Significant Decrease in Alcohol Use Disorder Symptoms Secondary to Semaglutide Therapy for Weight Loss:

A Case Series

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Abstract

Objective: Despite being a major cause of preventable death worldwide, alcohol use disorder (AUD) currently has only 3 FDA-approved pharmacotherapies. The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide has shown promise in preclinical studies for reducing alcohol consumption, but there are currently no randomized clinical trials that associate a decline in AUD symptoms with semaglutide use. This case series presents 6 patients with positive AUD screenings who were treated with semaglutide for weight loss. All subsequently exhibited significant improvement in AUD symptoms.

Methods: Retrospective chart review was utilized to identify patients treated with semaglutide for weight loss who also had positive screenings for AUD on the Alcohol Use Disorder Identification Test (AUDIT; score >8 considered positive) prior to initiation of semaglutide therapy. Six patients were identified who met these criteria. A paired *t* test was utilized to compare initial AUDIT scores with AUDIT scores after initiation of semaglutide therapy.

Results: All 6 identified patients (100%) had significant reduction in AUD symptomatology based on AUDIT score improvement following treatment with semaglutide (mean decrease of 9.5 points, $P<.001$).

Conclusions: This case series is consistent with preclinical data and suggests that GLP-1RAs have strong potential in the treatment of AUD. Additional randomized, placebo-controlled clinical studies are needed to fully assess the efficacy of semaglutide in treating AUD.

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Alcohol use disorder (AUD) is one of the most prevalent substance use disorders in the United States and is a leading cause of preventable death worldwide.[1] For nearly a century, AUD treatment has relied heavily on behavioral therapies such cognitive behavioral therapy and 12-step programs. More recently, pharmacologic therapies have gained traction, with proven efficacy for treating AUD. Currently, only 3 medications are approved by the US Food and Drug Administration (FDA) for the treatment of AUD: disulfiram, naltrexone, and acamprosate. Disulfiram functions by increasing the production of undesirable byproducts after alcohol use, leading to extreme nausea and potentially fatal neurologic sequelae, while naltrexone and acamprosate are anticraving medications that function by acting directly on neurotransmitter receptors stimulated by alcohol.[1] Even though FDA-approved medications are available, currently less than 2% of people with AUD in the United States receive pharmacotherapy using one of these drugs.[2]

One drug class with an intriguing potential for treating AUD is glucagon-like peptide-1 receptor agonists (GLP-1RAs). While GLP-1RAs were initially developed for the treatment of type 2 diabetes mellitus and have been FDA-approved for weight loss since 2014, continued preclinical research suggests they may also have utility in the treatment of substance use disorders. GLP-1 receptors are found throughout the body, including structures in the brain stem and mesolimbic dopamine pathway in the brain's reward system.[3] Preclinical research with both rodents and vervet monkeys has demonstrated that

Clinical Points

- Preclinical findings and anecdotal reports suggest that semaglutide might be an effective treatment for alcohol use disorder.
- In this case series, semaglutide therapy was associated with marked reductions in scores on the Alcohol Use Disorder Identification Test (AUDIT).
- At follow-up, all 6 patients (100%) had AUDIT scores consistent with "low-risk" drinking.

provision of GLP-1RAs, including semaglutide, results in substantial reductions in alcohol consumption in a number of research paradigms.[3] For example, 2 recent publications by Chuong et al[4] and Aranäs et al[5] demonstrated that treatment with semaglutide reduced binge-like alcohol consumption and dependence-induced alcohol drinking in rodents. Recently, a double-blind placebo-controlled trial examining the safety and efficacy of the first-generation GLP-1RA exenatide failed to meet its primary endpoint of reduced heavy drinking days in an AUD cohort, but a post hoc analysis found that exenatide did reduce heavy drinking in overweight participants.[6] The newest class of GLP-1RA molecules, such as liraglutide and semaglutide, have consistently demonstrated much greater clinical efficacy for diabetes control and weight loss in patients[7,8] and, importantly, have exhibited greater reductions in alcohol consumption in preclinical models.[9] Intriguingly, a recent nationwide cohort pharmacoepidemiology study found that patients with prescriptions for GLP-1 analogs had a lower incidence of alcohol-related events than those with prescriptions for dipeptidyl peptidase IV (DPP-IV) inhibitors.[10] To date, however, there are no published case series describing the response of AUD symptoms to treatment with the more recently developed GLP-1RAs (eg, liraglutide, semaglutide) and no randomized clinical trials in AUD patients using these medications.

