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Prospects of GLP-1 Therapies for Addiction and Mental Health Comorbidities—Quo Vadis? A Review

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IMPORTANCE Glucagon-like peptide-1 (GLP-1) therapies have revolutionized the management of chronic conditions like obesity and diabetes. Consistent with the overlap between feeding and metabolic pathways and those mediating addictive behaviors, growing evidence suggests that GLP-1 therapies may also be beneficial for treating alcohol and other substance use disorders (ASUDs). This review discusses the current landscape of GLP-1 therapies in the context of ASUDs, mental health considerations, and gaps and opportunities in this field.

OBSERVATIONS Preclinical evidence across several experimental models and species consistently shows that GLP-1 receptor agonists (GLP-1RAs) reduce drug intake and other addictive behaviors. Research to date has primarily focused on alcohol; however, nicotine, opioids, and psychostimulants have also been studied. Observational cohort studies using electronic health records suggest improvements in ASUD-related outcomes among people treated with GLP-1RAs for other indications. Randomized clinical trials (RCTs) have been limited, yielding mixed results but overall promising signals. Several RCTs are ongoing or about to start. Despite some early pharmacovigilance alarms, GLP-1RAs do not seem to cause or increase the risk of psychopathology (eg, depression, suicidal ideation and/or behavior). Some recent studies suggest beneficial effects of GLP-1RAs on mental health outcomes, but more work is needed.

CONCLUSIONS AND RELEVANCE The rationale for studying GLP-1 therapies for ASUDs is supported by preclinical and observational clinical evidence. RCTs are emerging and critically needed at this juncture to determine the safety and efficacy of GLP-1 therapies in people with ASUDs. Pending results from RCTs, GLP-1 therapies have the potential to be repurposed for ASUDs. However, there are several relevant questions in need of further investigation, including the specifics of treatment with GLP-1 therapies in the context of addiction (eg, dose, duration, tachyphylaxis, impact of discontinuation), individual differences and potential predictors of response, mechanisms of action, intersection with mental health and medical comorbidities, cost, and fair access to these treatments.

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Glucagon-like peptide-1 (GLP-1) is an incretin hormone mainly produced by intestinal L cells in response to food ingestion. By stimulating insulin secretion, inhibiting glucagon secretion, and slowing gastric emptying, GLP-1 regulates blood glucose levels and promotes satiety. GLP-1 exerts its physiological functions by activating GLP-1 receptors that are expressed in various peripheral tissues (eg, pancreas, liver, gastrointestinal tract, heart, kidneys) and brain regions (eg, hypothalamus, nucleus tractus solitarius, nucleus accumbens, ventral tegmental area, amygdala, hippocampus).[1]

Endogenous GLP-1 has a short half-life as it gets rapidly degraded by the dipeptidylpeptidase 4 (DPP-4) enzyme. GLP-1 receptor agonists (GLP-1RAs) are analogs of the endogenous GLP-1 with structural modifications that impede hydrolysis by DPP-4, resulting in extended half-lives and longer and stronger biological activity. DPP-4 inhibitors (DPP-4Is), on the other hand, boost endogenous GLP-1 levels by delaying its degradation. GLP-1RAs (starting with exenatide) and DPP-4Is (starting with sitagliptin) have been approved and used in clinical practice for approximately 2 decades to treat type 2 diabetes. More recently, the development of longer-acting GLP-1RAs with higher potency (eg, liraglutide and semaglutide) and those targeting more than 1 receptor (eg, tirzepatide) has been recognized as a major scientific breakthrough, mainly because of their remarkable antiobesity effects.[2,3] The GLP-1 system plays a critical role in regulating not only homeostatic but also hedonic food intake through central and peripheral pathways.[4,5] These mechanisms overlap with those underlying alcohol and other substance use disorders (ASUDs), and the cross talk between feeding and addictive behaviors provides a framework for studying GLP-1 therapies in the context of addiction.[6-8]

There has been an upswing of anecdotal reports from people taking GLP-1RAs for diabetes or obesity and experiencing uninten-

Table 1. Pharmacotherapies Approved by the US Food and Drug Administration (FDA) for Alcohol, Tobacco, and Opioid Use Disorders[a]

