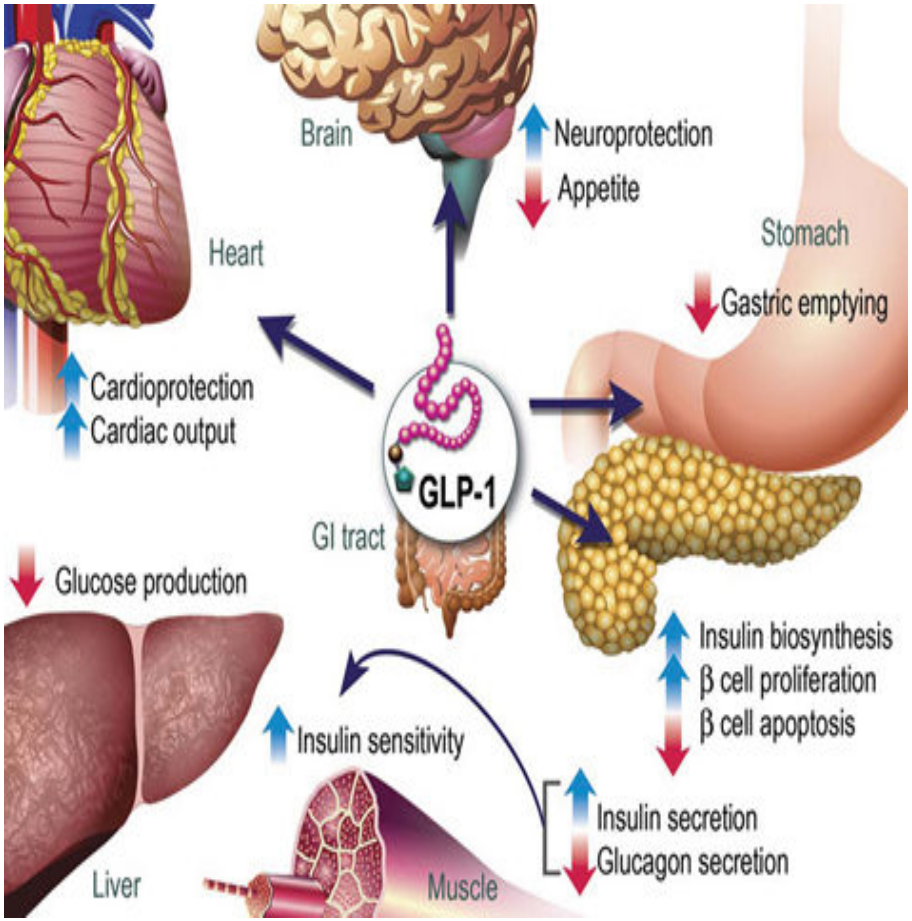
GLP-1 receptor agonists and the addicted brain

11.06.2025

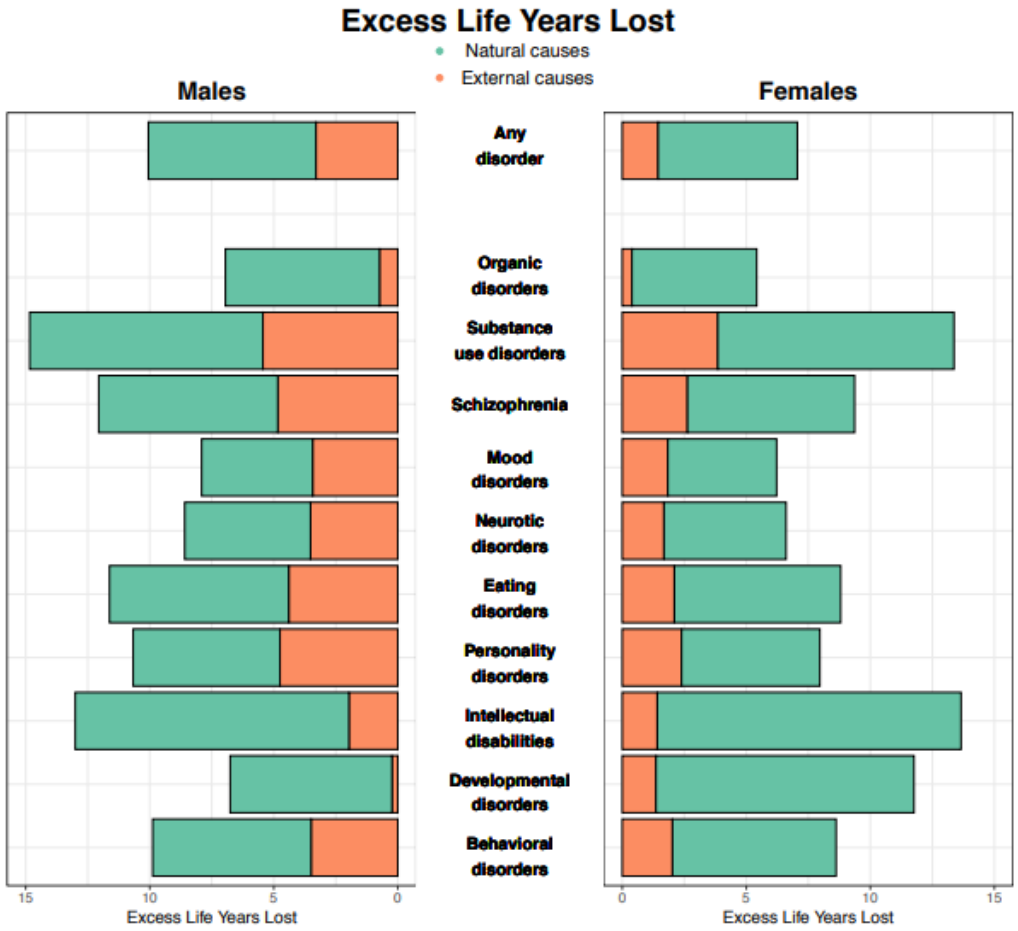
Anders Fink-Jensen, University of Copenhagen, Denmark

Glucagon-Like Peptide-1 (GLP-1)



Daniel J. Drucker, Cell Metabolism, 2006

Natural causes (e.g. general medical conditions) contribute to substantial part of the Excess Life Years Lost among patients with schizophrenia

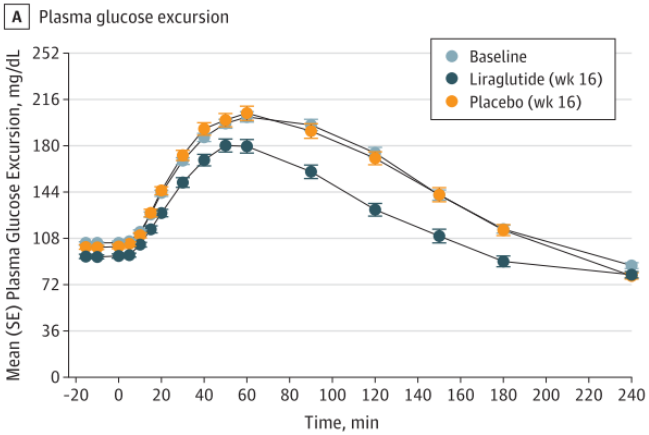


Plana-Ripoll et al. Lancet 2019

Effect of Liraglutide on Prediabetes in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial

Change in End Points between Baseline and Week 16.*

	Liraglutide n=47	Placebo n=50	Change between baseline and week 16 Liraglutide vs. placebo †	P Value
Clinical				
Body weight (kg)	-4.7 ± 0.5	0.5 ± 0.7	-5.3 (-7.0 to -3.7)	<0.001
Waist circumference (cm)	-4.0 ± 0.6	0.5 ± 0.7	-4.1 (-6.0 to -2.3)	<0.001
Body mass index (kg/m^2)	-1.6 ± 1.2	0.08 ± 0.2	-1.8 (-2.4 to -1.3)	<0.001



64% went from Prediabetes to non-Prediabetes in the liraglutide group compared to 16% in the placebo group

Larsen et al. JAMA Psychiatry 2017

Case reports type 2 DM patients 2010-2011

Medical treatment of Alcohol Use Disorder

GLP-1 and the reward circuitry

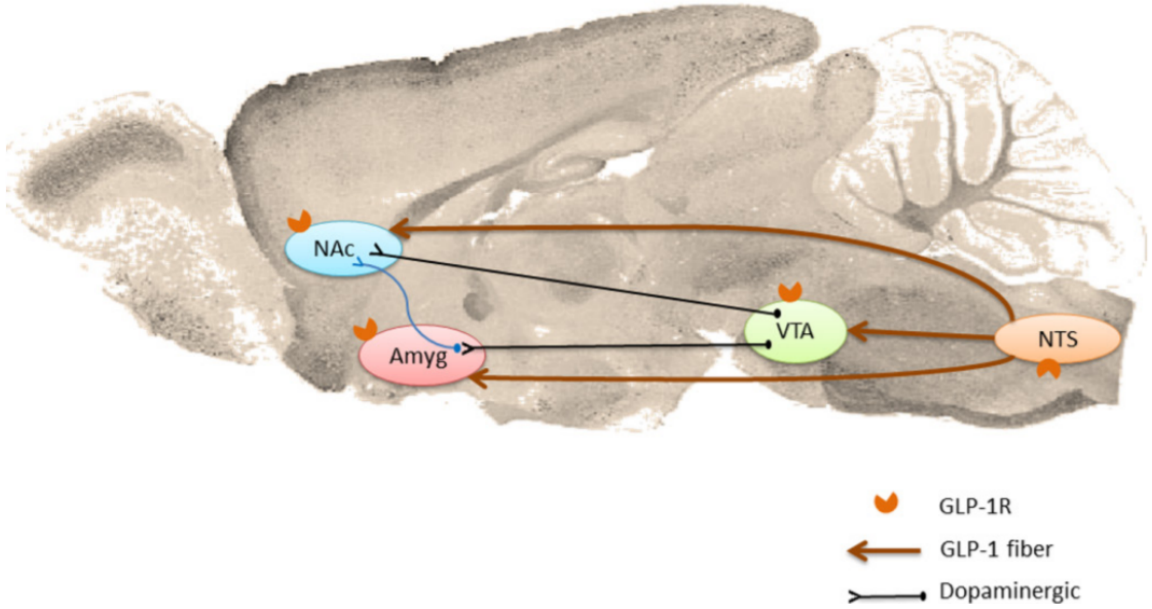
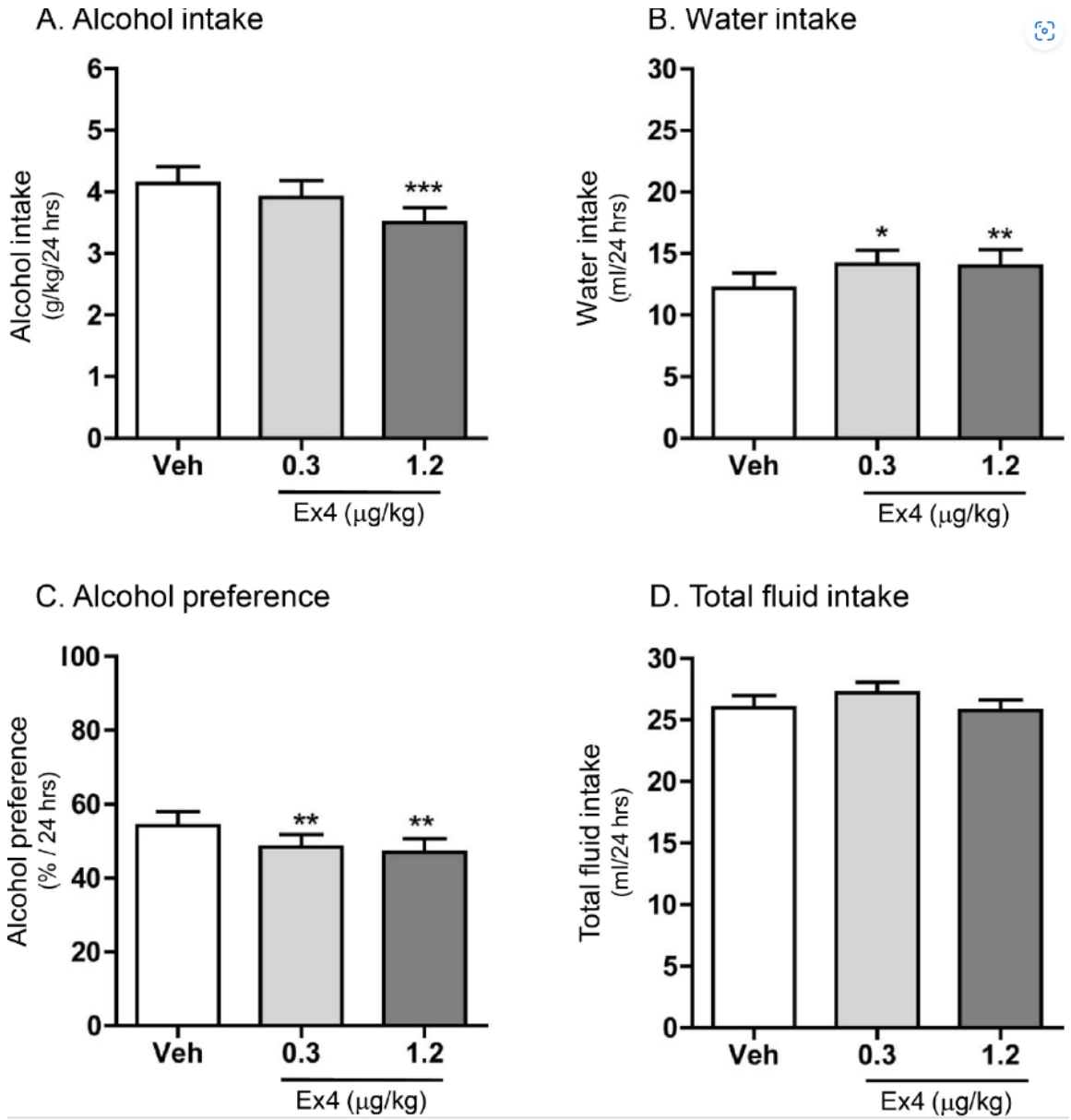


