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Review Article

Potential Therapeutic Role of GLP-1 Receptor Agonists in the Management of Opioid Use Disorders: A Literature Review

Skylar Bronson[1*], Kyla Groves[2], Seham Noorani[3], Danielle Boothe[4], Medha Gopal[2], Jonathan Quinonez[5]

[1]Department of Clinical Sciences, American University of the Caribbean School of Medicine, Cupecoy, Sint Maarten
[2]Department of Clinical Sciences, St. George's University School of Medicine, West Indies, Grenada
[3]Department of Clinical Sciences, Ross University School of Medicine, Miramar, Florida, United States
[4]Department of Clinical Sciences, St. Matthews University School of Medicine, Orlando, Florida, United States
[5]Department of Internal Medicine, River Oaks Treatment Center, Riverview, Florida, United States

*__Corresponding Author:__ Skylar Bronson, Email: skylarbronson@students.aucmed.edu

Abstract

Background: Opioid use disorder (OUD) is a global health crisis, contributing to significant public health challenges and economic loss. Although existing treatments are available, there is a critical need for novel therapeutic strategies. This review examined the potential of glucagon-like peptide-1 (GLP-1) receptor agonists, primarily used in diabetes management, as a repurposed treatment for OUD.

Methods: We explored preclinical studies that demonstrate how GLP-1 receptor agonists can modulate neurobiological pathways involved in opioid addiction, particularly dopaminergic signaling. We also reviewed initial human clinical trials examining the impact of GLP-1 receptor agonists on opioid self-administration, relapse behavior, and cravings.

Findings: Preclinical data suggest that GLP-1 receptor agonists can reduce opioid self-administration and relapse behavior in animal models. Early human clinical trials indicate promising results, showing a potential role for GLP-1 receptor agonists in reducing opioid cravings and improving treatment outcomes.

Conclusion: Although early findings are encouraging, further research is needed to confirm these results, optimize dosing regimens, and clarify the underlying mechanisms of action. Given the interplay between metabolic and neuropsychiatric factors in OUD, GLP-1 receptor agonists offer a unique therapeutic advantage. Large-scale clinical trials are essential to determine their long-term efficacy, safety, and integration into comprehensive OUD treatment plans.

Keywords: Dopamine, Neurobiology, Pharmacotherapy, Substance abuse, Relapse prevention

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Introduction

Opioid use disorder (OUD) is a global health crisis, contributing to significant public health challenges and economic loss.[1] Opioids, including natural, semi-synthetic, and synthetic compounds, interact with opioid receptors to reduce pain and are prescribed for acute and chronic pain, cancer, and palliative care. While effective, they can cause side effects such as drowsiness, euphoria, nausea, and constipation; at high doses, they may depress respiration and lead to fatal outcomes.[2] OUD is characterized by chronic opioid use, causing significant distress or impairment. Understanding OUD is essential for addressing opioid misuse and implementing appropriate treatment strategies.

Opioid use and related disorders are a global health challenge marked by rising prevalence and mortality. In 2021, about 296 million people reported drug use globally, with around 60 million using opioids. In 2019, opioids were responsible for nearly 80% of the 600,000 drug-related deaths worldwide, with about 25% due to overdose.[3] From 1999 to 2014, the U.S. saw a significant increase in opioid prescriptions and mortality, marking the onset of the opioid epidemic. Drug overdose deaths nearly tripled, with opioids involved in 60.9% of the 47,055 overdose deaths in 2014.[4] In 2019, overdose deaths reached 70,630, with about half involving synthetic opioids. Between 2013 and 2022, in the US alone, age-adjusted synthetic opioid death rates surged from 1 death per 100,000 to 22.7 deaths per 100,000 for the standard population, with the largest percent increase of death by overdose seen in the 65 + age group of 10% from 2021 to 2022, shown in Figure 1.[5] The COVID-19 pandemic appears to have accelerated this

