

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder

A Randomized Clinical Trial

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IMPORTANCE Preclinical, observational, and pharmacoepidemiology evidence indicates that glucagon-like peptide 1 receptor agonists (GLP-1RAs) may reduce alcohol intake. Randomized trials are needed to determine the clinical significance of these findings.

OBJECTIVE To evaluate the effects of once-weekly subcutaneous semaglutide on alcohol consumption and craving in adults with alcohol use disorder (AUD).

DESIGN, SETTING, AND PARTICIPANTS This was a phase 2, double-blind, randomized, parallel-arm trial involving 9 weeks of outpatient treatment. Enrollment occurred at an academic medical center in the US from September 2022 to February 2024. Of 504 potential participants assessed, 48 non-treatment-seeking participants with AUD were randomized.

INTERVENTION Participants received semaglutide (0.25 mg/week for 4 weeks, 0.5 mg/week for 4 weeks, and 1.0 mg for 1 week) or placebo at weekly clinic visits.

MAIN OUTCOMES AND MEASURES The primary outcome was laboratory alcohol self-administration, measured at pretreatment and posttreatment (0.5 mg/week). Secondary and exploratory outcomes, including prospective changes in alcohol consumption and craving, were assessed at outpatient visits.

RESULTS Forty-eight participants (34 [71%] female; mean [SD] age, 39.9 [10.6] years) were randomized. Low-dose semaglutide reduced the amount of alcohol consumed during a posttreatment laboratory self-administration task, with evidence of medium to large effect sizes for grams of alcohol consumed (β , -0.48; 95% CI, -0.85 to -0.11; $P = .01$) and peak breath alcohol concentration (β , -0.46; 95% CI, -0.87 to -0.06; $P = .03$). Semaglutide treatment did not affect average drinks per calendar day or number of drinking days, but significantly reduced drinks per drinking day (β , -0.41; 95% CI, -0.73 to -0.09; $P = .04$) and weekly alcohol craving (β , -0.39; 95% CI, -0.73 to -0.06; $P = .01$), also predicting greater reductions in heavy drinking over time relative to placebo (β , 0.84; 95% CI, 0.71 to 0.99; $P = .04$). A significant treatment-by-time interaction indicated that semaglutide treatment predicted greater relative reductions in cigarettes per day in a subsample of individuals with current cigarette use (β , -0.10; 95% CI, -0.16 to -0.03; $P = .005$).

CONCLUSIONS AND RELEVANCE These findings provide initial prospective evidence that low-dose semaglutide can reduce craving and some drinking outcomes, justifying larger clinical trials to evaluate GLP-1RAs for alcohol use disorder.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT05520775](https://clinicaltrials.gov/ct2/show/study/NCT05520775)

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Alcohol use is a leading modifiable cause of morbidity and mortality, accounting for an estimated 4% to 5% of disease burden and 2.6 million deaths per year globally.^{1,2} Alcohol is causally linked to more than 200 medical and disability conditions,² with increased risks of common diseases (including cardiovascular disease, liver disease, and cancers) accounting for a large proportion of alcohol-related morbidity.^{1,3,4} Increased incidence of alcohol-related liver disease since 2020 has contributed to a 29% increase in alcohol-related mortality in the US since 2016-2017.^{3,5,6} An estimated 178 000 US deaths per year are alcohol attributable,³ with further increases in rates of alcohol-related disease projected.^{4,7,8}

While roughly 29% and 11% of US adults meet lifetime and past-year criteria for alcohol use disorder (AUD), respectively,^{9,10} less than 10% of those with AUD report past-year treatment¹⁰ and less than 2% receive pharmacotherapy,¹¹ defining one of the largest known health care treatment gaps.¹² Underutilization of AUD medications is attributed to multiple factors, including few Food and Drug Administration (FDA)-approved therapies, limited awareness of these medications, and barriers related to stigma.^{12,13} Reduced alcohol intake, irrespective of abstinence, is associated with improved health outcomes.¹⁴⁻¹⁶ Medications that facilitate reductions in alcohol use while achieving broad clinical uptake would fill a critical unmet need.

Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) are incretin mimetic therapies with exceptional efficacy for the treatment of diabetes and obesity.¹⁷⁻¹⁹ Semaglutide, a long-acting GLP-1RA with superior efficacy to older GLP-1RA medications, received FDA approval for diabetes in 2017 and obesity in 2021.²⁰ Rapidly increasing prescription rates have been accompanied by reports of reductions in alcohol use and craving during treatment.^{21,22} These observations were predated by substantial preclinical evidence that GLP-1RAs reduce voluntary alcohol consumption and attenuate alcohol reinforcement,²³⁻²⁶ suggesting potential clinical applications of GLP-1RAs for AUD.²⁶⁻²⁹ Although experimental evidence for semaglutide-related reductions in alcohol intake remains specific to nonhuman studies,³⁰⁻³³ off-label prescribing for AUD is already reported, necessitating clinical trials.^{21,34} This prospective phase 2 randomized clinical trial evaluated the effects of once-weekly subcutaneous semaglutide in non-treatment-seeking adults with AUD.

Methods

Trial Design

This phase 2 clinical trial used a hybrid design, combining clinical outpatient and human laboratory components, to evaluate the effects of semaglutide in non-treatment-seeking adults with AUD. The outpatient sequence involved 9 weeks of medication or placebo (weeks 1-9) and a final assessment visit (week 10). Objective laboratory alcohol self-administration was assessed at pretreatment (prior to week 1) and between weeks 8 and 9 (at 0.5 mg/week). Other outcomes were assessed prospectively at weekly clinic visits. This investigator-initiated trial

Key Points

Question Does the glucagon-like peptide 1 (GLP-1) receptor agonist semaglutide reduce alcohol consumption and craving in adults with alcohol use disorder (AUD)?

