

WEBINAR



Alcohol Use Disorder Part 1

Epidemiology, Evidence-Based Treatments, and Emerging Therapeutics



Dr. Katie Witkiewitz
University of New Mexico



Dr. Lorenzo Leggio
NIDA/NIAAA Senior Investigator



Dr. Redonna Chandler
Addiction Policy Forum

SEPTEMBER 24 | 1:00 PM ET

addictionpolicy.org

Epidemiology and Evidence-Based Treatment for Alcohol Use Disorder

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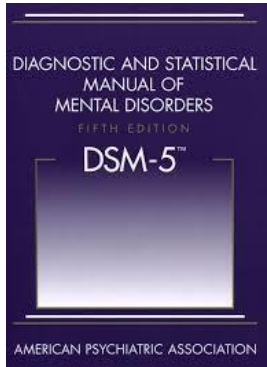
CENTER ON ALCOHOL,
SUBSTANCE USE
& ADDICTIONS

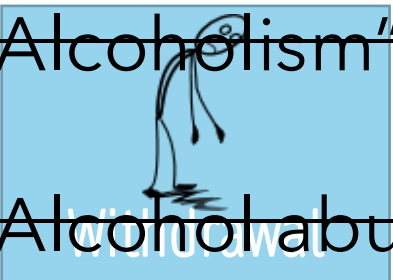
Disclosures

- Research reported in this presentation was supported by NIAAA under award numbers R01AA022328, R01AA025539, R01AA031159. The content does not necessarily represent the official views of the National Institutes of Health
- I am a participant in the Alcohol Clinical Trials Initiative, which in the past 36 months was supported by Eli Lilly, Indivior, and Imbrium
- I am on a Scientific Advisory Board and a consultant for Eli Lilly.

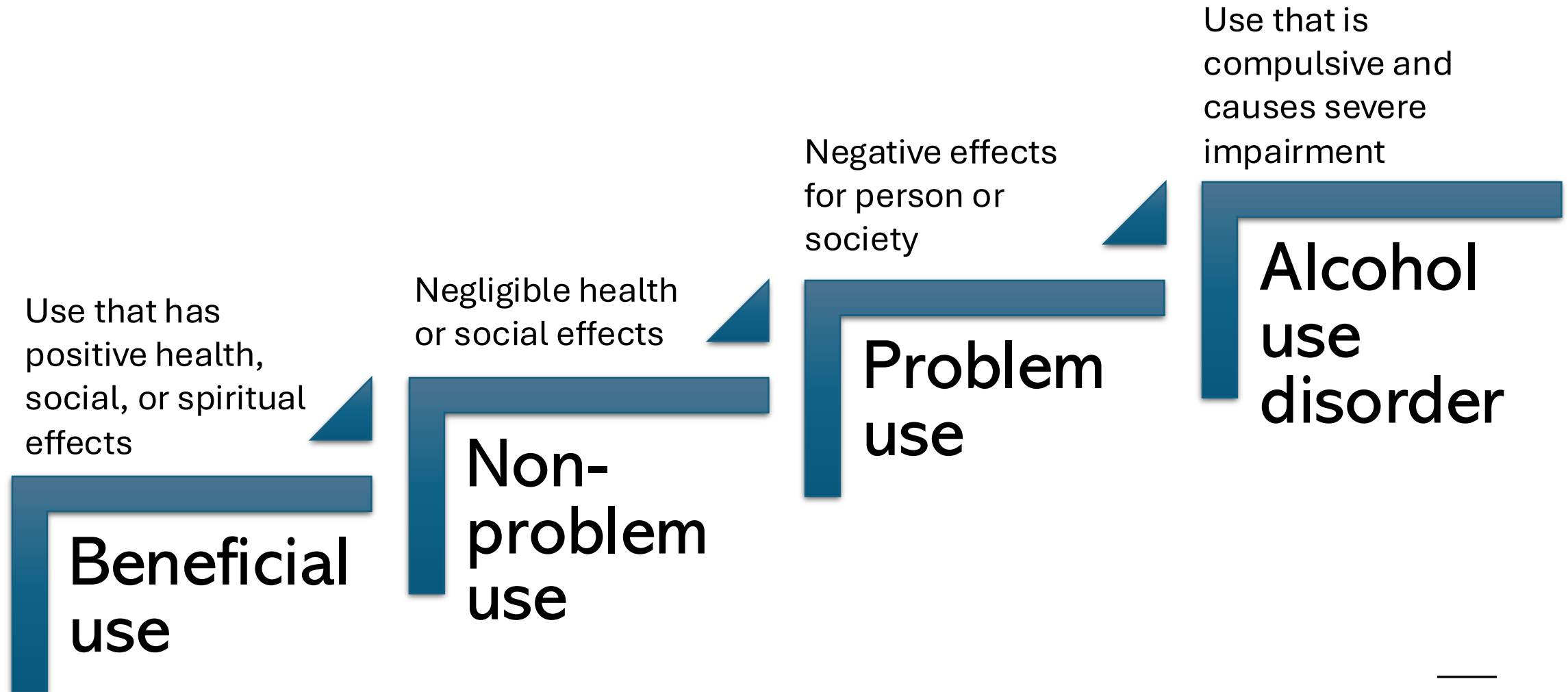
The views expressed in the presentation are my own and do not reflect any official policy of the Center on Alcohol, Substance Use, and Addictions (CASAA), the University of New Mexico, or the National Institutes of Health