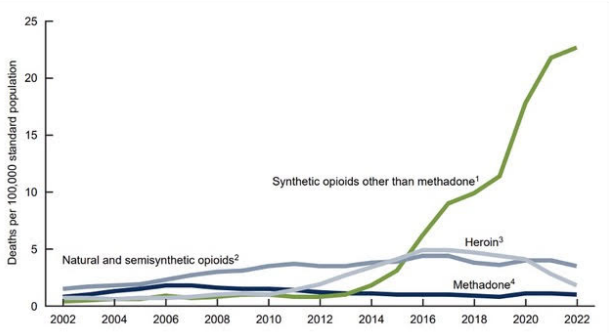

Figure 1. Age-adjusted opioid-related drug overdose death rates, by opioid category: United States, 2002–2022 [5]

(1) From 2002 to 2013, rates remained relatively stable, followed by an upward trend from 2013 through 2022. The rate of change varied over time, $p<0.05$.

(2) From 2002 to 2016, there was a notable upward trend, after which rates leveled off between 2016 and 2022. The pace of change differed across the observed periods, $p<0.05$.

(3) Between 2002 and 2016, rates rose significantly, with fluctuations in the rate of increase over time. This was followed by a stable period from 2016 to 2020, and then a marked decline from 2020 to 2022, $P<0.05$.

(4) From 2002 to 2006, rates increased significantly, then declined from 2006 to 2018, and remained stable from 2018 to 2022, $P<0.05$.

Notes: Drug overdose deaths were classified using ICD-10 underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Overdose deaths by drug type were identified using multiple cause-of-death codes: T40.1 (heroin), T40.2 (natural and semisynthetic opioids), T40.3 (methadone), and T40.4 (synthetic opioids excluding methadone). Age-adjusted death rates were computed using the direct method with the 2000 U.S. standard population. Deaths involving multiple opioid categories (e.g., both methadone and a natural/semisynthetic opioid) were counted in each relevant category. The proportion of overdose deaths specifying the drugs involved was between 75% and 79% from 2002–2013, rising from 81% in 2014 to 96% in 2022. Data source: National Center for Health Statistics, National Vital Statistics System, mortality data file. Access the data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db491-tables.pdf#4

existing trend.

Prescription opioid use rose from 3.5% in 1975 to over 9% in 2008. By 2009, 2.2 million Americans aged 12 or older used prescription opioids as their first illicit drug, second only to marijuana. In 2013, 169,000 individuals tried heroin for the first time.[6] Deaths from prescription opioids reached 16,000 in 2013, a 2.5-fold increase from 2001, while heroin deaths quintupled. Drug overdoses have surpassed motor vehicle crashes as the leading cause of accidental death in the United States, with about 100 daily fatalities, half from prescription opioids.[7]

Early opioid exposure increases the risk of OUD, with earlier initiation linked to worse outcomes. In 2011, 8.7% of 12th graders reported illegal prescription opioid use. Around 13% of high school seniors had used prescription opioids non-medically, and in 2009, 250,000 high school students had tried heroin.[8] The number of heroin users aged 18-20 years rose from 56,000 to 77,000 between 2008 and 2009. The 18-25 age group shows the highest opioid use, especially heroin, with rising use among youth from higher socioeconomic backgrounds.[6] Gender differences in seeking treatment for opioid use are less pronounced compared to other substance use disorders (SUDs).[6]

Overall, opioid use is a multifactorial crisis influenced by early initiation, social factors, and evolving drug markets. A multifaceted prevention and treatment strategy is needed.

Pathophysiology and Neurobiology of Opioid Addiction

Opioid addiction arises from complex neurobiological processes that disrupt the brain's natural reward and stress systems. When opioids bind to their receptors, they activate circuits involved in pleasure and reinforcement, leading to adaptive changes over time. Chronic exposure results in neuroadaptations within dopamine and opioid peptide systems in the ventral striatum and activation of stress systems in the extended amygdala. These include corticotropin-releasing factor, dynorphin, norepinephrine, and other modulators.[9]

This dysregulation contributes to heightened pain sensitivity (hyperalgesia) and negative emotional states (hyperkatifeia), which drive continued drug use through negative reinforcement. Animal models mirror these findings, showing elevated reward thresholds, anxiety-like behavior, and dysphoria following prolonged opioid use.[10]

Such neurobiological changes illustrate the chronic, relapsing nature of opioid addiction and emphasize the importance of treatments targeting both emotional and neurochemical pathways.

