GLP-1 Receptor Agonists and Substance Use Disorder: A Systematized Literature Review

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Abstract

Substance use disorder (SUD) is a significant cause of morbidity and mortality worldwide, and the incentive to discover effective and safe treatments is high given the large socioeconomic and healthcare system burden associated with SUD. SUD is a considerable challenge in medicine, partly due to the limited options for pharmacological treatment. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), which have become increasingly common in recent years as the evidence of their efficacy in metabolic disorders mounts, have also demonstrated potential benefit in treatment of addiction and SUD in preclinical data. This systematized review aimed to evaluate the current clinical evidence of efficacy in GLP-1RAs in SUD. Following PRISMA guidelines, a literature search was performed using the PubMed database. A total of 14 studies met the inclusion criteria. Analysis of the studies included in this review identified significant heterogeneity in methodology, population, and reported outcomes, however the preliminary evidence presented here suggests GLP-1RAs may have therapeutic benefit and offer a promising target for further research as a potential pharmacological tool in the treatment of SUD.

Introduction

SUD is defined by Health Canada as "a treatable medical condition that affects the brain and involves compulsive and continuous use despite negative impacts to a person, their family, friends, and others (1)." Substance use disorder (SUD) affects tens of millions of people worldwide (2). For individuals, SUD is associated with significant morbidity and mortality, and in wider society represents a substantial socioeconomic burden to health care and social services (3,4).

SUD treatment efficacy is comparable to that of other chronic medical conditions, typically requiring long-term treatment regimes, with failure to treat unfortunately often resulting in relapse (5–7). The pharmacopeia for addiction treatment is also sparse (8). Currently, only alcohol, nicotine, and opioid use disorders have FDA-approved medications for treatment while other substances, such as cannabis, stimulants, or inhalants do not (8). Interventions may be aimed at specific substances or behaviours have varying efficacy and resource demands (7,9).

Glucagon-like peptide-1 receptor agonist (GLP-1RA) use has exploded in recent years as the evidence of their efficacy in diabetes treatment, weight loss, and reduction of cardiovascular disease mounts (10,11). The drug is effective for treating a wide spectrum of conditions, suggesting the mechanism of action may be multifaceted, and not fully understood (6). One unexpected finding that has arisen from growing research surrounding this class of drugs is that its success in these clinical indicators may be related to an effect on addictive behaviour (6). GLP-1 agonists have an excellent safety profile and are already widely used (12). If they are found to be an effective addition to the arsenal of treatments for addiction, the potential positive health and social impact would be immense.

A significant body of research has investigated the mechanism of addiction and SUD. Reward pathway dysfunction, where certain areas of the brain associated with reward become dysregulated as a result of exposure to highly rewarding stimuli (i.e. substances of abuse), is thought to be a central element of addiction and SUD (13). Animal studies have found that GLP-1RAs directly influence the dopaminergic pathways involved in reward, and there is mounting evidence of GLP-1RA effectiveness in animal models of SUD (14). Animal models also suggest GLP-1RAs are involved with other central processes implicated in substance use, for example, stress and cognitive function (14). GLP-1RAs also impact peripheral systems that may also play a role in SUD, such as gastric motility and satiety (6,14).

The aim of this research project is to further establish how pharmacological agents can be used to treat addiction. Specifically, the goal of this review is **to summarize the current primary clinical research for GLP-1 agonists in the treatment of SUD.** It aims to evaluate the current evidence for the efficacy of GLP-1RAs for different substances of abuse, describe the current understanding of its mechanism in disrupting addiction, and which populations would benefit.

Methods

This review reports all items detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis – Search extension (PRISMA-Search) guidelines (15). This is a relatively new reporting guideline designed to support a systematic approach to literature reviews; a scoping review was not feasible for this study as screening was completed by one person.

Information Sources and Methods

The Medline database was searched using the PubMed platform. No study registries or grey literature were searched for the purpose of this review. Citation searching was also not performed. No additional studies or data was obtained by contacting other sources.

Search Strategies

The reproducible search for this database is available in Appendix I. The search was limited to articles published between January 1, 2000 and April 1, 2025. Test searches were performed to identify high-yield search terms and develop a search string that best fit the research question. No published search limitation was used. The initial search was performed on December 11, 2024, then rerun on April 18, 2025.

Peer review

The search strategy was developed with the assistance of librarian Margaret Banka from the University of Manitoba. A single reviewer reviewed all abstracts and sources to meet the requirements of this project.

Managing records

The database search yielded a total of 107 citations. Citations were uploaded into Covidence systematic review software (16) to assist with screening, review, and extraction. The extraction table is available in Appendix II. No duplicates were identified in the search.

Limits and restrictions

A set of limits and restrictions was created to guide the assessment of sources. To be included in this review, sources must

1. report findings relevant to of GLP-1 agonist use and SUD; and
2. report on empirical findings using quantitative, qualitative, mixed, or other appropriate methods; and
3. include human participants and / or patient data; and
4. be published in a peer-reviewed journal; and
5. be available as full text in English; and
6. be published between Jan 1 2000 and April 1 2025

Sources were excluded if they

1. did not report on findings relevant to the association between GLP-1 agonist use and SUD; or
2. were commentaries, or did not include empirical findings; or
3. reported solely on animal studies, were proof of concept studies, were protocols, were case studies, or did not include humans; or
4. were not published in peer-reviewed journals; or
5. were not available as full text in English; or
6. were published prior to Jan 1st 2000 or after April 1st 2025

Quality assessment

While not required for systematic literature reviews, this review included a quality assessment of sources using the 'Quality assessment with diverse studies (QuADS)' appraisal tool (17). The QuADS appraisal tool was developed for use in health service research systematic reviews to assess mixed- and multi-method studies by providing a framework to evaluate the quality of a source's reporting and methodology (17). A rubric was used to assess the source's methodological and reporting suitability and rigor (17, Additional Document 2). Studies were grouped into quartiles based on their relative rank order as determined by a single reviewer using the QuADS assessment tool. Boundaries of the quartiles were adjusted to create quartiles of similar size where all equally ranked sources were placed in the same quartile.

