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Semaglutide and Drug Craving: Emerging Perspectives in Addiction Psychiatry

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Abstract

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used for type 2 diabetes and obesity, has attracted interest as a potential modulator of drug craving and substance-related reinforcement. This mini-review examines mechanistic and clinical evidence across cocaine, alcohol, nicotine, and opioid use disorders. Preclinical studies implicate mesolimbic GLP-1 signalling in reward, cue reactivity, and consummatory behaviour. Human evidence remains limited but is most persuasive for alcohol use disorder, where randomized subcutaneous and oral semaglutide trials have reported improvements in selected drinking and craving outcomes; evidence for cocaine and nicotine remains preliminary or mixed, and opioid evidence is largely observational or protocol-level. A central interpretative challenge is whether apparent benefits reflect direct reward modulation or indirect effects of appetite suppression, gastrointestinal symptoms, weight loss, or metabolic improvement. Semaglutide is not an established pharmacotherapy for substance use disorders, and approved metabolic indications must remain distinct from investigational anti-craving use. Further trials should use substance-specific clinical outcomes, objective measures of consumption, formal mediation analyses, representative psychiatric populations, and longer follow-up.

Introduction: From Clinical Observation to Translational Hypothesis

Substance use disorders are chronic, relapsing psychiatric conditions in which motivational systems become biased toward substance-related stimuli. Craving is a multidimensional state elicited by conditioned cues, stress, drug priming, and affective states and is clinically relevant because of its association with continued use and relapse vulnerability.[1]

The therapeutic gap is particularly marked in cocaine use disorder: no medication is approved, and a recent network meta-analysis found no pharmacotherapy with consistent benefit across abstinence, cocaine use, craving, retention, and safety.[2] GLP-1 receptor agonists (GLP-1RAs), developed for type 2 diabetes and obesity, have consequently emerged as candidate modulators of addictive behaviour. A systematic review found a coherent preclinical signal but a small, heterogeneous human evidence base,[3] while a psychiatric review of semaglutide emphasized both potential benefits and unresolved safety questions.[4]

This mini-review was prompted by a case of a 54-year-old man with obesity and long-standing cocaine use in whom 12 weeks of subcutaneous semaglutide were temporally associated with a 13-kg weight reduction and a 58.9% decrease in Cocaine Craving

Questionnaire-Brief scores.[5] The observation is hypothesis-generating: concurrent reductions in weight and craving cannot distinguish direct reward modulation from appetite suppression, gastrointestinal effects, metabolic improvement, expectancy, or their interaction. The review therefore evaluates mechanistic plausibility, human evidence, clinical implications, and research priorities for semaglutide in addiction psychiatry.

Literature Identification and Scope

A targeted narrative search of PubMed/MEDLINE and Scopus was conducted from database inception to 15 September 2026, supplemented by ClinicalTrials.gov and backward citation tracking. Principal Boolean combinations included ("semaglutide" OR "GLP-1 receptor agonist" OR exenatide OR dulaglutide) AND ("drug craving" OR reward OR "substance use disorder" OR cocaine OR psychostimulant OR alcohol OR nicotine OR tobacco OR opioid OR cannabis), with agent- and substance-specific variants. Search syntax was adapted to each database using title/abstract and indexed terms where available. The rerun search retrieved a recently published randomized trial of oral semaglutide in alcohol use disorder not captured in the original search; it was added to the synthesis and Table 1.