What is alcohol use disorder (AUD)?

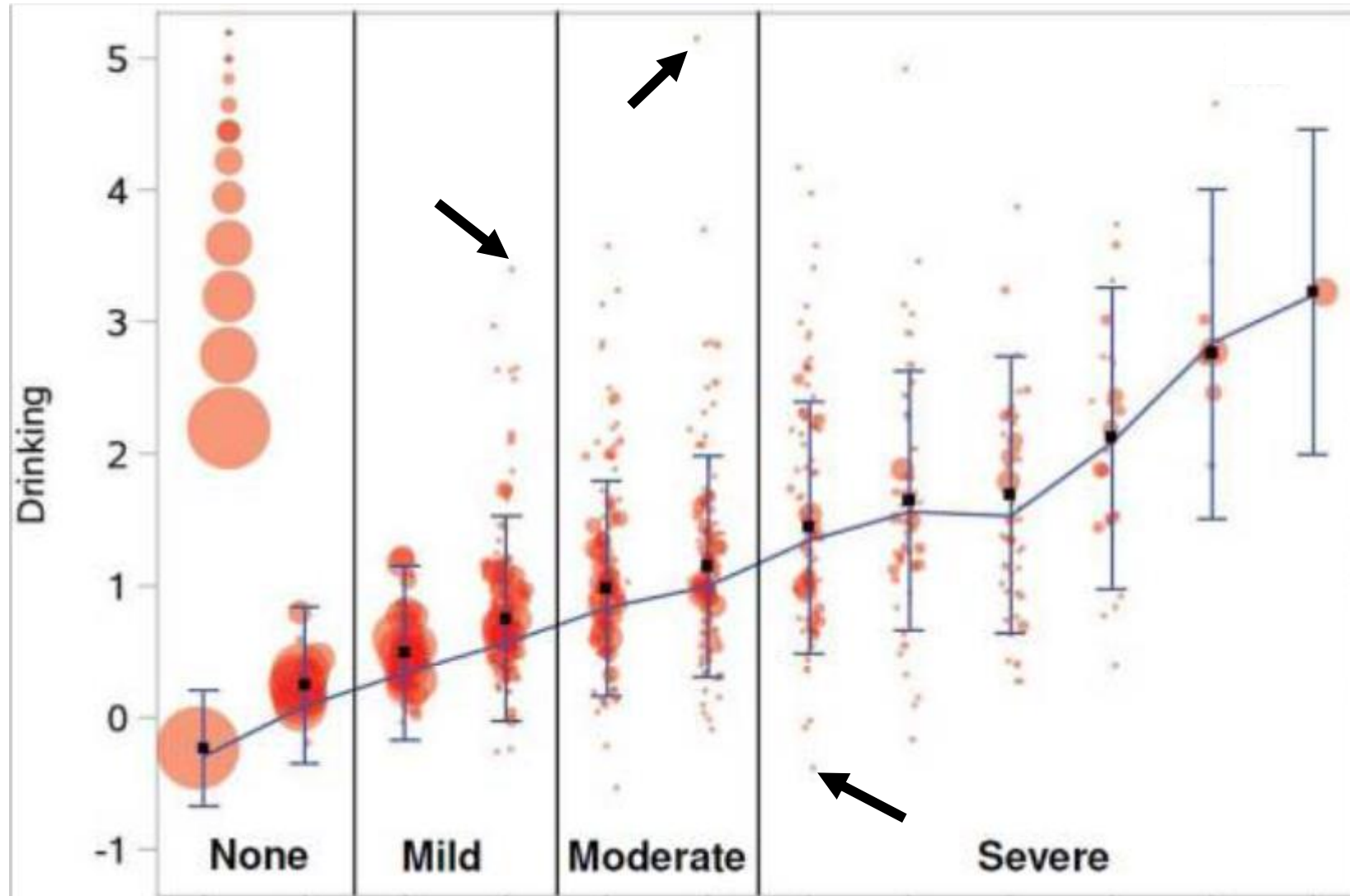


 "Alcoholism" Tolerance	 "Alcoholism" An individual with health alcohol use or social problems	 "Alcoholism" Health problems	 "Alcoholism" Drinking larger	Impairment caused by 2+ symptoms in past 12 months 2-3 symptoms = mild; 4-5 symptoms = moderate; 6+ = severe
 "Alcoholism" Missing work & life	 "Alcoholism" Alcohol use disorder or alcohol dependence	 "Alcoholism" Reduce activities	 "Alcoholism" Fail to reduce	
 "Alcoholism" Craving strong urge	 "Alcoholism" Hazardous use	 Time spent drinking		
"Alcohol abuse" Alcohol-related problems				

