2022. After propensity-score matching, the two cohorts (n=26566 in each group, mean age 51.2 years, 65.9% women, 15.8% black, 66.6% white, 6.5% Hispanic) were balanced. Matched cohorts were followed for one year after the index event. In patients with obesity or type 2 diabetes, semaglutide significantly decreased the risk for incident and AUD relapse when compared to non-GLP-1RA anti-obesity drugs like topiramate or naltrexone (**Table 3**) [22].

More recently, Lähteenvuo *et al.* analyzed Swedish nationwide registries to determine whether GLP-1RA use decreased the risk of hospitalization for AUD [22]. Among 227,868 individuals with AUD, semaglutide and liraglutide were associated with the lowest risks of hospitalization for both AUD and other SUDs. In contrast, other GLP-1RAs did not show similar effects. Surprisingly, except for naltrexone, FDA-approved AUD medications (acamprosate, disulfiram) were not associated with reduced hospitalization risk. Additionally, these medications were linked to a small but significant increase in suicide attempt risk (adjusted hazard ratio (aHR), 1.15, 95% CI, 1.08-1.22), whereas GLP-1RAs, including semaglutide, were not (semaglutide: aHR, 0.55, 95% CI, 0.23-1.30) (**Table 3**) [23]. These findings should be interpreted cautiously due to differing comparator groups and potential confounding [23].

While these observational studies cannot establish causality, their consistency across diverse populations and study designs strengthens the case for continued investigation of GLP-1RAs as therapeutic agents for AUD. GLP-1RAs are noteworthy as important candidates for upcoming randomized trials in AUD, as the epidemiological evidence in the metabolic and psychiatric domains has come together.

3.3. Safety and Considerations

The most reported side effects are gastrointestinal in nature—primarily nausea, vomiting, and diarrhea. These symptoms are generally dose-dependent and temporary but can lead to dehydration and, in rare instances, pre-renal acute kidney injury [24]. Despite the therapeutic potential of GLP-1RAs, concerns have been raised regarding potential neuropsychiatric side effects, including depressive symptoms and suicidality. Klausen *et al*. reported a case who died from suicide two months after discontinuing semaglutide; however, no causal link was addressed [15]. Similarly, several observational studies have also raised concerns about a potential link between GLP-1RAs and the increased risk of depressive symptoms and suicidality [25,26]. However, more recent evidence counters these concerns. Specifically, a large nationwide cohort study conducted in France found no short-term increase in suicide risk among users of GLP-1RAs [27]. Similarly, a meta-analysis of 27 randomized controlled trials reported no significant association between GLP-1RA use and suicidality [28]. Additionally, Lähteenvuo *et al.* reported that semaglutide was not associated with increased suicide risk, whereas FDA-approved AUD medications were linked to a modestly

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increased risk [23]. Additional studies have likewise found no clear association between GLP-1RA use and suicidality [29–33], further supporting the overall neuropsychiatric safety of this drug class.

4. Discussion and Future Perspectives

4.1. GLP-1RAs in AUD: Clinical Trial Evidence and Obesity Stratification

Clinical trials investigating the role of GLP-1RAs in AUD are still in the early stages, but initial findings are encouraging. GLP-1RAs are thought to influence motivation and reward-related behaviors primarily by modulating the brain's reward system, particularly dopamine signaling pathways in the mesolimbic circuit [34]. GLP-1 receptors are expressed in key regions involved in reward processing, including the nucleus accumbens and ventral tegmental area. Activation of these receptors has been shown to reduce drug-seeking behaviors [35,36]. Human neuroimaging studies, such as those by Klausen *et al*., confirmed these findings by demonstrating decreased activation in alcohol cue-reactive brain regions following exenatide administration [4]. Despite no significant reduction in heavy drinking days in patients with AUD overall, when patients were stratified by obesity status, as determined by BMI >30, significant reductions in heavy drinking days and monthly alcohol intake were observed in patients with BMI >30. Although the mechanisms underlying this differential response remain unclear, prior research has shown that pharmacokinetic and pharmacodynamic responses to GLP-1RAs vary between lean and obese individuals [37]. Specifically, intravenous exenatide infusion caused an 18.5-fold increase in insulin secretion in lean individuals compared with an 8.8-fold increase in obese individuals [37]. However, exenatide significantly inhibited the fMRI signal in amygdala, insula, hippocampus, and frontal cortex in response to food pictures in obese individuals, but it did not affect the brain fMRI signal in lean participants [37], suggesting that metabolic phenotype may influence modulate central nervous system responses.