Findings In this randomized clinical trial, relative to placebo, low-dose semaglutide reduced the amount of alcohol consumed during a posttreatment laboratory self-administration procedure. Over 9 weeks of treatment, semaglutide led to reductions in some but not all measures of weekly consumption, significantly reduced weekly alcohol craving relative to placebo, and led to greater relative reductions in cigarettes per day in a subgroup of participants with current cigarette use.

Meaning These results justify larger clinical trials of incretin therapies for AUD.

was conducted at the University of North Carolina (UNC)-Chapel Hill School of Medicine with oversight from the UNC institutional review board and under an investigational new drug exemption granted by the FDA. The trial protocol is in [Supplement 1](#). All participants provided written informed consent.

Participant Sample

Non-treatment-seeking adults with AUD were recruited via online and public advertisements. Primary inclusion criteria included age 21 to 65 years, reporting past-year *DSM-5* criteria for AUD, past-month endorsement of more than 7 (women) or more than 14 (men) standard drinks in a week with 2 or more heavy drinking episodes (4 or more drinks for women and 5 or more for men), and ability to attend weekly clinic visits and pretreatment and posttreatment laboratory sessions. Key exclusion criteria included currently seeking treatment for alcohol problems or actively attempting to reduce consumption; past use of GLP-1 receptor agonists; weight loss medications; body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) less than 23; past-year substance use disorder other than AUD, tobacco use disorder, or mild cannabis use disorder; recent (30-day) use of illicit drugs except cannabis; history of diabetes, and current medical or neurological illness precluding participation based on physician judgement. See the eMethods in [Supplement 2](#) for full eligibility criteria. Enrollment lasted from September 2022 to February 2024.

Study Procedures

Following written informed consent and eligibility confirmation, participants completed a pretreatment alcohol self-administration session before the week 1 medication visit. Participants then completed 8 additional medication or placebo visits (weeks 2-9), a posttreatment alcohol self-administration session (scheduled between weeks 8 and 9), and a discharge visit (week 10, no medication). See the eMethods in [Supplement 2](#) for additional procedural details.

Intervention

Subcutaneous semaglutide was administered according to standard practice, with dose increases every 4 weeks. To maximize safety and feasibility, only the 2 lowest dose sequences

(0.25 mg/week for weeks 1-4 and 0.5 mg/week for weeks 5-8) were used prior to primary outcome collection (between weeks 8 and 9). To obtain additional safety and prospective data, participants received a final dose increase (1.0 mg) at week 9, contingent on tolerability. The week 9 dose was treated as flexible and could be held at 0.5 mg or deferred for safety or practical reasons, based on physician judgement. Participants, investigators, and outcome assessors were blind to condition (see the eMethods in [Supplement 2](#) for additional placebo and blinding information).

Outcomes Assessment

Laboratory Alcohol Self-Administration

Objective self-administration (the primary outcome) was assessed by embedding human laboratory procedures in the trial design. Prior work supports the sensitivity of laboratory self-administration to detect pharmacotherapy effects.^{35,36} A standardized procedure³⁷ was used to estimate voluntary alcohol consumption and ability to delay drinking. Participants were presented with their preferred beverage and brand and could elect to delay drinking for up to 50 minutes for monetary reinforcement. Thereafter, participants were instructed to consume at their preferred pace to achieve preferred effects over 120 minutes.³⁷ The available alcohol amount (in grams) was determined with anthropometric formulas based on a pre-specified maximum breath alcohol concentration (BrAC) limit. BrAC was measured every 30 minutes after drinking onset. Estimated volume consumed (g-ETOH) and peak BrAC served as co-primary outcome measures. See the eMethods in [Supplement 2](#) for additional details.

Weekly Consumption and Craving

Weekly consumption was assessed using calendar-based methods³⁸ supplemented with daily logs to facilitate recall. Outcomes included average drinks per calendar day (registered secondary outcome), with additional quantity and frequency outcomes common to AUD trials (drinks per drinking day, number of heavy drinking days, number of drinking vs abstinent days), and weekly craving³⁹ examined as exploratory and hypothesis-generating outcomes. The proportion of participants with zero heavy drinking days served as an exploratory outcome relevant to FDA end points.⁴⁰ Cigarettes per day (registered secondary outcome) was assessed during calendar-based assessments.³⁸ See the eMethods in [Supplement 2](#) for additional information.

Additional Clinical and Safety Outcomes

Body weight and systolic and diastolic blood pressure were assessed weekly. Side effects, adverse events, and depression symptoms were queried weekly using standardized instruments.^{41,42}

Statistical Analyses

Power analyses informed a target sample of 48 randomized participants (see the eMethods in [Supplement 2](#) for rationale and full analysis plan). Primary, secondary, and exploratory outcomes were evaluated with linear mixed models and full information maximum likelihood estimation to accommodate

missing data (lme4 package version 35.5;⁴³ RStudio version 2024.04.2 + 764 [R Foundation]).

Models of weekly outcomes used intention-to-treat principles (all 48 randomized participants included). Primary intention-to-treat analyses of laboratory outcomes consisted of residualized change models testing medication effects on post-treatment self-administration (g-ETOH and peak BrAC; session 2) controlling for pretreatment levels (session 1). These models estimated medication effects on quantitative consumption during self-administration. Some participants elected not to engage in alcohol consumption, resulting in the presence of missing data for g-ETOH and peak BrAC. Thus, those who opted not to engage in the task contributed data to the intention-to-treat analyses for weekly drinking outcomes and non-self-administration laboratory outcomes (eg, delay time), but were modeled as having missing data for analyses of g-ETOH and peak BrAC, resulting in a sample of 25 with complete data for residualized change analyses. An exploratory model also tested mean BrAC across the session (see the eMethods in [Supplement 2](#) for full details and rationale for statistical models).

