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The Efficacy of GLP-1 Agonists in Treating Substance Use Disorder in Patients: A Scoping Review

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Abstract: Substance use disorder (SUD) continues to be a leading cause of morbidity and mortality with limited treatments. There is interest in expanding the use of GLP-1 agonists in treating SUD. However, evidence for safety and efficacy in humans is limited. This review aims to bridge the existing knowledge gap by establishing a baseline of literature in this area to inform future trials and clinical practice. Our inclusion criteria were English peer-reviewed manuscripts reporting on use of GLP-1, GIP, and/or glucagon receptor agonists in treatment of SUDs, excluding case studies. The literature search was performed in accordance to PRISMA guidelines. Five studies were included in this review examining the use of this medication in tobacco use disorder, alcohol use disorder, and cocaine use disorder. No studies regarding substance withdrawal syndrome were identified. The included studies varied widely in terms of patient selection, dose/formulation of GLP-1 agonists, and follow-up. The results of this scoping review are mixed, with 3 studies demonstrating positive results and 2 studies finding no efficacy of this medication on SUD outcomes. It is premature to prescribe this medication off-label to patients. Further research is needed to determine the efficacy of GLP-1 agonists in treating SUD.

Key Words: substance use disorder, glucagon-like peptide, GLP-1, treatment, metabolic disorder

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In the United States, mortality rates attributed to substance use disorder (SUD) have more than tripled over the last 2 decades and are estimated to cost over $3 trillion annually.[1,2] Current treatments often include medications for SUD, individual and group psychotherapies such as cognitive and behavioral therapies, and peer support. However, the problem continues to persist because of a variety of issues, including limited options for effective treatment. For example, studies have demonstrated current FDA-approved medications for alcohol use disorder (AUD) improve abstinence rates by less than 15%.[3,4] In this context, the growing morbidity and mortality of SUDs have prompted widespread interest in identifying alternative treatments.

Amidst their established role in diabetes and weight loss, glucagon-like peptide-1 (GLP-1) agonists are becoming increasingly recognized for their potential in addressing conditions outside of metabolic disease, ranging from Alzheimer disease to polycystic ovary syndrome.[5] GLP-1 is an anorexigenic peptide hormone released from the endocrine cells of the small intestine in response to nutrients in the gut lumen. Acting via an incretin effect, GLP-1 binds to GLP-1 receptors on beta cells of the pancreas, stimulating postprandial insulin secretion.[6] Recent studies show GLP-1 agonists increase satiety, improve cardiovascular function, and lower all-cause mortality,[7-9] which has led to a substantial increase in use. The literature establishes a well-known effect of GLP-1 agonists on mesolimbic regions in the central nervous system (ventral tegmental area, VTA; nucleus accumbens, NAc) that constitute food reward pathways and share structures with reward pathways involved in addiction to substances including alcohol, opioids, tobacco, etc.[10] GLP-1 agonists may play a role in the treatment of SUDs through their additional effects on reward circuits in the brain by blunting dopamine release and reducing responsiveness to cues for addiction.[11]

In this context, it is important to acknowledge the co-agonism of glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptor (GcgR) agonists, which have been combined with GLP-1 agonists for a synergistic effect. Tirzepatide, the first and only FDA-approved GLP-1/GIP co-agonist, was introduced in 2022. Cotadutide and efinopegdutide are examples of GLP-1/GcgR co-agonists currently undergoing clinical trials.

There has been interest in expanding the use of GLP-1 agonists and co-agonists in treating SUDs. Initially, the rise in the use of these medications has led to anecdotal findings that they reduce substance use and cravings. Subsequently, this class of medications was studied more extensively in animal models with overall promising results.[12] In recent years, human trials examining the use of GLP-1 agonists in treating SUDs have been conducted. However, the evidence from real-world clinical trials using these medications for SUDs is currently unclear.

We conducted a review of the evidence for use of GLP-1 agonists in the treatment of SUDs in humans. This review aims to bridge the existing knowledge gap by establishing a baseline of literature in this arena, inform future clinical studies, and further explore the tolerability, safety, and efficacy of GLP-1 agonists as a therapeutic modality for patients with SUDs.

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METHODS

Search Strategy

The search algorithm was developed with a medical librarian to search PubMed and APA PsychINFO from database inception through October 19, 2023. Search terms included the different forms of GLP-1, GIP, and glucagon receptor agonists including trade names along with SUDs by each individual substance (ie, alcohol, opioid, cocaine, stimulant, sedative, hallucinogenic, tobacco). For purposes of this review, all forms of GLP-1 agonists, including GIP/GcgR co-agonists, will be referred to as GLP-1 agonists, unless specified. Studies were identified and included, abiding by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] References were extracted and imported into Zotero, a reference manager. Duplicate articles were identified and removed. Each article was assigned a unique record number.