Table 1: Human Clinical Evidence on GLP-1 Receptor Agonists and Substance-Related Outcomes

Substance / study	Design and sample	GLP-1RA regimen	Craving-related outcome	Substance-use or behavioural outcome	Key metabolic / safety findings	Main interpretative limitation
Cocaine / Romeo, 2025[5]	Single-patient case report: 54-year-old man with obesity (BMI 35.4 kg/m²) and a 15-year history of cocaine use.	Semaglutide 0.25 mg once weekly, titrated to 1.0 mg by week 8; 12 weeks; concurrent behavioural counselling.	CCQ-Brief decreased from 5.6 to 2.3 (−58.9%).	No standardized quantitative or toxicology-verified cocaine-use, abstinence, or relapse endpoint was reported.	Weight decreased from 105 to 92 kg (−13 kg; −12.4%). Mild transient nausea and occasional diarrhoea; mood and anxiety remained stable or slightly improved.	Uncontrolled single case; concurrent counselling and SSRI withdrawal; substantial potential for expectancy, regression to the mean, and weight-loss-mediated effects.
Cocaine / Angarita et al., 2021[16]	Placebo-controlled, within-participant human laboratory study; n=13 non-treatment-seeking adults with cocaine use disorder.	Single exenatide 5 µg subcutaneous dose 3 h before cocaine self-administration.	Cocaine "wanting": 5.6±0.9 with exenatide vs 5.4±0.9 with placebo; p=0.46.	Cocaine infusions: 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.	Exenatide reduced circulating GLP-1 (p=0.03) and insulin (p=0.02); no acute efficacy signal on primary behavioural outcomes.	Very small sample; single acute low dose; short pretreatment interval; non-treatment-seeking population; no assessment of chronic exposure.
Cocaine / Yammine et al., 2023[17]	Open-label, single-arm case series; n=3 treatment-seeking patients with cocaine use disorder.	Extended-release exenatide 2 mg once weekly for 6 weeks plus weekly individual drug counselling.	Two of three participants showed reduced Brief Substance Craving Scale severity by week 6; the third showed fluctuating craving.	One participant achieved cocaine-negative urine screens during weeks 4–6; the other two continued to have cocaine-positive screens, and self-reported use was heterogeneous.	All three completed treatment. Mild treatment-related adverse events occurred in two participants; one serious adverse event (chest pain) was judged unrelated to study medication; no adverse-event-related discontinuations occurred.	n=3; no comparator; short duration; counselling co-intervention; descriptive outcomes and marked susceptibility to individual variability.
Alcohol / Klausen et al., 2022[18]	Randomized, double-blind, placebo-controlled trial; n=127 treatment-seeking patients with alcohol use disorder.	Exenatide 2 mg once weekly for 26 weeks plus standard cognitive-behavioural therapy.	Alcohol-cue fMRI reactivity was attenuated in the ventral striatum and septal area; no definitive global clinical craving effect was established.	Heavy-drinking-day treatment difference 6.0 percentage points (95% CI −7.4 to 19.4; p=0.37); no significant overall clinical alcohol reduction. Exploratory BMI>30 kg/m² subgroup analyses suggested benefit.	Gastrointestinal adverse events predominated. 58 of 127 participants completed the full 26-week trial.	Primary clinical endpoint was null; high attrition; obesity subgroup and neuroimaging findings were exploratory or based on subsets.
Alcohol / Probst et al., 2023[19]	Predefined secondary completer analysis of a smoking-cessation RCT; n=151 baseline drinkers who completed 12 weeks.	Dulaglutide 1.5 mg once weekly for 12 weeks plus varenicline 2 mg/day and behavioural counselling.	Alcohol craving was not the principal prespecified outcome and no separate clinically interpretable craving estimate was reported.	Alcohol consumption was 29% lower than placebo (relative effect 0.71, 95% CI 0.52–0.97; p=0.04).	Alcohol change was not correlated with smoking status. Parent trial primarily evaluated smoking cessation and metabolic outcomes.	Participants were not recruited for alcohol use disorder; completer-only secondary analysis; self-reported alcohol use; multiple co-interventions.
Alcohol / Hendershot et al., 2025[20]	Phase 2, double-blind randomized trial; n=48 non-treatment-seeking adults with alcohol use disorder.	Semaglutide 0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg in week 9; placebo-controlled.	Weekly alcohol craving decreased (β=−0.39, 95% CI −0.73 to −0.06; p=0.01).	Laboratory alcohol consumed: β=−0.48 (95% CI −0.85 to −0.11; p=0.01); peak BrAC: β=−0.46 (95% CI −0.87 to −0.06; p=0.03); drinks/drinking day: β=−0.41 (95% CI −0.73 to −0.09; p=0.04). No effect on average drinks/calendar day or drinking days.	Body weight decreased. Primary post-treatment laboratory assessment occurred after exposure to 0.5 mg/week.	Small sample; 9-week exposure; non-treatment-seeking cohort; multiple endpoints; limited inference regarding sustained remission or relapse prevention.