Results

A total of 107 sources were identified on PubMed using the search string. No duplicate studies were identified. 75 studies were excluded in the title and abstract screening. A further 18 studies were excluded during full-text review. Ultimately, 14 studies met the inclusion/exclusion criteria for extraction. A summary of the PRISMA search results are shown in Figure 1.

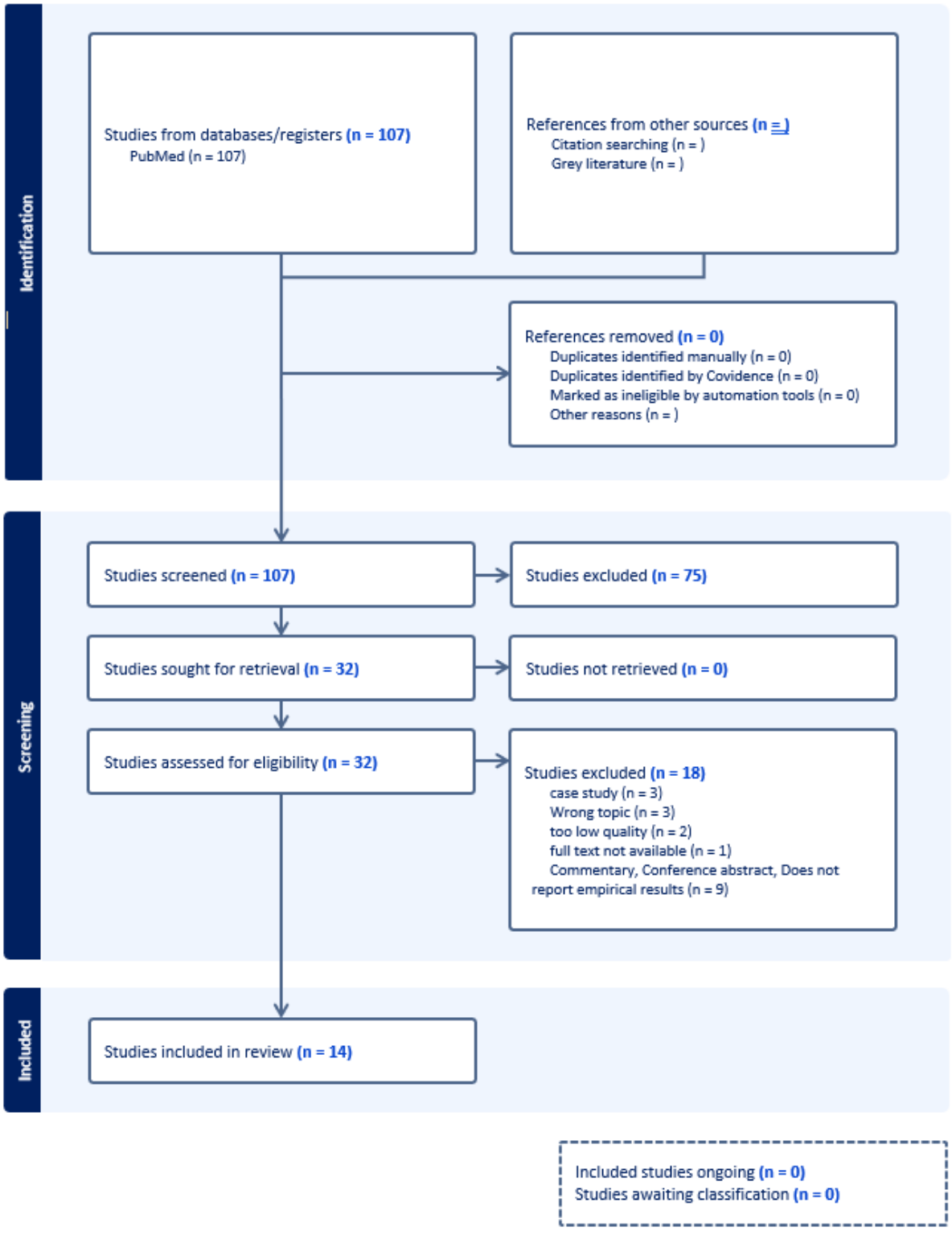

Figure 1: PRISMA flow diagram showing the results of search, screening, and inclusion process. Diagram generated using Covidence software (16).

Table 1: Summary of sources investigating the effects of GLP-1RAs on SUD.