The search algorithm is as follows: ("liraglutide" or "exenatide" or "dulaglutide" or "semaglutide" or "tirzepatide" or "lixisenatide" or "glp-1 agonist" or "glp-1 analog" OR "glucose-dependent insulinotropic peptide" or "gastric inhibitory peptide" OR "glucagon receptor agonist") AND ("'X' use disorder" OR "'X' abuse" OR "'X' withdrawal" OR "'X' addiction"), where each individual addictive disorder was searched. Additional studies were found from reviewing reference list of articles meeting inclusion criteria.

X = substance, alcohol, opioid, cocaine, stimulant, sedative, hallucinogenic, tobacco.

Inclusion/Exclusion Criteria

Our inclusion criteria were peer-reviewed manuscripts in the English language reporting on the use of GLP-agonists in the treatment of SUDs. Studies were excluded if they were nonhuman studies or did not describe the use of GLP-1 agonists related to the treatment of SUDs. Case reports, case series, and study protocols were also excluded.

Study Selection

Two authors (MRS, KO-B) independently screened titles and abstracts, followed by full text review for inclusion. The senior author (JS) resolved disagreements independently after title and abstract screening, as well as after full text review.

Data Extraction/Analysis

Two authors (MRS, KO-B) extracted the following data from the articles into a standardized electronic form: study population, study design, intervention (dosing, route, adjuncts), outcomes, and results, stratified by body mass index (BMI). Given the small number of studies and the heterogeneity of the studies in terms of design, this study was not amenable to meta-analysis.

RESULTS

A total of 308 studies were identified in the initial search, with 11 studies passing the title and abstract screen (Fig. 1; PRISMA). Six studies did not meet criteria. Two studies were excluded due to not being peer reviewed, 2 were excluded due to incorrect study design, and 2 were excluded for delineating a proposed protocol without results reported. Thus, in the full text review, a total of 5 studies met the criteria (Table 1). Of these 5 studies examining the effects of GLP-1 agonists in SUDs, 2 investigated tobacco use disorder, 2 studied AUD, and 1 examined cocaine use disorder. No studies regarding substance withdrawal syndrome were identified.

Tobacco Use Disorder

In examining the effect of GLP-1 agonists on tobacco use disorder, both Yammine et al. and Lengsfeld et al. conducted parallel-group, double-blind, placebo-controlled, randomized (1:1) controlled studies.[14,15] Yammine et al. enrolled 84 patients with prediabetes or overweight individuals who smoke (63.4% Black/African American, 69.5% male). Both groups received 21-mg tobacco replacement therapy (NRT) via patch and brief smoking cessation counseling. Participants were administered weekly subcutaneous (SQ) injections of exenatide (2 mg) with tobacco replacement therapy (NRT). Primary outcome measures were 7-day point prevalence abstinence (expired carbon monoxide level <5 ppm), cravings, withdrawal, and postcessation body weight. The results indicated that the intervention group exhibited significantly greater smoking abstinence at 6 weeks compared to placebo and NRT (46.3% vs 26.8%; RR, 1.70) and lower tobacco cravings at the end of treatment, with lower postcessation body weight.

Lengsfeld et al. published results on 244 individuals (96.9% Caucasian, 60.8% female) with no metabolic or weight criteria in a parallel-arm study comparing weekly dulaglutide (1.5 mg SQ) to placebo, with both groups also receiving varenicline (2 mg PO) daily, as well as behavioral counseling. The primary outcome was tobacco abstinence, and secondary outcomes were metabolic outcomes and cravings. The results showed no significant differences in these outcomes at 12 weeks between dulaglutide compared to placebo (63% vs 65%, respectively; difference in proportions, −1.9%; 95% CI, −10.7 to 14.4, $P = 0.86$). However, the dulaglutide did counteract postcessation weight gain and hemoglobin A1c (−2.9 kg [95% CI, −3.59 to −2.3; $P < 0.001$] and −0.25% [interquartile range {IQR}, −0.36 to −0.14; $P < 0.001$)], respectively, compared to placebo.

Alcohol Use Disorder

Two studies reported findings on the use of GLP-1 agonists in AUD. Klausen et al. conducted a double-blind, placebo-controlled, randomized controlled study in Denmark on 127 individuals with AUD (100% Caucasian, 59.8% male) who were randomized to receive either exenatide (2 mg SQ) weekly or saline placebo (2 mg SQ).[16] Both groups also received behavioral treatment. They did not find that exenatide was superior to placebo at 26 weeks or at 6 months after trial completion, but subgroup analysis of participants with obesity (BMI >30 kg/m^2) showed significant reduction in heavy drinking days by 23.6 percentage points (95% CI, −44.4 to −2.7, $P = 0.034$) and reduced total alcohol intake per 30 days by 1205 g (95% CI, −2206 to −204). Interestingly, in participants with BMI <25 kg/m^2, treatment with exenatide increased the number of heavy drinking days by 27.5% (95% CI, 4.7 to 50.2, $P = 0.024$) relative to the placebo group, though total