4.2. Observational Evidence and Real-World Relevance

Observational and real-world studies using large datasets and national registries provide compelling evidence of the association between GLP-1RA use and reduced alcohol-related outcomes. Studies from Denmark, the United States, and Sweden consistently found lower rates of alcohol-related hospital visits, intoxication events, and AUD recurrence among individuals taking GLP-1RAs compared to those on other antidiabetic or anti-obesity medications (**Table 3**). The convergence of findings across diverse populations and methodologies strengthens the case for a real therapeutic signal and suggests that these medications may exert beneficial effects across a range of real-world clinical contexts, including patients with comorbid conditions i.e., obesity and type 2 diabetes. While observational studies are valuable for detecting real-world patterns, they cannot establish causality and may be subject to confounding.

4.3. Safety Profile and Psychiatric Considerations

GLP-1RAs are generally well-tolerated, with gastrointestinal symptoms being the most common adverse events [36]. However, concerns have been raised about potential neuropsychiatric side effects, particularly suicidality. Although isolated case reports and some observational studies suggest a possible link [36,38], the majority of evidence, including large cohort studies and meta-analyses, has not demonstrated a significant increase in suicide risk [25,26]. On the contrary, Wang *et al.* reported that semaglutide may confer a lower risk for recurrence suicidal ideation compared to naltrexone or topiramate in patients with overweight or obesity, as compared to patients treated with non-GLP-1RA anti-obesity medication group (HR: 0.44, 96% CI: 0.32-0.60, n= 865 each group after propensity score matching) [8]. Some data suggest that GLP-1RAs may pose a lower suicide risk compared to traditional AUD medications, a finding that warrants further investigation [3]0. Xie et al. performed a retrospective study using the US Department of Veterans Affairs databases (n=

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1955135) and reported that GLP-1RA use was associated with a reduced risk of a series of SUDs including AUD, opioid use disorder, cannabis use disorder, and stimulant use disorder [39], and suicidal ideation, attempt, or intentional self-harm in patients with diabetes, as compared to patients with diabetes who initiating other anti-diabetes medications, including sulfonylureas, DPP-4 inhibitors or sodium−glucose cotransporter-2 inhibitors [39]. Additionally, a recent meta-analysis study showed that GLP-1RAs induced significant reductions in the depression rating scales compared to control treatments [4]0. These studies added to the body of evidence on the potential benefits of GLP-1RAs in the treatment of neuropsychiatric disorders. They also highlight the need for additional research into the biology and efficacy of GLP-1RAs as a primary or adjuvant treatment for the treatment of SUDs, psychotic disorders, and depressive disorders.

To date, three double-blind, randomized, placebo-controlled clinical trials have investigated the use of GLP-1RAs in AUD (**Table 3**). Notably, these studies have small sample sizes and short follow-up durations. Moreover, the heterogeneity in alcohol use patterns, treatment-seeking behavior, and comorbidities among patients complicates efforts to draw broad conclusions about efficacy. The study duration of the included studies listed in **Table 3** may not be sufficient to assess the long-term effects of GLP-1RAs on depressive symptoms. There were variations across included studies, including primary diagnosis (obesity, type 2 diabetes, or AUD), the agents and dosages of GLP-1RAs, and control treatments. Despite these limitations, the available evidence suggests that GLP-1RAs hold therapeutic promise for individuals with AUD.

A major limitation in current GLP-1RA clinical research is the frequent exclusion of individuals with comorbid psychiatric conditions, including co-occurring substance use disorders, depression, or suicidal ideation. Many trials enforce strict exclusion criteria for safety reasons, commonly omitting participants with recent psychiatric hospitalization, active, or a history of suicidal ideation, or a history of suicide attempts. While these precautions are ethically sound, they reduce the generalizability of findings and may obscure the true risk profile of GLP-1RAs in real-world AUD populations, where psychiatric comorbidities are prevalent. For example, individuals with AUD face elevated risks of both depression and suicidality, yet those most at risk are often underrepresented or entirely excluded from trials [41–43]. This is evident in the study by Hendershot *et al.* (see **Table 3**), which excluded participants with recent suicidal ideation, a history of suicide attempts, or psychiatric hospitalization within the previous six months. Although large-scale observational studies and meta-analyses to date have not found a significant association between GLP-1RA use and suicidality, existing trials may lack sufficient power or population diversity to detect such risks in individuals with AUD. Therefore, more inclusive and longer-term studies are needed to better assess both the therapeutic potential and safety of GLP-1RAs in this high-risk population.

4.4. Toward Precision Psychiatry and Future Directions

The efficacy of GLP-1RAs in treating AUD and metabolic diseases varies across agents [44,45], suggesting a need for individualized treatment strategies. Precision psychiatry is an emerging field that aims to tailor mental health care to individuals. To date, only three medications (disulfiram, acamprosate, and naltrexone) have been approved by the United States FDA for the treatment of AUD in the United States. Alcohol clinical trials have been conducted on more than 30 different drugs in the past three decades [46]. However, most of those clinical trials either showed no significant impact or the effect size was minimal [46]. This may be true, at least in part, due to **1**) the heterogeneity of AUD phenotypes and **2**) critical knowledge gaps underlying the pathophysiology of AUD and the mechanisms of action of the medications to treat AUD. Although DSM-5, a symptom-based tool, is used to assist in the diagnosis of mental disorders, its accuracy is not questionable. However, psychiatry lacks biological tools to evaluate or predict clinical outcomes using biological and objective measures. The promise of precision psychiatry lies in understanding the complex interplay of biological and environmental factors, ultimately leading to personalized diagnosis, treatment, and prevention strategies.