Medication	Primary mechanism(s) of action	Main clinical benefits	Common adverse effects
AUD[b]			
Disulfiram	Inhibition of aldehyde dehydrogenase	Deters alcohol drinking due to aversive effects (see right column) when alcohol is consumed	Drowsiness, nausea, vomiting, flushing headache, tachycardia
Acamprosate	Partial agonism of NMDA receptors; additional mechanisms include interaction with metabotropic glutamate and GABA-A receptors	Reduces return to any alcohol drinking and protracted withdrawal following abstinence	Diarrhea, insomnia, anxiety
Naltrexone	Antagonism of μ-, κ-, and δ-opioid receptors	Reduces heavy alcohol drinking and craving, reduces return to any alcohol drinking	Dizziness, nausea, headache, insomnia
TUD			
NRT[c]	Agonism of nicotinic receptors	Substitutes nicotine without harmful chemicals of tobacco products, reduces tobacco craving and withdrawal symptoms	Headache, nausea, dyspepsia, insomnia
Bupropion	Inhibition of norepinephrine and dopamine reuptake	Reduces tobacco craving and withdrawal symptoms	Dizziness, nausea, constipation, insomnia
Varenicline	Partial agonism of α4β2 nicotinic acetylcholine receptors	Reduces reinforcing effects of nicotine and tobacco craving	Headache, nausea, constipation, flatulence insomnia
OUD[d,e]			
Methadone	Agonism of μ-opioid receptors; additional mechanisms include antagonism of NMDA receptors and inhibition of serotonin and norepinephrine reuptake	Reduces opioid use, craving, and withdrawal	Drowsiness, dizziness, nausea, constipation, headache, QT interval prolongation
Buprenorphine	Partial agonism of μ-opioid and antagonism of, κ-, and δ-opioid receptors	Reduces opioid use, craving, and withdrawal	Drowsiness, dizziness, nausea, constipation, headache, insomnia
Naltrexone	Antagonism of μ-, κ-, and δ-opioid receptors	Reduces return to any opioid use and craving	Dizziness, nausea, headache, insomnia

Abbreviations: AUD, alcohol use disorder; GABA-A, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; NRT, nicotine replacement therapy; OUD, opioid use disorder; TUD, tobacco use disorder.

[a] There are no FDA-approved medications for other substance use disorders besides alcohol, tobacco, and opioid use disorders.

[b] Several benzodiazepines (eg, chlordiazepoxide, clorazepate, diazepam, and oxazepam) are FDA approved for acute alcohol withdrawal.

[c] NRT formulations approved by the FDA include gum, lozenge, oral inhaler, nasal spray, and transdermal patch.

[d] Lofexidine is FDA approved for acute opioid withdrawal.

[e] Naloxone and nalmefene are FDA approved for opioid overdose prevention and reversal.

tional reductions in alcohol and other substance use. These reports have been preceded by robust scientific evidence, from basic neuroscience and initial human studies, resulting in increased enthusiasm and investment of the biomedical research community to study GLP-1 therapies as potential novel treatments for ASUDs and possibly comorbid conditions. The need to identify and develop new effective treatments for people with ASUDs cannot be overstated; ASUDs are leading causes of morbidity and mortality, yet currently approved pharmacotherapies are very limited (**Table 1**). In this narrative review, we discuss the current landscape, existing evidence, and open questions on GLP-1 therapies in the context of ASUDs and mental health (**Figure**).