Alcohol + obesity / Klausen et al., 2026[21]	Randomized, double-blind, placebo-controlled trial; n=108 treatment-seeking adults with moderate-to-severe alcohol use disorder and BMI≥30 kg/m²; 88 completed the full intervention.	Semaglutide 0.25 mg once weekly with 4-weekly escalation to maximum tolerated dose or 2.4 mg; 26 weeks plus cognitive-behavioural therapy.	PACS change: −9.2 with semaglutide vs −6.1 with placebo; treatment difference −3.1 (95% CI −5.1 to −1.2; p=0.0020).	Heavy-drinking-day treatment difference −13.7 percentage points (95% CI −22.0 to −5.4; p=0.0015). Total alcohol: −467.5 g/30 days; drinks/drinking day: −1.5; PEth: −0.28 µmol/L.	GI events were common (nausea 57%; loss of appetite 35%). Completion 81%. Heavy-drinking reduction correlated with weight loss (ρ=−0.40; p=0.0038).	Obesity-only, single-centre sample; concurrent CBT; metabolic and gastrointestinal effects may partly explain parallel alcohol outcomes; correlation with weight loss does not establish mediation.
Alcohol / Schacht et al., 2026[22]	Phase 2 double-blind randomized trial; n=50 treatment-seeking adults with moderate-to-severe alcohol use disorder and BMI≥25 kg/m²; 47 completed 8 weeks.	Oral semaglutide 3 mg/day for 4 weeks, then 7 mg/day for 4 weeks, versus placebo.	Primary cue-elicited VAS craving at week 6 was not significant (b=−0.614, 95% CI −3.563 to 2.335; p=0.68). Naturalistic PACS craving decreased (b=−2.195, 95% CI −4.174 to −0.216; p=0.030).	Heavy-drinking days decreased (b=−0.580, 95% CI −1.012 to −0.148; p=0.008); drinks/drinking day decreased (b=−1.177, 95% CI −2.307 to −0.047; p=0.041); drinks/day was not significant (p=0.057).	47/50 completed treatment. Three semaglutide participants withdrew (two lost to follow-up; one allergic reaction considered probably medication-related).	Small, brief trial; all participants had overweight/obesity; current psychiatric disorders and suicidality risk were excluded; possible functional unblinding; no biological alcohol-consumption measure.
Nicotine / Lengsfeld et al., 2023[23]	Randomized, double-blind, placebo-controlled smoking-cessation trial; n=255 treatment-seeking smokers.	Dulaglutide 1.5 mg once weekly for 12 weeks plus varenicline 2 mg/day and behavioural counselling.	Smoking craving declined in both groups, with no significant between-group difference.	Biochemically confirmed abstinence at week 12: 63% with dulaglutide vs 65% with placebo; difference −1.9% (95% CI −10.7 to 14.4); p=0.859.	Weight change: −1.0 kg vs +1.9 kg; adjusted difference −2.9 kg (95% CI −3.59 to −2.3; p<0.001). GI symptoms: 90% vs 81%.	Adjunctive design with effective varenicline/counselling; 12-week endpoint; clear metabolic effect but null smoking-cessation effect.
Nicotine / Hendershot et al., 2026[24]	Phase 2a randomized, placebo-controlled trial; n=24 non-treatment-seeking daily smokers; 21 completed the primary outcome assessment.	Semaglutide 0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg in week 9.	Cigarette craving decreased (treatment×time β=−0.11, 95% CI −0.20 to −0.03; p=0.01).	Primary interactions were not significant for smoking resistance (β=0.16, 95% CI −0.07 to 0.40; p=0.16) or cigarettes smoked (β=−0.08, 95% CI −0.25 to 0.08; p=0.30). Exploratory change-score analysis suggested less laboratory smoking.	Body weight decreased (β=−0.04, 95% CI −0.05 to −0.03; p<0.001), with improvement in HbA1c relative to placebo.	Very small sample; primary smoking outcomes null; change-score analysis exploratory; non-treatment-seeking participants and no cessation attempt.
Opioids / Wang et al., 2024[25]	Electronic health-record target-trial emulation; 33,006 eligible patients with type 2 diabetes and opioid use disorder (3,034 semaglutide; 29,972 comparators); 1-year follow-up.	Routine clinical semaglutide prescribing; dose, titration, adherence, and behavioural treatment were not standardized.	Not measured.	Semaglutide was associated with lower opioid-overdose risk than comparator antidiabetic medications (HR range 0.32–0.58); illicit opioid use, abstinence, and remission were not directly assessed.	Population restricted to patients with type 2 diabetes; no prospective addiction-specific or psychiatric safety monitoring.	Observational design; residual confounding and confounding by indication; EHR coding limitations; overdose is not equivalent to reduced craving or opioid-use remission.