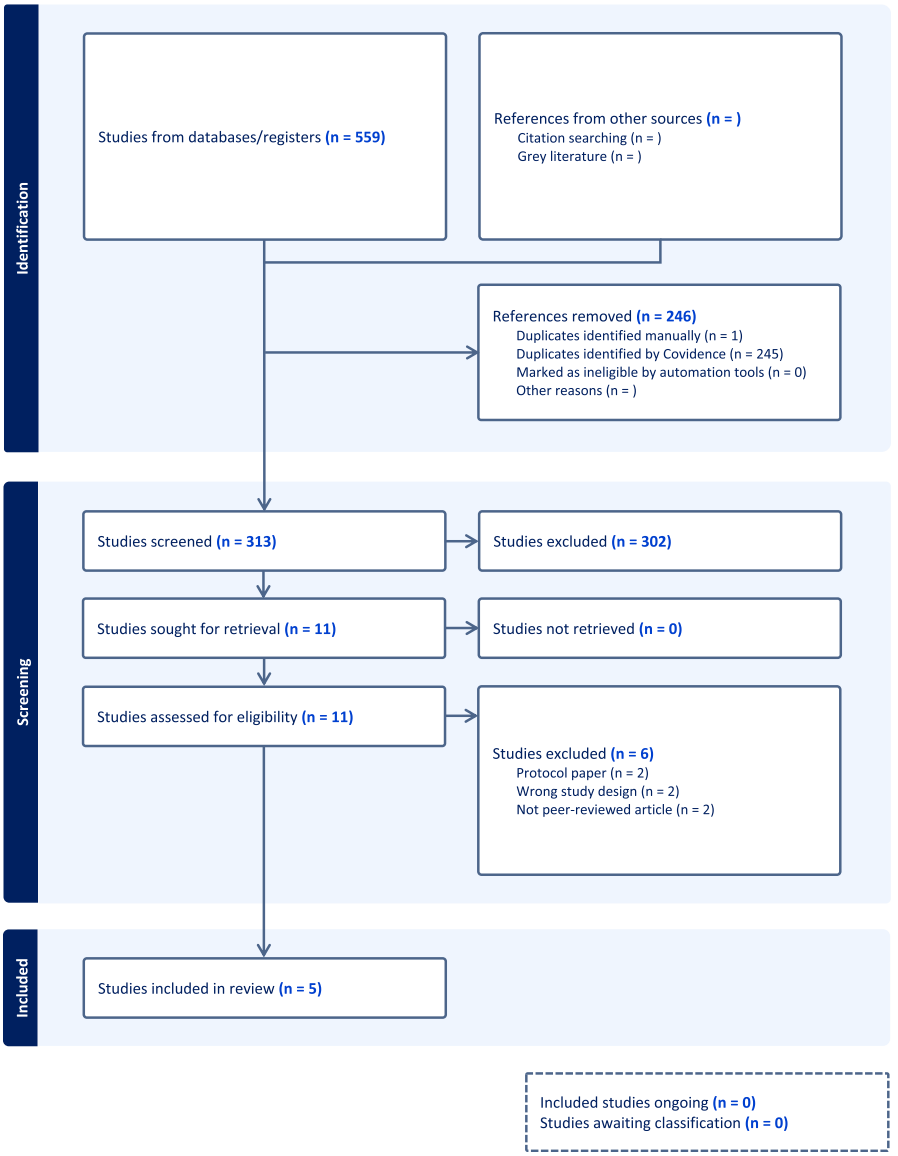

FIGURE 1. PRISMA flow diagram.

alcohol intake did not differ between the 2 groups. Exploratory analysis also showed that exenatide treatment resulted in reduction in fMRI alcohol cue reactivity in brain areas associated with addiction, specifically the ventral striatum, compared to the placebo group (mean difference [M] = −0.176, SEM = 0.075, P = 0.025). Investigators were unable to determine if overall ventral striatal brain responses were correlated with heavy drinking days in the overweight or obese subgroups due to insufficient sample size for subgroup analysis.

Wium et al. identified a cohort of new users of GLP-1 agonists (N = 38,454) compared to DPP-4 inhibitors (N = 49,222) in the Danish National Prescription Registry, where mean follow-up time was 4.1 years.[17] Here, GLP-1 agonists were compared to DPP-4 inhibitors on alcohol-related events as they are both diabetic drugs that were approved for patient use at similar times. DPP-4 inhibitors impede the DPP-4 enzyme, which breaks down GLP-1. As alcohol intake could not be measured from an epidemiological study, alcohol-related events were defined specifically as (1) hospital contacts with a main diagnosis of AUDs, (2) registered treatments for alcoholism in the National Registry of Alcohol Treatment, or (3) purchase of chlordiazepoxide or medication against alcohol dependence registered in the Danish National Prescription Registry. In this study, initiating GLP-1 agonist treatment was associated with lower risk of an alcohol-related event (hazard ratio = 0.46; 95% CI, 0.24–0.86) compared with initiation of DPP-4 inhibitor at 3 months and 1 year postinitiation of the GLP-1 agonist. However, for self-controlled analysis comparing alcohol use before starting and after starting GLP-1 treatment, the results demonstrated a lower risk of alcohol-related event after starting treatment, but only during the first 3 months. After this time, the risk of alcohol use actually significantly increased compared

