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Perspective

GLP-1 Diabetes/Obesity Medications in Alcohol and Substance Use Disorders: Heaven or Hell ?

Kenneth Blum[1-4]*, Panayotis K Thanos[5], Kai Uwe Lewandrowski[3,4,6], Morgan P Lorio[3,7], Debasis Bagchi[8], Frank Fornari[3], Marco Lindeau[3], Álvaro Dowling[3], Rafaela Dowling[3], Joao Paulo Bergamaschi[3], Rossano Kepler Alvim Fiorelli[4], Sérgio Luís Schimidt[4], Alireza Sharafshah[3,4], Rajendra D Badgaiyan[3], Sarah E Deemer[9] and Mark S Gold[9]

[1]Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel

[2]Division of Addiction Research and Education, Center for Sports, Exercise, and Mental Health, Western University of Health Sciences, Pomona, CA, USA

[3]Department of Neurobiology and Genetics, Origen Institute of Molecular Genetics and Neurobiology, Austin, USA

[4]Post-Graduate Program in Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil

[5]Behavioral Neuropharmacology and Neuroimaging Laboratory on Addictions, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biosciences, State University of New York at Buffalo, Buffalo, NY., USA

[6]Division Personalized Pain Research and Education, Center for Advanced Spine Care of Southern Arizona, Tucson, AZ., USA

[7]Orlando College of Osteopathic Medicine, Winter Garden, FL, USA

[8]Department of Pharmaceutical Sciences, Texas Southern University College of Pharmacy, Houston, TX, USA

[9]Department of Kinesiology, Health Promotion and Recreation, University of North Texas, Denton, TX USA

***Corresponding Author:** Kenenth Blum, Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel.

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Key Points

- GLP-1 receptors exist in the brain in the nucleus accumbens and ventral tegmental area
- GLP-1 agonist medications like Ozempic may work as anti-addiction agents
- GLP-1 agonists reduce food-seeking behavior, alcohol intake, cocaine reward, and improve other behavioral addictions (food, porn, gambling)
- Prior to administration status of patient DNA caution against prescribing GLP1 agonists in hypodopaminergia

- Potential Induction of altered dopaminergic function may lead to suicide by exacerbating existing dopaminergic dysfunction

Graphical Abstract

GLP-1 receptor agonists may influence addiction by modulating gut-derived interoceptive signaling, inflammatory tone, and mesolimbic dopamine circuitry within a distributed gut–brain–immune loop. While these agents may dampen pathological hyper-reinforcement, dopaminergic tone exists along a spectrum, and baseline vulnerability may influence therapeutic outcomes. Precision-guided monitoring is warranted.

Graphical abstract

Introduction

GLP-1 receptors in the brain have been identified in the nucleus accumbens (NAc) and ventral tegmental area (VTA), also sites where dopamine targets and the entire mesolimbic reward circuitry are found [1]. Early signals from preclinical models have demonstrated semaglutide reduced alcohol intake in humans as well as feelings of craving, extending their potential relevance to both substance and behavioral addictions.

In 2025, a phase 2 randomized, double-blind trial published in JAMA Psychiatry [2] demonstrated that low-dose weekly semaglutide significantly reduced alcohol craving, heavy drinking days, and drinking intensity in non-treatment-seeking adults with AUD. The magnitude of effect was equal to or greater than from FDA-approved AUD medications, despite lower doses and non-treatment-seeking status. This is pretty impressive, since many people who seek to consume less alcohol struggle mightily to succeed. This trial also moves such drugs from promising observational signals into controlled evidence supporting a novel treatment for alcohol use disorder (AUD),but not without real caution including potential suicide ideation [3]. Semaglutide significantly reduced alcohol intake of the subjects. The therapeutic effects appeared dose-related, strengthening at 0.5 mg/week.

Weight loss also occurred, and adverse effects were mild. Participants taking semaglutide showed a 48% reduction in the amount of alcohol consumed during a post-treatment laboratory simulation, with significantly lower drinks per drinking day [2]. Researchers suggested GLP-1 agonists like semaglutide may dampen brain cues triggering cravings. Notably, the magnitude of effects on heavy drinking and drinking intensity is comparable to—or greater than—those typically seen with approved AUD medications like naltrexone. This study provides the first prospective clinical evidence supporting this category of drugs as a promising, novel class for AUD, justifying larger trials in treatment-seeking and heavier-drinking populations. One very important caution is that in-part GLP1 agonists could reduce dopamine release inducing hypodopaminergia [4,5].

For decades, addiction has been conceptualized as a disorder of bad dopaminergic learning within the mesolimbic circuits of the brain [6]. Reward processes have been ascribed to dopamine-associated circuits. Notably, while external stimuli, such as food and drugs of abuse, are stimulators of dopamine -neuron activity, emerging evidence suggest that interoceptive signals also play a critical role. Along these lines, the gut-brain vagal axis has emerged as a key regulator, although its precise contribution to mesolimbic dopamine- signaling and behavior remains uncertain. *Ex vivo* and *in vivo* approaches across multiple scales to reveal that gut-brain vagal tone is essential for gating mesolimbic DA system activity and functions, modulating DA-dependent molecular and cellular processes, and scaling both food- and drug-induced reinforcement [7]. These findings challenge the traditional brain-centric view of reward processing, supporting a more integrated model in which vagus-mediated interoceptive signals intrinsically shape motivation and reinforcement. By uncovering the influence of gut-brain vagal communication on DA functions, this work provides insights into the neurobiology of adaptive and maladaptive reward, with broad relevance for eating disorders and addiction [8].