Data source and notes. Values are reported as presented in the cited primary publications. Craving-related outcomes are displayed separately from behavioural, laboratory, biochemical, or clinical substance-use outcomes because they are not interchangeable endpoints. Unless otherwise indicated, study medications were administered subcutaneously. During revision, numerical entries in Table 1—including sample sizes, dosing schedules, treatment duration, p-values, confidence intervals, completion data, and key safety findings—were rechecked against the cited primary publications.

Abbreviations. BMI, body mass index; BrAC, breath alcohol concentration; BSCS, Brief Substance Craving Scale; CBT, cognitive-behavioural therapy; CCQ-Brief, Cocaine Craving Questionnaire-Brief; CUD, cocaine use disorder; EHR, electronic health record; fMRI, functional magnetic resonance imaging; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HHD, heavy drinking days; HR, hazard ratio; PACS, Penn Alcohol Craving Scale; PEth, phosphatidylethanol; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor; VAS, visual analogue scale.

Titles and abstracts were screened for direct relevance to GLP-1RA exposure and substance-related outcomes; full texts were examined when they reported craving, cue reactivity, self-administration, consumption, abstinence, relapse, overdose, retention, or psychiatric safety. Human randomized, laboratory, observational, and clinically informative uncontrolled studies were prioritized. Overlapping reports were resolved in favour of the primary publication; secondary analyses were retained only for nonredundant substance outcomes, and preclinical studies only when needed to clarify mechanism.

Reporting and structure were informed by SANRA principles.[6] Study-level limitations were appraised

narratively across design, sample size, treatment-seeking status, agent specificity, duration, metabolic enrichment, co-interventions, attrition, outcome objectivity, psychiatric eligibility, and separation of craving from consumption or remission. Greater interpretive weight was given to randomized semaglutide trials with prespecified addiction outcomes, followed by randomized evidence from other GLP-1RAs or secondary substance outcomes, observational studies, uncontrolled reports, and mechanistic preclinical evidence. No meta-analysis, formal study-level risk-of-bias tool, or certainty-of-evidence framework was applied.[7]