Rationale for Exploring GLP-1 Receptor Agonists in OUD

OUD remains a significant public health crisis driven by the misuse of prescription and illicit opioids. The U.S. has faced three overlapping waves of overdose deaths: prescription opioids in the late 1990s, heroin in 2010, and synthetic opioids like fentanyl since 2013. The recent surge in fatalities is primarily attributed to illicit fentanyl, even as OUD prevalence remains steady. Opioid overdoses have tripled since the early 2000s, and unintentional poisoning is now the leading cause of injury-related death in Americans aged 1-44.[11]

Overprescribing plays a significant role, with many misuses linked to a single physician—patients treated by high-prescribing providers are significantly more likely to transition to long-term use.[12] Postoperative patients are particularly vulnerable, with orthopedic surgeons historically contributing substantially to prescription volume. Recent data have shown that between 0.1% and 10% of opioid-naïve patients develop new persistent opioid use after surgery, with pooled rates typically around 3%–7%.[13]

While medications like buprenorphine and clonidine are available, treatment capacity is limited, and new strategies are needed. GLP-1 receptor agonists, currently used for type 2 diabetes and obesity, have recently shown potential in treating SUDs.

Preclinical evidence suggests these agents reduce drug-seeking behaviors and withdrawal symptoms in animal models, indicating possible benefits in OUD. However,

human data are limited. A comprehensive review of existing literature is necessary to evaluate their therapeutic potential, identify knowledge gaps, and guide future clinical research.

By synthesizing available evidence, this review aimed to support the development of innovative treatment strategies for OUD, responding to the urgent need for more effective and accessible interventions.

Methods

A comprehensive search was performed on PubMed/MEDLINE using the keywords "GLP-1 receptor agonists", "opiate use disorder", "opioid use disorder", "addiction", "reward pathway", "neurobiology", "dopamine", "pharmacotherapy", "substance abuse", and "relapse prevention". All observational and trial studies conducted in either human or animal models were considered in our study. Exclusion criteria include grey literature, posters, abstracts, editorials, or commentaries. A total of 9 articles were included in the present study.

Results

Opioid use disorder has been increasing in prevalence. In 2022 alone, the U.S. reported 107,941 drug overdose deaths, underscoring the urgency of effective interventions.[13] This crisis stems from opioids' potent and addictive properties. Opioid receptors include mu, kappa, and delta, all producing analgesic effects. Mu receptors (in regions such as the cerebral cortex, periaqueductal gray, thalamus, nucleus accumbens, and amygdala) are chiefly associated with euphoria and physical dependence. Kappa receptors, located in the hypothalamus and periaqueductal gray, contribute to the dysphoric states experienced during withdrawal. Delta receptors, found in the basal ganglia, are thought to mediate anxiolytic effects.[14]

Current FDA-approved treatments for OUD include methadone, buprenorphine, and naloxone, which reduce cravings, mitigate withdrawal, and block opioid receptors, respectively.[15] While effective, these treatments have limitations, prompting interest in alternative therapies with fewer side effects. One such emerging option is GLP-1 receptor agonists.

Research on GLP-1 receptor agonists in OUD is predominantly preclinical. Although human trials are ongoing, data remain limited.[16,17] Bornebusch et al[18] conducted a study on mice that found no significant effect of GLP-1 agonists on opioid use.[17] However, subsequent studies using rats have yielded more promising results. Douton et al demonstrated that exenatide reduced cue-heroin-seeking behavior and drug-induced reinstatement.[19] Similarly, Evans et al showed that liraglutide, titrated to minimize gastrointestinal side effects, also reduced heroin-seeking behavior.[20] Zhang et al found that GLP-1 agonists attenuated addictive behaviors without compromising opioid-induced analgesia.[21]

Notably, positive findings have mostly come from rat models, while negative results were reported by Bornebusch et al[18] who used mice. This species difference may influence drug response and highlights the need to investigate further the physiological mechanisms underlying these effects.