TABLE 1. Summary of Studies of GLP-1 Agonists and Substance Use Disorder

Study	Population	Study Design	Intervention	Outcomes and Endpoints (Primary and Secondary)	Results
Lengsfeld et al., 2023	Nicotine use disorder (NUD) Adults who smoke with at least moderate cigarette dependence and expressed goal of abstinence N = 255 96.9% Caucasian 60.8% female Age, mean 43.2 Mean BMI 27.1 kg/m^2	Randomized control trial (parallel group, double-blind, placebo-controlled) Single center: University Hospital of Basel in Switzerland	Dulaglutide 1.5 mg weekly, subcutaneous for 12 wk (0.75 mg week 1; 1.5 mg weeks 2–12; N = 127) Control: normal saline (N = 128) All arms received oral varenicline (2 mg/d) + behavioral counseling	Primary: Abstinence at 12 wk (7-d point prevalence by self-report and exhaled CO ≤10 ppm) Secondary: Postcessation weight gain Glucose metabolism Cravings for smoking Smoking reduction (cigarettes/day)	No significant difference in abstinence rates at 12 wk between dulaglutide compared to placebo (63% vs 65%, respectively) Dulaglutide resulted in 2.9-kg difference in postcessation weight change compared to placebo Cravings for smoking and total cigarettes/day decreased in both groups without difference between groups Conclusion: Dulaglutide did not affect smoking abstinence rates but did mitigate postcessation weight loss
Yammine et al., 2021	Nicotine use disorder (NUD) Prediabetic (HbA1c 5.7%–6.4%) and/or overweight (BMI ≥25 kg/m^2) adults who smoke seeking treatment N = 84 63.4% Black/African American 69.5% male Age, mean 51.1 BMI data not reported	Randomized control trial (parallel-group, double-blind, placebo-controlled) Two centers: Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, Texas (N = 32) University of Texas Health Science Center at Houston (UTHealth) for Neurobehavioral Research on Addiction (CNRA) (N = 52)	Exenatide ER 2-mg weekly, subcutaneous for 6 wk (N = 41) Control: normal saline (N = 41) All arms received nicotine replacement (21 mg) via patch + smoking cessation counseling	Primary: Abstinence at 6 wk (7-d point prevalence by self-report and exhaled CO ≤5 ppm) Withdrawal symptoms Cravings for smoking Secondary: Postcessation weight gain	Exenatide increased smoking abstinence rates at 6 wk compared to placebo (46.3% vs 26.8%), respectively Exenatide reduced end of treatment cravings compared to placebo Subgroup (those who abstained) experienced reduced withdrawal symptoms with exenatide Postcessation weight gain was 5.6 lb lower in exenatide group Adverse outcomes (self-resolving injection site nodules) were reported more frequently in exenatide group (9.5% vs 2.3%) Conclusion: Exenatide as an adjunct to NRT patch improves abstinence, decreases cravings, and mitigates postcessation weight gain in adults who smoke vs NRT patch alone
Klausen et al., 2022	Alcohol use disorder (AUD) Treatment-seeking patients with mild-to-severe AUD N = 127 100% Caucasian 59.8% male Age, mean (52.1 and 52.5 in treatment vs placebo, respectively) Mean BMI 26.7 kg/m^2	Randomized control trial (double-blind, placebo-controlled) Four centers: All outpatient clinics in Copenhagen, Denmark	Exenatide 2 mg weekly, subcutaneous for 26 wk (N = 62) Control: normal saline (N = 65) All arms received AUD behavioral treatment (ie, motivational interviewing, cognitive behavioral therapy, and family therapy)	Primary: Reduction in number of heavy drinking days from baseline to 26 wk Secondary: Heavy drinking days 6 mo after treatment completion Total alcohol consumption fMRI alcohol cue reactivity Single-photon emission CT (SPECT) dopamine transporter availability	Exenatide was not superior to placebo in reducing the number of heavy drinking days at 26 wk or at 6-mo after trial completion Subgroup (BMI >30 kg/m^2) experienced reduction in heavy drinking days and total alcohol intake with exenatide Exenatide attenuated fMRI alcohol cue reactivity at week 26 in brain areas associated with addiction/reward Dopamine transporter availability lower in exenatide group Conclusion: Exenatide did not reduce heavy drinking days in AUD patients