The present study utilized a retrospective chart review to determine if GLP-1RA therapy for weight loss had an impact on alcohol intake in adult patients who presented for evaluation at an interdisciplinary obesity medicine and bariatric surgery clinic. Because individuals who undergo bariatric surgery are at increased risk of developing AUD postoperatively,[11] the clinic in question administers an Alcohol Use Disorders Identification Test (AUDIT) to all new patients and at all follow-up visits. The AUDIT survey is frequently used by clinicians to assess for AUD, as it inquires about self-reported frequency and quantity of alcohol use, in addition to information on mental state and experiences during use.[12] An AUDIT score above 8 is considered positive, with a score of 8–14 suggesting hazardous alcohol consumption, and a score ≥ 15 indicating moderate-severe alcohol use disorder.[13,14]

From March 2022 to October 2022, 79 new patients were seen by this clinic and completed AUDIT questionnaires at their intake appointments. Retrospective chart review was utilized to identify patients who both had a positive AUDIT screening test (AUDIT score ≥ 8) at their intake appointment and were later prescribed the GLP-1RA semaglutide for weight loss. Of the 79 patients who were screened, 6 patients met these criteria. One patient was concomitantly prescribed topiramate for weight loss, which is occasionally used off-label for treatment of AUD.[15] In the interest of presenting the most inclusive dataset, we have opted to include this patient in the case series. This resulted in a final sample size of 6 patients with positive AUDIT screenings who were then prescribed semaglutide therapy for weight loss. All patients gave their consent to publish the case reports, and the patient information has been deidentified. Here, we show that all 6 patients demonstrated significant reductions in AUDIT score after beginning semaglutide therapy for weight loss.

CASE PRESENTATIONS

Case 1

A 46-year-old female presented in October 2022 for evaluation prior to bariatric surgery. Medical history was significant for hypercholesterolemia. At her initial appointment, she weighed 78.80 kg (173.4 lb, body mass index [BMI] 30.8 kg/m^2) and had an AUDIT score of 13. She was prescribed semaglutide 0.25 mg weekly for weight loss. Four months after her initial presentation, the patient's weight had decreased to 71.60 kg (157.5 lb, BMI 28.0 kg/m^2), and her AUDIT score decreased to 5 (an 8-point decrease).

Case 2

A 39-year-old female presented in April 2022 for initial evaluation prior to bariatric surgery. The patient stated that she was gaining weight despite dietary changes, medication, and exercise. Medical history was significant for bipolar I disorder, binge eating disorder, attention-deficit/hyperactivity disorder, depression, major social stressors, and AUD. At her initial appointment, she weighed 113.60 kg (249.92 lb, BMI 35.99 kg/m^2) and had an AUDIT score of 20. She was prescribed topiramate 100 mg and semaglutide 0.25 mg for weight loss. Her semaglutide dose was ultimately increased to 1 mg weekly. At follow-up 8 months later, the patient's weight had decreased to 99.1 kg (218.0 lb, BMI 31.4 kg/m^2) and an AUDIT score of 6 was recorded (a 14-point decrease).

Case 3

A 24-year-old female presented in August 2022 for a medical weight loss evaluation. Medical history included binge eating disorder. At her initial appointment, she weighed 67 kg (147.4 lb, BMI 25.4 kg/m^2) and had an AUDIT score of 12. The patient reported a history of binge drinking. She was prescribed semaglutide 0.5

mg once weekly and behavioral therapy for weight loss. At a follow-up appointment 6 months later, the patient reported that her food cravings were completely controlled, and she was no longer binge drinking. Her weight had decreased to 61.7 kg (135.7 lb, BMI 23.4) and an AUDIT score of 2 was recorded (a 10-point decrease).