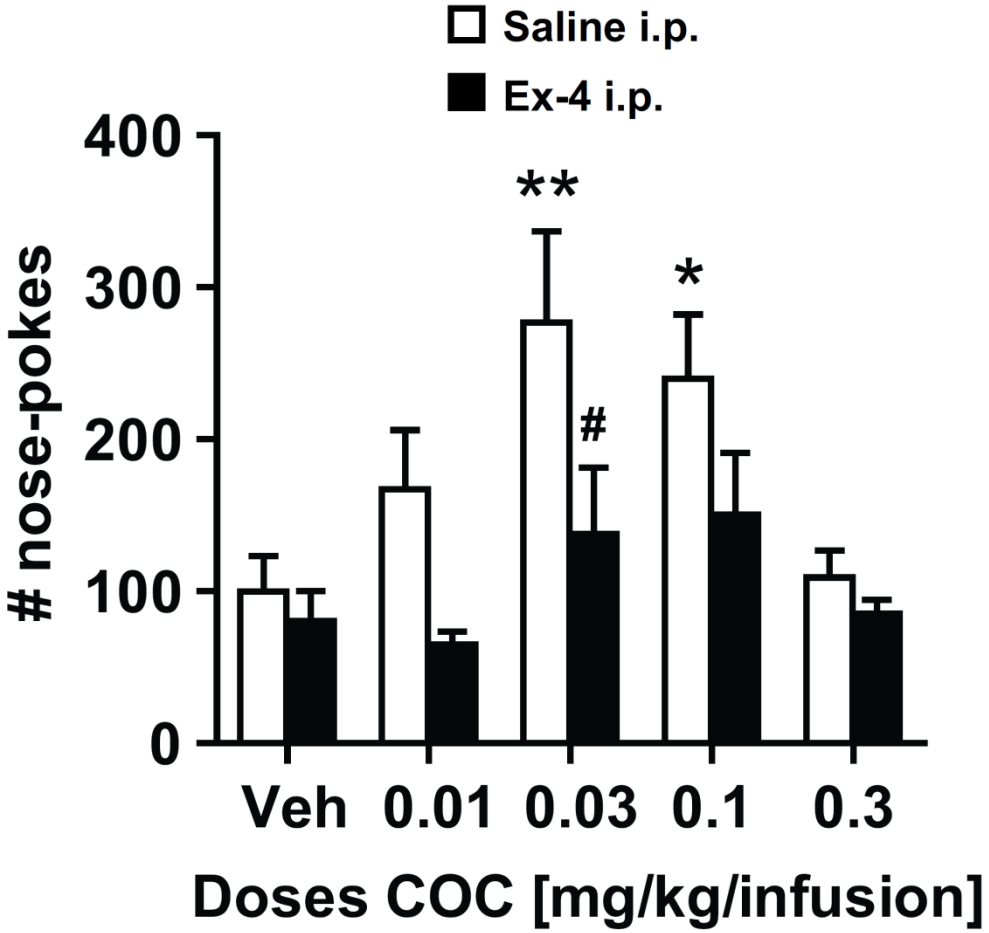
Figure 1. GLP-1 projection to mesocortico-limbic system. NTS (Nucleus of solitary tract), VTA (Ventral tegmental area), NAc (Nucleus accumbens), and Amyg (Amygdala).

Exendin-4 (Exenatide) and the Gila monster (Heloderma suspectum)

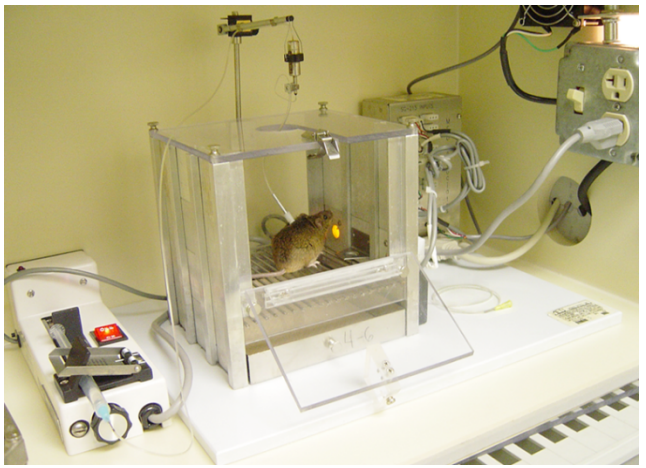


Egecioglu et al. Psychoneuroendocrinology, 2013

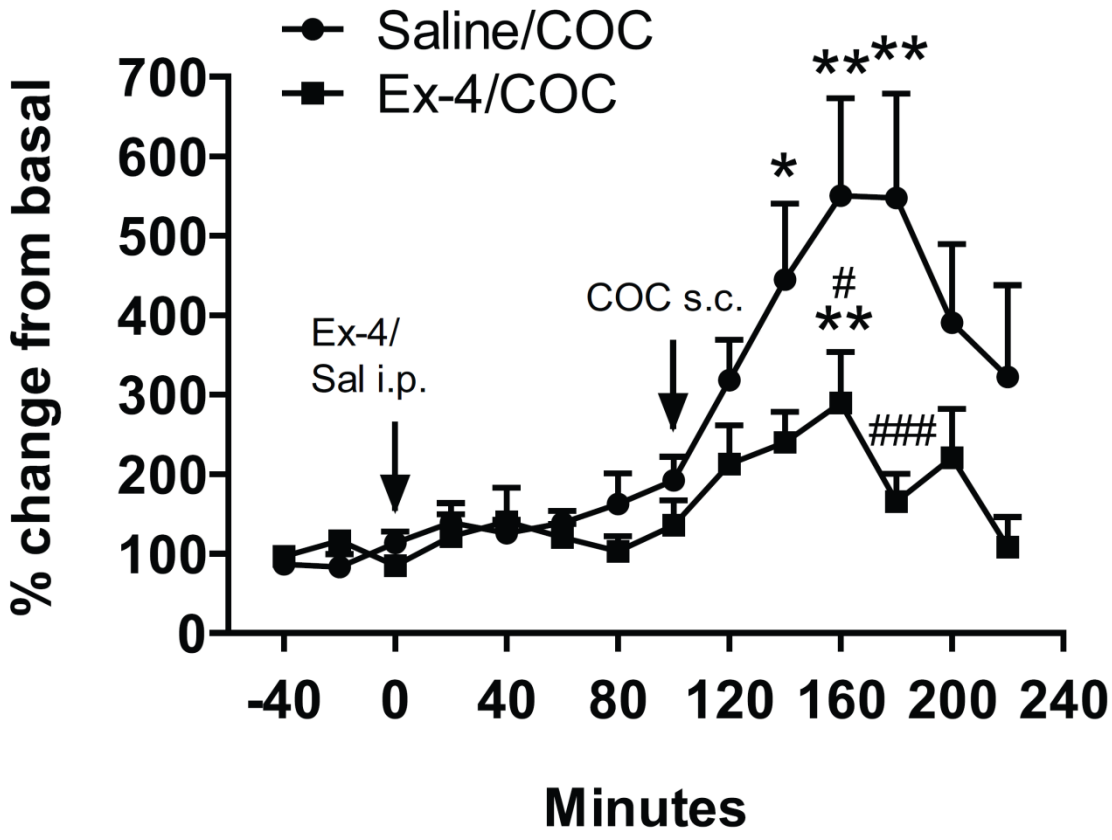
B

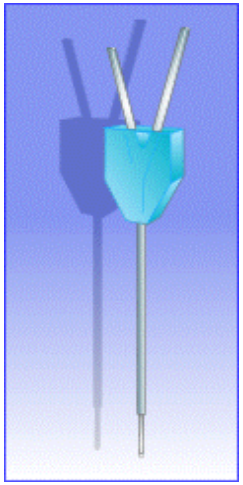


Pre-treatment with Ex-4 at 30 µg/kg i.p. shifted cocaine's dose-effect curve downward.



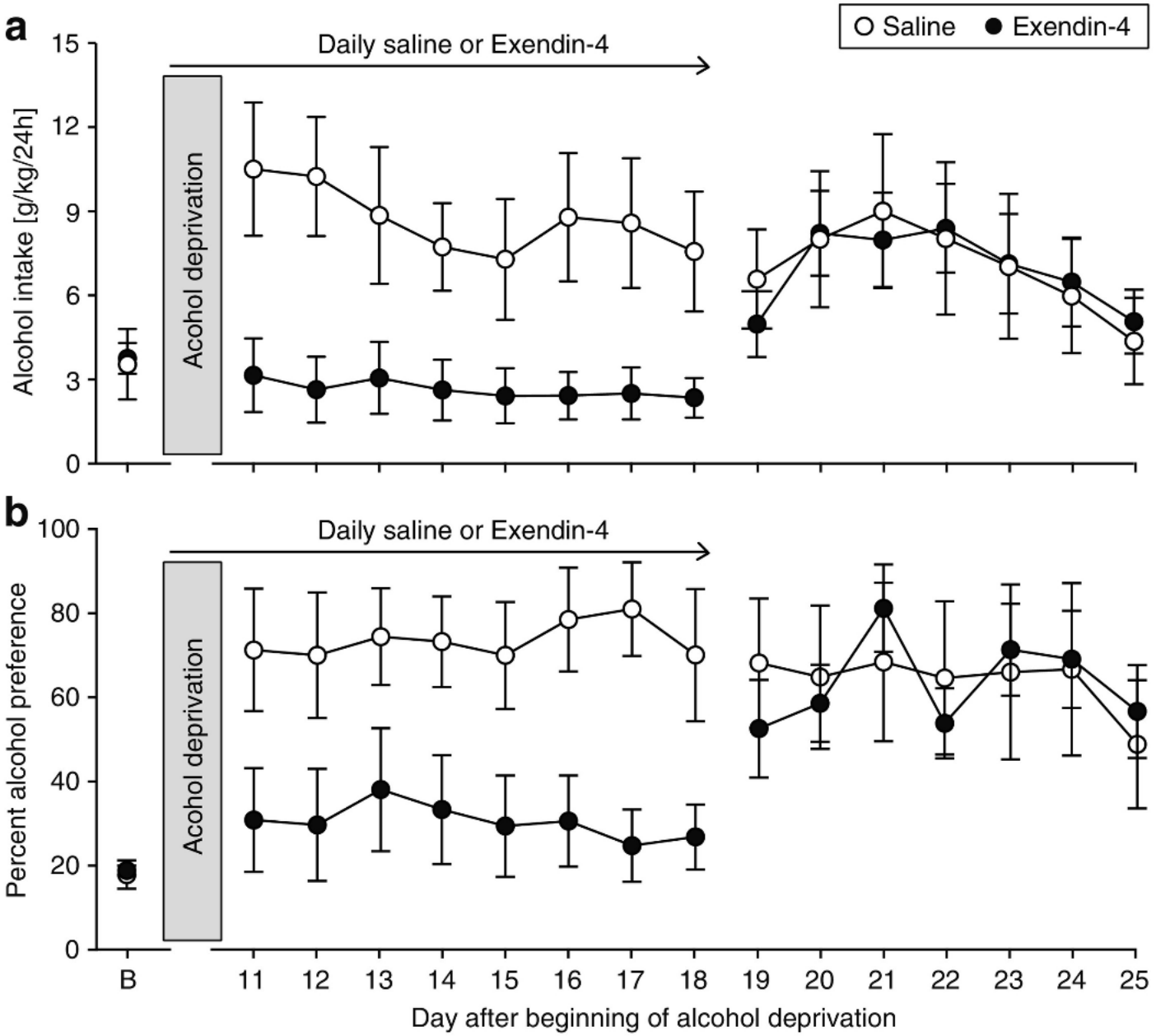
Sorensen et al. Physiology and behaviour 2015





Cocaine 30 mg/kg induced a significant increase in extracellular dopamine compared to basal levels. Ex-4 (30 µg/kg) significantly decreased the cocaine-induced dopamine efflux.

Sørensen et al. Physiology and behaviour 2015

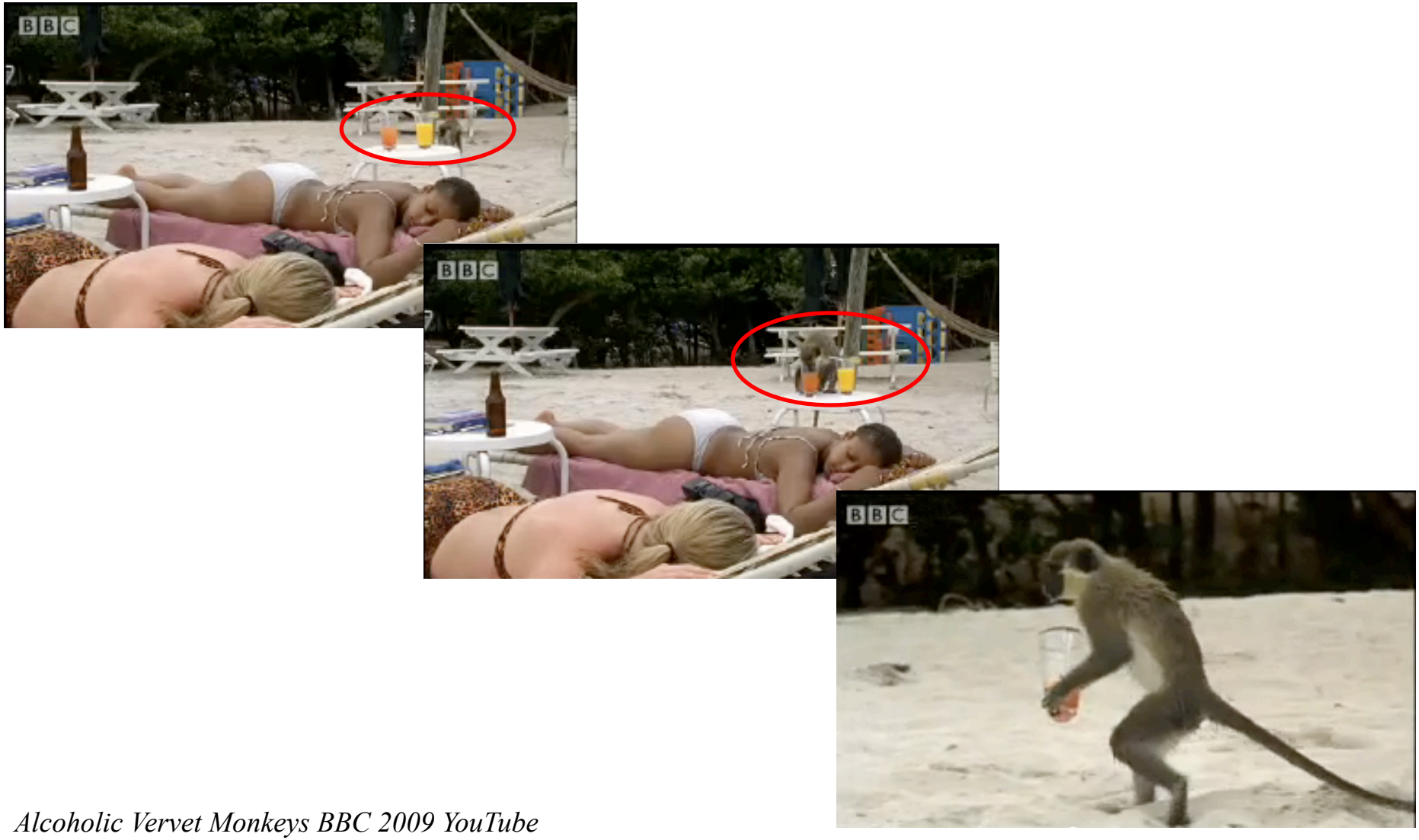


Thomsen et al. Pharmacol Biochem Behav. 2017

The Vervet Monkey (*Cercopithecus aethiops*) St. Kitts

St Kitts, Eastern Caribbean

Vervet Monkeys BBC YouTube



Alcoholic Vervet Monkeys BBC 2009 YouTube

BEHAVIOURAL SCIENCE FOUNDATION

Caribbean Primate Laboratory

BOX 428 ST KITTS, EASTERN CARIBBEAN

869-465-7280 (voice) 869-465-1089 (FAX)

Roberta Palmour

Academic title(s):

Professor, Department of Human Genetics, Department of Psychiatry

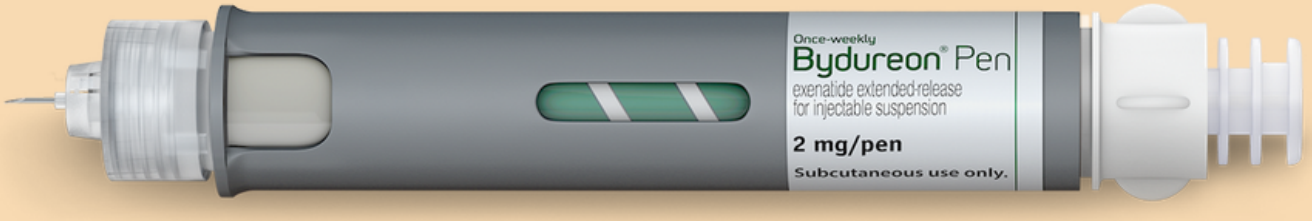

SUPERIOR
HIGH
WINE
DEMERARA
DISTILLERS
LIMITED
DEMERARA GUYANA
PRODUCT OF GUYANA
750 ml
69% ALC./VOL.