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GLP-1RAs are believed to influence alcohol-related behaviors by modulating the brain's reward system, particularly dopaminergic signaling in the mesolimbic pathway. To further elucidate the underlying mechanisms responsible for individual variation in drug treatment response, the patient-derived induced pluripotent stem cell (iPSC) model system offers a valuable platform for investigating the cellular and molecular effects of GLP-1RAs in the central nervous system. Importantly, these personalized models can recapitulate human brain tissue, which could be a useful tool to determine individual variability in drug response, potentially guiding future drug development and clinical trial design.

The effectiveness of GLP-1RAs varies, and it has been noted that this is due, at least in part, to differences in the molecular formula (**Table 2**). Consequently, the half-life and PK/PD profiles are different, suggesting a need for individualized treatment strategies [44,45]. Each drug, even within the same drug class, may possess distinct molecular profiles and mechanisms of action, thereby highlighting the necessity of patient-derived *in vitro* cell models to evaluate drug action in the brain [47–49]. Although current in vitro assays and in vivo models designed to discover potential therapeutic targets in psychiatry are useful, there is an urgent need to establish patient-derived model systems to complement studies that use other models for neuropharmacology research. The patient-derived iPSC model system offers distinct strengths, including **1)** working with cells that retain the patients' unique genetic background, **2)** the ability to recapitulate human brain tissue, and **3)** the ability to experimentally manipulate live brain-like cells, which is the beauty of the iPSC-based cell model system. Understanding of how GLP-1RAs work at the cellular and molecular levels could potentially identify new drug targets and drug repurposing opportunities for AUD. The patient-derived iPSC cell model could catalyze a paradigm shift that will add more mechanistic rigor to future clinical trials and revolutionize clinical practice for the treatment of AUD.

4.5. Beyond GLP-1RAs

With the technology evolving, it is conceivable to uncover novel therapeutic targets for AUD by employing a multi-omics framework and advanced systems biology techniques, using patient-derived iPSC model systems, and drugs as molecular probes, i.e., GLP-1RAs [47–50]. These research tools could offer a robust and reliable capability to detect potential pharmacological targets for future investigations.

One of the major challenges that we are currently dealing with is not a lack of data, but rather how we use the data that is already available from biobanks, public databases, clinical trials, preclinical studies, and real-world observation studies to generate a testable hypothesis. We should also point out that novel biological system network algorithms, machine learning, and artificial intelligence platforms have shed new light on disease mechanisms and underlying drug mechanisms, addressing critical challenges in big data-oriented biomedically complex systems [51–54]. These tools have already led to novel discoveries, thus laying the groundwork for testing novel therapeutic agents [55–57]. These integrated approaches offer two transformative opportunities: **1)** provide important new directions for the discovery of novel therapeutic targets for AUD treatment and **2)** catalyze a paradigm shift that will add more mechanistic rigor to future clinical trials.

Altogether, current literature indicates that GLP-1RAs represent a promising new direction in the pharmacologic management of AUD. Their central action on reward pathways, combined with robust real-world evidence of reduced alcohol-related harm and a generally favorable safety profile, suggests that GLP-1RAs could have clinical utility beyond metabolic diseases. As these findings continue to evolve, future research should prioritize larger, longer-term RCTs that evaluate GLP-1RAs across diverse patient populations, with careful attention to treatment motivation, psychiatric comorbidities, and long-term outcomes.

5. Conclusions

GLP-1 receptors are expressed in key brain regions involved in reward processing. While clinical research on GLP-1RAs in AUD is still in its early stages, preliminary findings are promising. Real-

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world evidence suggests that GLP-1 receptor agonists and analogs could be a compelling new avenue for the treatment of AUD. These medications offer a dual mechanism of action that aligns with the multifaceted nature of addiction by targeting both peripheral metabolic and central reward pathways. Although the evidence is emerging, recent clinical trials, large observational studies, and real-world data point to meaningful reductions in alcohol use, alcohol craving, and alcohol-related hospitalization. Going forward, future research is required to identify which subgroups of individuals, such as those with co-occurring obesity or metabolic disorders, may benefit the most. Furthermore, it is critical to enhance understanding of the long-term safety and efficacy of GLP-1RA in diverse populations. Nevertheless, GLP-1RAs may offer a novel and effective therapeutic strategy for AUD.

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