Case 4

A 38-year-old female presented in August 2022 for a follow-up appointment after receiving bariatric surgery 3 months prior. At the appointment, she weighed 125.2 kg (275.4 lb, BMI 47.5 kg/m^2) and had an AUDIT score of 13. Medical history was significant for asthma/lung disease, hypertension, hypercholesterolemia, depression, and hypothyroidism. Surgical history included cholecystectomy and a gastric sleeve. Semaglutide 0.25 mg weekly was prescribed for continued weight loss. Four months later, the patient's weight had decreased to 108.5 kg (238.7 lb, BMI 41.1 kg/m^2), and an AUDIT score of 6 was recorded (7-point decrease).

Case 5

A 60-year-old male presented in March 2022 for evaluation after medical obesity treatment. Medical history was significant for prediabetes, metabolic syndrome, binge eating disorder, hypertension, and hypercholesterolemia. At his initial appointment, the patient weighed 113.0 kg (248.6 lb, BMI 32.9 kg/m^2) and had an AUDIT score of 17. He was prescribed semaglutide 0.25 mg weekly for weight loss prior to bariatric surgery. This dose was increased to 0.5 mg weekly over the following months. Nine months after his initial appointment, the patient presented for follow-up. At this time, he weighed 105.5 kg (232.1 lb, BMI 30.7 kg/m^2) and had an AUDIT score of 6 (11-point decrease).

Case 6

A 51-year-old female presented in August 2022 for evaluation for medical weight management. The patient was open to implementing exercise routines and dietary modifications as part of her plan. Medical history was significant for vitamin B_{12} deficiency, insomnia, hypercholesterolemia, hyperesthesia, and breast cancer (in remission). At her initial appointment, the patient weighed 78.4 kg (172.5 lb, BMI 26.3 kg/m^2) and had an AUDIT score of 9. She reported a history of binge drinking. She was prescribed semaglutide 0.5 mg weekly for weight loss. One month later, the patient presented for follow-up with a weight of 77.7 kg (170.9 lb, BMI 26.09 kg/m^2), and an AUDIT score of 2 was recorded (7-point decrease).

RESULTS

Patients were predominantly (83.3%) female and had a mean ± SD age of 43.5 ± 12.3 years. Three patients (50%) were treated with 0.5 mg of semaglutide weekly, 2 (33.3%) were treated with 0.25 mg weekly, and 1 (16.7%) was treated with 1 mg weekly. The mean AUDIT score at intake was 14.0 ± 3.9, with a mean follow-up AUDIT of 4.5 ± 2.0 (Table 1, Figure 1). The mean decrease in AUDIT scores with semaglutide therapy was statistically significant relative to a null hypothesis of no change (mean [SD] change = 9.5 [2.7], paired $t_5 = 8.50$, $P < .001$). At follow-up, all 6 patients (100%) had AUDIT scores consistent with "low-risk" drinking.[14]

Table 1.
Changes in AUDIT Scores in Individuals Treated With Semaglutide

Case number (gender)	Age (y)	Initial AUDIT	Repeat AUDIT	Change in AUDIT score	Semaglutide dose (mg)
1 (F)	46	13	5	8	0.25
4 (F)	38	13	6	7	0.25
3 (F)	25	12	2	10	0.5
5 (M)	61	17	6	11	0.5
6 (F)	51	9	2	7	0.5
2 (F)	40	20	6	14	1.0