Effects of the GLP-1 receptor agonists exenatide (Bydureon®) and liraglutide (Victoza®) on alcohol consumption in African Vervet Monkeys

Thomsen et al. Psychopharmacology 2019

Exenatide (Bydureon®)
2.0 mg s.c. once weekly

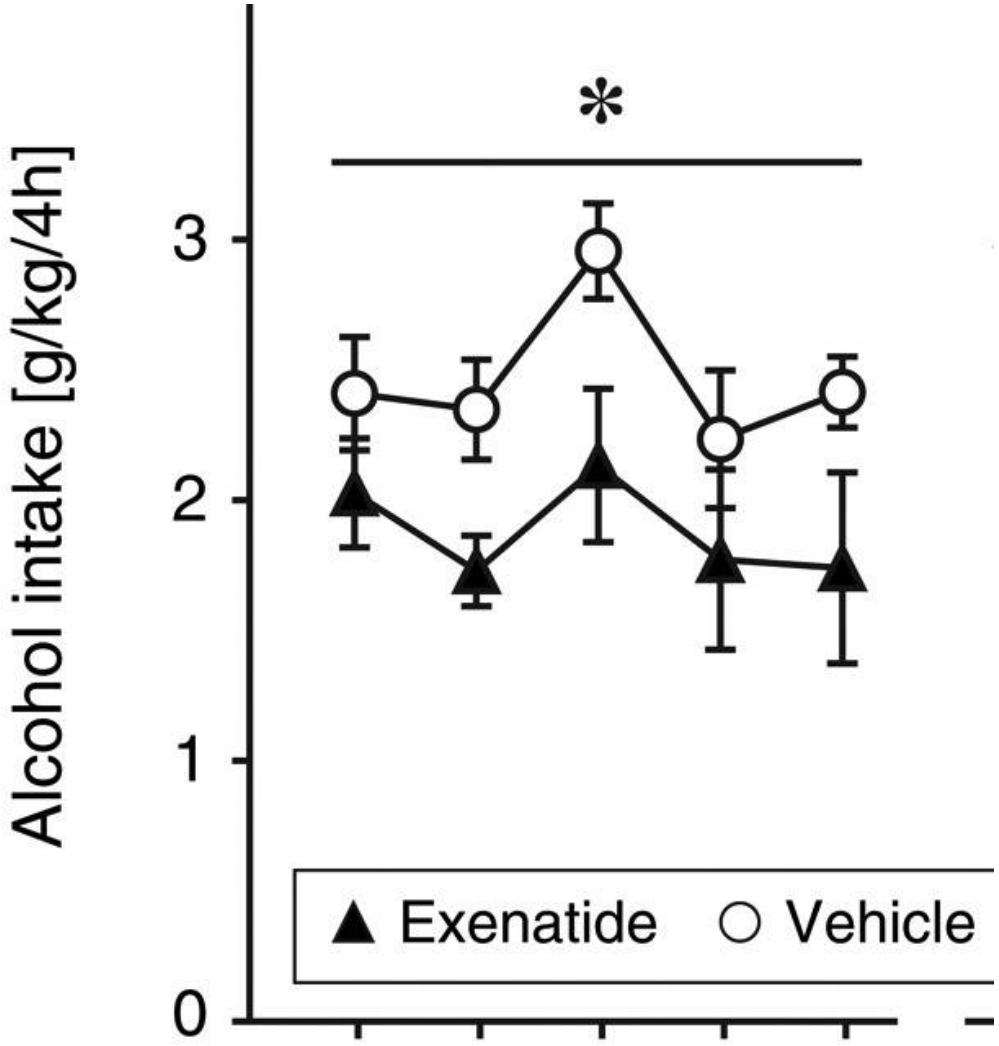
- Once-weekly, single-dose, prefilled pen with no titration
- Designed to be patient-friendly
- Can be used any time of day, with or without meals



Storage

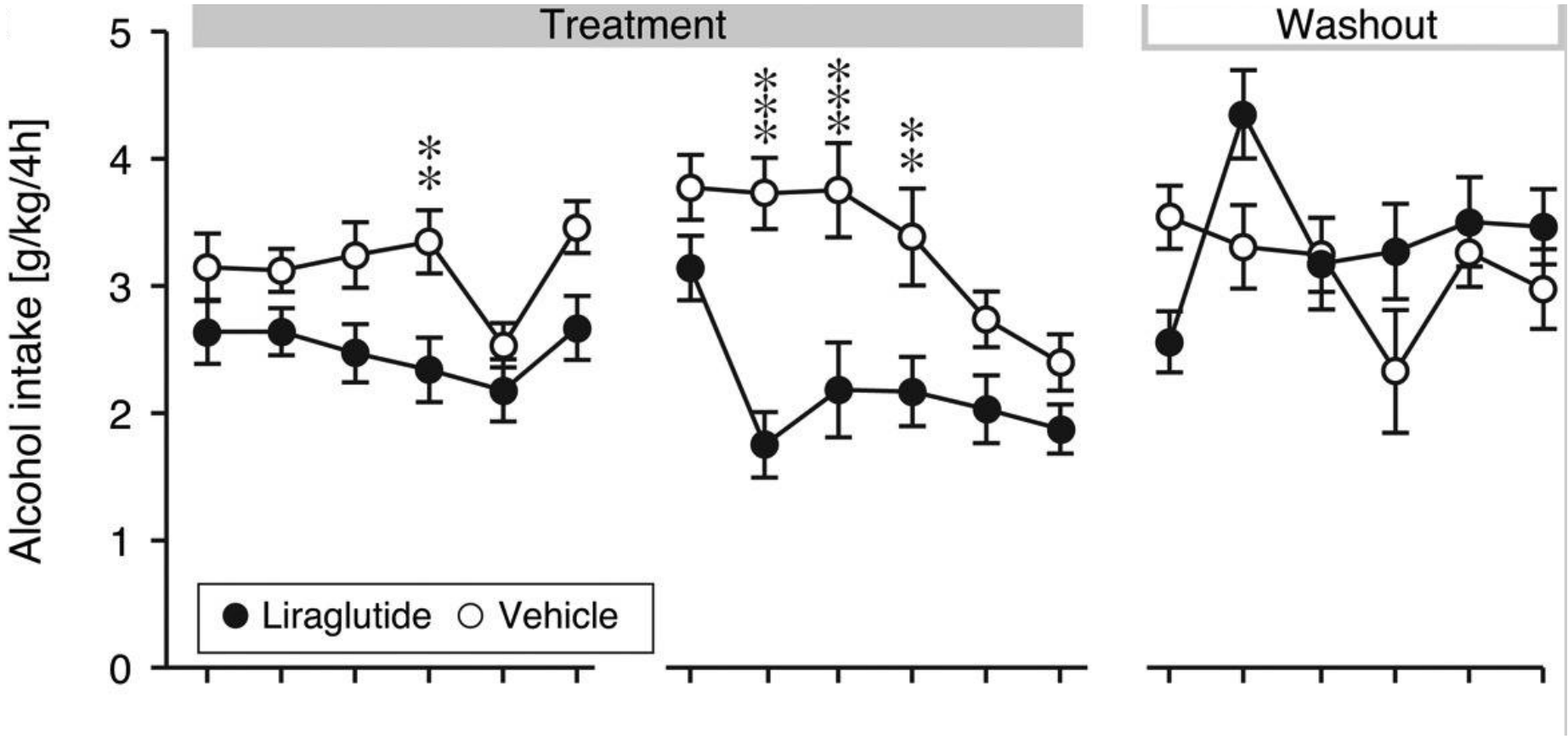
- Refrigerate 36°F to 46°F (2°C to 8°C)
- Do not freeze or use BYDUREON if it has been frozen
- Do not use BYDUREON past the expiration date
- Protect BYDUREON from light

Effect of exenatide, 0.04 mg/kg s.c. once weekly on alcohol consumption in African Vervet Monkeys



Liraglutide (Victoza®)
1.8 mg s.c. once daily

Effect of liraglutide, 0.05 mg/kg s.c. once daily on alcohol consumption in African Vervet Monkeys



Does Glucagon-like Peptide 1 (GLP-1) Receptor Stimulation Reduce Alcohol Intake in Patients With Alcohol Use Disorder?

Study design

- **Double-blind, randomized, placebo-controlled, 26-weeks clinical trial**

Patients

- **Out patients with a diagnosis of alcohol dependence between age 18 years and 70 years**

Sample size

- **In total 127 patients and 25 healthy subjects were included**

JCI insight

About Editors Consulting Editors For authors Publication ethics Transfers Advertising Job board Contact

Current issue Past issues By specialty Videos Collections JCI This Month

Clinical Medicine In-Press Preview Clinical trials Neuroscience Open Access | 10.1172/jci.insight.159863

Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial

Mette K. Klausen,[1] Mathias E. Jensen,[1] Marco Møller,[1] Nina le Dous,[1] Anne-Marie Ø Jensen,[1] Victoria A. Zeeman,[1] Claas-Frederik Johannsen,[1] Alycia M. Lee,[2] Gerda K. Thomsen,[3] Julian Macoveanu,[1] Patrick M Fisher,[3] Matthew P. Gillum,[4] Niklas R. Jørgensen,[5] Marianne L. Bergmann,[6] Henrik Enghusen Poulsen,[7] Ulrik Becker,[8] Jens Juul Holst,[9] Helene Benveniste,[10] Nora D. Volkow,[11] Sabine Vollstädt-Klein,[12] Kamilla W. Miskowiak,[13] Claus T. Ekstrøm,[14] Gitte M. Knudsen,[3] Tina Visboll,[15] and Anders Fink-Jensen[1]