Study	Population, Sample Size	Substance	Intervention	Duration	Study Design	Outcomes measured	Results	Quality Quartile
Angarita 2021 (18)	Non-treatment seeking individuals, 30-55 years old, meeting criteria for moderate to severe cocaine use disorder n = 13	Cocaine	Exenatide (at anti-diabetic dosing) 5 Î¼, 0.02 ml	4.5 hours per session	Randomized, double-blind, crossover, within-subject design.	Number of cocaine infusions in self regulated cocaine administration paradigm Cocaine induced euphoria Desire for cocaine	Exenatide administered at anti-diabetic dosing did not change cocaine-related behaviours (infusions) or subjective effects (euphoria and wanting cocaine) in people with cocaine use disorder	4
Hendershot 2025 (19)	Non-treatment-seeking adults with AUD n = 48	Alcohol, Tobacco	"Semaglutide (0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg for 1 week"p1	10 weeks	Double-blind, randomized, parallel-arm trial (mixed methods) (laboratory alcohol self administration, then changes in	Alcohol consumption before and after treatment in a laboratory self-administration paradigm Average drinks per calendar day Drinks per drinking day Number of heavy drinking day	Lower alcohol self-administration in semaglutide treatment group Semaglutide associated with fewer drinks per drinking day, reduced alcohol craving, and reductions in heavy drinking over time but did not affect average number of drinks per calendar	1

					alcohol consumption in craving at followup outpatient visits)	Number of drinking days versus abstinence days Cigarettes per day	day or number of drinking days Semaglutide associated with greater reduction of cigarettes per day	
Jensen 2020 (20)	Healthy individuals 18-40 years old without any history of SUD n = 10	N/A	Exenatide infusion (2.8µg non - diabetic subjects, 5µg diabetic subjects)	3h40m	Open-label, placebo-controlled, repeated-measures experiment	DAT availability on SPECT imaging	GLP-1R activation does not increase striatal DA uptake in vitro in humans	3
Klausen 2022 (21)	Treatment-seeking AUD patients n = 127	Alcohol	Exenatide 2mg subcutaneously once weekly combined with cognitive behavioural therapy	26 weeks, 6-month follow-up	Randomized, double-blinded, placebo-controlled clinical trial (mixed methods)	Total alcohol intake Number of heavy drinking days Number of days with no alcohol consumption fMRI measures of cue reactivity in the brain DAT availability	No reduction in number of heavy drinking days Reduction in heavy drinking days and total alcohol intake in obese subjects Decreased alcohol cue reactivity in ventral striatum and septal area on fMRI, and decreased DAT availability on	1

							SPECT in exenatide group relative to placebo	
Kuo 2025 (22)	Adults with T2D and AUD or ArLD initiated on GLP-1 RAs or DPP-4is n = 14,926	Alcohol	Semaglutide, Liraglutide or Dulaglutide	13 years	Retrospective cohort study	ArLD during follow-up period All cause mortality Recurrence of AUD	GLP-1RA treatment associated with reduced risk of ArLD incidence, decreased ArLD progression, lower rates of hepatic decompensation, reduced all-cause mortality, and lower rates of recurrent AUD	1
Lähtenvuo 2025 (23)	Residents of Sweden aged 16 to 64 years with diagnosis of AUD n = 227,866	Alcohol	GLP-1 agonists (exenatide, liraglutide, dulaglutide, and semaglutide), AUD medications (disulfiram, acamprosate, naltrexone)	17 years	Retrospective cohort study	Risk of hospitalization due to AUD and SUD Risk of hospitalization due to somatic reasons and suicide attempts	Semaglutide followed by liraglutide demonstrated lowest risks of AUD, SUD, and somatic hospitalization. No effect of GLP-1 agonists on suicide attempts. Reduced risk of AUD or SUD hospitalization with naltrexone use, but not overall for AUD medications. AUD	1

							medications associated with reduced somatic hospitalizations, but increased risk of suicide attempts.	
Probst 2023 (24)	Smokers aged 18 to 75 years, who were willing to quit smoking and willing to undergo treatment with varenicline n = 255	Alcohol, Tobacco	Dulaglutide, 0.75 mg/0.5 mL in the first week and then increased to 1.5 mg/0.5 m	12 weeks	Double-blind, randomized, parallel-arm trial	Total glasses of alcohol per week Correlation between reduction in alcohol consumption and smoking status Consumption of other drugs	Dulaglutide treatment group drank 29% less alcohol than placebo group No change in alcohol consumption in the subgroup of heavy drinkers No effect found in consumption of other drugs No correlation between reduction in alcohol consumption and smoking status	2
Qeadan 2025 (25)	Adults with a documented history of OUD or AUD n = 1,321,056	Alcohol, Opiod	Biglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide	2 years	Retrospective cohort study	Incidence of opioid overdose in OUD cohort or incidence of alcohol intoxication in AUD cohort in	GIP / GLP-1RA prescriptions associated with 40% lower rates of opioid overdose in people with OUD,	2

			and tirzepatide			individuals with T2D and or obesity	50% lower rates of alcohol intoxication in people with AUD. Effect present for patients with T2D, obesity, and both T2D and obesity	
Quddos 2023 (26)	Facebook, Instagram, and Reddit users in the United States n = 1,115	Alcohol	GLP-1RAs / GIPs (dulaglutide, exenatide, byetta, semaglutide, liraglutide, lixisenatide, rybelsus, mounjaro, tirzepatide, wegovy, ozempic, Trulicity)	14 years	Mixed methods (social media analysis, questionnaire)	Odds ratio of average drinks odds ratio of binge drinking drinks per drinking episode AUDIT score	Fewer drinks per episode alcohol use, fewer binge episodes, lower AUDIT scores , also reduction in self report of stimulating and sedative effects of alcohol after starting semaglutide or tirzepatide Reduced alcohol intake in obese patients using semaglutide or tirzepatide	4
Wang 2024 (27)	Obese patients with or without a pre-existing cannabus use disorder and who were prescribed	Cannabis	Semaglutide	12 month followup, and up to 3 year	Retrospective cohort study	Association of semaglutide with incident or recurrent cannabis use disorder in	Semaglutide was associated with a lower risk for both incident and relapse of cannabis use disorder compared	3