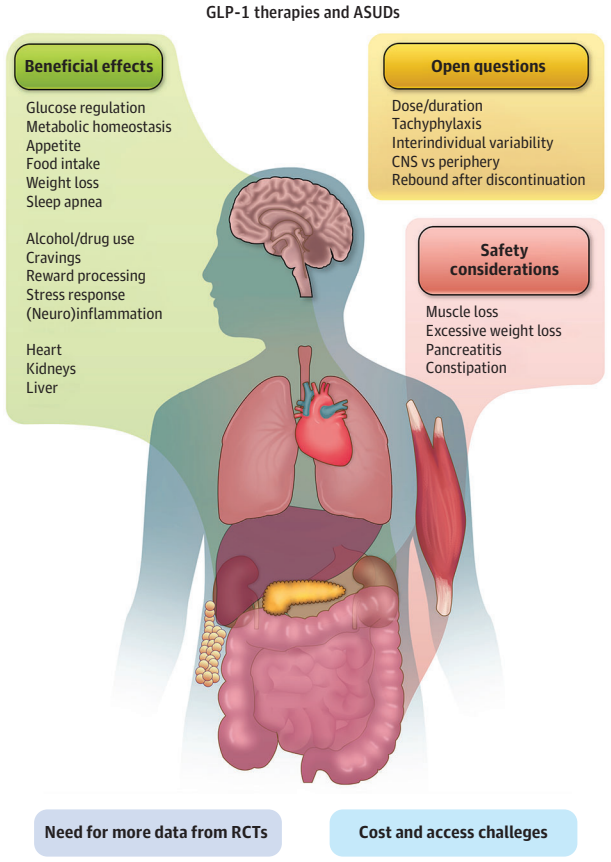
GLP-1 Therapies and Addiction

The majority of GLP-1 research in the addiction field to date has focused on alcohol, followed by nicotine, opioids, and psychostimulants. Several preclinical experiments in mice, rats, and nonhuman primates indicate that GLP-1RAs, administered systemically or centrally into relevant brain regions, reduce drug intake (using operant, choice, bingelike, and reinstatement models), drug reward (operationalized as conditioned place preference), accumbal dopamine release, and locomotor sensitization.[9,10]

Case series, survey analyses, and social media posts indicate that people who start semaglutide or tirzepatide report reductions in craving for and use of alcohol and nicotine.[11-14] Retrospective cohort studies analyzing the associations between GLP-1 therapies and ASUD-related outcomes in real-world electronic health records have been emerging. Such studies may signal potential efficacy but have inherent limitations (eg, confounding factors) and do not substitute randomized clinical trials (RCTs). One such study applied a discovery approach by including 175 health outcomes and found lower risk of ASUDs under GLP-1RAs compared with non–GLP-1RA antidiabetes medications.[15] Other pharmacoepidemiological studies have found GLP-1RAs to be associated with reduced risk of alcohol use disorder (AUD) incidence and recurrence, alcohol consumption, and alcohol-related events, intoxication, and hospitalization.[16-22] Unlike GLP-1RAs, receipt of DPP-4Is did not impact alcohol-related outcomes in cohort studies. This lack of effect with DPP-4Is has been confirmed in rodent experiments,[20,23] suggesting that increasing endogenous GLP-1 levels via DPP-4 inhibition is not sufficient to reduce alcohol seeking and/or intake and GLP-1R activation is needed to produce such effects. Beyond alcohol, observational cohort studies have also shown improvements in outcomes related to nicotine,[24,25] opioids,[18,26,27] and cannabis[28] in people receiving GLP-1RAs.

RCTs represent the criterion standard and are needed to study the safety and efficacy of GLP-1RAs for ASUDs (**Table 2**).[29-33] The first alcohol RCT yielded mixed results. Specifically, treatment with a first-generation GLP-1RA, extended-release exenatide, for 26 weeks did not reduce the number of heavy drinking days or total alcohol intake in people with AUD who also received standard cognitive-behavioral therapy. However, lower alcohol cue reactivity in the ventral striatum and septal area (functional magnetic resonance imaging) and lower dopamine transporter availability in the striatum, caudate, and putamen (single photon emission computed tomography) were found under ex-

Figure. Current Landscape and Main Beneficial Effects, Safety, Considerations, and Open Questions and Challenges With Glucagon-Like Peptide-1 (GLP-1) Therapies in Relation to Alcohol and Other Substance Use Disorders (ASUDs)



CNS indicates central nervous system; RCT, randomized clinical trial.