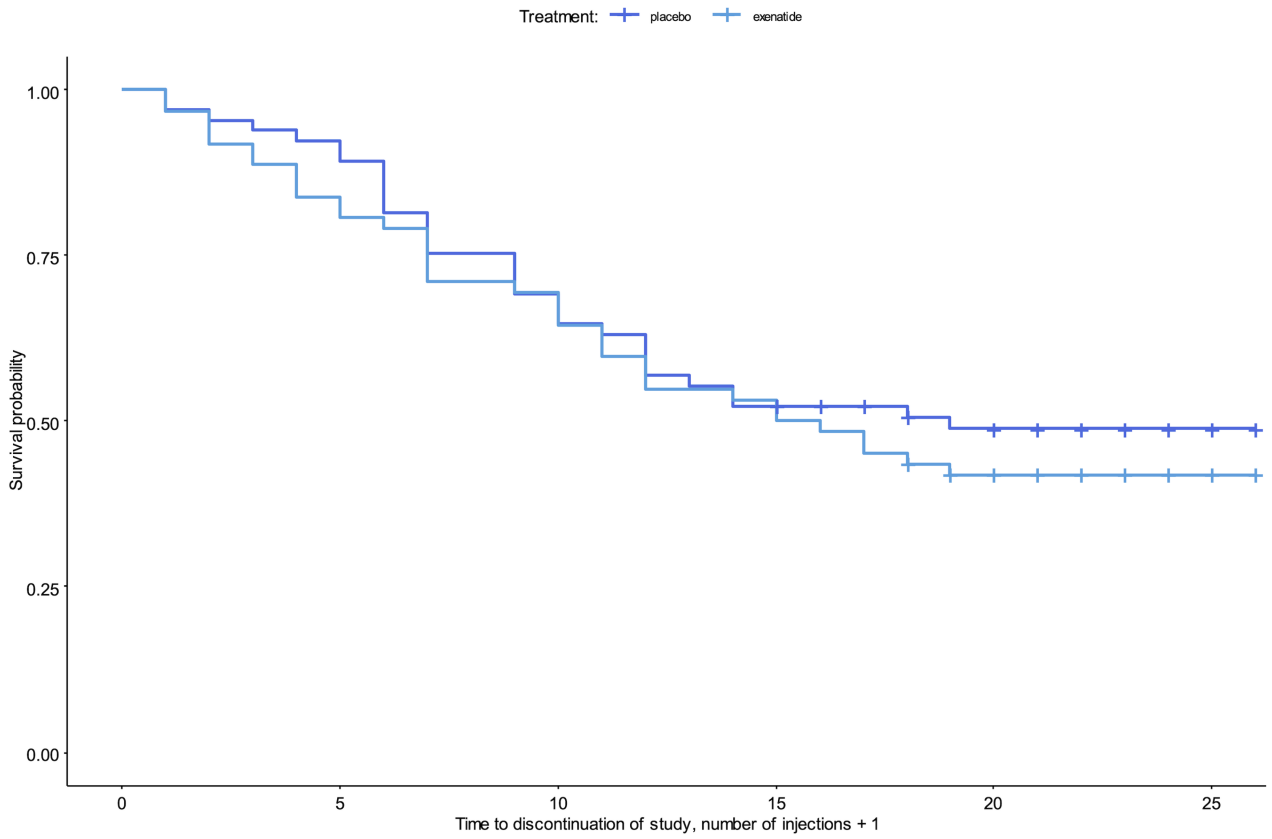
Published September 6, 2022 - More info

Table 1. Baseline demographic and clinical characteristics

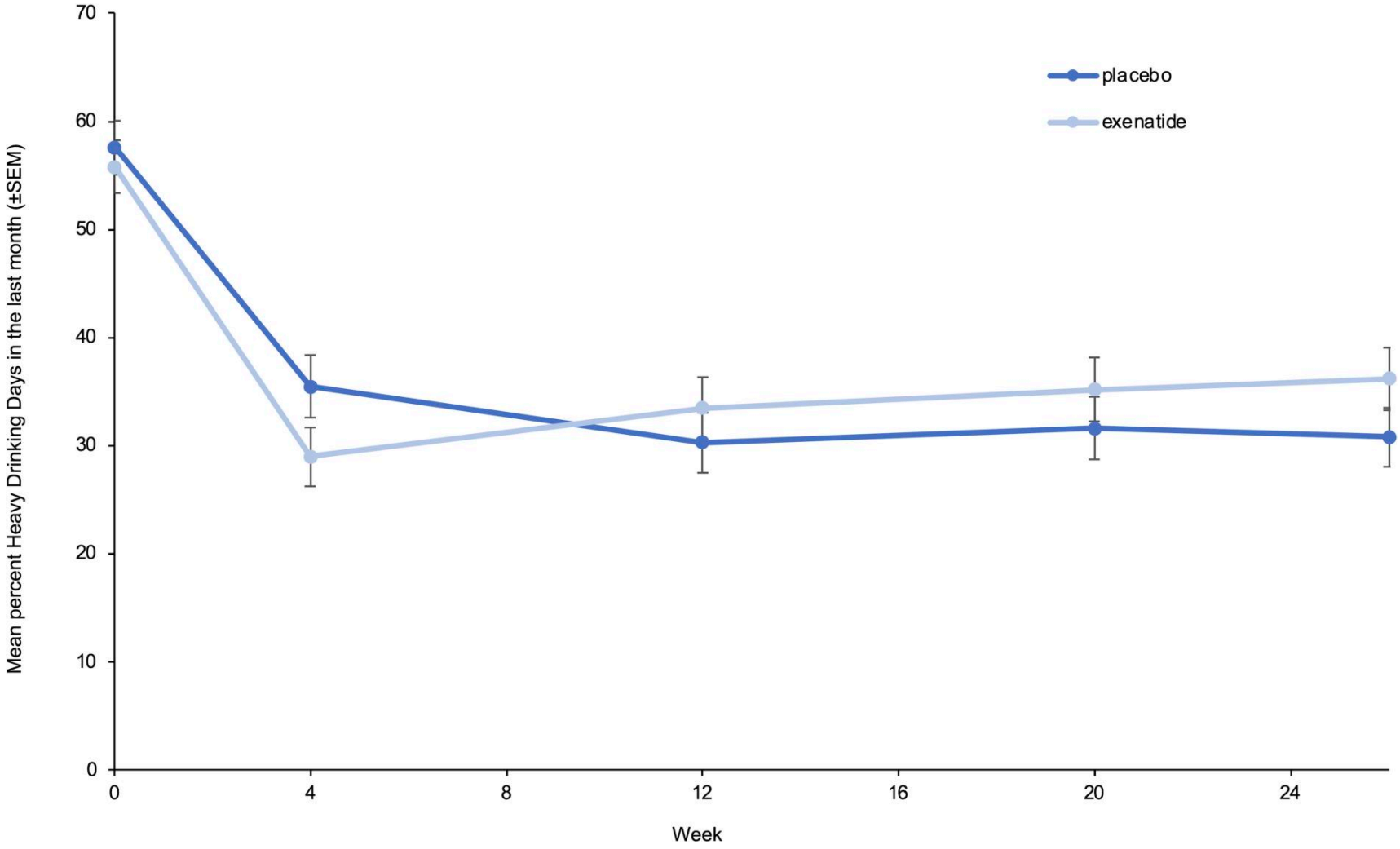
	Characteristics	Placebo (*n* = 65)	Exenatide (*n* = 62)
Sex[A]	Male, no. (%)	39 (60.0%)	37 (59.7%)
	Female, no. (%)	26 (40.0%)	25 (40.3%)
Age	Mean (SD)	52.5 (10.0)	52.1 (10.8)
	[A]Under 40 years of age, no. (%)	7 (10.8%)	8 (12.9%)
	[A]40 years of age and above, no. (%)	58 (89.2%)	54 (87.1%)
Social status	Cohabitation/married, no. (%)	36 (55.4%)	32 (51.6%)
	Data missing, no. (%)	1 (1.5%)	0 (0.0%)
Job	Job, no. (%)	31 (47.7%)	30 (48.4%)
	Data missing, no. (%)	19 (29.2%)	19 (30.6%)
Education	Lower secondary school, no. (%)	7 (10.9%)	9 (14.5%)
	Upper secondary school, no. (%)	3 (4.7%)	2 (3.3%)
	Vocational education/short-cycle higher education, no. (%)	22 (34.4%)	25 (40.3%)
	Medium-cycle higher education/higher education, no. (%)	32 (50.0%)	26 (41.9%)
AUDIT	Mean (SD)	25.9 (5.2)	25.6 (5.7)
ICD-10 Alcohol dependence	3 symptoms, no. (%)	14 (21.5%)	14 (22.6%)
	4 symptoms, no. (%)	16 (24.6%)	17 (27.4%)
	5 symptoms, no. (%)	16 (24.6%)	20 (32.3%)
	6 symptoms, no. (%)	19 (29.3%)	11 (17.7%)
DSM-5 Alcohol use disorder	Mild (2–3 symptoms), no. (%)	4 (6.2%)	7 (11.3%)
	Moderate (4–5 symptoms), no. (%)	7 (10.7%)	5 (8.1%)
	Severe (>5 symptoms), no. (%)	54 (83.1%)	50 (80.6%)
Heavy drinking days	Mean (SD)	17.3 (8.5)	16.7 (8.2)
Heavy drinking days, randomization strata	[A]5–11 heavy drinking days, no. (%)	22 (33.8%)	22 (35.5%)
	[A]12–17 heavy drinking days, no. (%)	13 (20.0%)	13 (21.0%)
	[A]18–23 heavy drinking days, no. (%)	10 (15.4%)	10 (16.1%)
	[A]24–30 heavy drinking days, no. (%)	20 (30.8%)	17 (27.4%)
Days without alcohol consumption/30 days	Mean (SD)	9.92 (7.9)	9.11 (7.3)
Total alcohol consumption (grams of alcohol/30 days)	Mean (SD)	2,430 (1,860)	2,370 (1,580)
Weight (kg)	Mean (SD)	82.1 (15.4)	82.8 (18.9)
BMI (kg/m^2)	Mean (SD)	26.7 (4.6)	26.7 (5.2)
HbA1c (mmol/mol)	Mean (SD)	33.2 (3.9)	34.9 (4.1)

AUDIT, Alcohol Use Disorders Identification Test; ICD-10, International Classification of Diseases, Tenth Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; BMI, body mass index (calculated as weight in kilograms divided by height in square meters); HbA1c, glycated hemoglobin.
[A]Randomization strata.

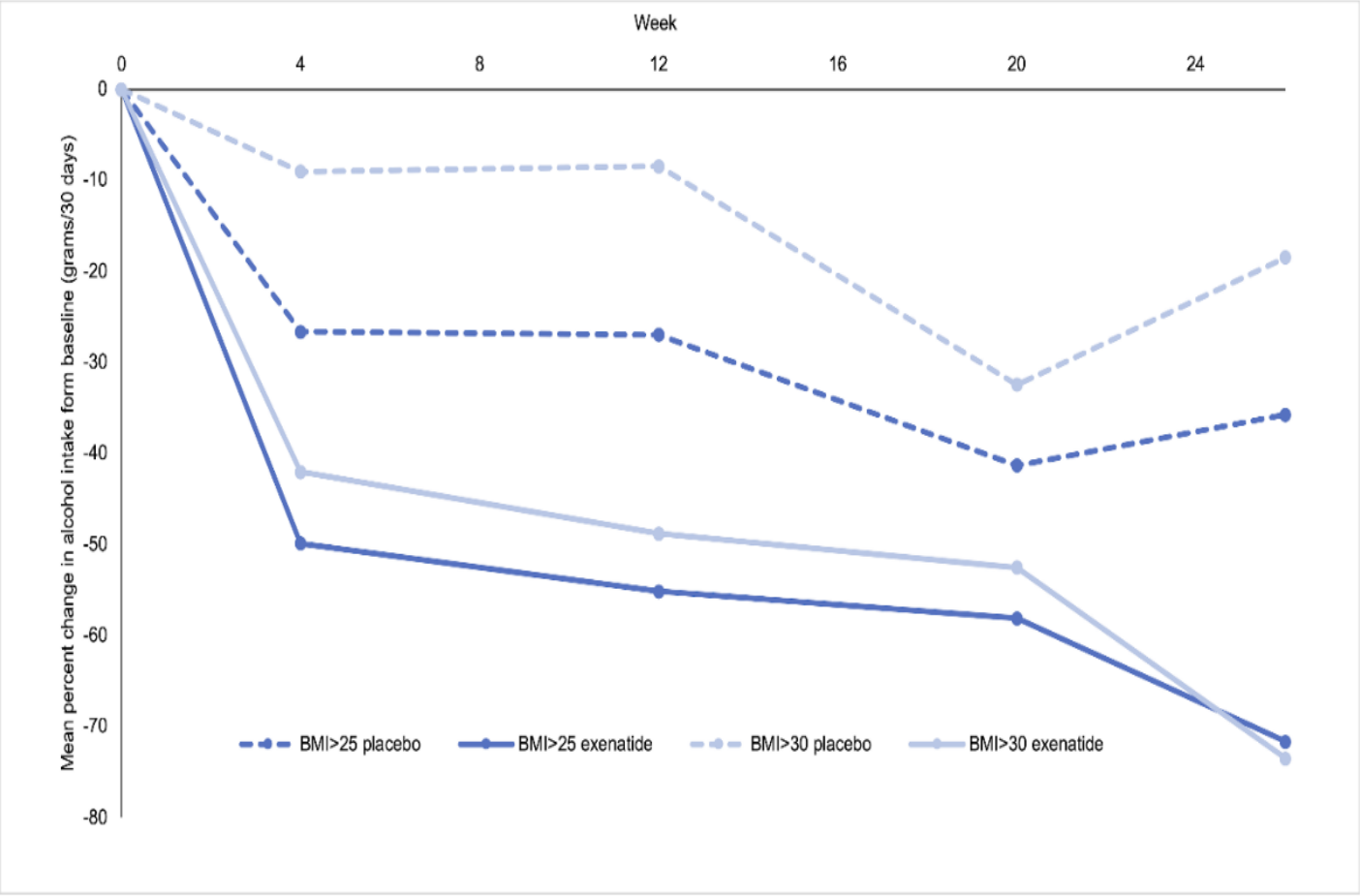
Kaplan-Meier survival curve of patients who withdrew from the trial or were lost to follow-up



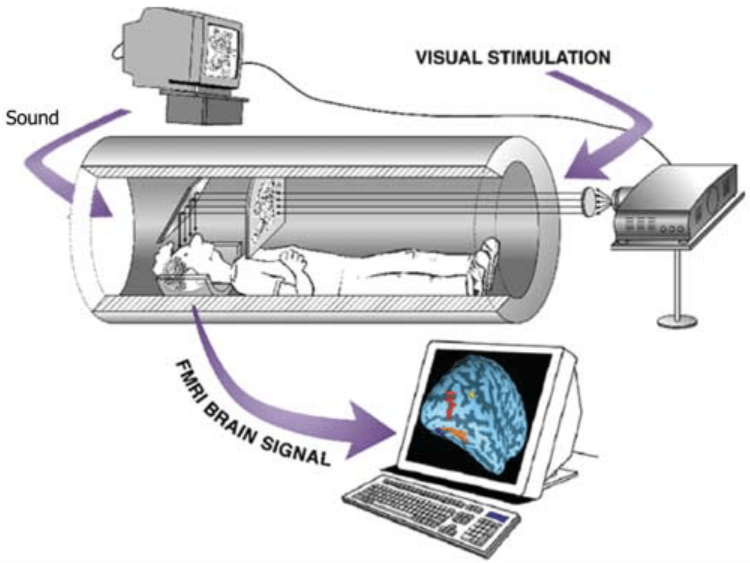
Reduction in heavy drinking days



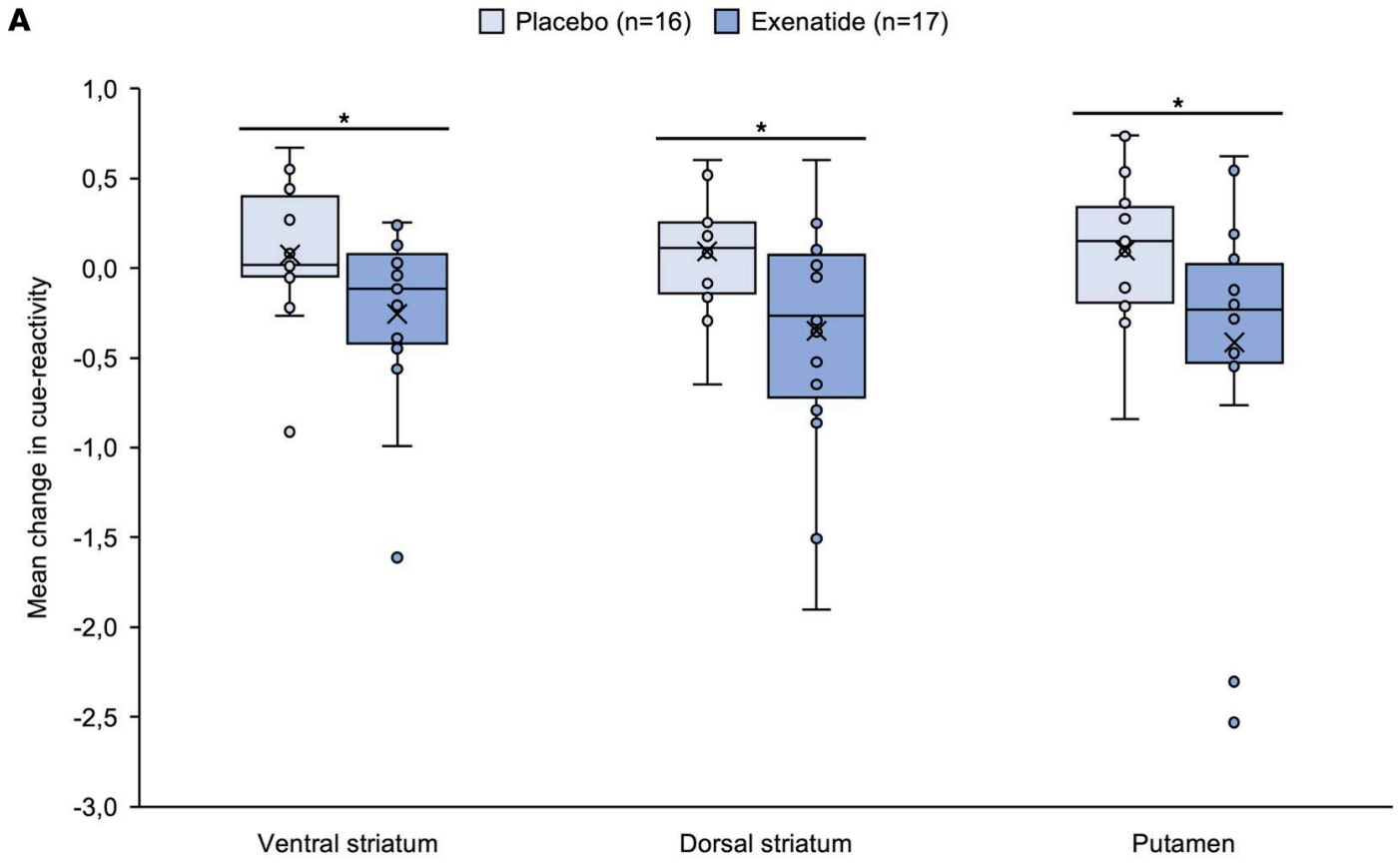
Change in mean percent total alcohol intake in BMI subgroups from baseline to week 26