Intention-to-treat linear mixed models of weekly outcomes included a random effect for participant, a fixed effect of time (study week, within-subject factor), medication group (semaglutide vs placebo, the primary effect of interest), treatment-by-time interaction, and covariates (see the eMethods in [Supplement 2](#) for full model details). A preplanned linear mixed model examining cigarettes per day (registered secondary outcome) was limited to those participants reporting cigarette smoking at baseline ($n = 13$; 7 in the placebo group and 6 in the semaglutide group), with restricted maximum likelihood estimation given the small sample size.

Because preliminary estimates of effect size are needed to inform future trials of GLP-IRAs, medication effect size estimates are reported in all models (β for linear mixed models and residualized change models; small effect: $\beta = 0.10$, medium: $\beta = 0.30$, large: $\beta = 0.50$). To compare effect sizes over the 2 dosage periods, Cohen d values computed for the monthly intervals corresponding with dosage (0.25 mg/week in weeks 1-4 and 0.5 mg/week in weeks 5-8) are presented for descriptive purposes, using percentage change from baseline to facilitate interpretation across outcomes. Cohen d (small effect: $d = 0.20$, medium: $d = 0.50$; large: $d = 0.80$) was computed in the R *lsr* package version 0.5.2.

Results

Sample Description and Retention

Of the 48 participants randomized, 34 (71%) were female and 14 (29%) were male. The mean (SD) age was 39.9 (10.6) years. Most had BMI greater than 30 ($n = 27$) or 25.0-29.9 ($n = 20$); 1 participant had BMI less than 24.9. On average, participants endorsed moderate AUD severity ([Table](#)). [Figure 1](#) presents the CONSORT diagram. Overall, 42 of 48 participants completed outpatient visits through week 9. All participants who completed posttreatment alcohol sessions received the required 4 doses at 0.5 mg/week. See the eResults in [Supplement 2](#) for full retention details.

Table. Pretreatment Characteristics by Treatment Group for All Randomized Participants

Characteristic	Mean (SD)		
	Placebo	Semaglutide	Total
Randomized, No.	24	24	48
Sex, No. (%)			
Female	17 (71)	17 (71)	34 (71)
Male	7 (29)	7 (29)	14 (29)
Age, y	39.0 (10.9)	40.6 (10.5)	39.9 (10.6)
Race, No. (%) ^a			
Asian	2 (8)	0	2 (4)
Black/African American	4 (17)	3 (13)	7 (15)
Hawaiian/Pacific Islander	0	0	0
White	18 (75)	21 (88)	39 (81)
Other (unspecified) or multiple	0	0	0
Hispanic ethnicity, No. (%) ^a	2 (8)	2 (8)	4 (8)
AUD symptoms, <i>DSM-5</i>	4.3 (2.0)	4.1 (1.5)	4.2 (1.7)
AUDIT	14.2 (6.5)	12.7 (5.6)	13.4 (6.0)
Alcohol consumption ^b			
Drinks/calendar day	3.0 (1.7)	2.7 (1.7)	2.9 (1.7)
Drinks/drinking day	4.5 (2.5)	3.8 (1.8)	4.2 (2.2)
Drinking days	19.6 (5.5)	20.8 (6.8)	20.2 (6.1)
Heavy drinking days	9.8 (5.5)	8.4 (7.9)	9.1 (6.8)
Alcohol craving, PACS score	12.2 (6.5)	11.9 (4.7)	12.0 (5.6)
Current smoking, No. (%) ^c	7 (29)	6 (25)	13 (27)
Cigarettes per day	14.0 (13.5)	8.0 (7.7)	11.2 (11.2)
WHO risk level, No. (%) ^d			
1	5 (21)	8 (33)	13 (27)
2	10 (42)	10 (42)	20 (42)
3	7 (29)	4 (17)	11 (23)
4	2 (8)	2 (8)	4 (8)
Weight, kg	93.1 (15.1)	95.4 (20.9)	94.2 (18.1)
BMI	31.7 (4.5)	32.4 (6.7)	32.1 (5.6)
BMI category, No. (%)			
BMI <30 male	5 (21)	4 (17)	9 (19)
BMI <30 female	4 (17)	8 (33)	12 (25)
BMI ≥30 male	2 (8)	3 (13)	5 (10)
BMI ≥30 female	13 (54)	9 (38)	22 (46)
Blood pressure			
Systolic	127.9 (18.7)	125.1 (16.2)	126.5 (17.3)
Diastolic	85.7 (14.7)	83.7 (10.6)	84.7 (12.7)
Heart rate	78.8 (14.1)	75.0 (10.7)	76.9 (12.6)
HbA _{1c}	5.16 (0.35)	5.09 (0.38)	5.13 (0.36)
Depression (CES-D score)	11.7 (10.0)	12.7 (7.4)	12.2 (8.7)

Abbreviations: AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CES-D, Center for Epidemiologic Studies Depression Scale; HbA_{1c}, hemoglobin A1C; PACS, Penn Alcohol Craving Scale; WHO, World Health Organization.

^a Race and ethnicity were collected via self-report for purposes of characterizing the sample.

^b Alcohol consumption during the 28-day period before baseline visit.

^c Defined as participants who smoked at least 1 cigarette per week during the 28-day baseline period.

^d WHO risk-level criteria are determined by sex-specific criteria for baseline reported alcohol consumption per week: level 1 = <40 g for male individuals and <20 g for female individuals; level 2 = 40-60 g for male individuals and 20-40 g for female individuals; level 3 = 60-100 g for male individuals and 40-60 g for female individuals; and level 4 = >100 g for male individuals and >60 g for female individuals.

