Glucagon-Like Peptide-1 Receptor Agonists Therapy: The Biological Bridge Across Comorbidities in Behavioral Health

CAROLINA L. HAASS-KOFFLER, PharmD, PhD; STEPHANIE L. FOSTER, MD, PhD

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INTRODUCTION

When providing comprehensive treatment to people with behavioral health conditions, comorbidity is the rule, rather than the exception. Approximately 50% of people with a mental illness also have a diagnosis of at least one additional chronic health problem, such as pulmonary, infectious, or cardiovascular diseases, with obesity and substance use disorders (SUDs) serving as significant predictors of individual health problem severity.[1] Patients with mental illnesses, including schizophrenia, major depression, and bipolar disorder, are known to exhibit a "mortality gap," with a reduced life expectancy compared to the general population.[2] Patients with schizophrenia, for example, exhibit a reduced life expectancy of 10–20 years.[3,4] Notably, despite the increased risk of suicide with severe mental illness, the primary cause of death in this group is cardiovascular disease. These findings reflect the importance of addressing comorbid physical health problems such as respiratory diseases, cancer and, most prevalently, cardiovascular disease resulting from obesity and hypertension.[5]

In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent an intriguing tool to potentially treat metabolic and mental health comorbidities simultaneously. Randomized clinical trials (RCTs) have established the efficacy of GLP-1 RAs in improving metabolic outcomes, and emerging preclinical and observational human data also suggest that GLP-1 RAs influence pathways relevant to stress[6] and reward processing[7,8] that could positively impact behavioral health outcomes, particularly in the realm of SUD. While these effects require further investigation using adequately powered RCTs with primary neuropsychiatric endpoints,[9] initial research suggests favorable impacts on mental health. As GLP-1 RAs become more widely available and are tested in a larger patient population, it is important to consider the current neuroscience and clinical evidence that shows how these tools may evolve for combined management of metabolic and mental health needs.

NEUROSCIENCE OF GLP-1 RECEPTOR AGONISM

GLP-1 is an endogenous peptide produced in the endocrine L cells of the intestine and the nucleus tractus solitarius of the brain, and its receptors are located in a host of regions throughout the gut and brain.[10] While early GLP-1 RA drugs were single-molecule therapies, the therapeutic landscape has since expanded to include dual-agonist approaches. Examples include FDA-approved tirzepatide, a GLP-1/Gastric Inhibitory Peptide (GIP) RA, and the investigational drug CagriSema, a combination of GLP-1/amylin analogue cagrilintide, which engage two pharmacologically distinct targets to maximize metabolic and behavioral outcomes. These dual agonists exert a powerful "double-hit" by operating simultaneously on receptors in the periphery and central nervous system. Peripherally, they enhance glycemic control and slow gastric emptying. With respect to alcohol, this blunts and delays the increase in blood alcohol concentration,[11] which can reduce immediate reinforcing effects.[12] Centrally, these medications penetrate the blood-brain barrier to target two distinct pathways: the GLP-1 component modulates dopamine signaling in the nucleus accumbens to dampen reward-seeking, and the second agonist (i.e. GIP or amylin) works synergistically in the hypothalamus and brainstem to increase satiety and further reduce the salience of addictive triggers. More recent Phase II and Phase III trials are systematically investigating this dual-target mechanism not only to improve metabolic dysfunction (weight loss and insulin sensitivity) but also to reduce behavioral responses, such as craving, that reinforce SUDs.

The more nuanced question that remains to be answered about GLP-1 RAs is: how exactly do they exert their effects on metabolic and reward pathways? A growing body of research suggests that the answer may lie in GLP-1 RAs modulating a shared biological substrate: chronic, systemic inflammation. Inflammation is a shared risk factor for metabolic and mental health disorders and can perpetuate comorbidity. For example, depression increases cortisol and inflammation, which can increase risk for type 2 diabetes.[13] Conversely, the physiological stress of chronic illnesses like diabetes or migraines promotes an inflammatory state that increases risk for major depressive episodes.[14] More recent clinical research is now also evaluating inflammation as a link between the development of PTSD[15] and comorbid alcohol use disorder (AUD).[16]