GLP-1 Signalling, Reward, and Drug Craving

GLP-1 signalling integrates peripheral metabolic information with central motivational processes. Preproglucagon neurons in the caudal nucleus tractus solitarius project to the ventral tegmental area (VTA) and nucleus accumbens,[8] and mesolimbic GLP-1 receptor activation reduces the rewarding value of palatable food without generalized locomotor suppression.[9] This is relevant to addiction because cue-triggered incentive salience ("wanting") can persist independently of hedonic "liking".[10]

Preclinical psychostimulant data support biological plausibility. Exendin-4 attenuates psychostimulant reward and accumbal dopamine responses,[11] reduces cocaine self-administration,[12] and suppresses cocaine-primed reinstatement through VTA GLP-1 receptors at doses not materially altering food intake or body weight.[13] GLP-1-responsive laterodorsal tegmental GABAergic projections to the VTA provide a complementary relapse-related pathway.[14] Semaglutide itself has reduced cocaine intake, motivation, reinstatement, and cocaine-evoked accumbal dopamine in rodents without increasing a nausea-like behavioural index.[15] Translation nevertheless remains uncertain because animal drug seeking is not equivalent to subjective human craving.

Clinical Evidence Across Substance Use Disorders

Human translation remains uneven. Table 1 summarizes the principal studies, separating craving from laboratory self-administration, real-world consumption, abstinence, relapse, and overdose. Evidence is interpreted by both study design and molecule specificity: randomized semaglutide trials with addiction-specific outcomes are most direct, whereas exenatide and dulaglutide studies mainly inform class-level plausibility.

Cocaine and Psychostimulant Craving

In 13 non-treatment-seeking adults with cocaine use disorder, a single 5-µg subcutaneous exenatide dose did not alter cocaine infusions, euphoria, or wanting.[16] A six-week open-label case series of extended-release exenatide 2 mg weekly plus counselling in three treatment-seeking patients showed good feasibility but heterogeneous cocaine-use and craving outcomes.[17]

The semaglutide case described above extends but cannot resolve this evidence base. Its uncontrolled design cannot separate pharmacological effects from expectancy, concurrent care, spontaneous fluctuation, regression to the mean, or weight-related change. No completed randomized trial has established semaglutide efficacy in cocaine use disorder; accordingly, the cocaine evidence remains mechanistically suggestive but of limited evidentiary strength, and exenatide findings cannot be assumed to establish a molecule-independent class effect.

Alcohol Use Disorder: The Strongest Human Signal

Alcohol use disorder provides the strongest human proof of concept. A 26-week randomized exenatide trial plus cognitive-behavioural therapy was negative for heavy-drinking days overall, although cue-related striatal/septal activity decreased and obesity subgroup findings were exploratory.[18] In a secondary smoking-cessation analysis, dulaglutide was associated with approximately 29% lower self-reported alcohol consumption, but participants were not recruited for alcohol use disorder and alcohol outcomes were secondary.[19] These studies support class-level plausibility rather than semaglutide-specific efficacy.

Semaglutide-specific evidence now includes three randomized trials. In 48 non-treatment-seeking adults with alcohol use disorder, nine weeks of low-dose subcutaneous semaglutide reduced laboratory alcohol consumption, peak breath alcohol concentration, drinks per drinking day, and weekly craving, without improving all drinking-frequency measures.[20] In 108 treatment-seeking adults with alcohol use disorder and obesity, 26 weeks of semaglutide plus cognitive-behavioural therapy reduced heavy-drinking days and several secondary alcohol, biomarker, craving, and somatic outcomes versus placebo plus therapy; gastrointestinal adverse effects were more frequent.[21]

An eight-week trial in 50 treatment-seeking adults with moderate-to-severe alcohol use disorder and BMI at least 25 kg/m^2 tested oral semaglutide 3 mg/day followed by 7 mg/day. The prespecified cue-elicited craving endpoint was negative, whereas heavy-drinking days, drinks per drinking day, naturalistic Penn Alcohol Craving Scale scores, and alcohol-related negative consequences improved; 47 participants completed treatment.[22] Thus, alcohol use disorder has the most robust human evidence base, but heterogeneity in route, dose, treatment-seeking status, metabolic enrichment, behavioural co-intervention, and endpoints limits generalization.