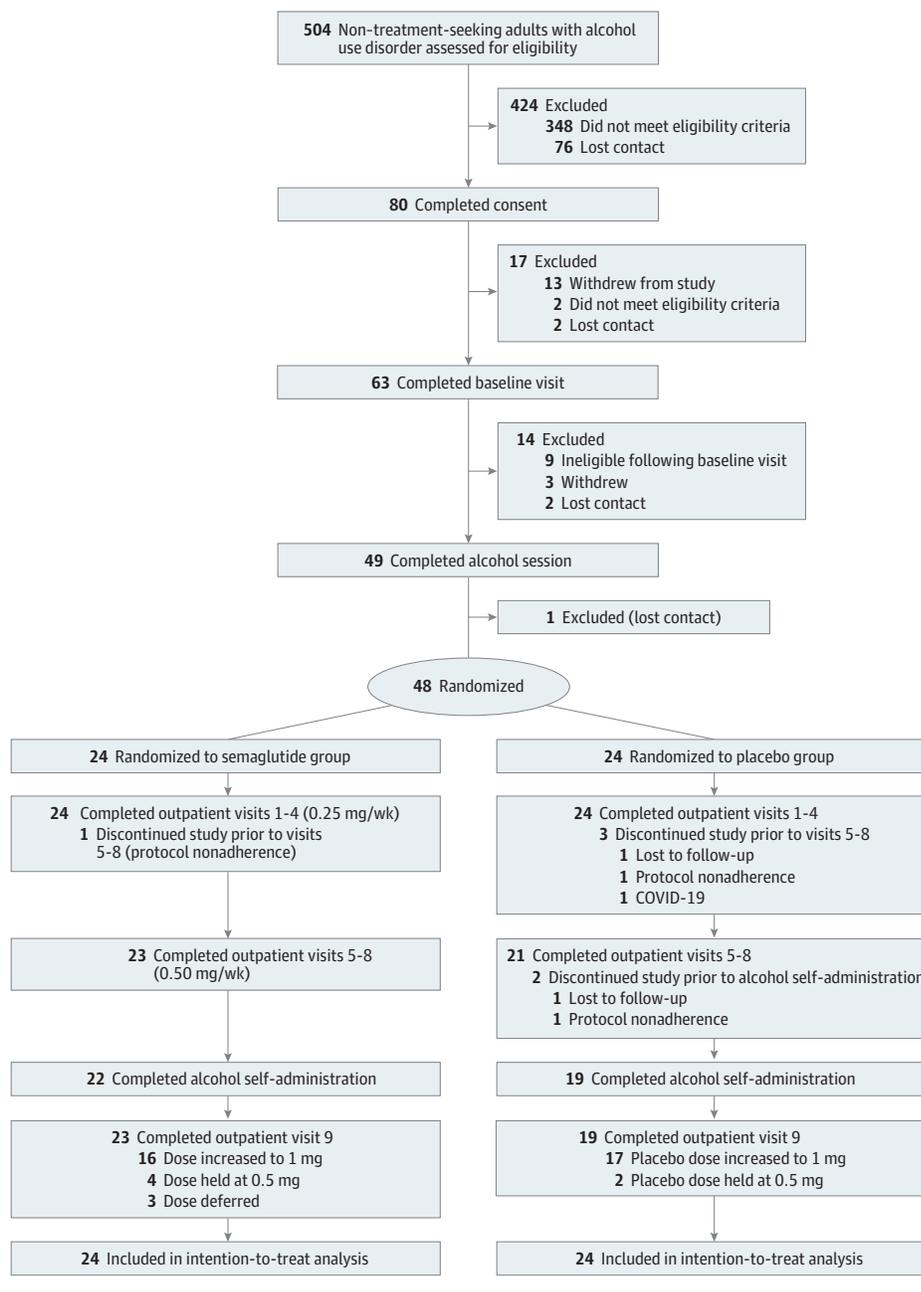
Laboratory Alcohol Self-Administration

Results of residualized change models indicated that semaglutide reduced posttreatment laboratory consumption with a medium to large effect size for grams of alcohol consumed (β , -0.48; 95% CI, -0.85 to -0.11; P = .01) and peak breath alcohol concentration (β , -0.46; 95% CI, -0.87 to -0.06; P = .03) (Figure 2). See the eMethods in Supplement 2 for additional model information and eTable 2 in Supplement 2 for full model results. Descriptive information on BrAC levels across time is depicted in Figure 2; the exploratory analysis of mean BrAC yielded a significant medication effect (β = -0.48, 95% CI, -0.87 to -0.09; P = .02). Medication condition did not predict engagement (vs abstinence) in the self-administration task or duration of delay time (eResults in Supplement 2).

Weekly Outcomes

Figure 3 shows prospective changes in weekly outcomes. Medication effects were nonsignificant for drinks per calendar day (β , -0.27; 95% CI, -0.63 to 0.09; P = .17) and significant for drinks per drinking day (β , -0.41; 95% CI, -0.73 to -0.09; P = .04). A significant treatment-by-time interaction indicated greater reductions in heavy drinking days over time in the semaglutide group relative to the placebo group (β , 0.84; 95% CI, 0.71 to 0.99; P = .04). There was no evidence that semaglutide altered number of drinking vs abstinent days (β , 0.90; 95% CI, 0.73 to 1.12; P = .89). Semaglutide significantly reduced weekly craving (β , -0.39; 95% CI, -0.73 to -0.06; P = .01). The analysis among individuals reporting current cigarette smoking yielded a significant time-by-treatment inter-

Figure 1. CONSORT Flow Diagram



action (β , -0.10 ; 95% CI, -0.16 to -0.03 ; $P = .005$), indicating relatively greater declines in cigarettes per day in the semaglutide vs placebo group over time (eFigure 2 in Supplement 2; eTable 3 in Supplement 2 presents all model results for weekly outcomes).