	semaglutide or non-GLP-1RA anti-obesity or diabetes medications n = 681,268			followup in T2D group		patients with obesity or T2D	to non-GLP-1 RA anti-obesity and anti-diabetes medications	
Wang 2024 (28)	New users of anti-diabetes medication with a diagnosis of T2D and TUD n = 222,942	Tobacco	Semaglutide, other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide), and other antidiabetic medications	1 year	Retrospective cohort study	Medical encounters for tobacco use disorder diagnosis Smoking cessation medications prescriptions	Fewer medical encounters for tobacco use disorder in semaglutide users compared to other anti-diabetic medications, including other GLP1-RAs Reduced smoking cessation medication prescriptions and counseling in both obese and non-obese semaglutide users.	2
Wang 2024 (29)	Obese patients with incident AUD diagnosis and no prior history of AUD, patients with recurrent AUD	Alcohol	Semaglutide	18 months, and 3.5 years for other group	Retrospective cohort study	Incident or recurrent AUD disagnosis	50 - 56% lower risk of incident and recurrent AUD diagnosis after 1 year in semaglutide users compared to	2

	diagnosis with obesity and a prior history of AUD, incident and recurrent AUD diagnosis with T2D n = 708,995						other anti-obesity medications. Reductions in incident and recurrent AUD in patients with and without T2D	
Wang 2024 (30)	patients diagnosed with both T2D and OUD and a history of one or more of obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, or stroke, prescribed semaglutide or other antidiabetic medications n = 33,006	Opiods	Semaglutide	12 months	Retrospective cohort study	Rate of opioid overdose	Lower risk of opioid OD in semaglutide users with comorbid T2D and OUD	4
Xie 2025 (31)	US veterans n = 1,955,135	Stimulants (eg cocaine), Cannabis, Alcohol, Opiods	Semaglutide, other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide,	Median of 3.68 years, (2.05 - 5.37) years	Retrospective cohort study	Rate of stimulant use, OUD, disorder, cannabis use disorder, AUD diagnosis	Reduction in risk of stimulant use disorder, OUD, cannabis use disorder, and AUD in GLP-1RA users	3

			tirzepatide and lixisenatide), and other antidiabetic medications					

Abbreviations: AUD (alcohol use disorder), AUDIT (alcohol use disorders identification test), ArLD (Alcohol related liver disease), DAT (dopamine transporter), GLP-1RA (Glucagon-Like Peptide-1 Receptor Agonist), GIPs (gastric inhibitor polypeptide), OUD (opioid use disorder), SPECT (single-photon emission computed tomography), SUD (substance use disorder), T2D (Type 2 diabetes), TUD (tobacco use disorder).

Description of sources

With respect to substances of abuse, nine sources reported outcomes related to alcohol (19,21–26,29,31), three on opioids (25,30,31), three on tobacco (19,24,28), two on cocaine/stimulants (18,31), and two on cannabis (27,31). Semaglutide (19,22,23,25–31), exenatide (18,20,21,23,25,26,28,31), and dulaglutide (22–26,28,31) were the most examined GLP1RAs, being represented in nine, eight, and seven studies, respectively.

Four studies included an experimental, randomized, controlled clinical element to their design (18,19,21,24). Of these, three assessed the impact of GLP-1RAs on alcohol consumption (19,21,24), one on tobacco consumption (19), and one on cocaine consumption (18). None of the sources with outcomes related to opioid or cannabis use included an experimental methodology. One study did not include any substance of abuse, and instead examined the expression of dopamine receptors in response to exenatide (20). Eight studies were observational cohort studies that used health care administrative data (22,23,25,27–31). One study analysed social media to assess the effects of semaglutide on alcohol consumption, and also included a remote questionnaire element in their study for a subgroup of patients (26). A summary of the extraction data from the studies included in this review is presented in Table 1.

