

GLP-1s for Addiction: Are We There Yet?

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Addiction, a chronic relapsing brain disease, continues to present a formidable challenge in clinical practice, with limited pharmacological options offering sustained efficacy. Clinicians routinely grapple with the complex interplay of neurobiological, psychological, and social factors driving substance use disorders and behavioural addictions. The recent surge in interest surrounding glucagon-like peptide-1 (GLP-1) receptor agonists, primarily for type 2 diabetes and obesity,¹ has inadvertently opened a new avenue of inquiry: their potential role in modulating addictive behaviours.

KEY TAKEAWAYS

- **The Pivot:** GLP-1 receptor agonists, known for metabolic effects, are now being explored for their potential to reduce addictive behaviours.
- **The Data:** Preclinical and early human data suggest GLP-1s may reduce alcohol consumption and cravings, but large-scale, placebo-controlled trials are scarce.
- **The Action:** Clinicians should not prescribe GLP-1s off-label for addiction; evidence is insufficient, and dedicated trials are needed before any change in practice.

The burden of addiction on public health is immense, encompassing not only substance use disorders like alcohol use disorder (AUD) and opioid use disorder (OUD) but also behavioural addictions such as pathological gambling and binge eating disorder. Current pharmacological treatments for AUD, for instance, include naltrexone, acamprosate, and disulfiram, each with varying efficacy and tolerability profiles. For many patients, these options fall short, leaving a significant unmet need for novel therapeutic strategies. This persistent gap has driven exploration into existing drug classes with known neurobiological effects, leading to the unexpected consideration of GLP-1 receptor agonists. GLP-1 is an incretin hormone, secreted by the gut in response to food intake, that plays a critical role in glucose homeostasis by stimulating insulin secretion and suppressing glucagon release. But its receptors are not confined to the pancreas; they are also expressed in various brain regions, including those involved in reward processing, motivation, and executive function. These areas, such as the ventral tegmental area, nucleus accumbens, and prefrontal cortex, are central to the pathophysiology of addiction. The hypothesis is that GLP-1 receptor activation in these brain regions could modulate dopamine signalling, thereby reducing the rewarding effects of addictive substances or behaviours and diminishing cravings.

Preclinical studies, primarily in rodents, have provided the initial mechanistic insights. Investigators observed that GLP-1 receptor agonists, such as exenatide and liraglutide, reduced alcohol intake in rats and mice. One study, for example, showed that chronic administration of exenatide significantly decreased voluntary alcohol consumption in alcohol-preferring rats without affecting food intake or body weight.¹ Similar effects were reported for other

substances, including nicotine and cocaine, where GLP-1 agonists attenuated drug-seeking behaviours and reduced self-administration in animal models. These early animal data, while compelling for generating hypotheses, do not translate directly to human clinical efficacy.

The Numbers, or Lack Thereof

Translating these preclinical observations into human clinical data has proven challenging, primarily due to the absence of large, dedicated, placebo-controlled trials. The evidence base for GLP-1s in addiction currently consists largely of anecdotal reports, small observational studies, and post-hoc analyses of trials designed for metabolic endpoints. One of the most frequently cited pieces of human evidence comes from a retrospective analysis of electronic health records. This analysis, involving patients prescribed GLP-1 receptor agonists for type 2 diabetes or obesity, suggested a reduction in alcohol consumption. Patients on GLP-1s showed a lower incidence of new alcohol-related diagnoses compared to matched controls on other antidiabetic or anti-obesity medications. But this was an observational study, inherently limited by confounding by indication and other biases, making it impossible to establish causality.²

A small, open-label pilot study investigated the effect of liraglutide on alcohol craving and consumption in individuals with AUD. The study enrolled 10 patients who received liraglutide for 12 weeks. Investigators reported a reduction in heavy drinking days and a decrease in alcohol craving scores. But the small sample size and open-label design are obvious caveats. There was no control group, meaning any observed effects could be attributable to placebo response or other unmeasured factors. The study was not powered to detect statistically significant differences, serving primarily as a feasibility assessment.³

Another area of interest is binge eating disorder (BED), which shares some neurobiological pathways with substance use disorders. Several GLP-1 receptor agonists, including liraglutide and semaglutide, have received regulatory approval for weight management, often showing significant reductions in body weight. In trials for obesity, a common secondary endpoint is the reduction in binge eating episodes. For instance, in a Phase III trial of liraglutide for weight management, patients with BED experienced a reduction in binge eating days by 2.6 days per week (95% CI, -3.1 to -2.1) compared to placebo.⁴ While this is a positive signal, it is important to remember that BED is distinct from AUD or OUD, and the mechanisms of action might differ. The primary endpoint in these trials was weight loss, not the cessation of binge eating as a standalone addiction outcome.