enatide compared with placebo. Notably, this study had a high dropout rate of more than 50%. An exploratory post hoc analysis showed that people with body mass index (BMI) greater than 30 (calculated as weight in kilograms divided by height in meters squared) decreased, whereas those with BMI less than 25 increased, their alcohol drinking under exenatide compared with placebo.[29] Secondary analysis of a smoking-cessation RCT found greater reduction in weekly alcohol consumption after 12 weeks of treatment with dulaglutide compared with placebo; changes in alcohol intake were not correlated with smoking status (abstinent vs still smoking) at the end of the study.[34] Recently, a 9-week RCT tested semaglutide in people with AUD and found that low-dose semaglutide significantly reduced the amount of alcohol self-administration in a human laboratory experiment. Furthermore, lower craving, drinks per drinking day, and heavy drinking days were found under semaglutide compared with placebo, while drinks per calendar day and number of drinking vs abstinent days were unchanged.[30] Although more studies are needed, the latter findings suggest that GLP-1RAs may not promote complete abstinence, at least in some individuals, but help reduce the amount of alcohol drinking. Of note, a large body of evidence indicates that, even without abstinence, reduction of alcohol use is associated with improvements in several health outcomes.[35-38] Accordingly, in addition to "abstinence," the US Food and Drug Administration (FDA) now accepts "no heavy drinking days" and recently qualified "2-level reduction in risk drinking level" as primary end points for AUD clinical trials.[39-41]

In the alcohol semaglutide RCT mentioned earlier, secondary analyses showed a significant reduction in the number of cigarettes smoked per day under semaglutide compared with placebo in a small subgroup who reported current cigarette use.[30] To date, 2 published RCTs have specifically examined GLP-1RAs for nicotine use. The first study tested extended-release exenatide as an adjunct to nicotine patch plus behavioral counseling and found higher nicotine abstinence and lower nicotine craving and withdrawal symptoms after 6 weeks of treatment with exenatide compared with placebo. Exenatide was also found to reduce postcessation weight in this study.[31] Because weight gain often follows smoking cessation and is a major deterrent to quitting, treatments that mitigate postcessation weight gain could encourage more quit attempts, support sustained abstinence, and improve overall health outcomes.[42,43] A secondary analysis of the aforementioned RCT found stronger benefits with exenatide in people with higher severity of cigarette smoking, no prediabetes or obesity, no or minimal depressive symptoms, and protected variant (GG) of rs16969968 on the cholinergic receptor nicotinic α-5 subunit (*CHRNA5*) gene.[44] Another nicotine RCT tested dulaglutide for 12 weeks as an adjunct to varenicline plus behavioral counseling and found no significant differences between dulaglutide and placebo on smoking outcomes.[32] Notably, the overall sample, regardless of the drug condition, showed significant reductions in nicotine craving and use (eg, >60% were abstinent at the end of study), which could have led to a ceiling effect. Consistent with the nicotine exenatide RCT,[31] dulaglutide significantly lowered postcessation weight during the treatment phase as assessed at the 3-month end point.[32] This study also included 2 follow-ups at 6 and 12 months after treatment, which showed similar weight gain across the 2 groups (dulaglutide vs placebo).[45] These findings suggest that attenuation of postcessation weight gain is not sustained once GLP-1RA treatment is discontinued, which is consistent with the broader notion in the obesity field that stopping GLP-1RAs typically results in weight regain.[46]

Despite robust preclinical evidence with opioids and psychostimulants, RCTs have been limited. Preliminary unpublished results from a 3- to 5-week RCT conducted in a residential opioid use disorder (OUD) treatment program indicate that liraglutide was safe and on average led to 40% reduction in opioid craving.[47,48] A small human laboratory found no changes in cocaine self-administration or subjective effects after a single dose of immediate-release exenatide vs placebo; these results must be interpreted with caution considering the study limitations, chiefly the use of a single dose of exenatide.[33] To our knowledge, no preclinical experiments or RCTs have investigated the effects of GLP-1 therapies on cannabis use.

In summary, preclinical and pharmacoepidemiological studies with GLP-1RAs indicate benefits across several addictive drugs. Data from RCTs have started to emerge (Table 2),[29-33] but additional well-designed and fully powered RCTs are needed to determine the safety and efficacy of GLP-1 therapies for ASUDs.[49,50]

GLP-1 Therapies and Mental Health

Considering the high comorbidity between ASUDs and other psychopathology and the well-established neurobiological role of GLP-1 in central or behavioral functions such as reward processing, stress

Table 2. Completed Randomized Clinical Trials (RCTs) With Glucagon-Like Peptide-1 (GLP-1) Therapies for Alcohol, Tobacco, and Opioid Use Disorders[a]