Drugs of abuse theoretically hijacked reinforcement learning [9]. But this new evidence indicates addiction is also a disorder in

which physiological signals—particularly from the gut, endocrine system, and immune system—continuously influence the brain, motivational states, seeking behavior for both food and substances and cognitive control [10].

The intestine as a primary reward sensor

The gastrointestinal tract is not merely a digestive center but also functions as a sensory organ for reward [11]. Enteroendocrine cells (EECs) detect luminal nutrients and send signals to the brain via endocrine, paracrine, immune, and direct neural mechanisms. A critical new advance was the recent identification of neuropod cells—specialized EECs capable of fast neurotransmission using glutamate or ATP [12]. These signals reach the brainstem in milliseconds. This mechanism is largely what improves issues with overeating as well as with excessive alcohol consumption and other issues when a person takes semaglutide.

Calorically dense substances (including alcohol) carry reinforcing properties beyond central nervous system effects. Addiction represents not only maladaptive central learning but also maladaptive interoceptive learning. An example of maladaptive learning is when gut-derived reward orders the body to eat more food or consume more fermented sugar-alcohol. Semaglutide may solve this problem by shutting off those commands but may cause other unwanted adverse effects [13-15].

Substances like opioids and nicotine may also be affected, although we are not yet sure, and improvement of excessive (or any) use may also occur through gut-mediated reinforcement pathways, although further research is needed. The intestine itself participates directly in the encoding of reward. With this stated and the known importance of dopamine in the brain -gut axis, the administration of GLP1 agonists must identify the dopaminergic genetic/epigentic trait /state of an individual prior to administration [Figure 1].

The reason for this difficult real-world step is based on the anti-dopaminergic effect of GL1 R agonists, especially in patients with known hypodopaminergia [16]. Overlaying gut sensory function is the gut microbiome, which is very important. Microbial metabolites influence vagal signaling and cytokine cascades that regulate mood and stress responsiveness [17]. The microbiome indirectly calibrates addiction vulnerability among those at risk; a problem resolved with medication. Addiction phenotypes may also include the microbial regulation of anxiety and dysphoria [18]. Thus, it may be possible for drugs like semaglutide to improve obesity, AUD, smoking, anxiety, and even depression, although further research is needed. Gut-derived hormones exert direct effects on motivational circuitry. GLP-1 receptors, ghrelin, and other hormones, acting on both hypothalamic homeostatic systems and mesolimbic dopamine pathways [19].

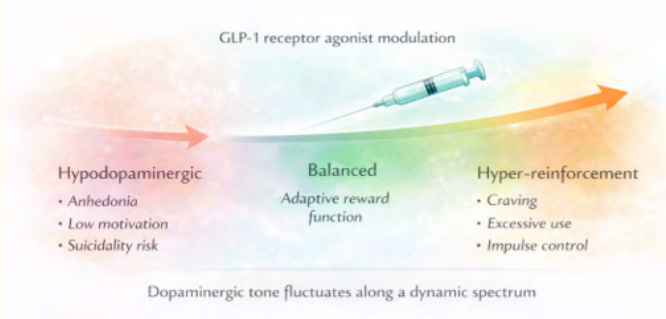

Figure 1: Conceptual framework of GLP-1 receptor agonist effects across the dopaminergic spectrum. Dopaminergic tone exists along a dynamic continuum ranging from hypodopaminergic states characterized by anhedonia and motivational deficits to hyper-reinforcement states associated with compulsive substance use. GLP-1 receptor agonists may reduce pathological reinforcement by dampening mesolimbic dopamine signaling, promoting movement toward balanced reward function. However, in individuals with baseline dopaminergic vulnerability, further suppression may have context-dependent neuropsychiatric consequences. This framework supports precision-based risk stratification in clinical application.

Inflammation destabilizes cognitive control

Inflammation is the final destabilizing pillar of the gut–brain–immune–reward model. Inflammation destabilizes the very circuits that support behavioral inhibition [20]. Chronic inflammation impairs prefrontal cortex function, increases anhedonia, and heightens stress sensitivity—and these are all core features of severe addiction. GLP-1 inhibitors may improve this chronic inflammation, which may be another reason why these medications are effective in many people [21]. Neuroimaging studies have correlated inflammatory markers with reduced executive control, translating biologically into an impaired resistance to craving.

Resolve the inflammation, and executive control normalizes. At least, theoretically.

Addiction as a closed-loop failure

These research insights and findings support reconceptualizing addiction as a closed-loop systems failure, involving the gut, microbiome, endocrine signaling, immune tone, and brain reward circuits. The intestine senses reward, hormones bias motivation, and inflammation erodes control. Dopaminergic plasticity remains central but is continuously modulated and influenced by peripheral physiology. Treatment extends beyond the brain to include gut health, metabolic signaling, and inflammation. Conversely, relapse is shaped by stress physiology and immune tone rather than purely by learning [22].