Continued next page

TABLE 1. *(Continued)*

Study	Population	Study Design	Intervention	Outcomes and Endpoints (Primary and Secondary)	Results
Wium-Andersen et al., 2022	All new patients starting use of GLP-1 agonists and dipeptidyl peptidase 4 (DDP-4) inhibitors in Denmark from 2009 to 2017 N = 87,676 GLP-1 (N = 38,454) DPP-4 (N = 49,222) BMI data not reported	Cohort study (new user, active comparator) Single country: Entire population of Denmark Patients identified from nationwide registries (Danish National Prescription Registry; Danish Civil Registration System)	Association between the use of GLP-1 agonists and alcohol-related events vs the use of DPP-4 inhibitors Exposure: GLP-1 agonists Comparator: DPP-4 inhibitors*	Alcohol-related events defined as any of the following: Hospital contacts with a main diagnosis of AUD Registered treatments for AUD Purchase of medications for treatment of alcohol withdrawal or dependence	Initiation of GLP-1 treatment was associated with lower risk of an alcohol-related event vs initiation of DPP-4 during the first 3 mo of medication use (hazard ratio = 0.46 [95% CI, 0.24–0.86]) and also 1 y after medication use (hazard ratio = 0.62 [95% CI, 0.45–0.85]) Compared to self-controlled nontreatment phase, initiation of GLP-1 treatment was associated with lower risk of an alcohol-related event (IRR, 0.74 [95% CI, 0.56–0.97]) Conclusion: Compared with DPP-4 users, patients who start treatment with GLP-1 have a lower incidence of alcohol-related events
Angarita et al., 2021	Cocaine use disorder (CUD) Adult nontreatment-seeking patients with moderate-to-severe cocaine use disorder N = 13 76% African American 92% male Age, mean 45 BMI data not reported	Randomized control trial (double blind; placebo-controlled; crossover; within-subject design) Single center: Clinical Neuroscience Research Unit (CNRU) at Connecticut Mental Health Center (CMHC)	Single dose (pretreatment) of exenatide 5 μg, subcutaneous, 3 h before cocaine administration Control: normal saline Pretreatment phase followed by drug-by-drug interaction (DDI) phase where patients received IV cocaine administration in 3 ascending dose orders of 4, 8, and 16 mg/70 kg DDI phase followed by 90 min cocaine self-administration phase	Primary: Number of cocaine infusions Visual analog scale of wanting cocaine Visual analog scale of euphoria Secondary: GLP-1, insulin, and amylin blood levels	Low-dose exenatide did not alter cocaine self-administration (8.5 ± 1.2 vs 9.1 ± 1.2; $P = 0.39$), euphoria (a (4.4 ± 0.8 vs 4.1 ± 0.8; $P = 0.21$), or wanting of cocaine (5.6 ± 0.9 vs 5.4 ± 0.9; $P = 0.46$) Exenatide vs placebo reduced levels of GLP-1 ($P = 0.03$) and insulin ($P = 0.02$) Self-administered cocaine also reduced levels of GLP-1 ($P < 0.0001$), insulin ($P < 0.0001$), and amylin ($P < 0.0001$) Conclusion: Low-dose exenatide does not alter cocaine self-administration, self-reported euphoria, or desire for cocaine in patients with CUD

*Similar to GLP-1 agonists, DPP-4 inhibitors treat diabetes; both medications received drug approval in Denmark at about the same time.

to baseline during the late exposed time from 4 to 12 months (hazard ratio = 1.23 [1.02–1.49]), then normalized back to baseline between 13 and 24 months.

Cocaine Use Disorder

Finally, Angarita et al. conducted an inpatient study, examining the effects of a GLP-1 agonist on cocaine self-administration. The authors designed a double-blind, placebo-controlled, crossover randomized controlled trial in 13 non–treatment-seeking adults with cocaine use disorder (76% African American, 92% male).[18] The design included the following phased approach: (1) administration of low-dose exenatide (5 μg SQ) versus normal saline placebo; (2) a drug-by-drug interaction phase in which patients received ascending doses of IV cocaine administration; and (3) a self-administration phase in an inpatient unit. The amount of cocaine self-administered was then recorded. The results demonstrated that low-dose exenatide did not alter cocaine self-administration (8.5 ± 1.2 vs 9.1 ± 1.2; $P = 0.39$), euphoria (4.4 ± 0.8 vs 4.1 ± 0.8; $P = 0.21$), or wanting of cocaine (5.6 ± 0.9 vs 5.4 ± 0.9; $P = 0.46$).

DISCUSSION

This review explores the evidence base for using GLP-1 agonists, traditionally utilized in metabolic disorders, as a novel approach to treat SUDs. Given the interest in expanding the use of these medications outside of metabolic disease, it is important to understand the existing evidence to inform clinical decision-making and identify gaps in the literature in humans.