Functional Magnetic Resonance Imaging (fMRI)

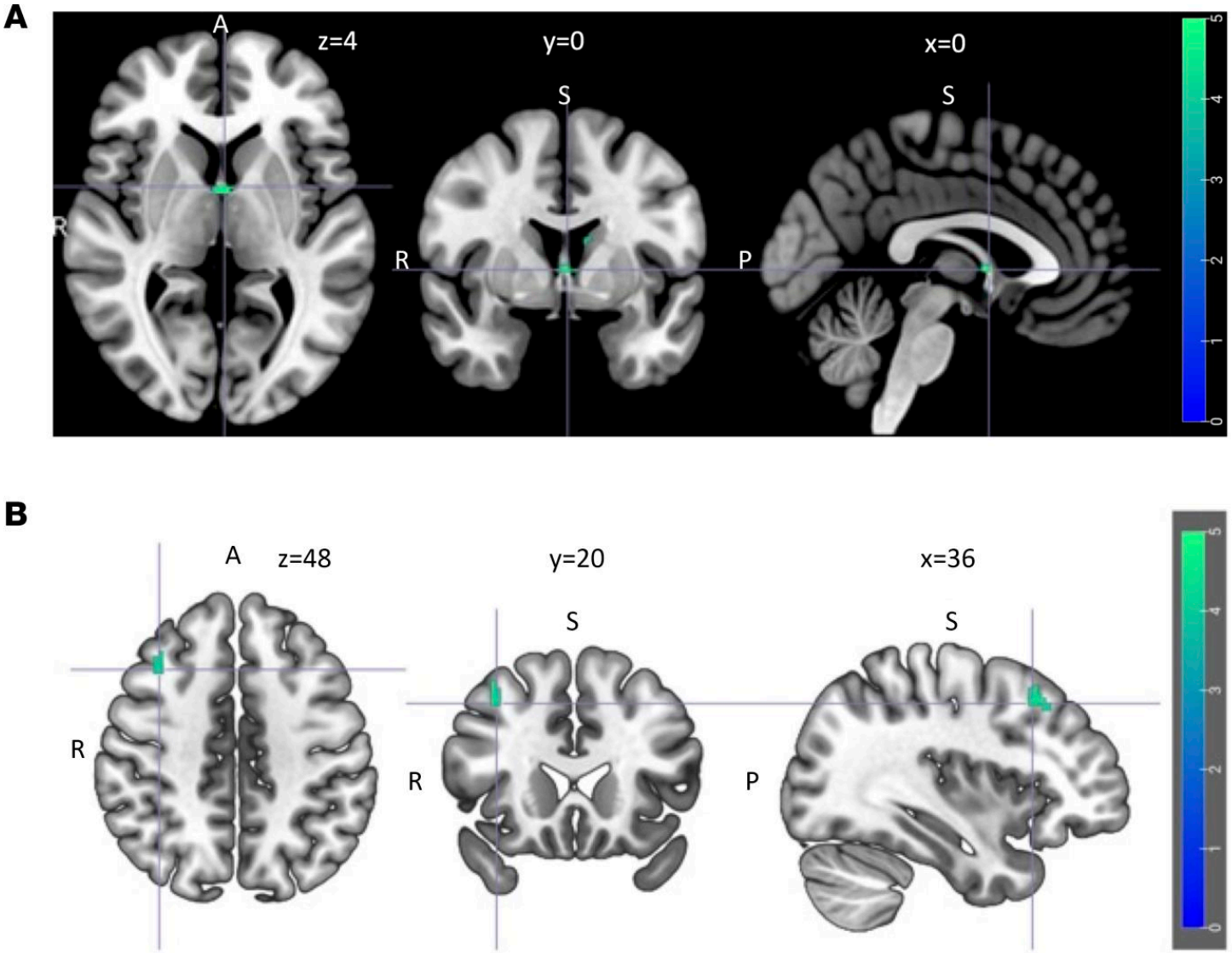


fMRI ALCUE ROI results



fMRI ALCUE whole-brain results

Septal area, left caudate, right middle frontal gyrus



POSITIVE REINFORCEMENT PRODUCED BY ELECTRICAL STIMULATION OF SEPTAL AREA AND OTHER REGIONS OF RAT BRAIN[1]

JAMES OLDS[2] AND PETER MILNER

McGill University

Stimuli have eliciting and reinforcing functions. In studying the former, one concentrates on the responses which come after the stimulus. In studying the latter, one looks mainly at the responses which precede it. In its reinforcing capacity, a stimulus increases, decreases, or leaves unchanged the frequency of preceding responses, and accordingly it is called a reward, a punishment, or a neutral stimulus (*cf.* 16).

Previous studies using chronic implantation of electrodes have tended to focus on the eliciting functions of electrical stimuli delivered to the brain (2, 3, 4, 5, 7, 10, 12, 14). The present study, on the other hand, has been concerned with the reinforcing function of the electrical stimulation.[3]

so that a response produced electrical stimulation; during extinction, the stimulator was turned off so that a response produced no electrical stimulation. Each *S* was given a percentage score denoting the proportion of his total acquisition time given to responding. This score could be compared with the animal's extinction score to determine whether the stimulation had a positive, negative, or neutral reinforcing effect. After testing, the animal was sacrificed. Its brain was frozen, sectioned, stained, and examined microscopically to determine which structure of the brain had been stimulated. This permitted correlation of acquisition scores with anatomical structures.

Electrode Implantation

Electrodes are constructed by cementing a pair of enameled silver wires of 0.010-in. diameter into a Lucite block, as shown in Figure 1. The parts of the wires which penetrate the brain are cemented together to form a needle, and this is cut to the correct length

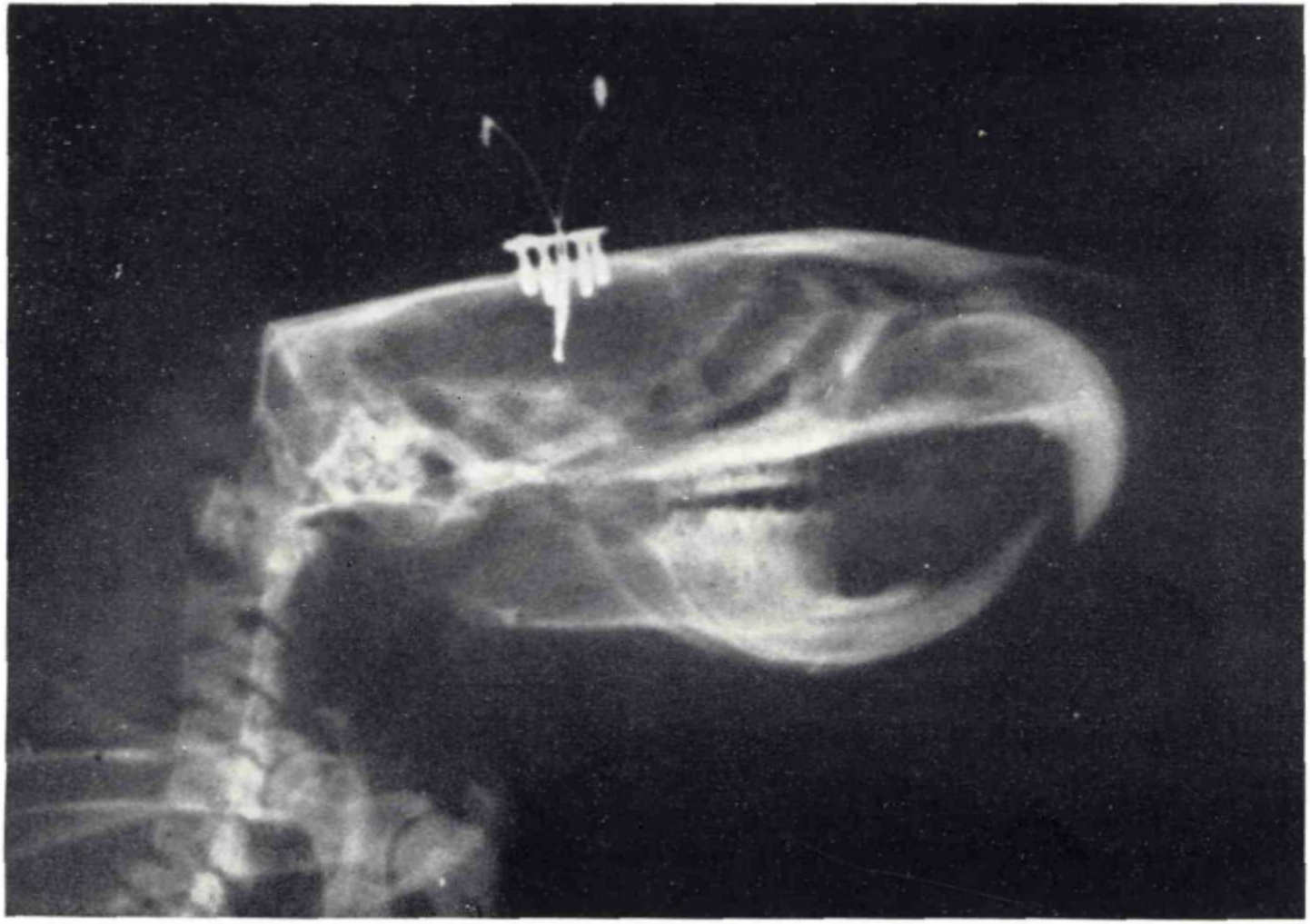


FIG. 2. X ray showing electrode in place in intact animal. There are two wires insulated completely from each other, stimulating the brain with their tips.

RESULTS

Locus

In Table 1, acquisition and extinction scores are correlated with electrode placements.

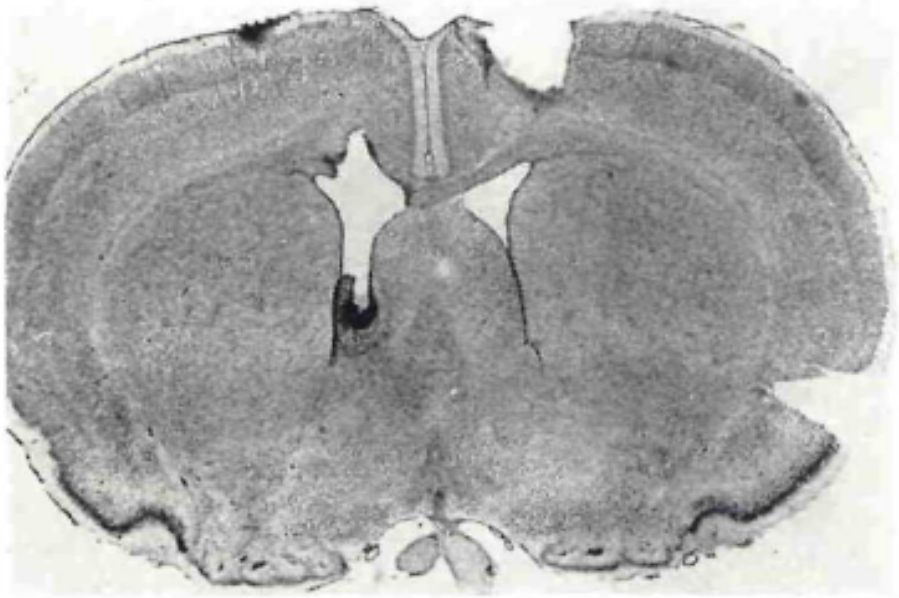


FIG. 3. Photomicrograph showing the electrode track in a cresyl-violet–stained brain section. The section is 1 mm. in front of the anterior commissure. The electrode protruded through the lateral ventricle and its stimulating tip was in the septal area.