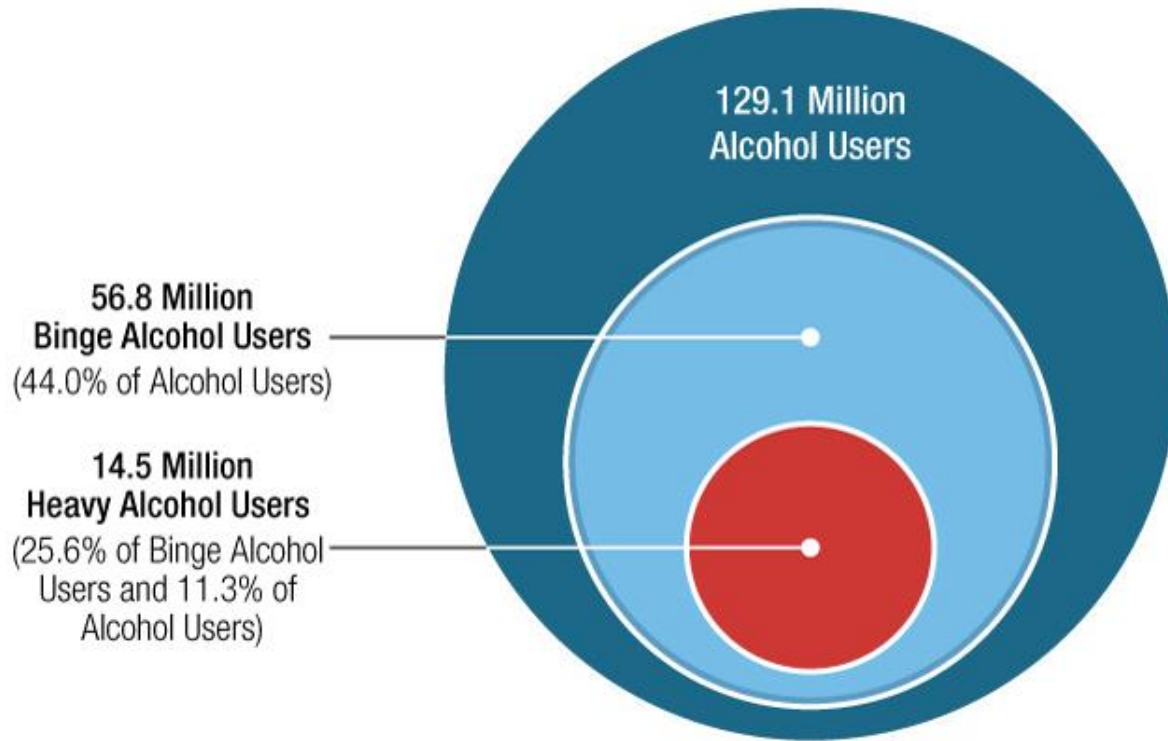
Alcohol use $\neq$ disorder



Alcohol use $\neq$ disorder



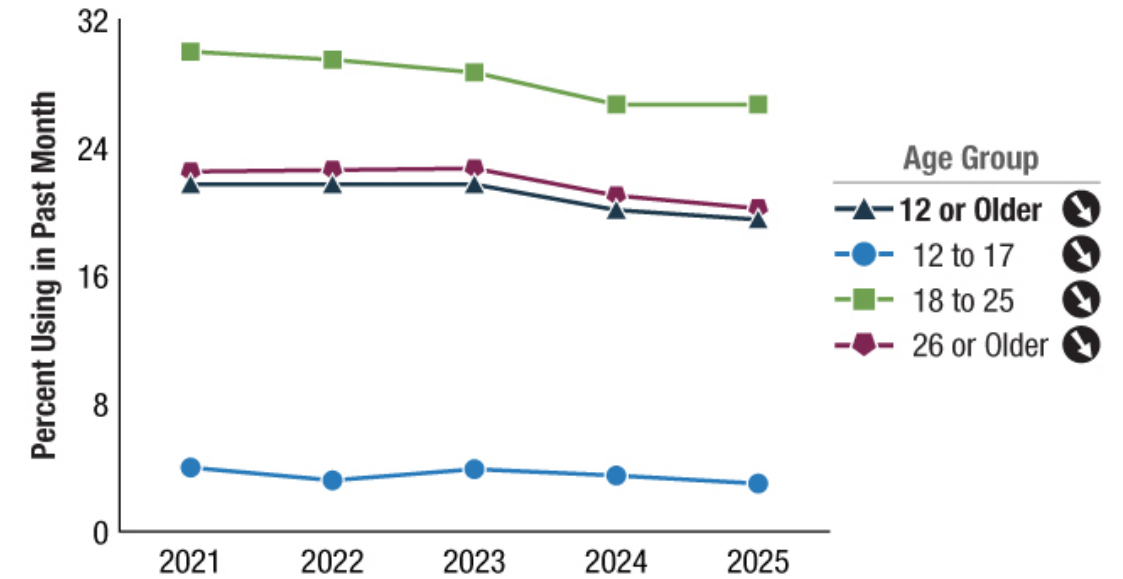