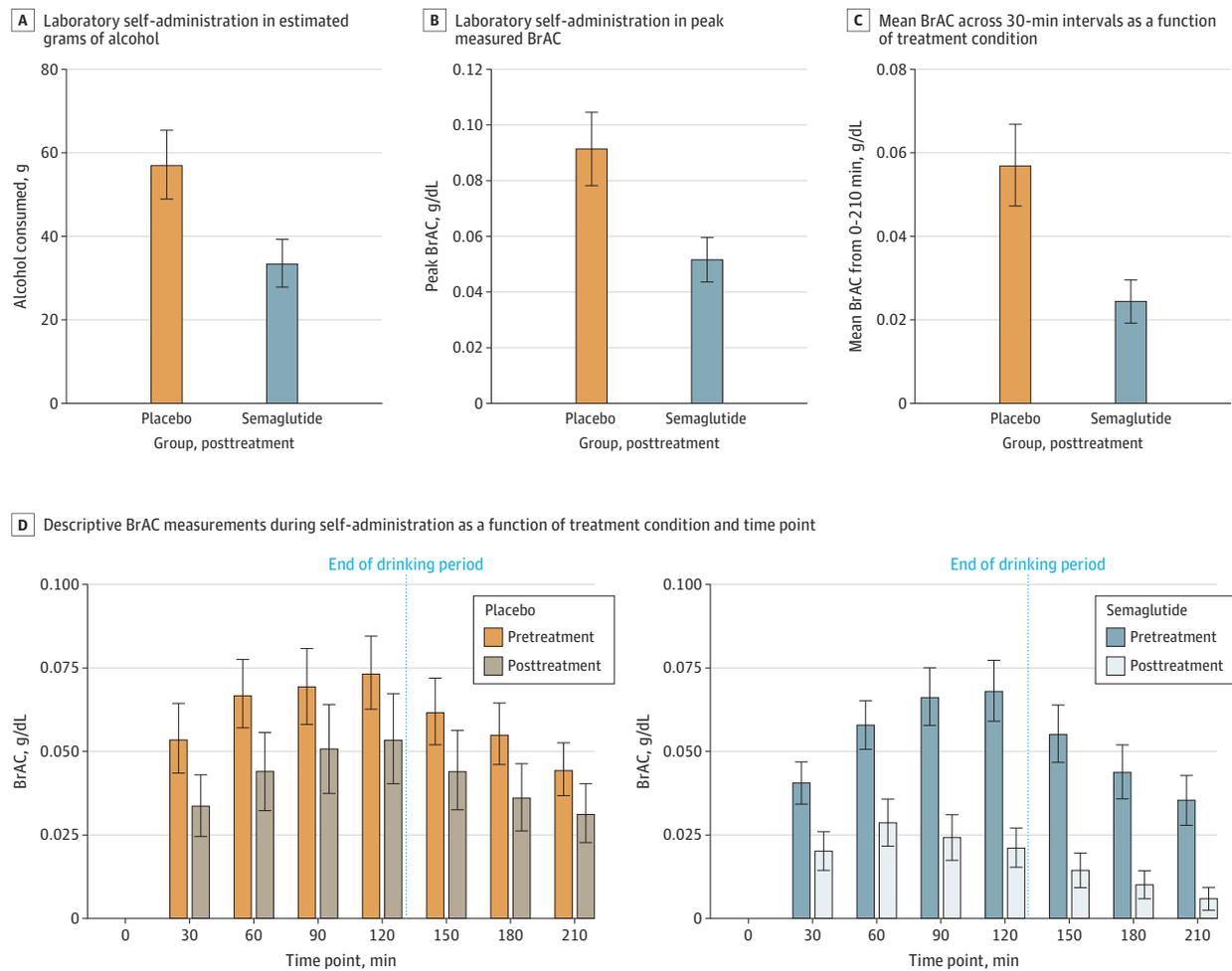
Figure 4A-E depicts monthly changes from baseline with estimated effect sizes. Medication effect sizes were mostly small (by convention, Cohen $d = 0.20$) through week 4 and increased during weeks 5 to 8, with large effect sizes (defined as $d = 0.80$) observed for drinks per drinking day and heavy drinking days. Comparing the proportion of participants with zero heavy drinking days by group and treatment period

(Figure 4F) showed that the likelihood of zero heavy drinking days increased significantly from weeks 1 through 4 to 5 through 8 in the semaglutide group (z score, -2.93 ; $P = .003$), with no other significant comparisons.

Weight and Safety and Adverse Effect Outcomes

Body weight (kg) change at discharge averaged -5% in the semaglutide group (mean [SD], -5.05% [3.56] vs 0.18% [2.5] in the placebo group; time-by-treatment interaction: β , -0.07 ; 95% CI, -0.08 to -0.05 ; $P < .001$) (Figure 3). No significant medication effects for hemoglobin A_{1c}, blood pressure, or depression scores were observed. Participants treated with sema-

Figure 2. Laboratory Self-Administration



Laboratory self-administration, measured in estimated grams of alcohol (A) and peak measured breath alcohol concentration (BrAC; B). Bars depict posttreatment alcohol self-administration following treatment week 8 (0.5 mg/wk), controlling for pretreatment self-administration among those without missing data on the self-administration procedure (n = 25; 12 in the placebo

group and 13 in the semaglutide group). C. Mean BrAC measured across 30-minute intervals as a function of treatment condition. D. Descriptive BrAC measurements during self-administration as a function of treatment condition and time point. Bars depict group means and whiskers standard errors.

glutide reported expected adverse effects, which were largely mild in severity (eTable 1 in Supplement 2). No serious adverse events, adverse interactions with alcohol, or treatment-related discontinuations were recorded.