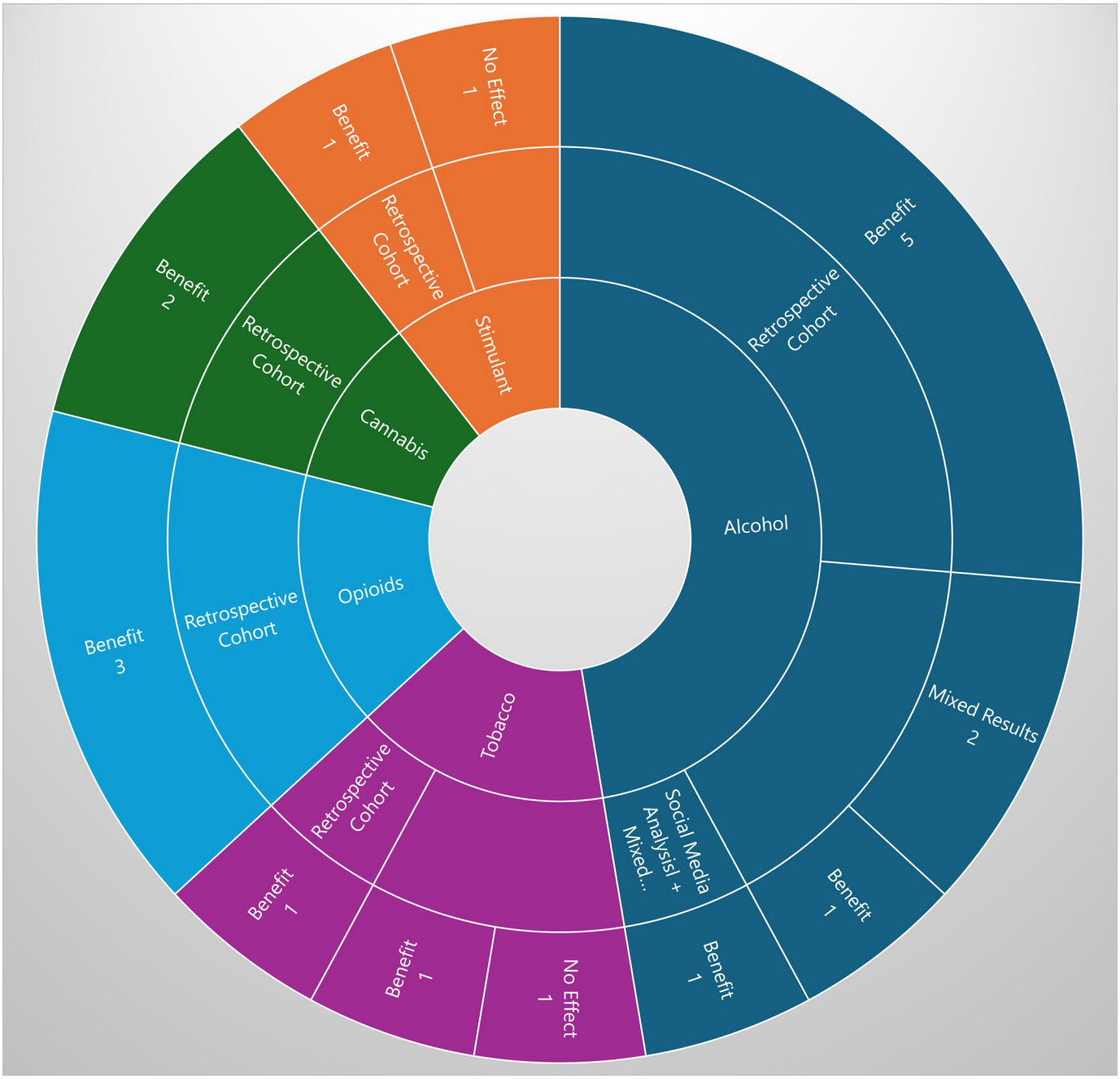

Figure 1. Sunburst diagram representing a summary of the reported efficacy of GLP-1RAs organized by substance of abuse and study methodology. Efficacy was judged based on analysis of results relating to the main outcomes reported in the source. Sources that evaluated outcomes related to multiple sources of abuse (19,24,25,31) are represented in multiple substance categories accordingly.

Description of subject/sample population substance use

Eleven studies evaluated patient populations with a SUD (18,19,21–23,25,27–31), while two studies examined patients with history of substance use but did not specify that they met criteria for a SUD (24,26), and one study included only healthy volunteers who did not meet criteria for any SUD (20).

Detailed summary of findings

The review will now detail the findings of each source, organized by substance of abuse.

Types of Substances

Alcohol use was the substance of abuse most examined in research on GLP-1RAs in our search and was examined in nine studies. See Figure 1 for a depiction of the sources by substance of abuse and methodology.

Probst (24), in a secondary analysis of experimental data, analyzed alcohol consumption in a study of participants treated for nicotine addiction. They found that after 12 weeks of dulaglutide treatment, participants drank 29% less alcohol than the placebo group (24). The decrease in alcohol consumption seen in the dulaglutide group was consistent regardless of baseline alcohol consumption (24). This study also performed further subgroup analysis, but did not find evidence to suggest that the consumption of other drugs was impacted by dulaglutide (24).

Hendershot (19) found that non-treatment-seeking participants with alcohol use disorder consumed less alcohol post-treatment with eight weeks of low-dose semaglutide compared to placebo in a laboratory-based self-administration paradigm. Self-report data collected using daily logs in the same participants demonstrated a reduction in both number of drinks per drinking day and in alcohol craving, although the total number of drinks per calendar day and the number of drinking versus abstinence days were not impacted (19).

In treatment-seeking patients with alcohol use disorder, Klausen (21) found that subjects who received once weekly 2mg subcutaneous exenatide over twenty-six weeks of treatment combined with cognitive behavioural therapy did not demonstrate a reduction in the total number of heavy drinking days compared to a control group that received cognitive behavioural therapy alone. This result was maintained at a six month follow-up. Subgroup analysis of obese patients, however, did find a reduction in both the number of heavy drinking days and total alcohol consumption in the exanatide group compared to the control group (21). Analysis of fMRI data demonstrated significantly attenuated cue reactivity in the ventral striatum and septal area to alcohol in the experimental group (21). This study also evaluated the dopamine transporter availability in the brain using SPECT imaging. Although there was no difference at baseline, after treatment the exenatide treatment group demonstrated lower dopamine transporter availability in the striatum, caudate, and putamen relative to the control group on SPECT imaging (21).

A social media analysis performed by Quddos (26), which analyzed social media discussions about GLP-1RAS on Reddit, Facebook and YouTube, found that posters with obesity reported a reduction in alcohol consumption while using GLP-1 agonists. A web-based survey of current alcohol users with obesity was also performed using participants recruited from the same social

media platforms (26). The effects of semaglutide and tirzepatide on alcohol use and effects were evaluated through a within-subjects design of the same patient's self-report pre- and post-treatment, and by comparison to a control group that did not use these medications. Semaglutide and tirzepatide use were associated with lower self-report of alcohol consumption, and also a reduction in both the stimulating and sedative effects of alcohol (26).

In a retrospective analysis of electronic health records, Qeadan (25) found that in adults with a diagnosis of alcohol use disorder, use of any GLP-1RA / GIP (glucose-dependent insulinotropic polypeptide) medication was associated with 50% lower rates of alcohol intoxication over a follow-up period of two years from an initial GLP-1RA/GIP prescription. This effect was also demonstrated in patients with T2D, obesity, or both T2D and obesity (25).