2025 U.S. Data



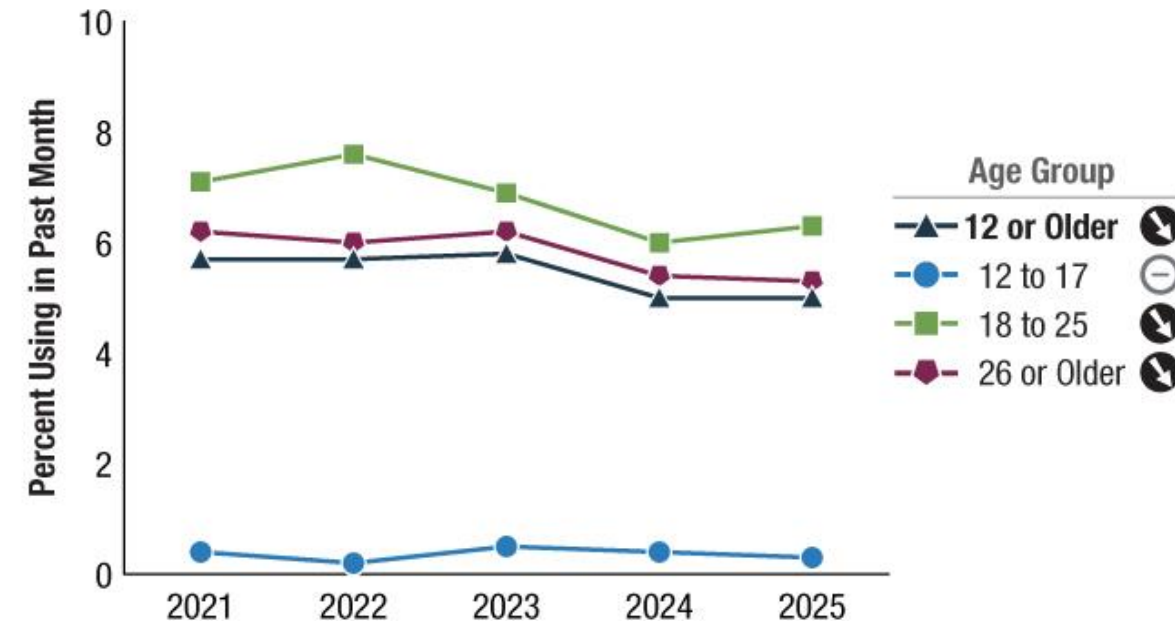
Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days