The utility of GLP-1 agonists as a treatment for SUDs was first proposed in response to anecdotal reports. However, several animal studies demonstrated promising results, as detailed in a review by Brunchmann et al. in 2018, kindling the progression to human trials.[12] To date, 3 studies have demonstrated results showing that GLP-1 agonists may be beneficial in treating SUDs.[14,16,17] Interestingly, in all 3 of the positive studies, the reduction in substance use was seen in patients with preexisting metabolic disease. Specifically, Yammine et al. demonstrated a reduction in tobacco use enrolling only overweight/prediabetic patients, and Klausen et al. demonstrated a reduction in alcohol-related events in a subgroup analysis of patients with BMI >30 kg/m^2. Surprisingly, Klausen et al. reported that patients with BMI <25 kg/m^2 experienced a significant increase in heavy drinking days after receiving GLP-1 agonist treatment. The third positive study, a cohort study of patients with AUD by Wium et al., did not report weight, though patients were independently started on a GLP-1 agonist likely with metabolic indications. While the exact mechanism linking metabolic disease and SUD has yet to be elucidated, a possible hypothesis is due to the shared brain circuitry in the reward pathways that are seen in disordered eating (including binge eating) and substance use, especially given that patients with metabolic disorder are at a higher propensity for maladaptive reward-related eating behavior.[19,20] Further research is needed to elucidate the target patient population for GLP-1 agonists in SUD. According to Dr Fink-Jensen, senior author of the Klausen et al. study, the group will repeat the study exclusively in patients with BMI >30 kg/m^2.[21]

It is important to note that the formulation of GLP-1 agonists administered varied across studies (Table 2). As background, the first GLP-1 agonist, exenatide,[22,23] was approved by the FDA in 2005. Since then, liraglutide,[24] albiglutide,[25] dulaglutide (Trulicity),[26] lixisenatide (Adlyxin in the United States),[27] and semaglutide were developed,[28] as listed in chronological order. In 2022, the first dual GLP-1 and GIP agonist, tirzepatide was approved by the FDA.[29,30] These drugs have sequentially evolved to largely increase plasma half-life and increase GLP-1 receptor activation potency.[31] In the 2 studies demonstrating positive effect on substance use in overweight/prediabetic individuals, both studies used exenatide weekly (2 mg SQ), which is the standard treatment dose used for diabetes.[14,16] The study conducted by Angarita et al. in individuals with cocaine use disorders showed minimal effect after a subclinical dose of exenatide (5 μg SQ).[18] The authors suggested that a larger dose may have resulted in a different outcome.[18] However, Lengsfeld et al. used dulaglutide weekly (0.75 mg week 1, then 1.5 mg week 2–12) in individuals with tobacco use disorder, but found no difference in abstinence rates, despite the treatment resulting in a 2.9-kg difference in postcessation weight loss.[15]

It may also be useful to consider the different sequence homologies of these medications (Table 2). For example, in comparing dulaglutide to exenatide, dulaglutide has increased sequence homology to endogenous GLP-1, with improved efficacy for primary indications (ie, blood glucose, HbA1c, and weight loss) in diabetes/obesity studies.[32] However, even using a formulation with the increased sequence homology, Lengsfeld et al. did not find a significant difference in tobacco abstinence. However, it is difficult to compare across substance use disorders.[15] Given the advent of "twincretins," which include GLP-1 and GIP co-agonists (ie, tirzepatide),[29,30] and triple agonists targeting GLP-1, GIP, and GcgR receptor activity (ie, orforglipron, retatrutide), these formulations may have varying efficacy in their modulation of the reward pathway involved in addiction behavior.[33,34] Further investigation is needed within singular substance use disorders to determine if increased sequence homology to endogenous GLP-1 in the formulation of these medications is correlated with increased abstinence from substance use. It is also

TABLE 2. Comparison of Formulations and Doses by Study Included

Drug	Doses in Studies	Homology to Native GLP-1 (%)	Typical Route, Dose, and Frequency	Tmax	Half-Life
Exenatide (long-acting)	Yammine et al.—2 mg Klausen et al.—2 mg Angarita et al.—5 μg	53	2 mg SQ weekly	2.5–5.1 h	3.3–4.0 h
Dulaglutide	Lengsfeld et al.	90	0.75–1.5 mg SQ weekly	24–72 h	5 d

SQ indicates subcutaneous injection.

TABLE 3.. Current Ongoing Clinical Trials, as Listed on clinicaltrials.gov (as of May 2024)

Author	Study Title	Population	Study Design	Intervention	Outcomes and Endpoints (Primary and Secondary)	Status
Eric Devine, PhD	The effects of exenatide, a GLP-1 agonist, on alcohol self-administration in heavy drinkers	Alcohol use disorder Adults with alcohol use disorder Mean BMI not reported	Double-blind, randomized, placebo-controlled, crossover trial	Immediate release exenatide 5 mcg on day of self-administration trial vs placebo injection	Primary: Alcohol consumption within 2 h in lab	Terminated due to COVID-19 with results
Mette Kalusen, MD, PhD	Does semaglutide reduce alcohol intake in patients with alcohol use disorder and comorbid obesity? (SEMALCO)	Alcohol use disorder Adults with alcohol use disorder BMI >30 kg/m^2	26-wk long, double-blind, randomized, placebo-controlled trial	Semaglutide injection once weekly titrated to maximum 2.4 mg vs placebo injection	Primary: Percentage-point reduction in total number of heavy drinking days Secondary: Change in heavy drinking days Total alcohol consumption Days without alcohol consumption Time to relapse (first alcohol intake, first heavy drinking day) Time to relapse to heavy drinking day World Health Organization Alcohol cravings Biomarkers, including labs and fMRI alcohol cue reactivity Metabolic measurements and biomarkers	Recruiting
Mehdi Farokhnia, MD	Semaglutide Therapy for Alcohol Reduction (STAR): A Proof-of-Concept Phase II Clinical Trial	Alcohol use disorder Adults with alcohol use disorder BMI 25–50 kg/m^2	20-wk long, double-blind, randomized, placebo-controlled trial	Semaglutide injection once weekly titrated to maximum 2.4 mg vs placebo injection	Primary: Adverse events and proportion of participants reaching maximum dose Change in total number of alcohol-containing drinks per week. Secondary: Other self-reported alcohol-related outcomes (heavy drinking days, drink per drinking days, WHO drinking levels) Effect on PEth levels as a biomarker of alcohol use Effect on cravings for alcohol or food fMRI cue reactivity	Recruiting