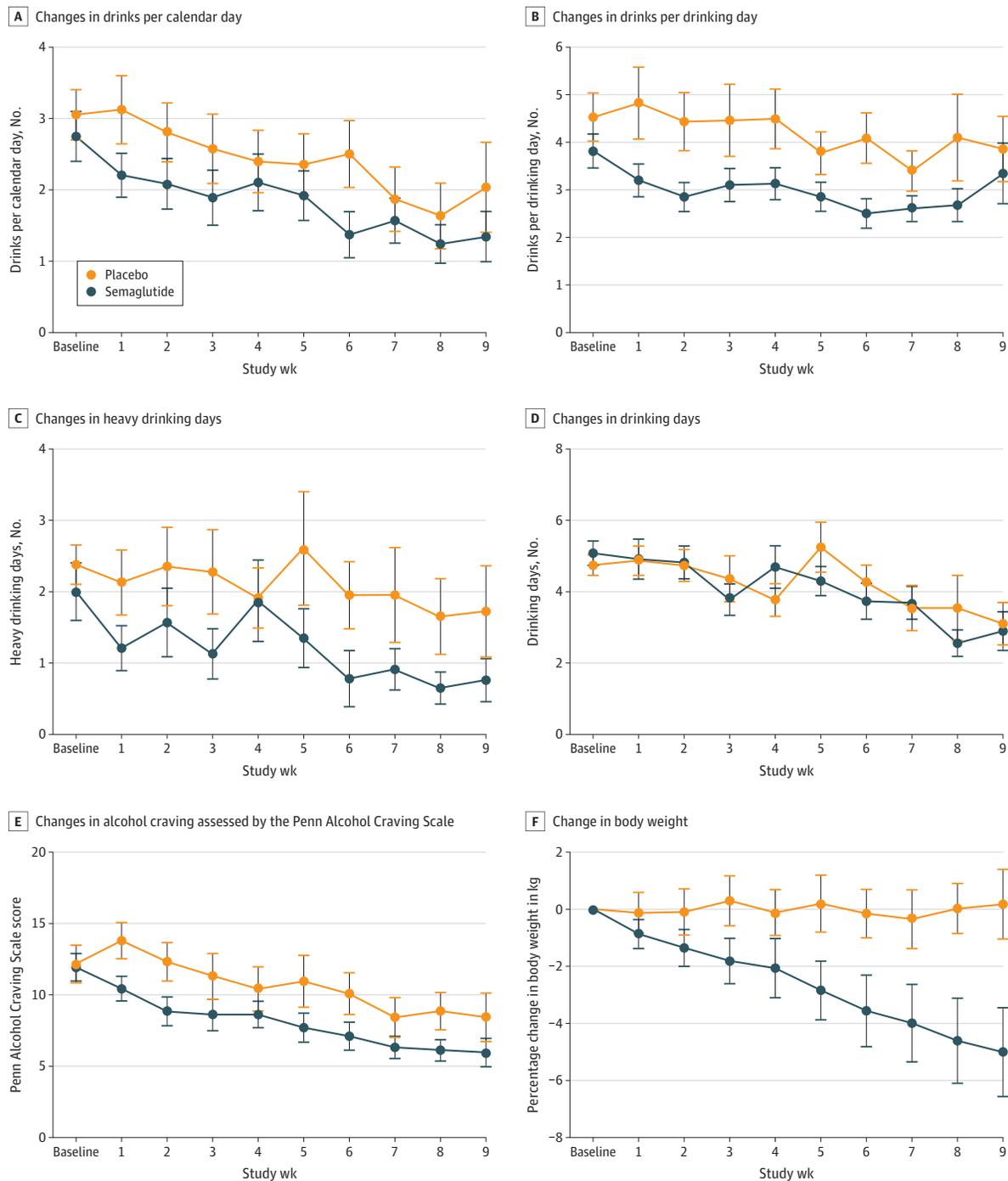
Discussion

Preclinical studies have demonstrated GLP-1RA-induced suppression of voluntary alcohol intake and attenuation of behavioral and neurochemical measures of alcohol reward.²³⁻²⁶ Although most of these studies tested older GLP-1RAs (including exenatide and liraglutide), recent studies show that semaglutide reduces self-administration in mice, rats, and nonhuman primates.³⁰⁻³³ Separately, anecdotal and media reports of incidental reductions in alcohol use, first noted with older GLP-1RAs,⁴⁴ have increased markedly alongside escalations

in semaglutide prescriptions.^{21,22} Off-label prescribing of GLP-1RAs for AUD is already reported, necessitating data from controlled trials.^{21,34}

This prospective clinical trial examined changes in laboratory and naturalistic alcohol consumption following weekly semaglutide treatment. Residualized change models of laboratory self-administration indicated that semaglutide reduced g-ETOH and peak BrAC among participants who engaged in a self-administration task at posttreatment, with evidence of medium to large effect sizes. Additionally, an exploratory analysis found that semaglutide reduced mean BrAC across the posttreatment self-administration session, with descriptive data suggesting the possibility of earlier de-escalation in consumption among participants treated with semaglutide, perhaps consistent with a satiety effect (Figure 2). For weekly drinking outcomes, medication effects on number of drinks per calendar day were nonsignificant; however,