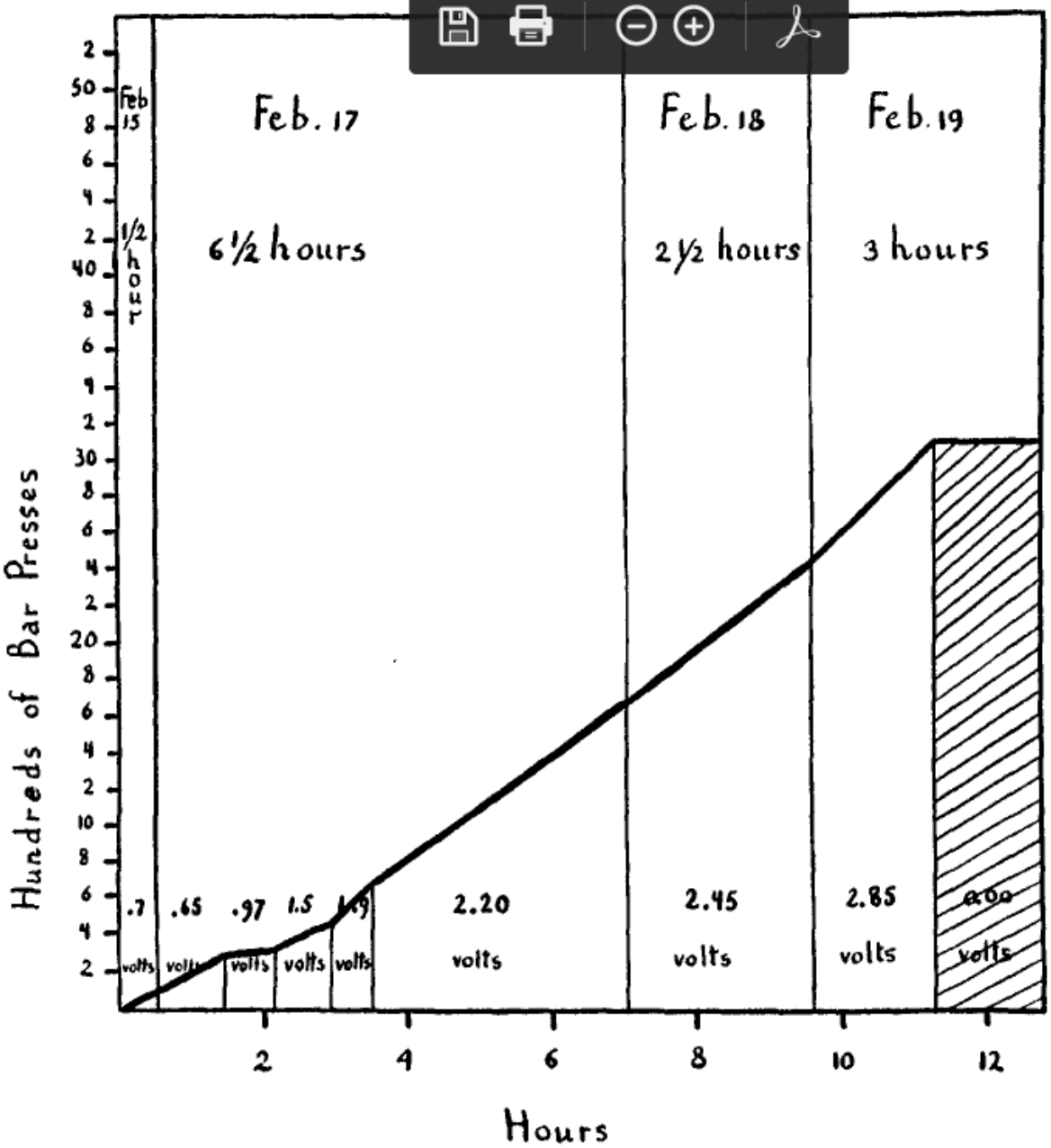


FIG. 5. Smoothed cumulative response curve for rat No. 32. Cumulative response totals are given along the ordinate, and hours along the abscissa. The steepness of the slope indicates the response rate. Stimulating voltages are given between black lines. Cross hatching indicates extinction.

The Vervet Monkey (*Cercopithecus aethiops*) St. Kitts

Semaglutide (Ozempic®)
1.0 mg s.c. once weekly

Semaglutide (Wegovy®)
2.4 mg s.c. once weekly

JCI insight

About Editors Consulting Editors For authors Publication ethics Publication alerts by email Transfers Advertising Job board Contact

Current issue Past issues By specialty Videos Collections

Research Article Endocrinology Neuroscience Open Access | 10.1172/jci.insight.170671

The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission

Vicky Chuong,[1,2] Mehdi Farokhnia,[1] Sophia Khom,[3,4] Claire L. Pince,[1,2] Sophie K. Elvig,[2] Roman Vlkolinsky,[3] Renata C.N. Marchette,[2] George F. Koob,[2] Marisa Roberto,[3] Leandro F. Vendruscolo,[5] and Lorenzo Leggio[1]

Authorship note: VC, MF, and SK contributed equally to this work and share first authorship. MR, LFV, and LL jointly supervised this work and share senior authorship.

Published May 16, 2023 - More info

Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats

*Cajsa Aranäs, Christian E. Edvardsson, Olesya T. Shevchouk, Qian Zhang, Sarah Witley, Sebastian Blid Sköldheden, Lindsay Zentveld, Daniel Vallöf, Maximilian Tufvesson-Alm, and Elisabet Jerlhag**

Department of Pharmacology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

eBioMedicine 2023;93: 104642

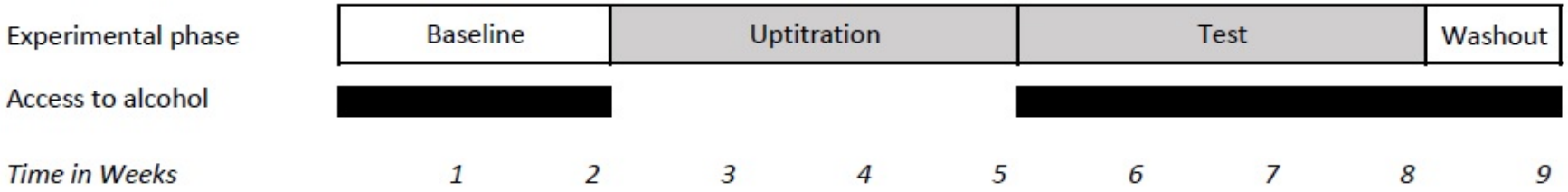
Published Online 7 June 2023

https://doi.org/10.1016/j.ebiom.2023.104642

Summary

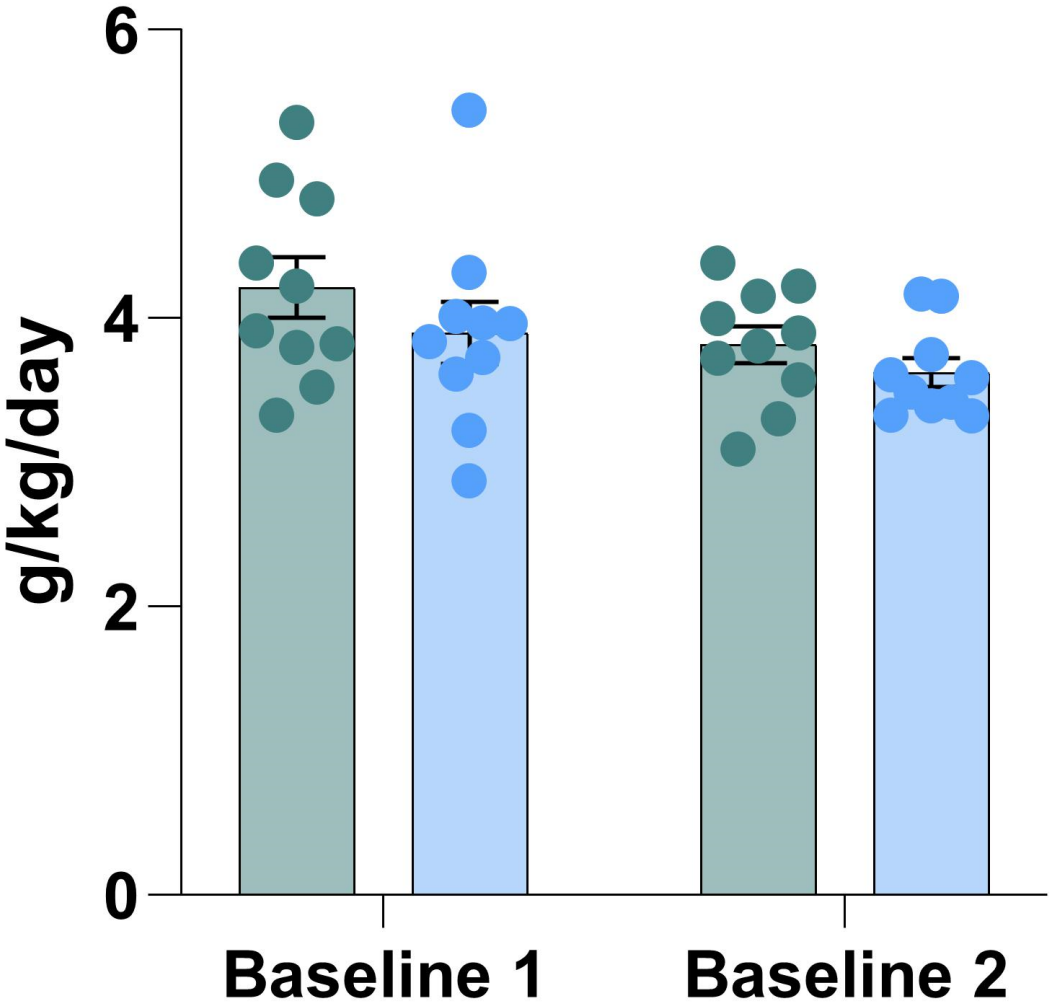
Background Glucagon-like peptide1 receptor (GLP-1R) agonists have been found to reduce alcohol drinking in rodents and overweight patients with alcohol use disorder (AUD). However, the probability of low semaglutide doses, an agonist with higher potency and affinity for GLP-1R, to attenuate alcohol-related responses in rodents and the underlying neuronal mechanisms is unknown.

Effect of semaglutide 0.05 mg/kg s.c. twice weekly on alcohol consumption in African Vervet Monkeys



Fink-Jensen et al, 2024

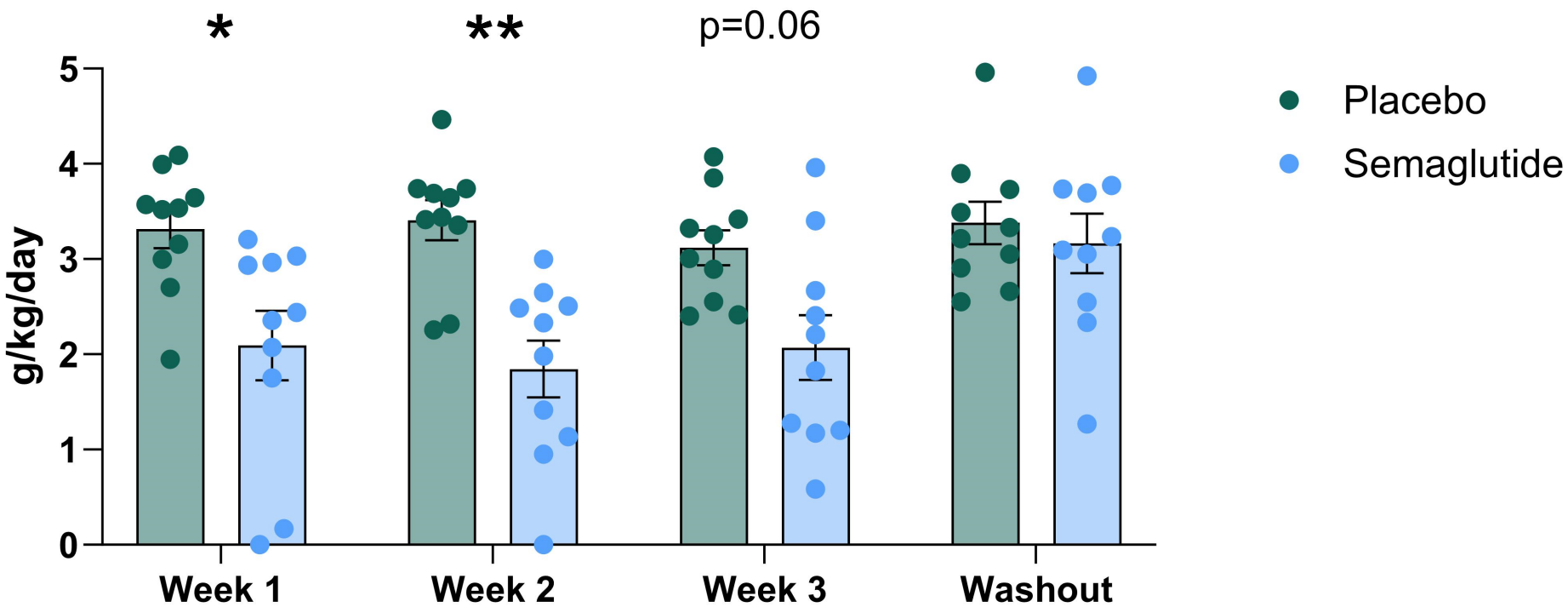
Alcohol consumption



Placebo

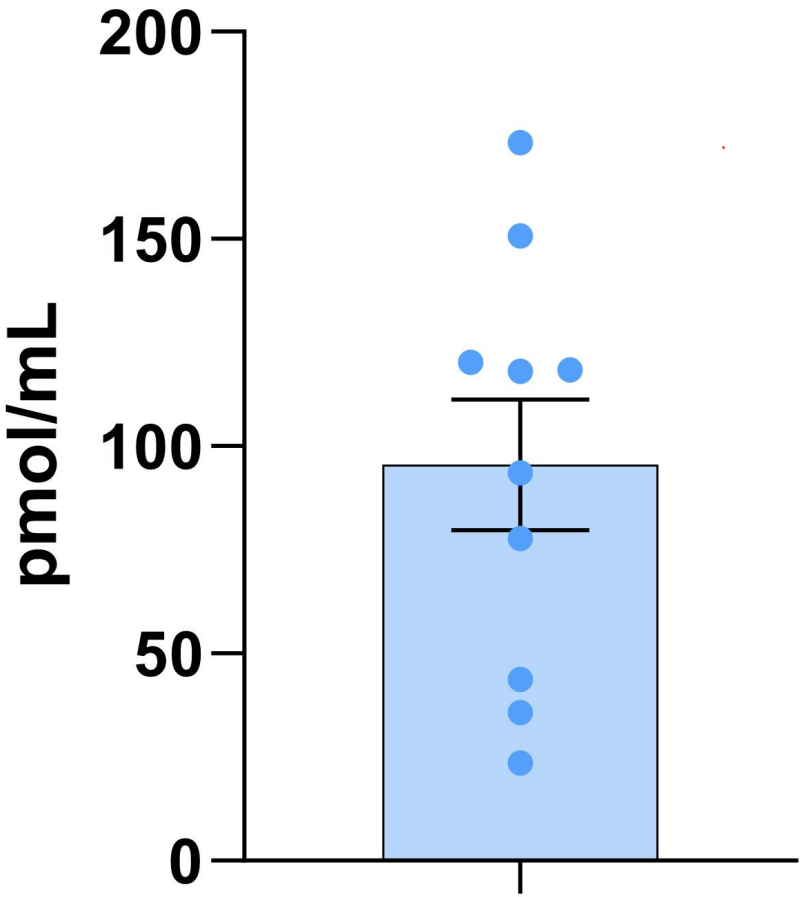
Semaglutide

Fink-Jensen et al, 2024



Fink-Jensen et al., 2024

Semaglutide plasma concentration



Fink-Jensen et al., 2024
(Radioimmunoassay originally described by Deacon et al. J Endocrinol 2002)