Medication target dose	Duration design	Participants sample size	Main outcomes	Source/ ClinicalTrials.gov ID
AUD[b]				
Exenatide 2 mg/wk	26 wk Outpatient, between-participant RCT of once weekly exenatide vs placebo (plus behavioral treatment)	Treatment-seeking individuals with AUD N = 127 randomized N = 58 completed	No significant differences between the 2 groups in the number of heavy drinking days or total alcohol intake. Significantly reduced brain functional magnetic resonance imaging cue reactivity under exenatide than placebo. Significantly lower brain single photon emission computed tomography dopamine transporter availability under exenatide than placebo Significantly greater reduction in the number of heavy drinking days and total alcohol intake under exenatide than placebo among participants with BMI[c] >30 (exploratory analysis).	Klausen et al,[29] 2022 NCT03232112
Semaglutide 1 mg/wk	9 wk Outpatient, between-participant RCT of once weekly semaglutide vs placebo	Nontreatment-seeking individuals with AUD N = 48 randomized N = 42 completed	Significantly lower laboratory alcohol self-administration under semaglutide than placebo. Significantly greater reduction in drinks per drinking day, heavy drinking days, and alcohol craving under semaglutide than placebo. No significant differences between the 2 groups in drinks per calendar day or number of drinking vs abstinent days. Significantly greater reduction in cigarettes per day under semaglutide than placebo among cigarette smoking participants (N = 13).	Hendershot et al,[30] 2025 NCT05520775
Semaglutide 2.4 mg/wk	26 wk Outpatient, between-participant RCT of once weekly semaglutide vs placebo (plus behavioral treatment)	Treatment-seeking individuals with AUD and comorbid obesity N = 108 randomized	Unpublished	NCT05895643
TUD[d]				
Exenatide 2 mg/wk	6 wk Outpatient, between-participant RCT of once weekly exenatide vs placebo (plus nicotine patch and behavioral treatment)	Treatment-seeking smokers with comorbid prediabetes and/or overweight N = 84 randomized N = 69 completed	Significantly higher ratio of smoking abstinence and significantly lower craving scores under exenatide than placebo. Significantly lower withdrawal scores under exenatide than placebo among abstainers (no significant differences among nonabstainers). Significantly lower postcessation weight under exenatide than placebo.	Yammine et al,[31] 2021 NCT02975297
Dulaglutide 1.5 mg/wk	12 wk Outpatient, between-participant RCT of once weekly dulaglutide vs placebo (plus varenicline and behavioral treatment)	Treatment-seeking smokers N = 255 randomized N = 204 completed	No significant differences between the 2 groups in the ratio of smoking abstinence or craving scores. Significantly lower postcessation weight under dulaglutide than placebo.	Lengsfeld et al,[32] 2023 NCT03204396
Liraglutide 3 mg/d	32 wk Outpatient, between-participant RCT of once daily liraglutide vs placebo (plus behavioral treatment)	Treatment-seeking smokers with comorbid obesity or BMI ≥27 and weight-related medical problems N = 40 randomized	Unpublished	NCT03712098
Semaglutide 1 mg/wk	9 wk Outpatient, between-participant RCT of once weekly semaglutide vs placebo	Nontreatment-seeking smokers N = 24 randomized	Unpublished	NCT05530577
OUD[e]				
Liraglutide 3 mg/d	3-5 wk Inpatient, between-participant RCT of once daily liraglutide vs placebo (plus behavioral treatment with or without buprenorphine/naloxone)	Treatment-seeking individuals with OUD N = 25 randomized	Unpublished	NCT04199728

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; OUD, opioid use disorder; TUD, tobacco use disorder.

[a] There are no completed RCTs with GLP-1 therapies for other substance use disorders. A small human laboratory with a single dose of immediate-release exenatide found no effects on cocaine self-administration or subjective effects.[33] Trials NCT06252623 and NCT06691243 are ongoing for cocaine use disorder.

[b] Examples of ongoing RCTs with GLP-1 therapies for AUD are as follows: NCT06015893, NCT05891587, NCT05892432, NCT06994338, NCT06727331, NCT06817356, and NCT06409130.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Examples of ongoing RCTs with GLP-1 therapies for TUD are as follows: NCT05610800 and NCT06173778.