Discussion

GLP-1 Receptors

GLP-1 receptor agonists are widely used in treating diabetes and obesity, with semaglutide, liraglutide, and exenatide being the most common agents. Their mechanisms of action have sparked interest in their potential for treating substance use disorders.

GLP-1 is a peptide that acts as both an incretin hormone and a neurotransmitter, produced by intestinal L cells in response to food intake.[21] Its receptors are expressed throughout the body, including the pancreas and brain. GLP-1 promotes glucose-dependent insulin secretion, decreases glucagon levels, delays gastric emptying, and reduces appetite. These functions underlie its use in diabetes and obesity management.

Beyond metabolic regulation, GLP-1 also influences the brain's reward system. GLP-1 receptors are found in the mesolimbic dopamine system, including the nucleus tractus solitarius (which projects to the ventral tegmental area) and the nucleus accumbens, key regions involved in reward and addiction. This has opened the door to exploring GLP-1 agonists as modulators of addictive behavior.

Preclinical Evidence

Animal studies have demonstrated that GLP-1 receptor agonists can reduce the rewarding effects of opioids, stimulants, and alcohol.[22-24] They also appear to offer neuroprotection and modulate the hypothalamic-pituitary-adrenal (HPA) axis, both of which are relevant to the adverse effects of chronic substance use.[25,26]

Although clinical data are limited, early results are encouraging. For example, a pilot study of patients with alcohol use disorder found that liraglutide reduced both cravings and alcohol consumption.[27]

Together, the preclinical and early clinical findings support the GLP-1 system as a potential target for addiction therapies, including OUD. The proposed mechanisms, such as reward pathway modulation, stress response regulation, and neuroprotection, may contribute to a broader understanding of addiction's neurobiology.

However, human data are still lacking. Continued preclinical and clinical research will be essential to validate GLP-1 receptor agonists as effective treatments for OUD. In addition to agonist-based therapies, exploring the role of GLP-1 receptor antagonism may also provide new insights into reducing opioid use. The following section outlines potential mechanisms by which GLP-1 receptor

modulation, particularly through antagonism, could influence opioid-related behaviors.

Hypothesized Pathways for GLP-1 Receptor Antagonists in Reducing Opiate Use

1. Reduced Cravings and Modulation of Reward Circuitry

- GLP-1 receptors are expressed in key components of the mesolimbic reward pathway, particularly in the ventral tegmental area (VTA) and nucleus accumbens (NAc), regions critical for dopamine-mediated reinforcement.[23]
- As shown in Figure 2A, activation of GLP-1 receptors in the VTA reduces dopamine release in the NAc in response to addictive drugs, including opioids. This suppression of drug-induced dopamine signaling leads to attenuated rewarding effects and, consequently, reduced drug-seeking behavior. Moreover, GLP-1 may modulate glutamatergic inputs into the VTA, dampening excitatory signals that potentiate craving.[22] This dual action on dopaminergic and glutamatergic systems represents a central mechanism through which GLP-1 agonists may reduce cravings and the reinforcing properties of opioids.
- Antagonism of GLP-1 receptors may paradoxically reduce opioid-induced dopaminergic surges by modulating feedback inhibition loops in these circuits. GLP-1 receptor antagonists may also interfere with opioid-induced increases in extracellular dopamine levels in the NAc, thereby reducing the reinforcing properties of opioids and lowering cue-induced cravings.[22]

2. Modulation of Stress Response

- Chronic opioid use disrupts the hypothalamic-pituitary-adrenal (HPA) axis, leading to heightened stress responses and increased vulnerability to relapse.[28]
- GLP-1 receptors are expressed in the paraventricular nucleus of the hypothalamus (PVN) and brainstem structures involved in stress regulation. By modulating