GLP-1 RA-mediated reduction of peripheral inflammation is well established, and its effect is greater than other FDA-approved anti-diabetic drugs.[17] They act as powerful anti-inflammatory agents, lowering circulating cytokines (e.g. IL-6),[18] C-reactive protein (CRP),[19] and inhibiting activation of microglia, the immune cells of the brain.[20] This attenuation of systemic and central inflammation is thought to help mood symptoms by alleviating the "fog" associated with depression,[21] and reduce the salience of rewarding stimuli, effectively quieting both, and substance-related craving in patients with SUD.[22] Importantly, real-world data obtained from patient electronic health records has shown that GLP-1 RAs are associated with a lower risk of suicidal ideation and self-harm compared to other diabetes medications,[23,24] though whether this can be attributed to decreased neuroinflammation remains to be tested. Future studies will need to examine possible anti-neuroinflammatory mechanisms of GLP-1 RAs more closely, ideally with a combination of biomarker and neuroimaging approaches to determine whether GLP-1 RAs decrease central inflammation in a manner that functionally alters reward or limbic circuits.

CLINICAL TRIAL HIGHLIGHTS

After early trials demonstrated the ability of GLP-1 RAs to reduce metabolic dysfunction, additional studies sought to investigate the effectiveness of GLP-1 RAs on a broader array of conditions spanning physical and behavioral health. In particular, the ability of GLP-1 RAs to reduce craving-like preoccupation with food (i.e., "food noise"),[25-27] along with GLP-1 receptor expression in addiction circuitry, and reports of incidental decreases in substance use while on GLP-1 RAs spurred interest in these medications as treatments for AUD[28] and other SUDs.[29] To date, GLP-1 RA effects on AUD have been the most studied, with encouraging initial results.

While the first GLP-1 RA RCT testing found no reduction in heavy drinking days with exenatide compared to placebo,[30] subanalysis identified decreased drinking among individuals with BMI >30, raising the question of whether GLP-1 RAs might be more effective at reducing drinking in obese individuals. Another RCT evaluating nicotine abstinence following smoking cessation found no difference in abstinence with dulaglutide due to a strong placebo effect.[31] However, a secondary analysis found that dulaglutide *was* associated with a significant decrease (29%) in weekly drinking.[32] Notably, the dulaglutide study population was predominantly obese, adding further support to GLP-1 RAs potentially exhibiting stronger effects in this population. GLP-1 RA mediated reduction in drinking is also supported by an RCT that found semaglutide reduced alcohol craving and drinks per drinking day.[33] Clinical trials for other SUDs remain in early stages but will also examine GLP-1 RAs for cocaine use disorder (NCT07227948),[34] cannabis use disorder (NCT07523633), and opioid use disorder (NCT04199728,[35] NCT06548490).

Clinical trials are also exploring the utility of GLP-1 RAs in other meaningful areas of mental health, particularly with respect to mitigating the metabolic side effects of antipsychotic use. A recent study in Denmark found that semaglutide significantly decreased blood glucose, decreased body weight, and increased physical quality of life among patients with schizophrenia, obesity, and prediabetes.[36] Additional work demonstrates similar effects in patients on clozapine without affecting clozapine concentration or worsening psychotic symptoms.[37] These findings are particularly meaningful, as the metabolic side effects of antipsychotics are a common reason for treatment discontinuation. While it remains to be seen whether GLP-1 RAs could be a primary treatment for conditions like bipolar disorder or psychotic disorders, they may indirectly improve mental health outcomes by mitigating antipsychotic-induced metabolic side effects and thereby increasing adherence to treatment. Clinical trials in the future should examine the impacts of GLP-1 RAs on antipsychotic initiation and adherence.

CONCLUSION

Overall, research suggests that there is great potential for GLP-1 RA therapies to address comorbid medical and mental health conditions, though additional studies are needed. GLP-1 RAs are currently approved for metabolic indications, and RCTs will need to specifically test GLP-1 RAs with a variety of mental health outcomes before these medications can be utilized for such purposes. If supported by the evidence, their use would be well-suited for collaborative care settings, particularly with respect to management of SUDs. Within an integrated care system, GLP-1 RAs could facilitate treatment by curbing dysregulated appetite, improving physical functioning, and/or reducing craving intensity, potentially allowing for more effective engagement with behavioral therapies. By addressing comorbid conditions through a shared mechanism of inflammation, GLP-1 RAs represent an exciting area of ongoing research with multiple potential disease applications.

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Authors

Carolina L. Haass-Koffler, PharmD, PhD, Center for Alcohol and Addiction Studies, Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University; Department of Behavioral and Social Sciences, School of Public Health, Brown University; Carney Institute for Brain Science, Brown University, Providence, RI.

Stephanie L. Foster, MD, PhD, Center for Alcohol and Addiction Studies, Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, RI.

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Correspondence

Carolina Haass-Koffler, PharmD, PhD
carolina_haass-koffler@brown.edu