Wang (29) performed a retrospective cohort study using electronic health records to compare rates of alcohol use disorder diagnosis in obese semaglutide users compared to other anti-obesity medications. Their results demonstrated that semaglutide prescription was associated with a 50–56 % reduced risk of both incident and recurrent alcohol use disorder diagnosis after one year when compared to other anti-obesity medications (29).

Lähteenvuo (23) analyzed Swedish electronic health records to identify all residents aged 16 – 64 years old with alcohol use disorder, then assessed their risk of hospitalization for various causes over a 17 year window. Comparison between various GLP1-RAs (exenatide, liraglutide, dulaglutide, and semaglutide) and alcohol use disorder medications (disulfuram, acamprosate, and naltrexone) found that semaglutide, followed by liraglutide, were the agents associated with the lowest risk of somatic hospitalization (23). They also found that "among patients with alcohol use disorder and comorbid obesity/type 2 diabetes, the use of semaglutide and liraglutide

were associated with a substantially decreased risk of hospitalization due to alcohol use disorder. This risk was lower than that of officially approved alcohol use disorder medications." (23, p94)

Kuo (22) performed a retrospective cohort study using TriNetX (32) healthcare administrative data in patients with diabetes and either alcohol use disorder or alcohol related liver disease, and compared outcomes in patients who had been started on either a GLP-1RA or a DPP4i. They found that the group using GLP-1RAs had reduced risk of recurrent AUD (22). They also found that GLP-1RAs showed a reduced risk of incidence and progression of alcohol related liver disease, and all cause mortality (22).

In a retrospective analysis of U.S. veteran health care data, Xie (31) looked for changes in the frequency of various health outcomes after initiation of various anti-diabetic medications. They found initiation of a GLP-RAs was associated with a reduced risk of alcohol use disorder, opioid use disorder, cannabis use disorder, and stimulant use disorder (31).

Opioids

Three studies examined the impact of GLP1-RAs on opioid use disorder. No sources were identified in the search that used experimental methods to examine outcomes related to opioid use.

In a retrospective analysis of electronic records, described above in the alcohol section, Qeadan (25) found that “among individuals with opioid use disorder, those with a GIP/GLP-1 RA prescription had a 40% lower rate of incident opioid overdose compared to those without a GIP/GLP-1 RA prescription“ (p244). This effect was also demonstrated in patients with type 2 diabetes, obesity, or both type 2 diabetes and obesity (25).

Wang (30) analysed health care administration data to identify patients diagnosed with type 2 diabetes, a diagnosis of at least one of several comorbidities (obesity, hypertension, hypercholesteremia, hyperlipidemia, heart disease, or stoke), and opioid use disorder who were prescribed either semaglutide or other antidiabetic medications, over a six year period. They found that in patients with type 2 diabetes and opioid use disorder, semaglutide was associated with a reduced risk of overdose (30).

Cocaine / Stimulants

Angarita (18) found that a single acute treatment of 5ug exenatide, administered to non-treatment seeking individuals with moderate to severe cocaine use disorder prior to a self-administration paradigm, had no effect on the amount of cocaine used, or on the subjective measures of cocaine induced euphoria or desire for cocaine in comparison to placebo.

Tobacco

In a mixed methods study performed by Hendershot (19), described above in the alcohol section, analysis of self-report logs of cigarette users enrolled in the study identified a treatment-by-time interaction that predicted greater reductions in cigarettes use for the experimental group receiving semaglutide relative to placebo over time during the eight weeks of treatment.

One of the secondary outcomes assessed in Probst (24), a mixed methods analysis described above in the alcohol section, assessed whether the decrease in alcohol consumption that was seen after 12 weeks of dulaglutide treatment was correlated with smoking status (i.e. abstinent versus

continued cigarette use). They found that smoking status was not correlated with reduction in alcohol consumption (24).

Wang (28) analysed healthcare administrative data to assess the frequency of various types of health care visits related to tobacco use disorder within 1 year of prescription of various antidiabetic medications. They found a lower risk of medical encounters for tobacco use disorder diagnosis in patients using semaglutide in comparison to other anti-diabetes medications (28). They also found that "semaglutide was associated with reduced smoking cessation medication prescriptions and counseling. Similar findings were observed in patients with and without a diagnosis of obesity (30, p1).

Cannabis

Wang (27) compared rates of incident and recurrent cannabis use disorder using the TriNetX database in patients prescribed semaglutide in versus other non GLP-1RA anti-diabetic or anti-obesity medications. At 12-month follow-up, there was a lower risk for cannabis use disorder in the cohort prescribed semaglutide (27). In a subgroup analysis in patients with diabetes, the risk of incident and recurrent risk of cannabis use disorder at three years was assessed. There was a significantly lower risk of incident cannabis use disorder, however no significant reduction in recurrent cannabis use disorder (27). The reduced risk at three years was found to be attenuated over time (27).

Other outcomes

Jensen (20) described a series of three experiments investigating the effect of exenatide on dopamine uptake and dopamine transporter expression. Two of the experiments included animal data and are not described in this review. In the experiment on human subjects, the effect of an acute intravenous exenatide infusion on levels of dopamine transporter expression was analyzed using SPECT imaging in 10 healthy volunteers. They found no effect of acute exenatide infusion on DAT expression in humans in this small pre-clinical trial (20).

Discussion

This systematized review sought to characterize the current body of human research investigating the effects of GLP-1RAs on SUD. GLP1-RAs have only recently entered mainstream clinical use, limiting the opportunities to study these drugs for potential applications outside of diabetes and obesity. Indeed, none of the studies identified in this review were published prior to 2020. In contrast to this relatively short timeframe, given the nature of the research question, this review includes results contingent on many variables, including numerous GLP1-RA agents, substances of abuse, and study methodologies. While this variability does not permit definitive conclusions, it offers the opportunity to make comparisons that can help inform ongoing research.