Nicotine and Other Substance Use Disorders

Nicotine findings illustrate the distinction between craving and cessation. In 255 treatment-seeking smokers

receiving varenicline and counselling, adjunctive dulaglutide did not improve biochemically confirmed abstinence or craving but attenuated post-cessation weight gain.[23] In a phase 2a trial of 24 non-treatment-seeking daily smokers, semaglutide reduced weekly cigarette craving, whereas prespecified treatment-by-time effects for smoking resistance and cigarettes smoked were not significant.[24] The former informs class-level plausibility; the latter remains too small for definitive clinical inference.

For opioid use disorder, an electronic health-record target-trial emulation associated semaglutide exposure with lower overdose risk among patients with type 2 diabetes but did not measure craving, illicit use, abstinence, or remission and remains vulnerable to residual confounding.[25] A protocol now evaluates 12 weeks of semaglutide in 200 patients receiving buprenorphine or methadone who continue nonprescribed opioid use, with urine toxicology, craving, ecological assessment, and follow-up.[26] Human evidence for methamphetamine, cannabis, and polysubstance use remains insufficient; craving is an intermediate endpoint, not a surrogate for remission.

Direct Reward Modulation or Indirect Metabolic Effects?

A central interpretative problem is whether semaglutide-related reductions in craving reflect substance-specific reward modulation or broader changes in appetite, consummatory motivation, gastrointestinal physiology, weight, and metabolic status. A direct central mechanism is plausible because GLP-1 receptor activation alters activity in human insular, amygdalar, orbitofrontal, and striatal reward regions.[27] Food-cue attenuation, however, cannot be assumed to represent reduced drug-cue responsivity.

Indirect explanations are equally plausible. Semaglutide reduces energy intake, hunger, food craving, and preference for energy-dense foods,[28] and effects on appetite and intake can persist without significant delayed gastric emptying at week 20.[29] Gastrointestinal symptoms may suppress consumption without changing reward valuation, and intake suppression can be partly dissociable from nausea-like responses across GLP-1RAs and doses.[30] Longer-term data also suggest partially distinct trajectories for energy intake, appetite, food reward, and weight loss.[31]

In the 26-week alcohol-use-disorder/obesity trial, reductions in heavy drinking correlated with weight loss.[21] This does not establish mediation: parallel changes may reflect common treatment exposure, metabolic phenotype, time-varying confounding, or gastrointestinal effects. Formal mediation requires temporally ordered repeated measures and explicit indirect-effect models, ideally with active comparators producing similar weight loss. Trials should therefore measure craving, appetite, nausea, weight, glycaemia, and substance consumption repeatedly and incorporate objective use measures and drug-cue paradigms.

Clinical Implications and Psychiatric Safety

Semaglutide should not be prescribed solely for drug craving or replace evidence-based addiction treatment. Its most defensible present context is a patient who independently meets an approved indication under applicable regulatory labelling (e.g., type 2 diabetes or obesity), while craving and substance consumption are monitored as exploratory outcomes. Approved metabolic use must remain distinct from an investigational anti-craving indication.

Psychiatric safety findings are broadly reassuring but incompletely generalizable. STEP post hoc analyses found no clinically meaningful increase in depressive symptoms or suicidal ideation with semaglutide 2.4 mg, but major psychopathology was generally excluded.[32] A Scandinavian active-comparator cohort found no increased risk of suicide death, self-harm, depression, or anxiety among GLP-1RA initiators, although small risk increases could not be excluded.[33] Pharmacovigilance data have shown a modest disproportionality signal for depressive disorders with semaglutide, but spontaneous reports cannot establish incidence or causality.[34] In a retrospective chart review of 226 GLP-1RA recipients, pre-existing depression and anxiety were stable in most patients, while new or worsening psychiatric manifestations occurred in a minority.[35]