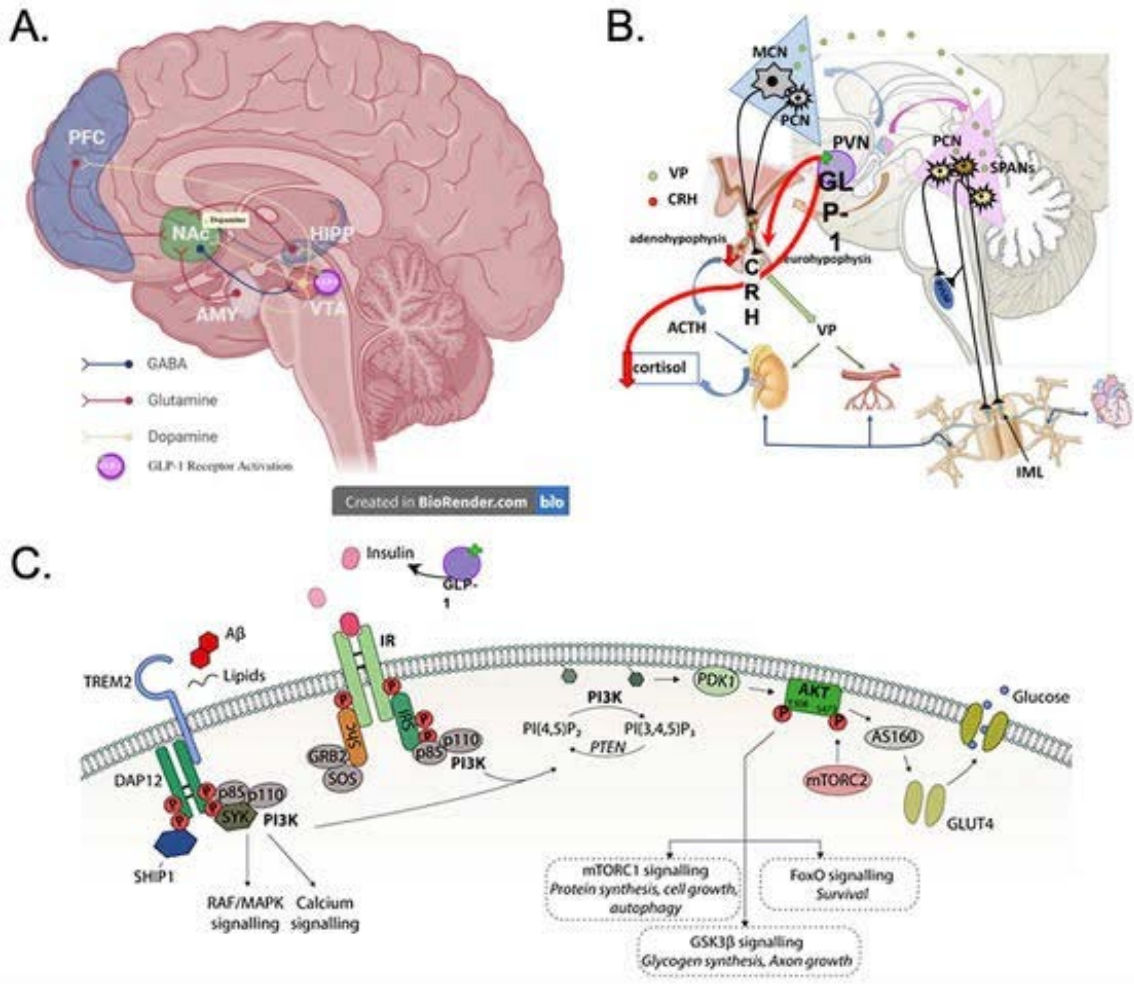

Figure 2. Hypothesized Pathways for GLP-1 Receptor Antagonists in Reducing Opioid Use
A. Reduced Cravings and Modulation of Reward Circuitry: GLP-1 receptor activation in the VTA leads to decreased dopamine release in the NAc, highlighting the modulation of reward circuitry.
B. Modulation of Stress Response: GLP-1 receptor activation in the PVN leads to the modulation of the HPA axis, resulting in reduced CRH and cortisol levels.
C. Neuroprotective and Anti-inflammatory Effects: GLP-1 receptor activation leads to the PI3K/Akt pathway, resulting in reduced neuroinflammation and enhanced neuronal survival

corticotropin-releasing hormone (CRH) output and dampening the HPA response, GLP-1 agonists may normalize stress signaling as shown in Figure 2B.[26] This may reduce the intensity of withdrawal-associated dysphoria and anxiety, thus lowering relapse risk. Animal models have demonstrated that GLP-1 agonists reduce corticosterone levels and exhibit anxiolytic effects in stress paradigms.