Heavy Alcohol Use is defined as binge drinking on 5 or more days in the past 30 days

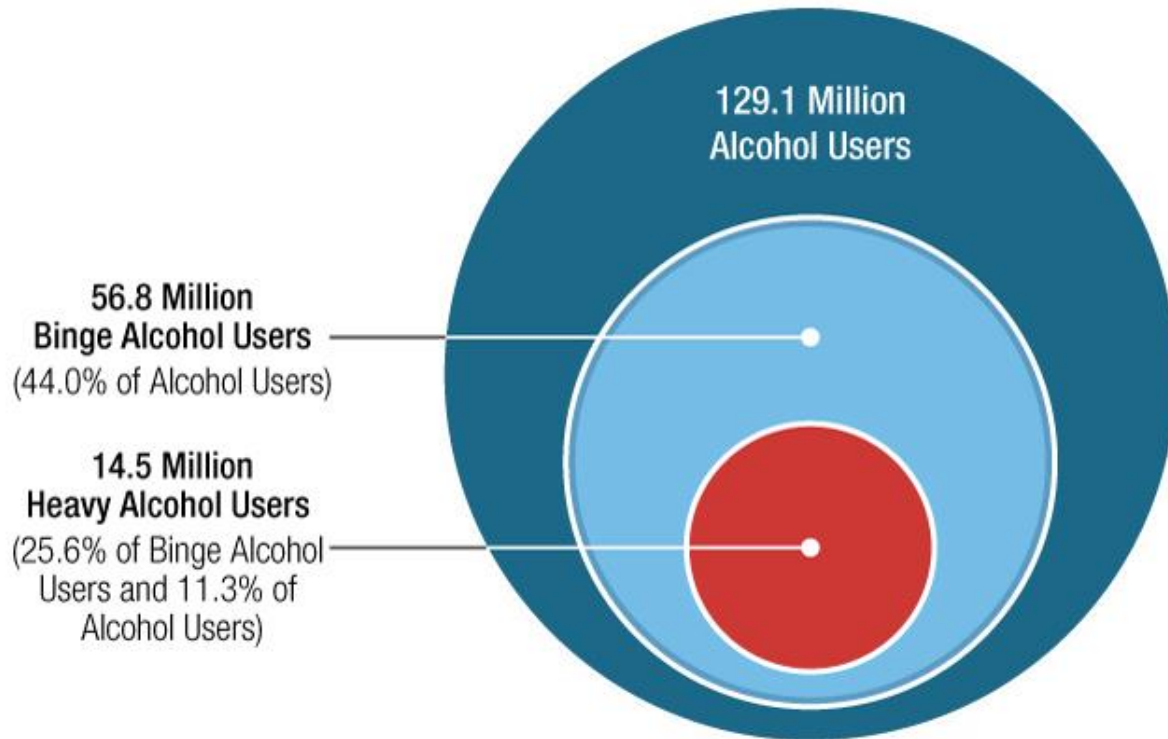
Past Month Binge Alcohol Use 2021-2025



Past Month Heavy Alcohol Use 2021-2025



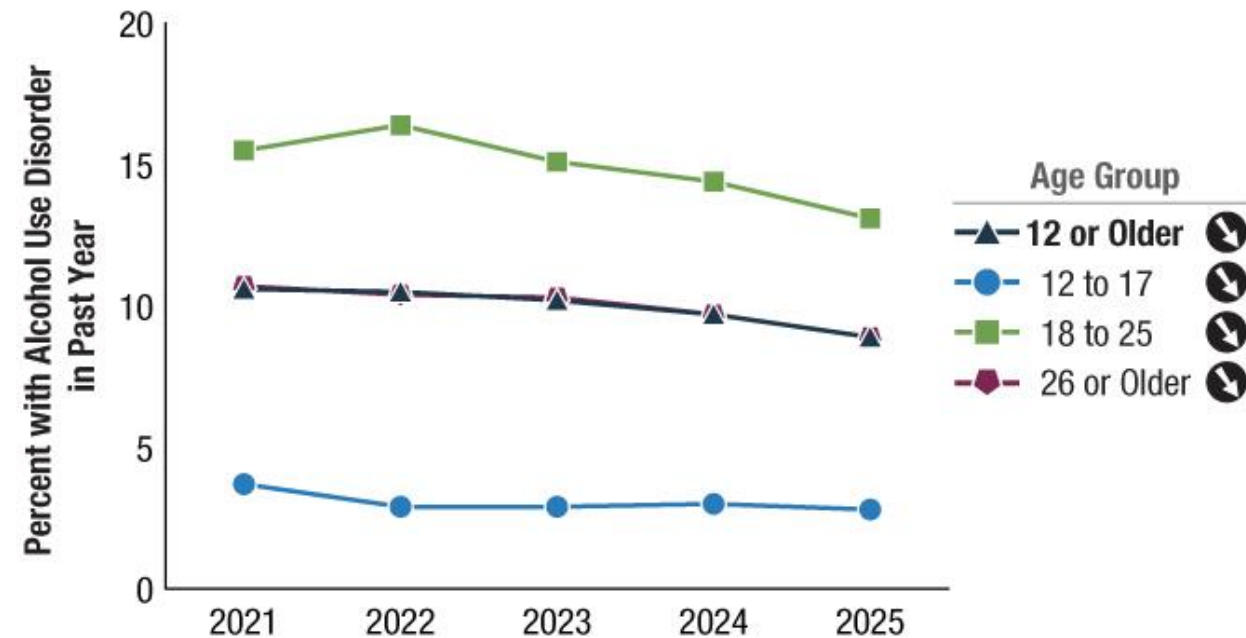
2025 U.S. Data



Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days

Heavy Alcohol Use is defined as binge drinking on 5 or more days in the past 30 days

Past Year Alcohol Use Disorder: Among People Aged 12 or Older; 2021-2025 (13.1% in 2025; 4.7 million people)



The treatment gap

Condition	Proportion of people untreated, %
Schizophrenia	32.2
Depression	56.3
Dysthymia	56.0
Bipolar disorder	50.2
Panic disorder	55.9
Generalised anxiety disorder	57.5
Obsessive–compulsive disorder	57.3
Alcohol misuse or dependence	78.1

Sources: Kohn 2004; Wittchen 2005; World Health Organization 2005.