Figure 3. Prospective Changes in Weekly Alcohol Outcomes



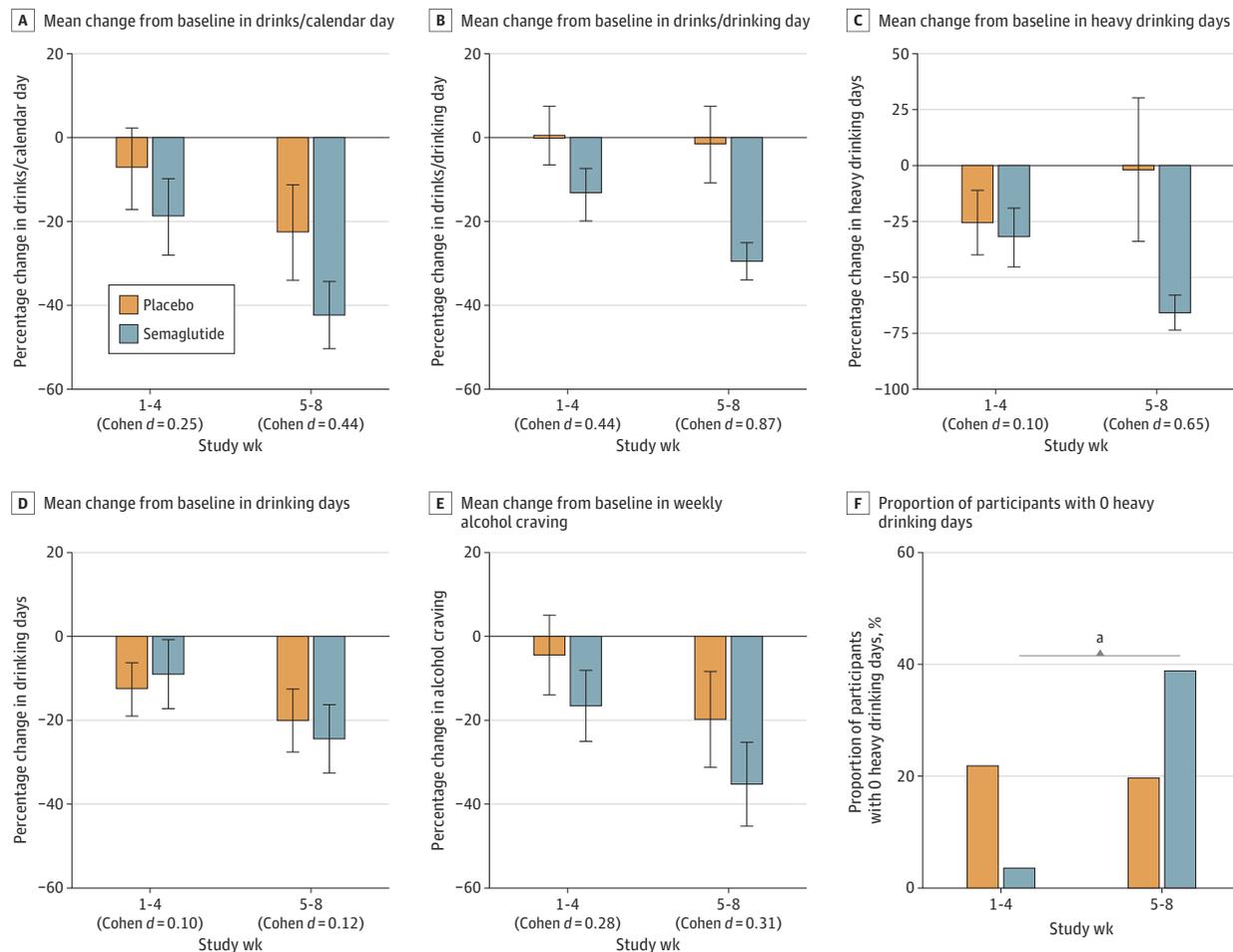
A, n = 39-48 across weeks (18-24 in the placebo group and 21-24 in the semaglutide group). B, n = 31-48 (15-24 in the placebo group and 16-24 in the semaglutide group). C, n = 39-48 (18-24 in the placebo group and 21-24 in the semaglutide group). D, n = 39-48 (18-24 in the placebo group and 21-24 in the semaglutide group). E, n = 41-48 (19-24 in the placebo group and 22-24 in the semaglutide group). F, n = 41-48 (19-24 in the placebo group and 22-24 in

the semaglutide group). Alcohol craving was measured via the Penn Alcohol Craving Scale (0-30). Data points depict group means and standard errors for weekly measurements of the outcome. Medication commenced at week 1. Weekly time points indicate data collected at the end of the week following that week's injection (eg, week 1 drinking data were measured at week 2 and reflect the week following the week 1 injection).

semaglutide significantly reduced alcohol craving and drinks per drinking day, also interacting with treatment week to predict reductions in heavy drinking days. Consequently, the pro-

portion of participants with zero heavy drinking days increased significantly in the semaglutide group across the 2 dose phases. Semaglutide did not alter the proportion of abstinent

Figure 4. Medication Group Differences in Weekly Drinking and Craving as a Function of Treatment Period



A-E, Bars depict group means for changes from baseline on alcohol consumption and craving outcomes during treatment weeks 1-4 (0.25 mg/wk) and 5-8 (0.5 mg/wk) and whiskers indicate standard errors. Effect size estimates (Cohen *d*) reflect medication vs placebo group differences on the outcomes presented. Conventional benchmarks are *d* = 0.20 for a small effect, *d* = 0.5 for a medium effect, and *d* = 0.8 for a large effect. Numbers of participants across weeks were 43-47 for all models (placebo: 23 in weeks 1-4

and 20 in weeks 5-8; semaglutide: 24 in weeks 1-4 and 23 in weeks 5-8). For visual presentation, panel C excludes the data from 1 participant with an extreme outlier >4 SD above the mean. F, Proportion of participants with zero heavy drinking days by treatment condition and dose (weeks 1-4, 0.25 mg/wk; weeks 5-8, 0.5 mg/wk).

^a*P* < .005.

vs drinking days. Though limited by a small subsample, an analysis of participants reporting current cigarette use revealed a significant medication-by-time interaction on changes in cigarettes per day.