- GLP-1 receptor antagonists may reduce HPA axis hyperactivity by blocking excessive CRH release, normalizing downstream adrenocorticotropic hormone (ACTH) and cortisol production. This could help alleviate the hyperkatifeia seen during opioid withdrawal, mitigating relapse driven by negative reinforcement.

3. Neuroprotective and Anti-Inflammatory Effects

- Prolonged opioid exposure induces neuroinflammation, oxidative stress, and damage to neural circuits involving cognition and emotion.[29]
- GLP-1 receptor agonists have demonstrated neuroprotective properties by activating pathways such as PI3K/Akt and MAPK, shown in Figure 2C, which promote neuronal survival and reduce apoptosis. Additionally, GLP-1 signaling reduces microglial activation and pro-inflammatory cytokine release (e.g., TNF-α, IL-1β), which are elevated in opioid-related neurotoxicity.[25] These actions may help preserve brain structure and function in individuals with OUD, offering long-term benefits beyond symptomatic relief.
- GLP-1 receptor antagonists may downregulate microglial activation and reduce levels of pro-inflammatory cytokines. This could protect against opioid-induced synaptic remodeling and neurodegeneration, particularly in reward-related and cognitive brain regions. Additionally, GLP-1 antagonism may promote neuronal homeostasis by modulating intracellular pathways such as PI3K/Akt and MAPK, offering neuroprotection in chronic opioid exposure.

Comparison with Other Pharmacological Treatments for OUD

Opioid Agonists (e.g., Methadone, Buprenorphine)

These medications alleviate withdrawal symptoms and cravings by activating opioid receptors.[16] While effective for symptom management, they do not target the dysregulated reward or stress systems implicated in addiction, a key area where GLP-1 receptor antagonists may have an advantage.

Opioid Antagonists (e.g., Naltrexone)

Opioid antagonists block opioid-induced euphoria by competitively inhibiting receptor activation, similar to the proposed mechanism of GLP-1 receptor antagonists.[15] However, unlike GLP-1 receptor antagonists, they lack effects on stress modulation and neuroprotection.

Other Medications (e.g., Clonidine, Lofexidine)

These agents help manage the physical symptoms of opioid withdrawal but do not address the underlying neurobiological processes of reward dysregulation or emotional stress.[30]

In summary, GLP-1 receptor antagonists offer a potentially novel therapeutic approach to reducing opioid use by targeting multiple pathways (reward modulation, stress regulation, and neuroprotection) that current treatments do not fully address. Further research is essential to assess their efficacy and safety in human populations.

Limitations and Gaps in Current Research

Methodological Limitations

One key limitation is the reliance on observational studies, which inherently carry the risk of bias and confounding variables. For example, the study by Bezin et al. used a nested case-control analysis based on healthcare databases to assess the association between GLP-1 receptor agonist use and thyroid cancer risk.[31] While such large-scale databases provide valuable insights, they are susceptible to misclassifying outcomes and exposures, potentially leading to biased estimates. Additionally, the lack of specific coding for certain outcomes, such as medullary thyroid cancer, necessitated the development of alternative definitions, introducing uncertainty into the results.

Furthermore, many preclinical studies exploring the effects of GLP-1 receptor agonists on addictive behaviors are limited to animal models, often exclusively male rats. This limitation raises concerns about the generalizability of findings to diverse human populations. For instance, the study by Evans et al demonstrated the efficacy of liraglutide in reducing cue- and drug-induced heroin-seeking in male rats but did not investigate potential sex differences or replicate the findings in female animals.[20] Such limitations hinder our understanding of the translational potential of GLP-1 receptor agonists in humans.