Efficacy

Most studies in this review found that GLP-1RAs are associated with improvements in the SUD related outcomes described in their study. Alcohol use disorder had the most evidence in favor of its efficacy. Alcohol was represented by studies using various methodologies and included all

four studies rated in the highest quality quartile. Cocaine/stimulant use disorder had the smallest body of favourable evidence, with one retrospective cohort analysis showing reduced rates of cocaine/stimulant use disorder associated with GLP-1RA use. This mirrors the current evidence in animal studies, wherein GLP-1RAs have the most evidence of a benefit in animal models of alcohol use disorder, and little evidence suggestive of benefit for stimulants (14). While different SUDs may share some underlying mechanisms, there is also variability in the physiologic and behavioural components of different substances of abuse(17,20). For example, alcohol consumption may be subject to greater impact of the peripheral effects of GLP-1RAs on factors like satiety, gastric motility, and glucose metabolism, given its method of ingestion and high caloric value in comparison to other substances of abuse (6).

Dose size

The effect of dosing in humans is an important clinically relevant question. In the case of semaglutide, for example, Ozempic and Wegovy include the same active ingredient marketed for different applications based on their dosage (33). Specifically, the dose given for obesity is higher than doses prescribed for diabetes (33). Because many of the observational studies collected data and separated cohorts into diabetic and obesity cohorts, indirect inferences can be made about dose, given that the prescribed dosage would correspond to whether it was prescribed for diabetes or obesity. Many of the sources commented that the effect was present for both type 2 diabetes and obesity medications, however Wang (29) found that although the effect on alcohol use disorder was present in both populations, the effect was greater in the obesity group than in the diabetes group. In another example, Wang (27) found that at the 12-month follow-up there was a reduction in recurrent cannabis use disorder in both the type 2 diabetes and

obesity group, however the reduction was not statistically significant in non-obese individuals. In the experimental arm of Hendershot (19), they also described a greater effect size in weeks 5-8 of their study relative to weeks 1- 4, which they attributed to a treatment-by-time effect, but might also be explained by the higher doses used in weeks 5-8. Both of the studies which included experimental arms and had negative results (18,21) were at antidiabetic dosing. Taken together, these studies suggest that higher doses may result in larger effects on SUD dose. Because the mechanisms of SUD are unclear, and these studies included other significant confounding variables such as metabolically relevant comorbidities, further experimental studies to eliminate these confounding variables are required to assess this question in depth.

Dose Timing / treatment-by-time

The timing of medication effects is another variable of interest. Using intravenous infusion, two experimental studies assessed the impact of GLP-1Ras on acute administration, on the timescale of hours from initial drug administration. Angarita (18) used a single acute pre-treatment paradigm with exenatide, which did not show any reduction in cocaine self-administration. In Jensen (20), dopamine transporter availability measured by SPECT imaging in the 60 minutes following initiation of exenatide infusion was unchanged in human subjects. The failure to show an effect after a single acute administration contrasts with animal studies where single doses of exenatide resulted in decreased cocaine seeking behaviour in rats (34) and mice (35).

Inferences can also be drawn about the variable of timing of administration from studies that evaluated the effectiveness of GLP-1RAs over longer timeframes. After 26 weeks of treatment, Klausen (21) reported significant reduced alcohol cue reactivity, based on fMRI imaging, and

dopamine transporter availability, based on SPECT analysis, in areas of the brain associated with reward and addiction in comparison to a placebo group. These physiological changes were not reflected by a decrease in their primary behavioural outcome of decreased number of drinking days (21). These results suggest that some neurobiological changes are not acutely impacted by GLP-1RA administration, and instead may accrue over time.

As described above in the discussion about effect of dose size, Hendershot (19) reported a significant treatment-by-time effect with a small effect for reduction in cigarettes per day in weeks 1-4, and a larger effect size seen in weeks 5-8 of their trial. Hendershot (19) also demonstrated a significant treatment-by-time effect with a greater reduction in heavy drinking days over time relative to placebo. Analysis of administrative health care data by Wang (28) found the reductions in tobacco use disorder related health care presentations was present as early as 30 days from prescription of GLP-1RAs, with the effect size plateauing at 180 days. Few of the studies incorporated analysis of effectiveness over long term GLP-1RA use, however Wang (27) found that the initial effect of reduced incident recurrent cannabis use disorder codes was attenuated in their long term (three year) follow-up.

GLP-1RA agent

Among studies comparing specific GLP1-RAs, semaglutide was most commonly reported as the most effective agent for SUD. This is consistent with data suggesting semaglutide is one of the most effective GLP1-RAs for weight loss and diabetes (36), although the SURPASS-2 study found that tirzepatide was more effective in both weight loss and diabetes (37). Different agents possess unique pharmacokinetic and pharmacodynamic characteristics, which may make them

better suited to certain clinical applications (38). One plausible explanation for the reported effectiveness of semaglutide when compared against other GLP1-RAs is the relatively tolerability of its side effect profile (37), which may translate to better medication adherence. It's worth noting that most of the sources identified by this review did not compare between GLP1RA agents. Of the six sources that did (23,26–30), four shared the same lead author. All four Wang papers used similar population, methods, and analyses, and identified semaglutide as the most effective agent (27–30). Any comparisons between effectiveness of different GLP1-RA agents based on this review is therefore subject to a significant risk of bias.