Recent reports linking semaglutide or related drugs (including tirzepatide, a GLP-1/GIP dual receptor agonist) to alcohol-related outcomes have relied on observational or anecdotal data.^{22,45,46} The only prior randomized trial in an AUD sample⁴⁷ found that exenatide—the first approved GLP-1RA—did not reduce overall consumption, but exploratory analyses indicated potential efficacy within a high-BMI (≥ 30) subgroup.⁴⁷ Exploratory subgroup comparisons here (eFigure 3 in Supplement 2) did not indicate a similar pattern, suggesting the need to study efficacy across BMI levels. Although differences in sample characteristics or study design could contribute to differential evidence for efficacy across

these 2 trials, the superior efficacy of semaglutide vs exenatide is likely the simplest interpretation.

Preliminary estimates of medication effect sizes yielded notable findings. Effect sizes approximated the small range (Cohen *d* = 0.20) during weeks 1 to 4 (0.25 mg/week), increasing during weeks 4 to 8 (0.5 mg/week). Effect sizes for heavy drinking days and drinks per drinking day reached the large range (*d* > 0.80) at the 0.5 mg/week dose, with objective laboratory data also suggesting large effect sizes on self-administration. By comparison, approved (and effective) AUD medications, including naltrexone, generally show small effect sizes in both clinical trials^{15,48,49} and laboratory studies of self-administration and other outcomes.^{35,50} While preliminary, the current effect size estimates are promising, especially considering those observed for FDA-approved AUD treatments.^{51,52} These findings are especially notable in that this study used the 2 lowest clinical doses of semaglutide, whereas

doses for weight reduction reach 2.4 mg/week. Considering greater effects of semaglutide on other medical outcomes (eg, weight loss) with increasing dose and treatment duration, higher doses would presumably yield greater effects on alcohol reduction. However, safety profiles at higher doses in this population require careful evaluation. The extent of weight loss in the semaglutide group (~5% on average), though similar to that observed at these doses in populations with overweight or obesity, has additional safety risks for people with normal or low weight, necessitating evaluation of which doses (and which GLP-1RAs) optimally balance safety and efficacy in substance use disorder samples.

The focus on non-treatment-seeking participants has important considerations, one being that semaglutide-related reductions in drinking quantity occurred absent volitional attempts to reduce drinking. In contrast to treatment-seeking participants, this sample is arguably representative of the majority of those with AUD exposed to GLP-1RAs in general medical settings. Considering both the rapid adoption of GLP-1RAs and the demonstrated health benefits of net reductions in alcohol use,⁵³ GLP-1RA-related reductions in consumption—when considered at large scale—could lead to improved health outcomes that are not currently appreciated. Recent pharmacoepidemiology results⁵⁴ appear consistent with this possibility. Moreover, given low utilization of FDA-approved AUD therapies,¹¹ the number of those with AUD receiving GLP-1RA medications already greatly exceeds the number who receive FDA-approved AUD medications. In this context, the broad uptake of GLP-1RAs presents an ideal scenario for medication repurposing, with potential to help reduce the wide treatment gap associated with AUD.

Evidence that semaglutide showed minimal effects on proportion of drinking vs abstinence days—with the largest effect sizes observed for drinking quantity and heavy drinking—also has possible clinical implications. The potential for selective effects on quantitative reductions in drinking could render GLP-1RAs well suited to nonabstinence goals,^{14-16,53} which are a preferred treatment goal for many with AUD. Notably, laboratory self-administration results also suggested no medication effects on delay time or abstinence (eResults in Supplement 2). Studies with treatment-seeking samples are needed to determine whether GLP-1RAs can facilitate abstinence or prevent relapse.

Though limited by a small subsample, a notable secondary finding was evidence for medication-related reductions in cigarettes per day among those reporting cigarette use. Based on preclinical evidence that GLP-1RAs reduce voluntary nicotine self-administration,⁵⁵ recent studies have evaluated GLP-1RAs for smoking cessation and prevention of postcessation

weight gain.^{56,57} Should GLP-1RAs prove efficacious for both alcohol reduction and smoking cessation, potential health implications could be substantial. Alcohol and cigarette use (along with obesity) are leading preventable causes of mortality and preventable cancer deaths,^{58,59} making individuals who smoke and drink heavily—including those with overweight or obesity—a priority population.⁶⁰⁻⁶² Despite efforts to advance pharmacotherapies for concurrent AUD and tobacco use disorder,⁶³⁻⁶⁶ no medication is approved for both conditions.⁶²

Limitations

Among several study limitations are the modest sample size and short-term treatment duration, both reflecting the phase 2 stage of this trial. The use of low-dose semaglutide to maximize safety and feasibility likely limited detection of significant effects. However, the effect sizes observed at low doses are encouraging and provide information for estimating sample sizes for future trials. Another limitation is the moderate level of AUD severity of this sample, with consumption levels below those of most treatment-seeking samples. While this sample might reasonably approximate populations encountered in general medical settings, studies with heavier drinkers are necessary. Larger trials that address these questions while prioritizing FDA-accepted efficacy end points⁴⁰ will ultimately inform the potential of GLP-1RAs as an emergent class of AUD therapies.^{21,34}

Conclusions

Since the FDA approval of the first AUD medication (disulfiram) in 1951, only 2 medications (naltrexone and acamprostate) have received subsequent FDA approval for AUD.^{12,52} The rate of 1 new approval every 20 to 25 years is inadequate and is in stark contrast with the pace of FDA approvals for diabetes medications, which now outnumber AUD medication approvals 20-fold. Should additional phase 2 and phase 3 clinical trials support repurposing 1 or more GLP-1RAs for AUD, these treatments could have broad clinical infiltration, with potential to bypass many traditional impediments to the uptake of AUD medications, including low public and provider awareness and stigma toward AUD treatments. Importantly, the increasing clinical uptake of GLP-1RAs would presumably reduce prescribing barriers, including in primary care, where AUD treatments have proven difficult to bring to scale. These possibilities call for larger clinical trials to evaluate efficacy of GLP-1RAs and other incretin therapies for AUD. Given numerous GLP-1RAs at various stages of development, future studies need not be limited to a single medication.

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