Addiction-trial safety findings should remain population-specific. The oral semaglutide alcohol trial excluded current psychiatric disorders, elevated suicidality risk, and psychotropic medication use other than antidepressants, limiting inference for complex dual diagnoses.[22] Clinicians using semaglutide for an approved metabolic indication in patients with substance use disorders should assess substance severity, withdrawal risk, mood, anxiety, psychosis, eating-disorder pathology, suicidality, nutrition, concomitant medications, and weight trajectory, and monitor psychiatric symptoms and gastrointestinal tolerability during titration.

Research Priorities for Addiction Psychiatry

Future research should progress to adequately powered, substance-specific randomized trials. The registered landscape remains concentrated in alcohol and nicotine use disorders, with fewer cocaine and opioid studies and marked heterogeneity in agents, metabolic eligibility, and endpoints.[36] Trials should prespecify analyses by obesity, glycaemic status, sex, psychiatric comorbidity, baseline craving, and concurrent treatments.

Craving should not be the sole efficacy endpoint. Ecological momentary assessment can distinguish tonic,

cue-elicited, and momentary craving and test whether real-world changes precede reduced use.[37] Subjective outcomes require objective corroboration: cocaine trials can use the proportion of cocaine-negative urine samples,[38] and alcohol studies can incorporate phosphatidylethanol.[39] Longer treatment and post-discontinuation follow-up are important because register-based evidence suggests substance-related hospitalisation risk may vary during exposure and after cessation.[40]

Mechanistic work should combine repeated appetite, nausea, weight, glycaemic, affective, and substance measures with mediation analysis. Rodent data on alcohol intake, relapse-like drinking, and accumbal dopamine can inform translational designs,[41] while pragmatic comparisons with approved alcohol-use-disorder medications can address effectiveness in patients with concurrent metabolic dysfunction.[42] Future programmes can therefore be organized around four priorities: clinical efficacy, mechanism, psychiatric safety, and durability. Head-to-head work should also determine whether benefit is semaglutide-specific, extends to dual incretin agonists, persists after discontinuation, and adds value to established psychosocial and pharmacological care.

Conclusion

Semaglutide is biologically plausible but remains investigational for drug craving and substance-related reinforcement. Human evidence is most persuasive in alcohol use disorder, where multiple randomized semaglutide trials provide convergent but endpoint-heterogeneous signals; cocaine, nicotine, opioid, and other substance findings remain preliminary, mixed, or indirect. Reduced craving cannot be equated with abstinence or remission, and direct reward modulation cannot yet be separated reliably from metabolic or gastrointestinal pathways. Semaglutide should therefore not be considered an established pharmacotherapy for substance use disorders. Its potential role warrants substance-specific randomized trials with objective outcomes, mediation analysis, longer follow-up, and prospective psychiatric safety monitoring.

List of Abbreviations

GLP-1: glucagon-like peptide-1

GLP-1RA: glucagon-like peptide-1 receptor agonist

STEP: Semaglutide Treatment Effect in People with obesity

VTA: ventral tegmental area

Declarations

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Conflict of Interest

The author declares no conflict of interest.

Authors' Contributions

Vincenzo Maria Romeo conceived the review, defined its scope and conceptual framework, identified and critically evaluated the relevant literature, interpreted the available evidence, drafted the manuscript, revised it critically for important intellectual content, and approved the final version for submission.

Ethics Approval and Consent to Participate

Not applicable. This article is a narrative mini-review and does not report original research involving human participants, human biological materials, or identifiable clinical data. The previously published case report discussed in the manuscript is cited solely as part of the existing scientific literature, and no additional patient information is presented.

Data Availability Statement

No original datasets were generated or analysed for this narrative mini-review. All information discussed in the manuscript was derived from the published literature and publicly available sources cited in the reference list.

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