Semaglutide for Alcohol Use Disorder

To the Editor: Alcohol use disorder (AUD) is a significant global health issue, contributing to 5% of the global disease burden and causing 140,000 deaths related to alcohol use annually in the United States.[1,2] Since 2020, alcohol-related deaths in the United States have surged by 29%, primarily due to liver disease.[3] Despite these consequences, the treatment landscape for AUD remains largely unchanged, with only 2% of patients receiving pharmacotherapy. This is attributed to the limited efficacy and low acceptability of current US Food and Drug Administration–approved treatments, such as disulfiram, acamprosate, and naltrexone, often used alongside psychological strategies like cognitive-behavioral therapy and 12-step programs.[1] However, high relapse rates persist, suggesting the importance of finding better treatments, as reducing drinking, even without full abstinence, can improve health outcomes.

Ali et al[4] published a review in the PCC examining the potential of glucagon-like peptide-1 (GLP-1) receptor agonists in treating psychiatric and substance use disorders, demonstrating promising results in autism-related disorders and depression. The authors noted that GLP-1 agonists are associated with a decreased risk of alcohol-related events, such as withdrawal and dependence.[4] Here, we further explore the potential mechanisms underlying the relationship between GLP-1 agonists and AUD and outline human studies exploring semaglutide for AUD.

GLP-1 receptor agonists affect brain reward pathways beyond their metabolic effects. In animal models, semaglutide consistently reduces alcohol intake. Other GLP-1 analogs, like exenatide, dulaglutide, and liraglutide, also show promise by dampening dopamine release in reward centers. GLP-1 is synthesized in specific brain stem neurons and acts as a neurotransmitter, projecting to areas involved in reward regulation, such as mesocortical limbic dopamine pathways, ventral tegmental area, and nucleus accumbens, which are crucial to alcohol's reinforcing effects. Observational studies in humans have shown that semaglutide reduces AUD risk by 50%–56% within 12 months compared to other antiobesity medications.[5] Alcohol consumers with a body mass index of 30 kg/m^2 or higher reported significant reductions in alcohol consumption among those taking semaglutide or tirzepatide.[6]

One randomized phase 2 trial evaluated the effects of weekly semaglutide on alcohol consumption and cravings in adults with AUD.[7] Semaglutide significantly reduced drinking amounts and peak blood alcohol concentration during a self-administration task, with medium to large effect sizes. Although it did not change the number of abstinence days, it reduced drinks on drinking days and lowered cravings, according to patient reports. However, this study had a short duration, relatively small doses, and a modest sample size with lower alcohol consumption levels than typically seen in treatment-seeking populations.[7]

Phase 3 trials evaluating semaglutide for AUD are underway, assessing its efficacy, tolerability, and safety. Despite its promise, the high cost may hinder widespread adoption, potentially leading to underutilization.[8] Therefore, we must consider whether GLP-1 receptor agonists will become an accessible and reliable option for AUD. If randomized clinical trials confirm their safety and efficacy, this unexpected application of GLP-1 receptor agonists could transform AUD treatment, marking a potential breakthrough in the field. The future of AUD treatment hangs in the balance, carrying significant implications for broader public health.

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