Another limitation is the lack of human studies in this area. Most research on GLP-1 receptor agonists has been conducted in animal models or through observational studies. One possible cause for the lack of clinical trials in humans is the difficulty in obtaining funding and complying with strict ethical regulations, which can delay the implementation of human studies.[32] In addition to regulatory burdens, logistical hurdles, such as recruiting individuals with OUD who are often medically and socially vulnerable, present further challenges. Ethical concerns about withholding standard care or exposing participants to potential relapse must be balanced with

the scientific need for placebo-controlled trials. Designing ethically sound, pragmatic studies that integrate with existing treatment programs may help address these concerns.[16] The limited number of rigorous, controlled clinical trials in human populations poses a challenge to confidently assess the therapeutic potential and safety of GLP-1 receptor agonists. This gap underscores the urgent need for well-designed human studies to validate the findings from preclinical research and provide a robust evidence base for clinical applications.[33]

Areas requiring further investigation

Despite the promising findings from preclinical and preliminary clinical studies, several critical gaps remain in our understanding of the therapeutic role of GLP-1 receptor agonists in OUD management.

There is a critical need for more extensive and rigorous clinical trials to confirm the preliminary efficacy of GLP-1 receptor agonists in reducing opioid cravings and preventing relapse in humans. While early trials have shown promise, larger-scale studies with more extended follow-up periods are necessary to evaluate the long-term safety and effectiveness of these agents.[33]

Future studies should prioritize randomized controlled trial (RCT) designs with well-defined primary endpoints such as craving reduction, relapse rates, and retention in treatment. Multi-center collaboration can facilitate adequate sample sizes and improve generalizability. Adaptive trial designs may also allow iterative adjustments based on interim data, increasing feasibility and ethical acceptability.[34] Integrating existing medication-assisted treatment protocols could serve as a framework for practical trials.

The mechanisms underlying the effects of GLP-1 receptor agonists on addictive behaviors are still not fully elucidated. Future research should focus on unraveling the neurobiological pathways through which GLP-1 receptor agonists modulate addiction-related processes, including dopamine signaling and reward circuitry. This requires interdisciplinary approaches combining neurobiology, pharmacology, and behavioral science.[33]

Given the heterogeneity of OUD and the complexity of addiction, studies should explore the potential differential effects of GLP-1 receptor agonists based on individual characteristics such as sex, genetic predisposition, and comorbidities. Understanding how these factors influence treatment response can inform personalized therapeutic approaches tailored to the unique needs of patients.[34]

There is a pressing need for translational research to bridge the gap between preclinical findings and clinical applications. This includes investigating the optimal dosing regimens, formulations, and routes of administration of GLP-1 receptor agonists for treating OUD and assessing their potential interactions with existing pharmacotherapies and behavioral interventions.[33]

Conclusion

Opioid use disorder remains a persistent and complex public health challenge, with current treatment options often limited in their ability to fully address the underlying mechanisms that drive relapse and continued use. GLP-1 receptor agonists, initially used to manage metabolic disorders, show potential as a therapeutic approach helpful in regulating stress responses, modulating reward pathways, and providing neuroprotective effects. Early findings from research have shown encouraging results in reducing opioid-seeking behaviors and suggest benefits for craving reduction and treatment outcomes. Despite these promising signals, significant work remains to determine their safety, long-term efficacy, and integration into existing treatment strategies. Advancing this line of research through large, well-designed clinical trials will be essential to clarify the role of GLP-1 receptor agonists in the management of opioid use disorder and to realize their potential as part of a comprehensive, mechanism-based approach to care.

Author's Contribution

Conceptualization: Skylar Bronson, Kyla Groves, Seham Noorani, Danielle Boothe, Jonathan Quinonez.
Supervision: Kyla Groves.
Writing-original draft: Skylar Bronson, Kyla Groves, Seham Noorani, Danielle Boothe, Medha Gopal, Jonathan Quinonez.
Writing-review & editing: Skylar Bronson, Kyla Groves, Danielle Boothe.

Competing Interests

There have been no conflicts of interest.

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Ethical Approval

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