[e] Examples of ongoing RCTs with GLP-1 therapies for OUD are as follows: NCT06548490, NCT06639464, and NCT06651177.

response, cognition, and neuroprotection, it is important to evaluate the intersection of GLP-1 therapies and mental health from at least 3 standpoints, as detailed next.

First, a key question in the field is whether GLP-1RAs cause significant anhedonia, affecting general survival behaviors (eg, feeding, sex, sleep) that may lead to, or worsen, depressive symptoms, including life-threatening conditions (eg, suicidal ideation and/or behavior). From a neurobiological perspective, this concern aligns with the expression of GLP-1 receptors in several relevant brain regions and the broad effects of GLP-1RAs on behaviors and pathways that are essential for survival. In fact, GLP-1RAs reduce not only appetite, food intake, and food reward but also some other caloric and

noncaloric ingestive behaviors (eg, the intake of water, saccharine, sucrose, etc), as well as addictive and seeking behaviors, as discussed previously. This concern is also legitimate for at least 2 more reasons: (1) the well-known bidirectional relationship between mental health conditions (eg, depression, anxiety, cognitive deficits) and metabolic disorders like diabetes[51] and obesity,[52] which are 2 FDA-approved indications for GLP-1RA treatment, and (2) precedents in the history of medication development for weight management, such as the development, approval, and subsequent withdrawal of the cannabinoid receptor 1 antagonist rimonabant in Europe due to neuropsychiatric adverse effects, including severe mood disorders, depression, and suicide.[53] Case in point, the prescribing information of GLP-1RAs approved for obesity states that suicidal ideation and/or behavior have been reported in clinical trials with other weight management products and patients receiving GLP-1RAs should be monitored for the emergence or worsening of depressive symptoms and suicidal ideation and/or behavior. Besides this generic warning, lately the concern came to light due to some reports (eg, by the Icelandic drug surveillance system) of suicidal ideation and/or self-injury in patients taking GLP-1RAs, prompting the European Medicine Agency (EMA), FDA, and other regulatory agencies to conduct thorough reviews of this matter. The alarms triggered by postmarketing surveillance have been accompanied by a few published reports. A pooled analysis of phase 2 and 3a RCTs testing liraglutide for weight loss, including data from both adverse-event reporting and prospective questionnaires (eg, Patient Health Questionnaire-9 and Columbia-Suicide Severity Rating Scale), found a small numerical imbalance in increased risk of suicidal ideation and/or behavior with liraglutide through adverse event reporting (9 vs 2 patients on liraglutide vs placebo, respectively) but not with the prospective questionnaires.[54] More recently, a case-control pharmacovigilance study of 36 172 078 reports in the World Health Organization global database identified 107 cases of suicidal and/or self-injurious adverse reaction associated with semaglutide and 162 cases associated with liraglutide. Analyses identified significant disproportionality only for semaglutide-associated suicidal ideation, which remained significant in people who were also taking antidepressants and/or benzodiazepines.[55] Other pharmacovigilance studies have yielded mixed results with some showing more reported than expected rates of depression and suicidal ideation and/or behavior (ie, disproportionate reporting) under GLP-1RAs,[56,57] whereas others indicated no associations.[58,59] In interpreting these results, it is important to keep in mind the limitations of pharmacovigilance data and disproportionality analyses, as well as confounding factors (eg, confounding by indication), all of which limit the ability to establish causal links.[60,61] Case in point, mendelian randomization studies, which examine potential causality between an exposure and an outcome, have shown that GLP-1RAs do not increase suicide risk.[62,63] A number of large-scale analyses (eg, data from 4 of the obesity Semaglutide Treatment Effect in People With Obesity [STEP] trials,[64] the UK Clinical Practice Research Datalink,[65] the US Medicare administrative data,[66] and several recent meta-analyses[67-72]) have found no associations between GLP-1RAs and increased risk of psychiatric adverse events including depression and suicidal ideation and/or behavior.