Addiction is not merely synaptic plasticity in the nucleus accumbens [Figure 2]. It is also a disorder of gut–brain–immune–reward coupling, in which the intestine senses reward, the microbiome shapes stress, hormones bias motivation, and inflammation destabilizes control. So, addiction is a disorder in which peripheral signals continuously shape central motivational states, stress reactivity, and behavioral control. Situating addiction within this system-level framework opens new avenues for integrated treatment strategies that target the whole person.

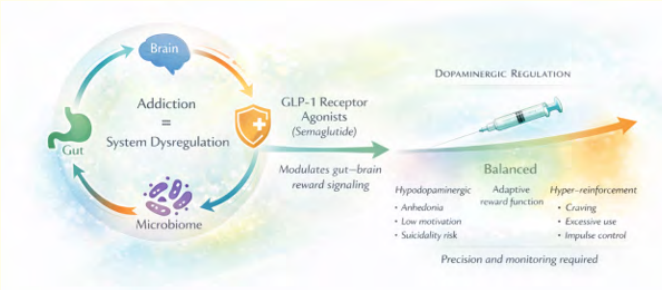

Figure 2: Conceptual model of addiction as a closed-loop gut–brain–reward disorder. Addiction is reframed as a systems-level dysregulation involving continuous bidirectional interactions between gut-derived interoceptive signaling, microbiome-mediated stress modulation, inflammatory tone, and mesolimbic dopamine circuitry. Peripheral physiology shapes reinforcement learning and executive control rather than merely responding to central neural changes. GLP-1 receptor signaling represents a potential point of therapeutic modulation within this distributed loop.

Addiction (both substance and behavioral) is fundamentally a disorder of reward learning, impulse control, and stress reactivity involving dopamine function —but all of these intersect with gut–brain signaling. Vagal afferents from the gut project to the dopaminergic brain regions. Sugar and fat activate these circuits synergistically. The gut can act as a sensory organ for reward, not just nutrition. Addictive drugs hijack dopamine signaling already modulated by gut-derived signals [23]. Synaptic plasticity in the nucleus accumbens represents one element within a distributed system whose parameters are set by peripheral physiology. Addiction thus resembles other complex chronic diseases—like diabetes or autoimmune disorders—where central symptoms emerge from multi-organ dysregulation [24].

Policy statement

GLP-1 receptor agonists (GLP-1 RAs) represent a biologically plausible and increasingly evidence-supported adjunctive strategy for alcohol and substance use disorders, grounded in their effects on mesolimbic reward circuitry, gut–brain vagal signaling, metabolic hormones, and inflammatory tone (1,6–10). Randomized controlled evidence now demonstrates that weekly low-dose semaglutide significantly reduces alcohol craving, heavy drinking days, and drinking intensity in adults with alcohol use disorder, with effect sizes comparable to or exceeding those of currently FDA-approved AUD pharmacotherapies, even in non-treatment-seeking populations [2].

At the same time, policy must proceed with caution. Preclinical, pharmacogenomic, and mechanistic data indicate that GLP-1 RAs can modulate dopaminergic tone and, in susceptible individuals with baseline hypodopaminergia, may exacerbate reward deficiency states, affect mood regulation, and potentially increase vulnerability to suicidality [3,6,16]. These risks underscore the need for structured monitoring rather than indiscriminate off-label use.

Accordingly, GLP-1 RAs should be positioned in clinical policy as adjunctive, investigational therapeutics for substance use disorders, not as replacements for established evidence-based addiction treatments. Coverage and clinical use should prioritize patients with comorbid metabolic disease (obesity, type 2 diabetes) and alcohol or substance use disorders, incorporate longitudinal assessment of craving, consumption, mood, and cognitive control,

and support participation in registries and pragmatic trials to further define benefit–risk profiles [2,13-15,22].

Given the emerging understanding of addiction as a closed-loop gut–brain–immune–reward disorder rather than a purely brain-centric disease, future policy frameworks should encourage integrated treatment models that align metabolic, neuropsychiatric, and behavioral care while continuing to refine precision-based risk stratification strategies [7,8,17-24]. While we insist on real caution prior to prescribing such as family history of SI and other psychiatric issues, continued research related to both clinical and basic science [25-27] research.

Conclusion

Addiction is not just synaptic plasticity in the nucleus accumbens. It is also a disorder of gut–brain–immune–reward coupling, in which the intestine senses reward, the microbiome shapes stress, hormones bias motivation, and inflammation destabilizes control. Recognizing addiction as a system-level disorder situates neural mechanisms within the physiological context determining their expression. This perspective opens new avenues for integrated treatment strategies addressing the whole person. We may just have a successful means of treating addiction with semaglutide and related drugs, although more research is needed. Still, the outlook is hopeful.

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Author Contribution

KB and MSG developed the initial draft ; KUL developed the figures; and all authors edited, commented and approved the final version of this manuscript.

Conflict of Interest

KB owns all ip linked to both GARS and KB220.

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