Open access Protocol

BMJ Open

Does semaglutide reduce alcohol intake in Danish patients with alcohol use disorder and comorbid obesity? Trial protocol of a randomised, double-blinded, placebo-controlled clinical trial (the SEMALCO trial)

Mette Kruse Klausen ,[1] Tugba Kuzey,[1] Julie Niemann Pedersen,[1] Signe Keller Justesen,[1] Line Rasmussen,[1] Ulla B Knorr,[1,2] Graeme Mason,[3] Claus Thorn Ekstrøm,[4] Jens Juul Holst ,[5] George Koob,[6] Helene Benveniste,[7] Nora D Volkow,[8] Gitte M Knudsen,[2,9] Tina Vilsbøll ,[2,10] Anders Fink-Jensen[1,2]

Research

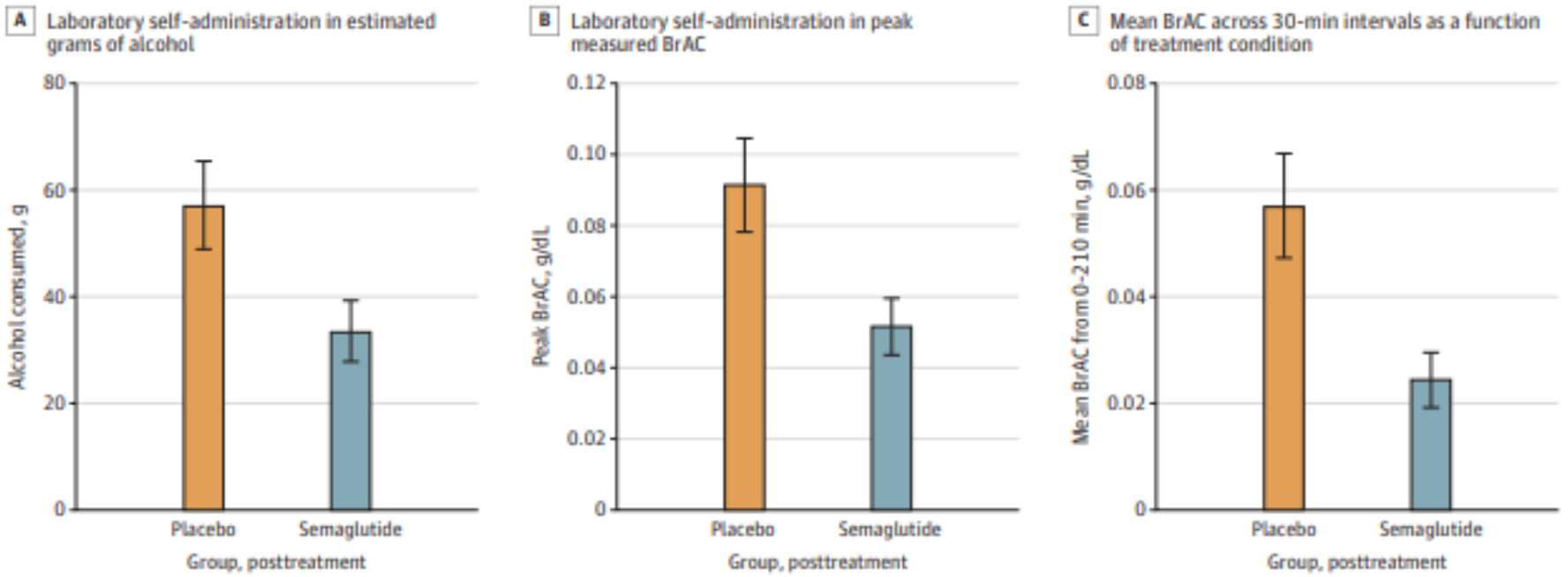
JAMA Psychiatry | Original Investigation

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder
A Randomized Clinical Trial

Christian S. Hendershot, PhD; Michael P. Bremmer, MA; Michael B. Paladino, BS; Georgios Kostantinis, BA; Thomas A. Gilmore, BA; Neil R. Sullivan, BA; Amanda C. Tow, MD, PhD; Sarah S. Dermody, PhD, CPsych; Mark A. Prince, PhD; Robyn Jordan, MD, PhD; Sherry A. McKee, PhD; Paul J. Fletcher, PhD; Eric D. Claus, PhD; Klara R. Klein, MD, PhD

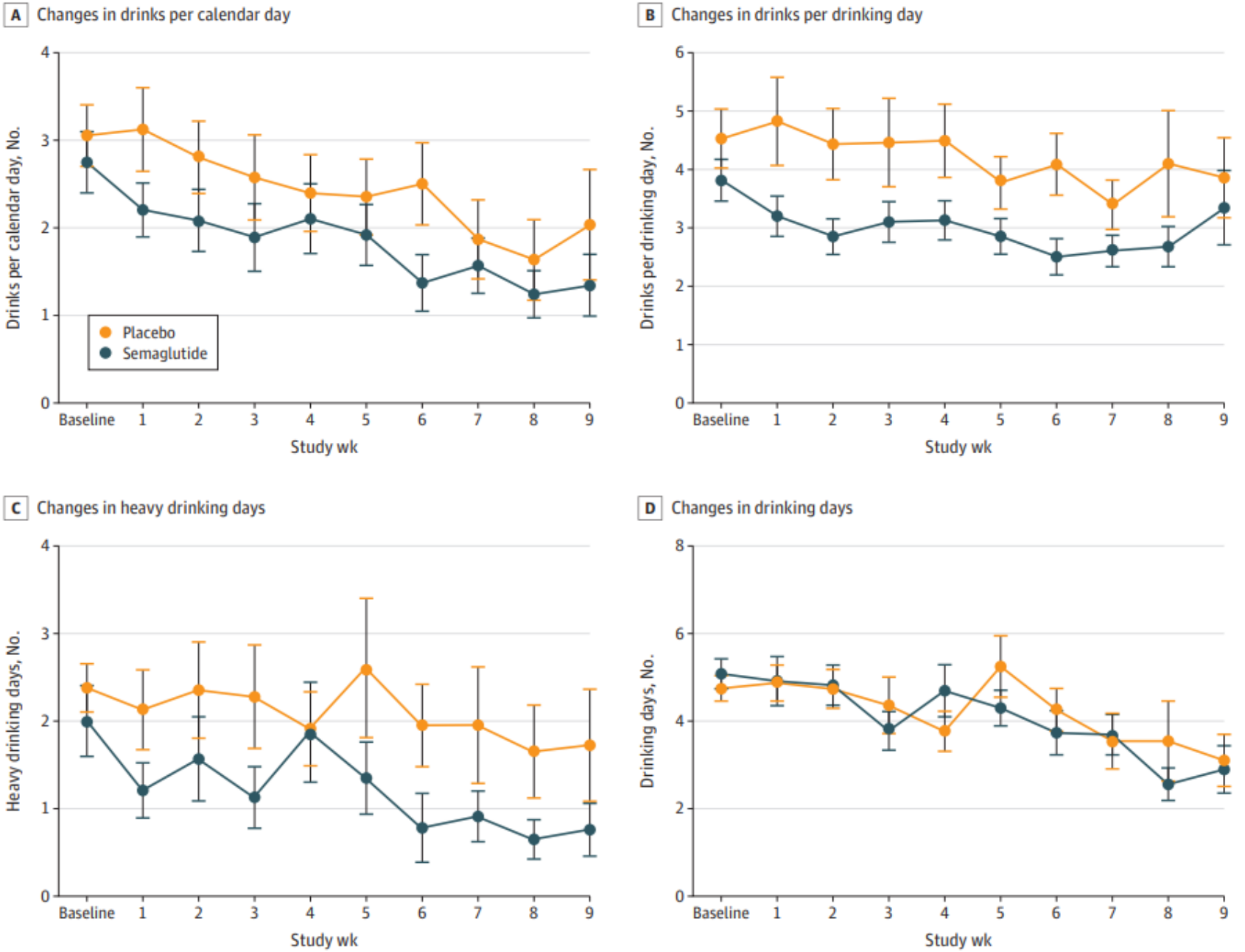
Hendershot et al., JAMA Psychiatry 2024

Figure 2. Laboratory Self-Administration



Hendershot et al., JAMA Psychiatry 2024

Figure 3. Prospective Changes in Weekly Alcohol Outcomes



nature communications

Article

https://doi.org/10.1038/s41467-024-48780-6

Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population

Received: 8 November 2023

Accepted: 8 May 2024

Published online: 28 May 2024

Check for updates

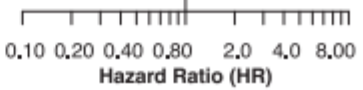
William Wang[1], Nora D. Volkow[2] ✉, Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] & Rong Xu[5] ✉

Alcohol use disorders are among the top causes of the global burden of disease, yet therapeutic interventions are limited. Reduced desire to drink in patients treated with semaglutide has raised interest regarding its potential therapeutic benefits for alcohol use disorders. In this retrospective cohort study of electronic health records of 83,825 patients with obesity, we show that semaglutide compared with other anti-obesity medications is associated with a 50%-56% lower risk for both the incidence and recurrence of alcohol use disorder for a 12-month follow-up period. Consistent reductions were seen for patients stratified by gender, age group, race and in patients with and without type 2 diabetes. Similar findings are replicated in the study population with 598,803 patients with type 2 diabetes. These findings provide evidence of the potential benefit of semaglutide in AUD in real-world populations and call for further randomized clinical trials.

(a)

Incident AUD diagnosis in patients with obesity and no prior history of AUD during 12–month follow–up time period (comparison between propensity–score matched cohorts)

Population	semaglutide cohort	non–GLP–1RA anti–obesity medications cohort	HR (95% CI)
Overall (n = 26,566/cohort)	0.37% (98)	0.73% (193)	0.50 (0.39–0.63)
Women (n = 17,977/cohort)	0.22% (40)	0.44% (79)	0.50 (0.34–0.73)
Men (n = 6,903/cohort)	0.59% (41)	1.14% (79)	0.50 (0.35–0.74)
age <= 55 years (n = 15,767/cohort)	0.30% (48)	0.61% (96)	0.49 (0.35–0.70)
age > 55 years (n = 10,440/cohort)	0.48% (50)	0.86% (90)	0.54 (0.38–0.76)
Black (n = 4,107/cohort)	0.32% (13)	0.71% (29)	0.43 (0.23–0.83)
White (n = 17,861/cohort)	0.35% (62)	0.67% (120)	0.51 (0.38–0.69)
No T2DM (n = 17,609/cohort)	0.39% (68)	0.60% (106)	0.64 (0.47–0.87)
T2DM (n = 8,696/cohort)	0.30% (26)	0.90% (78)	0.32 (0.20–0.49)



JAMA Network Open

Research Letter | Psychiatry

Semaglutide and Opioid Overdose Risk in Patients With Type 2 Diabetes and Opioid Use Disorder

William Wang; Nora D. Volkow, MD; QuangQiu Wang, MS; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; Rong Xu, PhD

Molecular Psychiatry

www.nature.com/mp

IMMEDIATE COMMUNICATION OPEN

Check for updates

Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study

William Wang[1], Nora D. Volkow[2]✉, Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] and Rong Xu[5]✉

FDA Drug Safety Communication

Update on FDA's ongoing evaluation of reports of suicidal thoughts or actions in patients taking a certain type of medicines approved for type 2 diabetes and obesity

Preliminary evaluation does not suggest a causal link

01-11-2024 FDA Drug Safety Communication

The U.S. Food and Drug Administration (FDA) has been evaluating reports of suicidal thoughts or actions in patients treated with a class of medicines called glucagon-like peptide-1 receptor agonists (GLP-1 RAs; see the list in Table 1 below). These medicines are used to treat people with type 2 diabetes or to help those with obesity or overweight to lose weight. Our preliminary evaluation has not found evidence that use of these medicines causes suicidal thoughts or actions.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02672-2

Association of semaglutide with risk of suicidal ideation in a real-world cohort

Received: 31 July 2023

Accepted: 30 October 2023

Published online: 05 January 2024

Check for updates

William Wang[1], Nora D. Volkow[2] ✉, Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] & Rong Xu[5] ✉

Concerns over reports of suicidal ideation associated with semaglutide treatment, a glucagon-like peptide 1 receptor (GLP1R) agonist medication for type 2 diabetes (T2DM) and obesity, has led to investigations by European regulatory agencies. In this retrospective cohort study of electronic health records from the TriNetX Analytics Network, we aimed to assess the associations of semaglutide with suicidal ideation compared to non-GLP1R agonist anti-obesity or anti-diabetes medications. The hazard ratios (HRs) and 95% confidence intervals (CIs) of incident and recurrent suicidal ideation were calculated for the 6-month follow-up by comparing propensity score-matched patient groups. The study population included 240,618 patients with overweight or obesity who were prescribed semaglutide or non-GLP1R agonist anti-obesity medications, with the findings replicated in 1,589,855 patients with T2DM. In patients with overweight or obesity (mean age 50.1 years, 72.6% female), semaglutide compared with non-GLP1R agonist anti-obesity medications was associated with lower risk for incident (HR = 0.27, 95% CI = 0.200.32–0.600.36) and recurrent (HR = 0.44, 95% CI = 0.32–0.60) suicidal ideation, consistent across sex, age and ethnicity stratification. Similar findings were replicated in patients with T2DM (mean age 57.5 years, 49.2% female). Our findings do not support higher risks of suicidal ideation with semaglutide compared with non-GLP1R agonist anti-obesity or anti-diabetes medications.

Suicide is a serious and preventable public health concern with 759,028 people reported worldwide to have died from suicide in 2019 (ref. 1). Suicide is among the top 10 leading causes of death and the fourth among people aged 15–29 years[2]. Suicide death rates vary according to demographics, with males having 2–3 times higher rates than females and people older than 85 years having some of the highest rates globally[3]. In the United States, provisional data from the Centers for Disease Control and Prevention calculated that in 2022 over 49,449 individuals died by suicide, with suicide rates among the highest in people aged between 25 and 34 years of age and over 75 years of age[4].