Second, emerging work suggests that GLP-1RAs may have beneficial effects on mental health. Although benefits for binge eating disorder and bulimia nervosa are expected,[73] some studies suggest that GLP-1RAs could mitigate mood disorders,[74] which contradicts the aforementioned concerns. In addition to the role of GLP-1 in promoting neurogenesis and neuroprotection and improving cognition, these putative benefits might be related to the impact of GLP-1RAs on metabolism, stress, and/or (neuro)inflammation, all of which are also mechanisms implicated in mood disorders.[75-79] For example, retrospective cohort studies using TriNetX electronic health records report lower incidence of suicidal ideation and/or behavior among people treated with GLP-1RAs compared with propensity score–matched controls.[80,81] A meta-analysis of 5 RCTs and 1 prospective cohort study found improvement in depression rating scale scores in people on GLP-1RAs compared with control treatments.[82] Notably, in a mendelian randomization study that included more than 3 million people and assessed 7 common mental health disorders, GLP-1RAs reduced the risk of major depressive disorder.[83] While potentially intriguing, the evidence that GLP-1RAs may improve psychiatric outcomes is not well established yet.

Third, people with mental health disorders, especially those with severe mental illness, are at increased risk of metabolic dysfunction and are often treated with medications that lead to adverse metabolic effects, including weight gain, diabetes, and dyslipidemia.[84] Antipsychotics, especially second-generation ones like clozapine and olanzapine, are strongly associated with weight gain. Some other psychiatric medications like antidepressants and mood stabilizers can also have such effects but to a lesser extent. GLP-1RAs may mitigate drug-induced weight gain and other metabolic adverse effects in people taking medications for psychiatric conditions, as indicated by several meta-analyses.[85-89]

In summary, despite some reports concerning increased risk of depression and suicide in people taking GLP-1RAs, a larger and more robust body of evidence does not support such an association. Both the EMA[90] and FDA[91] have issued statements that current data do not support a causal link between GLP-1RAs and suicidal ideation and/or behavior. On the other hand, adjunct GLP-1 therapies may benefit patients with mental illness who take medications with known drug-induced weight gain and other metabolic adverse effects. Current evidence on the possible role of GLP-1RAs to improve depression and other psychopathology is insufficient, calling for more research, especially prospective studies with psychiatric measures as primary outcomes

Open Questions and Future Directions

Despite promising data from preclinical and observational human studies and significant excitement in the media and the scientific community to repurpose GLP-1 therapies for ASUDs, it is important not to put the cart before the horse, mainly because the number and quality of published RCTs have been very limited (Table 2).[29-33] Given the existing preliminary yet promising evidence, GLP-1 therapies deserve rapid and rigorous testing for ASUDs; several RCTs are ongoing or about to start. To move the field forward, here we highlight some of the key gaps, promises, and open questions in this arena (Figure):

- What is the optimal dose and duration of treatment with GLP-1 therapies for ASUDs? Preliminary studies suggest that benefits on ASUD-related outcomes might emerge with lower doses and/or durations compared with weight-lowering and glucose-regulating ef-

fects, but more studies are needed. Clinicians' experience and data from longer studies in the obesity field indicate that (A) diminished response and tolerance (also known as tachyphylaxis) may develop after chronic treatment with GLP-1 therapies (of note, this phenomenon seems to occur only for appetitive, gastric, and weight-lowering, but not glucose-regulating, effects), and (B) discontinuation of GLP-1 therapies is often associated with weight regain. A key question in need of further investigation is whether the effects of GLP-1 therapies on addictive behaviors and drug intake are also subject to tolerance after chronic use and/or regain after discontinuation.