Joseph P Schacht, PhD	Randomized, controlled trial of Rybelsus (semaglutide) among adults with alcohol use disorder (AUD)	Alcohol use disorder Adults with alcohol use disorder of at least moderate severity Adults with BMI ≥25 kg/m^2	8-wk long, double-blind, randomized, placebo-controlled trial	Semaglutide (oral) daily titrated up to 7 mg/d vs matched placebo All participants engage in a computerized behavioral intervention	Primary: Adverse effects and tolerability Alcohol cue-elicited craving and alcohol consumption Secondary: Number of drinks per day Percentage of heavy drinking days	Recruiting
William Simmons, PhD	Semaglutide therapy for alcohol reduction Tulsa	Alcohol use disorder Adults with alcohol use disorder BMI 25–50 mg/kg^2 Single Center: Oklahoma State University	12-wk long randomized, double-blind, placebo-controlled clinical trial	Semaglutide injection once weekly titrated to 1.0 mg vs placebo injection	Primary: Number of weekly alcohol drinks Secondary: Change in drinking habits Adverse events and tolerability Changes in amount/types of food choices Biomarkers fMRI cue reactivity and task-related activity	Recruiting
Christian Hendershot, PhD	Human laboratory screening of semaglutide for alcohol use disorder	Alcohol use disorder Adults with alcohol use disorder	9-wk long randomized, double-blind, placebo-controlled clinical trial	Semaglutide injection once weekly titrated to 1.0 mg vs placebo injection	Primary: Alcohol consumption Breath alcohol concentration Secondary: Alcohol and nicotine cravings Daily alcohol and cigarette use Subjective sedation and stimulation from alcohol Metabolic measurements and biomarkers	Completed, no results posted
Christian Hendershot, PhD	Effects of semaglutide on nicotine intake and smoking lapse	Nicotine use disorder Adults smoking 5+ cigarettes daily on average over the past year BMI >25 kg/m^2	9-wk long, double-blind, placebo-controlled, parallel arm pilot study	Semaglutide injection once weekly titrated to 1.0 mg vs placebo injection	Primary: Nicotine self-administration in observed lab Duration to smoking reinstatement Secondary: Daily cigarette smoking Cigarette craving, motivation Metabolic measurements and biomarkers	Recruiting
Rebecca L Ashare, PhD,	Glucagon-like peptide-1 receptor agonists as novel pharmacotherapies for nicotine dependence	Nicotine use disorder Adults smoking 10+ cigarettes daily on average over the past 6 mo. BMI ≥27 kg/m^2	32-wk long randomized, double-blind, placebo-controlled, parallel arm pilot study with 1 between-subjects factor of medication group (liraglutide vs placebo)	Liraglutide injection pen daily titrated up to 3 mg/d vs placebo injection pen	Primary: Smoking abstinence Secondary: Body weight, calories consumed	Completed, no results posted.

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TABLE 3. *(Continued)*

Author	Study Title	Population	Study Design	Intervention	Outcomes and Endpoints (Primary and Secondary)	Status
Scott Bunce, PhD	Use of a GLP-1R agonist to treat opioid use disorder	Opioid use disorder Adults diagnosed with opioid use disorder seeking treatment for residential treatment plan for at least 4 wk	33-d long, double-blind, placebo-controlled, parallel assigned study	Liraglutide injection pen daily titrated up to 3 mg/d vs placebo injection pen	Primary: Self-reported drug craving Change in ambient drug craving Secondary: Metabolic measurements and biomarkers Adverse events Vital signs	Completed, no results posted

unclear if the effect of these medications on metabolic markers (ie, fasting blood glucose, HbA1c, weight loss) is directly proportional to the effects on substance craving and use.