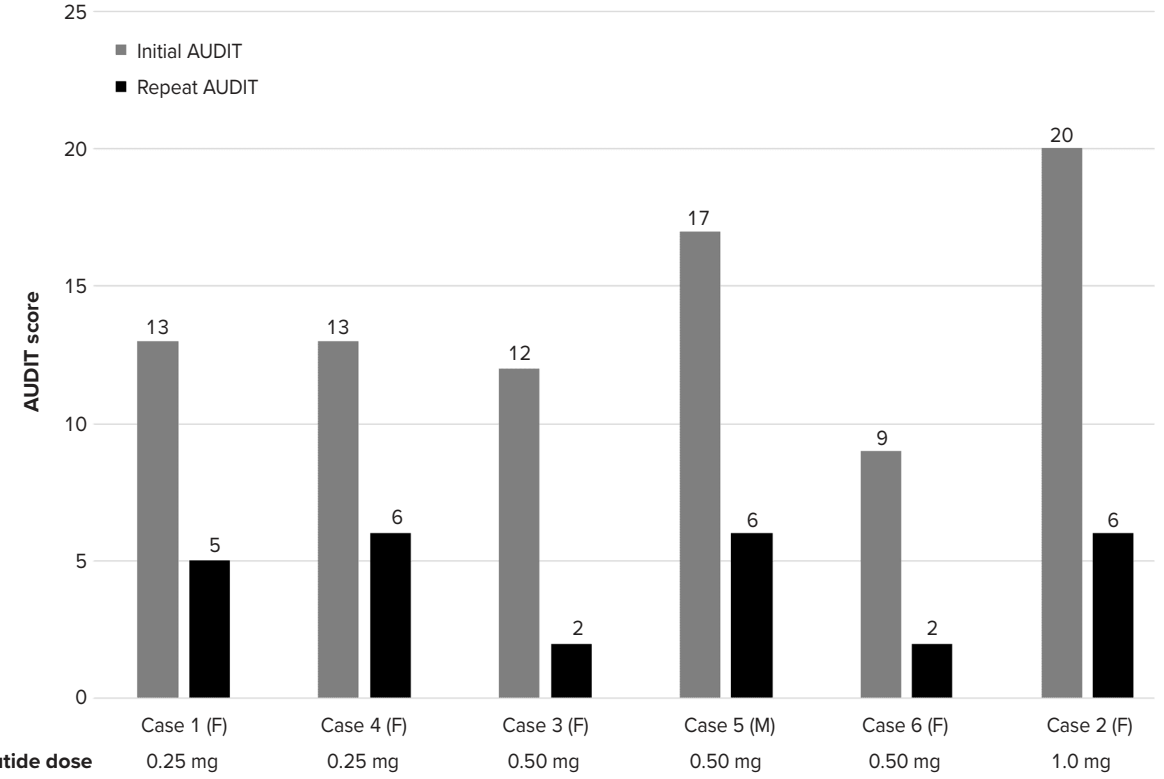
Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, F = female, M = male.

DISCUSSION

Globally, AUD has a 20% lifetime prevalence[16] and is a highly morbid condition. As previously described, there are currently only 3 FDA-approved pharmacologic treatments for AUD, with a heavy reliance on complementary behavioral therapies.[17] This case series highlights the potential for a new and potentially highly effective treatment for AUD that also has known benefits on the regulation of blood sugar, cardiovascular health, and weight loss.

In this study, we utilized retrospective chart review to assess the impact of semaglutide therapy on alcohol consumption as evidenced by changes in AUDIT scores. During treatment for weight loss with the GLP-1RA semaglutide, all individuals in this case series exhibited marked improvement in AUDIT scores, consistent with a clinically significant reduction in alcohol intake in their daily lives. This pattern occurred even though alcohol cessation/reduction was not the intended target of therapy, and no formal or standardized behavioral intervention was implemented for patients with positive AUDIT screenings. Interestingly, the reduction in AUDIT score was observed even in patients with minimal weight loss. For example, patient 6 lost only 1% of her total body weight but had a 77% (7-point) reduction in AUDIT score in a 1-month period. Similarly, patient 3 was prescribed semaglutide with a starting BMI of 25.4 kg/m^2 (classified as "overweight" rather than "obese"), which represents off-label use for this medication. Despite the minimal weight loss this patient underwent to reach a normal BMI of < 25 kg/m^2, she too demonstrated a significant

Figure 1.
Change in AUDIT Scores for Patients Included in the Case Series



Abbreviations: AUDIT = Alcohol Use Disorders Identification Test, F = female, M = male.