Population

The majority of the studies which performed retrospective cohort analysis using medical administrative data used the same database, TriNetX (32), which includes data from a large number of American healthcare institutions (22,27–30). These studies showed largely positive results, suggesting relative improvement in various SUD related health outcomes associated with GLP1-RA use. Three other sources analyzed health records for cohort analysis, which corroborated the results found in the TriNetX data. Xie (31) found a reduction in risk of SUDs when analyzing data of nearly two million U.S. military veterans, while Lähteenvuo (23) demonstrated benefits to SUD in Swedish residents. Qeadan (25), used Cerner Real-World Data (39), a de-identified database that also includes health care data from the United States, found reduced rates of alcohol intoxication presentations in a cohort of GLP-1RA users with alcohol use disorder.

One significant confounding variable in any of the health administrative data analyses presented in this review is that the vast majority of patients prescribed GLP-1RA have diabetes, obesity, or both. How the interaction of these comorbid conditions impacts the effect of GLP1RAs on SUD is unclear, as is the degree to which these results will generalize to other populations.

One comparison of interest in the population of experimental studies is whether patients were treatment-seeking or non-treatment-seeking. In a study including only non-treatment seeking individuals, Hendershot (19) found a reduction in heavy drinking over time with semaglutide use in comparison to placebo, while Klausen (21) did not find a reduction of heavy drinking days with exenatide use relative to placebo in a study that included only treatment-seeking individuals. An important difference between these two study designs was that the Klausen (21) study included cognitive behavioural therapy for both the treatment and nontreatment groups. The authors posit that the strength of the effect of cognitive behavioural therapy in the placebo group could have hidden an effect that might otherwise have been detected when compared to a control group with no treatment (21). Regardless, differences in efficacy of SUD treatments between treatment-seeking and non-treatment-seeking individuals is of clinical interest. From a practical standpoint concerning future clinical research, taking this potential reduction on effect size into account during study design and power analysis may be necessary given that treatment-seeking subjects are likely to also be engaged with cognitive behavioral therapy by ethical necessity.

What does this review add to the existing literature?

At least two other recent PRISMA reviews have described the existing research on the effect of GLP-1Ras on SUD in humans. Both of these studies, authored by Shen (40) and Martinelli (41), found mixed results concerning efficacy. Each review identified five studies that met their inclusion/exclusion criteria. Three sources were identified in these reviews that were not captured by the search methodology employed in this study. Two RCTs studying the effects of tobacco were described in both reviews; Lengsfeld (42) found that dulaglutide treatment did not improve smoking abstinence when compared against placebo, while Yammine (43) found that exenatide in conjunction with nicotine patch use resulted in higher rates of abstinence compared to placebo. Shen (2024) also included a retrospective cohort analysis of Danish healthcare administrative data performed by Wium-Anderson (44), which found that GLP-1RAs were associated with lower rates of alcohol related healthcare interactions when compared against other anti-hyperglycemic medications (specifically DPP4s) and non-treatment. In comparison to Shen (40) and Martinelli (41) this review includes a greater number of sources, largely represented by the inclusion of more sources that analyzed healthcare administrative data. These large-scale retrospective cohort analyses of healthcare administrative data have the benefit of analyzing large sample populations to assess for trends. Although this methodology has significant limitations, it is a valuable approach in pre-clinical research where large-scale RCTs would not be ethical or practical.

Limitations

Several limitations must be considered when interpreting the findings of this review. Although the methodology for this systematized review followed the well-established PRISMA guidelines, additional reviewers during the title and abstract screening, full text review, extraction, and

quality analysis would have yielded results with greater reliability and validity. The decision to search a single database excluded several studies identified in other systematic reviews. Despite the small number of studies reviewed, there is little overlap between recruitment practices, methodology, or analysis. Further, given the wide variety of variables and outcomes analysed in each of these studies, direct comparisons within this review cannot be made without significant confounding variables. All the studies included in this review included subjects from, or reviewed data from, populations in resource-rich nations, and it is unclear whether these results are representative of other populations. High-risk populations, for example, children and adolescents, minority cultural and ethnic groups, LGBTQ2S+ communities, and geographically isolated populations, were not well represented in this review.

Conclusions

This systematized review found that GLP-1RAs may have the potential to impact SUD in humans. While most of the studies presented here indicated a benefit of GLP1-RAS on SUD, some showed no effect. Alcohol was the substance of abuse best represented in this review, being studied by various methodologies, and demonstrated mixed results regarding the efficacy of GLP-1RAs on alcohol use disorder outcomes. The heterogeneity of outcomes, methodologies, substances of abuse, and specific GLP1-RAs, precludes definitive conclusions at this early stage of investigation into this topic. Given the magnitude of the negative impact SUD has worldwide, and the sparsity of viable treatment options, future research that better characterizes the impact of GLP-1RAs on SUD is warranted.

Appendix I: Search String

The Medline database was searched using the PubMed platform. The reproducible search for this database is

(("substance use" OR "addictions") OR (substance related disorders[MeSH Terms])) AND ((glucagon-like peptide-1 receptor agonist[MeSH Terms]) OR (glp-1 agonist OR semaglutide OR ozempic OR liraglutide OR exenatide OR dulaglutide OR lixisenatide OR tirzepatide))

The search was limited to publications from Jan 1st 2000 to April 1st 2025. The initial comprehensive literature search was performed on December 11, 2024 then rerun on April 18th 2025. The search strategy was developed with the assistance of librarian Margaret Banka.

Appendix II: Extraction template

Title

Lead author

Primary objective / research question

Year

Study design

Length of study/intervention

Intervention (drug)

Population

Sample Size

Location/Setting

Targeted outcomes (related to SUD)

SUD as a primary or secondary outcome?

Findings

Main conclusions as it pertain to SUD

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