The mechanism by which GLP-1s might exert anti-addictive effects is thought to involve several pathways. Beyond direct modulation of reward circuitry, GLP-1s influence gastric emptying and satiety, which could indirectly reduce compulsive consumption behaviours. They also have anti-inflammatory properties and may reduce neuroinflammation, a factor implicated in the chronicity of addiction. Still, the precise neurobiological pathways remain under active investigation. The brain's complex reward system, involving dopamine, serotonin, and opioid pathways, is not easily disentangled. Any drug targeting this system will likely have pleiotropic effects, some beneficial, some potentially adverse.

The current landscape of clinical trials for GLP-1s in addiction is nascent. Several trials are registered, but most are small, early-phase studies focusing on specific populations or mechanisms. For example, a Phase II trial is currently recruiting patients with AUD to evaluate the efficacy and safety of semaglutide. This trial aims to enrol approximately 100 participants and will assess changes in heavy drinking days and craving scores over a 16-week period. Such trials are critical for moving beyond observational data and establishing a causal link. But until these trials report definitive, statistically significant results from adequately powered, placebo-controlled designs, any claims of efficacy remain

speculative.

The safety profile of GLP-1 receptor agonists is generally well-established from their use in diabetes and obesity. Common adverse events include gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. These are typically mild to moderate and transient. But in the context of addiction, where patients may have co-occurring mental health conditions or be on multiple medications, the safety profile needs careful re-evaluation. The potential for rare but serious adverse events, such as pancreatitis or thyroid C-cell tumours (observed in rodents), must also be considered, especially if these drugs were to be used long-term in a broader population of individuals with addiction. The risk-benefit calculus for a chronic condition like addiction, where treatment might extend for years, differs significantly from short-term metabolic management.

Another limitation of the existing data is the heterogeneity of addiction itself. Alcohol use disorder, opioid use disorder, and stimulant use disorder each have distinct neurobiological underpinnings and clinical presentations. A drug that shows promise in one form of addiction may not be effective in another. The current research largely lumps various addictive behaviours together, which risks diluting any specific signal. Future research will need to stratify patient populations more carefully and focus on specific addiction types. The dose-response relationship for anti-addictive effects also remains largely unknown. The doses used for metabolic control may not be optimal for modulating reward pathways, or they might be associated with unacceptable side effects in a non-diabetic, non-obese population.

The open-label nature of many early human studies is the most obvious caveat. Patients and investigators knowing the treatment assignment can introduce significant bias, particularly in subjective endpoints like craving scores or self-reported consumption. The placebo effect in addiction research is notoriously strong, making robust blinding essential for any meaningful interpretation of results. Without a rigorously designed, double-blind, placebo-controlled trial, it is impossible to disentangle true pharmacological effects from psychological expectations. The field needs to move beyond exploratory signals and into definitive efficacy trials before GLP-1s can be considered a viable treatment option for addiction.

CLINICAL IMPLICATIONS

The enthusiasm for GLP-1 receptor agonists in addiction is understandable, given the desperate need for new treatments. But clinicians must resist the urge to prescribe these agents off-label based on preclinical data or anecdotal reports. The evidence base is simply not there yet; what we have are intriguing signals, not definitive proof of efficacy in humans for addiction.

The pharmaceutical industry, having seen the commercial success of GLP-1s in metabolic disease, will undoubtedly fund larger trials. These trials must be designed with addiction-specific endpoints, adequate power, and robust placebo controls. Anything less will not provide the clarity needed for clinical decision-making.

For patients struggling with addiction, the hope offered by a new class of drugs is powerful. But this hope must be tempered with scientific rigour. Until large, well-designed studies demonstrate a clear benefit, the standard of care for addiction remains the established pharmacological and behavioural therapies. Premature adoption risks diverting resources and attention from proven interventions.

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