decrease in her AUDIT score at her follow-up 6 months later. To our knowledge, there are no published studies to date examining the interaction between semaglutide and AUD in humans. Experimental studies have thus far been limited to pre-preclinical rodent models focusing on the effects of semaglutide on neurotransmission and alcohol consumption: in 2 studies involving rodents, alcohol intake and withdrawal-induced relapse-drinking were both decreased in rodents exposed to semaglutide.[5,18] In another animal study, semaglutide was shown to reduce binge drinking in mice and have an inhibitory effect on the central amygdala and infralimbic cortex, potentially modulating GABA function.[4] The present case series strongly supports the results of these preclinical data, with 100% of patients demonstrating significant reduction in alcohol consumption during semaglutide therapy, despite not being prescribed the medication for this purpose.

None of the patients in this case series reported side effects from GLP-1RA therapy, and to our knowledge there are no AUD-specific risks or contraindications that would prevent patients with AUD from undergoing therapy with GLP-1RAs. Nevertheless, given semaglutide's effectiveness for weight loss, semaglutide likely would not be appropriate for AUD patients having a BMI near or below 18.5 kg/m^2.

As with all retrospective chart review studies, confounding variables may be present. This study took place in a multidisciplinary, university-based, bariatric surgery and obesity medicine clinic that treats patients of all insurance statuses (including self-pay, Medicare/Medicaid, and private insurance), but which does require referral from a primary care provider. The patient population is diverse and contains individuals from a variety of socioeconomic classes and a spectrum of medical and psychiatric histories. No medical or psychiatric illnesses, including substance use disorders, exclude patients from treatment in this clinic. However, there may be a self-selection bias as individuals with severe or function-limiting substance use disorders may be less likely to have a primary care provider to make a referral to the clinic or may be less likely to seek medical care or maintain consistent follow-up in an outpatient clinic setting. Another potentially confounding variable is the administration of the AUDIT questionnaire itself. While no formal or standardized intervention was implemented for individuals who had positive AUDIT screenings, it is plausible that simply answering the questionnaire may have caused some patients to alter their alcohol consumption behaviors.

Another limitation of this study includes the variable follow-up times between intake and follow-up AUDIT

questionnaires. This is due to variation in individualized treatment plans. For the purposes of this case series, minimum and maximum follow-up intervals were not predetermined, and only 2 time points were measured. Because of this, we do not have enough information to determine if the significant reduction in AUDIT scores seen with semaglutide therapy persists long-term. Larger, randomized controlled longitudinal trials are needed in order to determine if this treatment effect is replicable and, if so, whether reduction in drinking behaviors persists with time. If these patterns do persist, GLP-1RAs such as semaglutide could indeed represent a breakthrough in medical therapy for AUD.

It is important to note that in addition to semaglutide, 1 patient (case 2) received topiramate off-label for weight loss. Prior evidence demonstrates that topiramate may be effective in treating AUD.[15] The patient exhibited the same overall pattern of responses to semaglutide as the other cases, dropping from an AUDIT score of 20 down to a 6. This represents the largest overall drop in AUDIT score among the 6 patients, although 2 of the other patients exhibited larger percent changes in AUDIT scores. Case 2's large drop in AUDIT score could reflect individual variability in response to the drug, or it could reflect the combined therapeutic effect of the 2 drugs (semaglutide *and* topiramate).

CONCLUSION

GLP-1RAs including semaglutide have gained significant popularity due to their beneficial metabolic effects including blood sugar regulation, cardiovascular protection, and weight loss. While animal models have shown that semaglutide has strong potential for treating AUD in humans, this case series is the first of its kind to demonstrate that potential in humans. Though the results of this case series are promising, gold standard randomized, placebo-controlled clinical trials (RCTs) are needed to further explore the potential efficacy and safety of semaglutide for treating AUD. Multiple RCTs are currently underway to assess the efficacy of semaglutide in AUD, and we believe that until these data are available, evidence-based practice requires that providers point patients toward the psychological and pharmacologic interventions that have already been validated.[1]

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