Thus, a concern for the U.S. Food and Drug Administration (FDA) and other regulatory agencies that approve medications for human use is to minimize the risks that these medications increase suicidal ideation. Although preapproval trials are required to show a lack of suicidal ideation, their predictive accuracy for safety is constrained by the relatively limited number of patients included[5]. To address this, regulatory agencies have established several post-marketing surveillance methods that can lead to 'black box' labels for the highest safety-related warning or potential drug removal. However, the sensitivity and accuracy of these methods have been questioned[6]. A study

JAMA Internal Medicine | Original Investigation

Psychiatric Safety of Semaglutide for Weight Management in People Without Known Major Psychopathology

Post Hoc Analysis of the STEP 1, 2, 3, and 5 Trials

Thomas A. Wadden, PhD; Gregory K. Brown, PhD; Christina Egebjerg, PhD; Ofir Frenkel, MD; Bryan Goldman, MS; Robert F. Kushner, MD; Barbara McGowan, PhD; Maria Overvad, MD; Anders Fink-Jensen, MD

IMPORTANCE Obesity is associated with numerous psychosocial complications, making psychiatric safety a consideration for treating people with obesity. Few studies have investigated the psychiatric safety of newly available antiobesity medications.

OBJECTIVE To evaluate the psychiatric safety of subcutaneous semaglutide, 2.4 mg, once weekly in people without known major psychopathology.

CONCLUSIONS AND RELEVANCE The results of this post hoc analysis suggest that treatment with semaglutide, 2.4 mg, did not increase the risk of developing symptoms of depression or suicidal ideation/behavior vs placebo and was associated with a small but statistically significant reduction in depressive symptoms (not considered clinically meaningful). People with obesity should be monitored for mental health concerns so they can receive appropriate support and care.

Editor's Note page 1312

Related article page 1301

Supplemental content

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: _____ **DATE:** _____

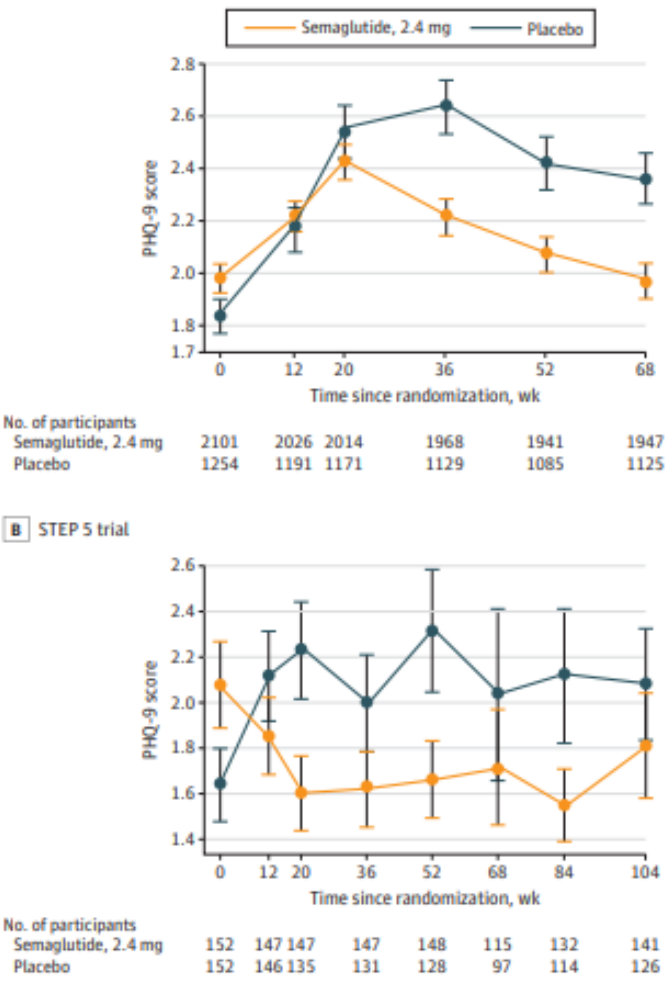
Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

TOTAL:

Figure. Patient Health Questionnaire 9 (PHQ-9) Scores Over Time During the STEP 1, 2, 3, and 5 Trials



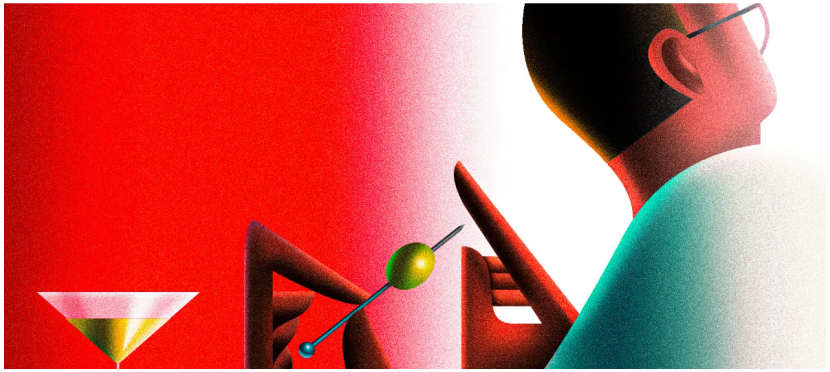
Data are mean PHQ-9 scores over time from baseline to week 68 for STEP 1, 2, and 3 (A) and to week 104 for STEP 5 (B). Error bars represent the SD of the mean. Data are for the in-trial period for all participants in the safety analysis set.

The New York Times

Some People on Ozempic Lose the Desire to Drink. Scientists Are Asking Why.

As the diabetes drug gains more attention, a surprising side effect has emerged.

Give this article 726



The Atlantic

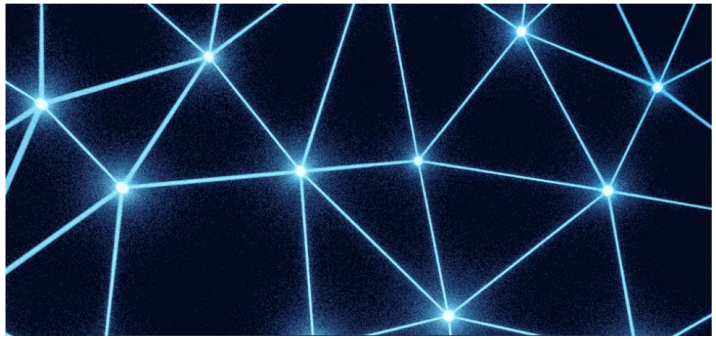
Popular Latest Newsletters Sign In

HEALTH

Did Scientists Accidentally Invent an Anti-addiction Drug?

People taking Ozempic for weight loss say they have also stopped drinking, smoking, shopping, and even nail biting.

By Sarah Zhang



THE WALL STREET JOURNAL.

SIGN IN SUBSCRIBE

Ozempic Might Help You Drink and Smoke Less

Animal studies suggest GLP-1 drugs alter behaviors associated with reward and pleasure

MEDICINE

Hot weight loss drugs tested against addiction

Clinical trials will gauge whether GLP-1 analogs curb drug and alcohol cravings

By **Mitch Leslie**

When the diabetes treatments known as GLP-1 analogs reached the market in 2005, doctors advised patients taking the drugs that they might lose a small amount of weight. Talk about an understatement. Obese people can drop more than 15% of their body weight, studies have found, and two of the medications are now approved by the U.S. Food and Drug Administration (FDA) for weight reduction. A surge in demand for the drugs as slimming treatments has led to shortages. "This class of drugs is exploding in popularity," says clinical psychologist Joseph Schacht of the University of Colorado School of Medicine.

But patient reports and animal studies have yielded tantalizing signs that the drugs may spur another unexpected and welcome effect: fighting addiction. Most early trials were disappointing, but they used less potent versions of the drugs. Now, at least nine phase 2 clinical trials are underway or being planned to test whether the more powerful compound semaglutide and its chemical cousins can help patients curb their use of cigarettes, alcohol, opioids, or cocaine. Hopes are high. Semaglutide (sold under the trade names Wegovy, Ozempic, and Rybelsus) "is truly the most exciting drug for the last few decades," says neuropharmacologist Leandro Vendruscolo of the U.S. National Institute on Drug Abuse.

If the results of the new trials are positive, addiction science could have its own "Prozac moment," says clinical neuroscientist W. Kyle Simmons of the Oklahoma State University Center for Health Sciences. In the 1980s, that drug brought a sea change to psychiatry, becoming part of popular culture and leading to the wider use of antidepressants.

Scientists have long been searching for new addiction drugs. Although FDA has approved several, including three for patients with alcohol use disorder, these medicines only work for a small percentage of people who try them. And the pharmaceutical industry has not delivered new compounds, in part because companies believe patients won't stick with treatments, making their development a poor investment, says clinical neuroscientist Lara Ray of the University of California, Los Angeles. The last "new" drug treatment for alcohol use disorder received FDA approval in 2006—and it was an injectable version of a drug, naltrexone, that had been available since the 1980s.

So when patients taking GLP-1 analogs for diabetes or weight loss reported that their hankering for substances such as alcohol and nicotine declined, researchers and doctors in the addiction field perked up. "You usually don't hear people say that a drug makes them less interested in drinking," Schacht says.

Researchers are still probing how GLP-1 analogs might pull off that feat. The drugs replicate the effects of the hormone glucagon-like peptide-1; by prodding its receptors in the pancreas, they stimulate release of insulin and trigger other beneficial responses, which explains how they help people with diabetes. But several structures in the brain also produce GLP-1 or carry receptors for the hormone—including brain areas that are involved in our reward pathways, which drive us to pursue pleasurable activities such as eating tasty food or hanging out with friends. Addiction involves "hijacking of the reward pathways in the brain," says behavioral neuroscientist Patricia Grigson of the Pennsylvania State University College of Medicine. Researchers think GLP-1 analogs spur weight loss in part by quelling activity of this system, and the same mechanism could explain why people who take the medications report they are less motivated to drink and smoke.

Studies in rodents and primates have supported that mechanism and confirmed that the drugs diminish the desire for substances such as alcohol, fentanyl, nicotine, and heroin. Clinical psychiatrist Anders Fink-Jensen of the University of Copenhagen and colleagues even demonstrated that the drugs work in an incorrigible group of drinkers:

ILLUSTRATION: DENIS NOVIKOV/ISTOCKPHOTO ADAPTED BY N. JESSUP/*SCIENCE*

https://doi.org/10.1038/s41591-023-02634-8

GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders

Lorenzo Leggio, Christian S. Hendershot, Mehdi Farokhnia, Anders Fink-Jensen, Mette Kruse Klausen, Joseph P. Schacht & W. Kyle Simmons

Preclinical and initial human studies suggest that glucagon-like peptide-1 receptor agonists may be promising treatments for alcohol use disorder, but existing approved treatments should be used until safety and efficacy is demonstrated in clinical trials.

The development and rapid clinical adoption of potent and long-lasting glucagon-like peptide-1 receptor agonists (GLP-1RAs) is quickly changing the landscape of diabetes and obesity treatment. In particular, semaglutide (marketed as Ozempic, Wegovy and Rybelsus) has attracted attention among the general public for its remarkable effects on weight loss. The explosive growth of its use in clinical practice has been accompanied by an important ancillary finding: frequent anecdotal reports of reductions in alcohol use and other addictive behaviors. These observations, which we have heard ourselves from patients and providers, are being amplified by media and public attention and have led to discussions about potential clinical applications of semaglutide and other GLP-1RAs for addictive disorders, especially alcohol use disorder (AUD). We write as leaders of clinical trials currently underway in North America and Europe to evaluate the efficacy of semaglutide for AUD to encourage clinicians and patients to be prudent and avoid placing supposition before science.

Initial evidence from animal and human studies

Preclinical work on the effects of GLP-1RAs on the consumption of alcohol and other substances started more than a decade ago. Research on mice, rats and non-human primates carried out by independent laboratories and using several alcohol-related models (which reflect key phenotypic aspects of excessive alcohol consumption and AUD) has produced consistent evidence that GLP-1RAs reduce the rewarding properties of alcohol and other addictive drugs such as nicotine, opioids and cocaine, leading to reduced motivation for and intake of these drugs (reviewed in ref. 1). Recent studies by Chuong et al.[2] and Aranäs et al.[3] in mice and rats independently provide support for an effect of semaglutide on reducing alcohol consumption and modulating other phenotypes and behaviors relevant to AUD.

Although research in humans has also suggested a relationship between alcohol consumption, AUD and the endogenous GLP-1 system[4–6], there is a lack of randomized controlled trials (RCTs). A recent study using information from nationwide registers of the Danish population reported that patients taking GLP-1RAs had lower incidence of alcohol-related events compared with those taking dipeptidyl peptidase IV inhibitors[7].

The only RCT including patients with AUD showed that the first-generation GLP-1RA exenatide was not superior to placebo on the primary alcohol consumption outcomes in the full sample, although a secondary analysis showed that exenatide reduced alcohol use in a subgroup who had AUD and comorbid obesity[8]. Furthermore, activity induced by alcohol cues in brain areas related to reward processing was reduced in the exenatide group[8]. Compared with more recently developed GLP-1RAs such as semaglutide, exenatide has reduced sequence homology to endogenous GLP-1, and has been shown to have less of an effect on blood glucose and weight in diabetes and obesity studies. This inconclusive research in humans emphasizes the need for prospective RCTs with GLP-1RAs — including semaglutide — in patients with AUD. Such RCTs are underway, and human studies with GLP-1RAs are expanding to include patients with other substance use disorders[9,10].

Repurposing drugs

The surge in clinical and anecdotal reports of decreased alcohol use in people taking semaglutide for diabetes and obesity should not be ignored. AUD is a leading cause of mortality and morbidity[11], but compared with other chronic diseases such as cancers, hypertension, diabetes and depression, there is a very small number of US Food and Drug administration (FDA)-approved medications for AUD (acamprosate, disulfiram and naltrexone). These drugs also have low uptake (less than 2% in the USA[12]) due to several factors, including patients' reluctance to seek treatment, lack of addiction training among healthcare providers and considerable stigma surrounding AUD and addiction[11].

Developing new medications is a difficult, expensive and time-consuming process; drug repurposing, therefore, has the potential to expedite much-needed treatment options for AUD. There are

Acknowledgement
GLP-1 Alcohol Projects

Clinical Project

Mette Kruse Klausen
Mathias Jensen
Nina le Dous
Amanda Brunchman
Anne-Marie Østergaard
Marco Jensen
Victoria Zeeman
Claas Johannsen

Tina Vilsbøll

Gitte Moos Knudsen
Gerda Krogh Thomsen
Peter Steen Jensen
Kamilla Miskowiak

Alycia Lee
Sabine Vollstädt-Klein

Jens Juul Holst
Bolette Hartmann
Claus Ekstrøm

Helene Benveniste
Nora Volkow

Preclinical Projects

Morgan Thomsen
Gitta Wöertwein
Pia Weikop
Anna Molander

India Reddy
Aurelio Galli

Emil Egecioglu
Elisabet Jerlhag

Roberta Palmour
Maurice Ptito

REGION H Mental Health Services