There are several reasons why the use of GLP-1 agonists in SUD would be beneficial. First, obesity and AUD in particular are frequently comorbid, as there is evidence of a genetic link.[35] Furthermore, a meta-analysis found that over 1 in 5 patients with AUD also have metabolic syndrome.[35] Additionally, there may be secondary metabolic benefits. For example, both studies in our review investigating this medication in tobacco use disorder demonstrated mitigation in postcessation weight gain, which might make these medications potentially useful agents to individuals who consider postcessation weight gain as a barrier to tobacco abstinence.[14,15] Furthermore, many psychotropic medications, namely, dopamine antagonists, are highly associated with metabolic syndrome.[36] Given the high comorbidity of SUDs with other mental illnesses necessitating treatments with psychotropic medications, it is possible that this medication could offset some of the long-term complications of mental health treatment.

However, there are challenges to consider. First, these medications are generally only available in subcutaneous injection form. An oral form of semaglutide exists. An inhaled form of semaglutide and an implantable device (ITCA650) are currently undergoing clinical trials.[31] Furthermore, as these medications have continued to be studied, side effects such as nausea, vomiting, constipation, and diarrhea (related to GLP-1 agonist-induced delayed gastric emptying and satiety) have been noted.[37] Of the studies detailed in this review, incidence of adverse events varied. In the Yammine et al. and Klausen et al. studies, which each used 2-mg weekly exenatide, no patients withdrew because of treatment side effects, though they did report symptoms ranging from subcutaneous nodules to GI symptoms. The Klausen et al. study demonstrated increased alcohol intake in patients with BMI <25 kg/m^2. In the Lengsfeld et al. study, which used the dulaglutide formulation, 10 patients withdrew because of adverse effects, specifically GI symptoms. However, all participants were also treated with varenicline, which also causes nausea, pointing to a possible synergistic effect. In the Angarita et al. study, which used 5-μg exenatide, no adverse side effects were observed. These side effects are confirmed by the literature, as exenatide has demonstrated a lower risk of vomiting compared to dulaglutide.[38,39] Studies have also demonstrated a higher risk of pancreatitis, bowel obstruction, and gastroparesis, even compared to other weight loss drugs.[40] In fact, the American Society of Anesthesiologists issued a statement encouraging patients to hold the medication preoperatively because of reports of risk of aspiration.[41] Furthermore, there is anecdotal evidence for increased depression and suicidal ideation, which is especially important given the high comorbid nature of SUD and major depressive disorder.[42] However, recent studies demonstrate no association between GLP-1 agonists and increased suicidal ideation.[43,44] However, further research is needed to determine the safety and tolerability of these medications.

Identifying an ideal target population also requires further investigation. Klausen et al. demonstrated an increase in heavy drinking days in patients with BMI <25 kg/m^2, raising questions

about safety in the general population. In addition, prior research on individuals undergoing bariatric surgery shows substance use can increase after rapid weight loss, potentially due to pharmacokinetic changes or increased cravings.[44] Furthermore, given the short-term follow-up in most of these studies, it is unclear whether the effects of these medications on substance use will persist. The cohort study conducted by Wium et al. had a mean follow-up period of 4.1 years and saw a decrease in alcohol-related events for 3 months after initiating treatment, followed eventually by a return to baseline.[17] Finally, while this review included all substances, given the comorbid nature of malnourishment and SUD, the use of GLP-1 agonists may not be appropriate for all SUDs.

Another concern worth noting is access and affordability of this drug. Health equity remains a paramount issue, especially in the United States. SUD is associated with living in a disadvantaged socioeconomic neighborhoods.[45] GLP-1 agonists are costly. One study demonstrated using GLP-1 agonists instead of insulin costs $54,851 versus $29,115 per case of all-cause mortality and hospital hypoglycemia prevented.[46] However, as generic forms become available, access may also improve.

The strengths of this review include an extensive search including all common substance use and withdrawal disorders as delineated by the *DSM-5*. We abided by PRISMA guidelines and used 2 independent reviewers with a third senior author resolving disagreements. Furthermore, most papers included were double-blind, placebo-controlled, randomized controlled studies. Moreover, while several of the studies used self-report as a primary outcome, this information was corroborated with biomarkers such as exhaled CO_2 for both nicotine trials and PEth levels for the Klausen et al. study. Limitations of this review are exclusion of non-English language studies. Case reports and case series were also not included. In terms of study limitations, there was homogeneity of patients included in several studies, specifically in terms of gender and race, limiting generalizability to a larger population. Moreover, in the Klausen et al., Yammine et al., and Lengsfeld et al. studies, GLP-1 agonists were used in addition to standard treatments, and not as standalone treatments. Furthermore, given the paucity of studies meeting criteria, meta-analysis was not possible.

In summary, the results of this review are mixed. Further research is needed to determine the efficacy of GLP-1 agonists in treating SUD. To our knowledge, there are ongoing trials examining different formulations of GLP-1 agonists in AUD, opioid use disorder, tobacco use disorder, and cannabis use disorder with varying BMIs (Table 3). Although preliminary results demonstrate these medications may benefit certain subgroups, specifically overweight/prediabetic/diabetic patients, it is premature to prescribe this medication off-label to patients. Given the risks and mixed outcomes of GLP-1 agonists on SUDs, further research is needed to elucidate the efficacy, safety, and tolerability of these medications in patients with SUD.

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