- Like any other treatment, GLP-1 therapies are unlikely to work for all patients with ASUDs. In fact, estimates suggest that 1 in 5 people do not lose substantial weight when taking GLP-1 therapies (often labeled as nonresponders). Therefore, it is important to study individual differences and predictors and moderators of response to optimize treatment. Although higher severity of ASUDs is likely associated with a higher magnitude of response (eg, more reduction in alcohol drinking), some studies suggest that GLP-1 therapies may also help people with less severe ASUDs. Could response to GLP-1 therapies vary based on the stage, length, and/or type of addiction (eg, early vs late stage, reward vs relief vs habit intake)? How about pharmacogenetic variants, likely on the GLP-1 receptor, that could contribute to differential response? Some RCTs have found baseline BMI as a possible moderator, but findings have been mixed with no clear direction, and cohort studies show no associations between BMI and ASUD-related outcomes in people treated with GLP-1 therapies. Some preclinical studies suggest possible sex differences (mostly higher response in females), whereas the majority of literature does not support a clear sex difference in ASUD-related outcomes in response to GLP-1 therapies. Nevertheless, studies in the ASUD field should continue to explore factors that contribute to interindividual variability in treatment response.
- The safety of GLP-1 therapies in people with ASUDs must be rigorously studied and closely monitored. Although these are generally safe medications, some potential adverse effects in this particular population require careful attention, eg, increased risk of pancreatitis in people with AUD, worsening of constipation in people with OUD, and other gastrointestinal events such as gastroparesis, intestinal obstruction, and biliary disease. Muscle loss, malnutrition, and further weight loss in people with low BMI are also potential concerns. Less common and under investigation adverse events such as acute kidney injury and optic neuropathy should also be monitored. Although recent evidence is reassuring, the risk of new-onset or worsening of psychopathology (eg, depression) cannot be ruled out.
- Many people with ASUDs use more than 1 drug and often present with not only psychiatric but also medical comorbidities. The notion that GLP-1 therapies might work across several addictive drugs and help people with polysubstance use is very appealing and in need of testing. If GLP-1 therapies are approved and used for addiction treatment, patients with or at increased risk of medical comorbidities may also gain ancillary benefits in terms of metabolic factors and the well-documented beneficial effects of GLP-1 therapies on cardiovascular, hepatic, and renal systems.
- Beyond safety and efficacy, mechanistic studies are needed to inform how GLP-1 therapies work in relation to ASUDs. In addition to regulating appetitive and consummatory behaviors, several mechanisms have been proposed, including, but not limited to, their impact on reward processing, cognitive function, neuroprotection, inflammation, stress regulation, pain and aversion, taste and smell, thirst and fluid intake, and interoception. Contribution of central vs peripheral pathways and understanding the crosstalk between GLP-1 therapies and the blood-brain barrier, especially in the context of ASUDs, are other key questions and areas of research.
- In addition to classic solo GLP-1RAs, several novel compounds are being developed and tested, eg, nonpeptide, small molecule GLP-1RAs and polyagonists that target not only GLP-1 receptors but also other receptors and pathways. These novel compounds typically have enhanced tolerability and potency, as well as ancillary benefits, and it will be important to examine their potential impact on ASUD-related outcomes. The safety and efficacy of combining GLP-1 therapies with FDA-approved medication for ASUDs (Table 1) is another area in need of further investigation.
- Although scientifically intriguing, we should also acknowledge the elephant in the room, ie, issues surrounding access to and uptake of GLP-1 therapies, mainly arising from high cost, payer stance, and varied or complex insurance coverage. Could such issues exacerbate health inequalities, especially for conditions like obesity and addiction that disproportionately affect underserved populations? Of note, access to GLP-1 therapies has been reported to be harder for obesity than diabetes, likely due to stigma, biases, and lack of education. A similar scenario is likely to happen if GLP-1 therapies are approved for ASUDs, as both obesity and ASUDs are highly stigmatized conditions. Solutions such as broadened insurance coverage and availability or uptake of generic versions require concerted efforts at multiple levels, including health care professionals, patients, insurers, drug manufacturers, nonprofit organizations, regulatory agencies, and governments. As the prescription, uptake, and knowledge about GLP-1 therapies are rapidly increasing, patients may be more likely to request and accept, and clinicians may be more likely prescribe these medications compared with other FDA-approved options that are often considered specialized treatments. In other words, with equitable and efficient distribution, GLP-1 therapies have the potential to facilitate a paradigm shift by expansion of addiction treatment beyond specialized settings and incorporating such treatments in other clinical settings, including primary care.

Conclusions

In conclusion, preclinical studies, pharmacoepidemiological analyses, and some initial RCTs indicate that GLP-1 therapies could be repurposed for ASUDs and added to the addiction treatment toolbox. Although promising, several unanswered questions call for additional research and rigorous testing of the safety, efficacy, mechanisms of action, and other aspects of GLP-1 therapies in addiction medicine.

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