Thornicroft et al. 2010 doi:10.1192/apt.bp.107.004481

EPIDEMIOLOGY OF RECOVERY FROM ALCOHOL USE DISORDER

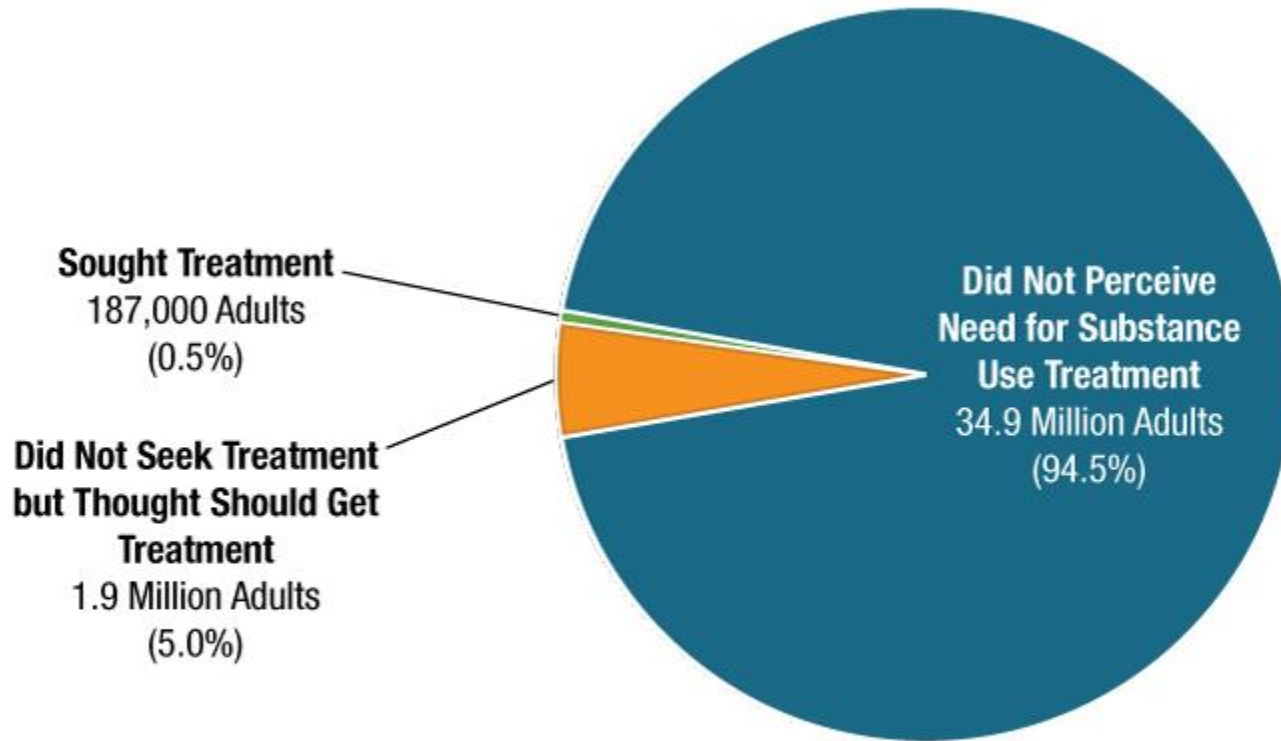
Jalie A. Tucker,¹ Susan D. Chandler,¹ and Katie Witkiewitz²

¹Department of Health Education and Behavior and the Center for Behavioral Economic Health Research, University of Florida, Gainesville, Florida

²Department of Psychology and the Center on Alcoholism, Substance Abuse, and Addictions, University of New Mexico, Albuquerque, New Mexico

“Approximately 70% of persons with alcohol use disorder and alcohol problems **improve without interventions** (natural recovery), and fewer than 25% utilize alcohol-focused services. **Low-risk drinking is a more common outcome** in untreated samples”

2025 U.S. Data



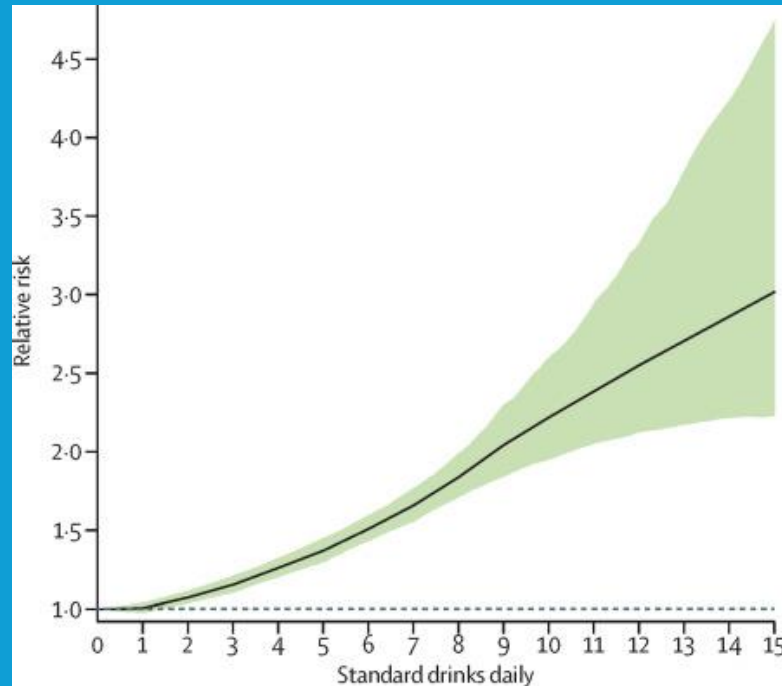
Among 5% who perceived a need, but did not get treatment... Why?

- Thinking they should have been able to handle their alcohol or drug use on their own (82.5%),
- **Not being ready to stop or cut back on using alcohol or drugs (68.4%)**
- Not being ready to start treatment (67.7%)
- Not having enough time for treatment (54.3%)

38.1 Million Adults with a Substance Use Disorder Who Did Not Receive Substance Use Treatment

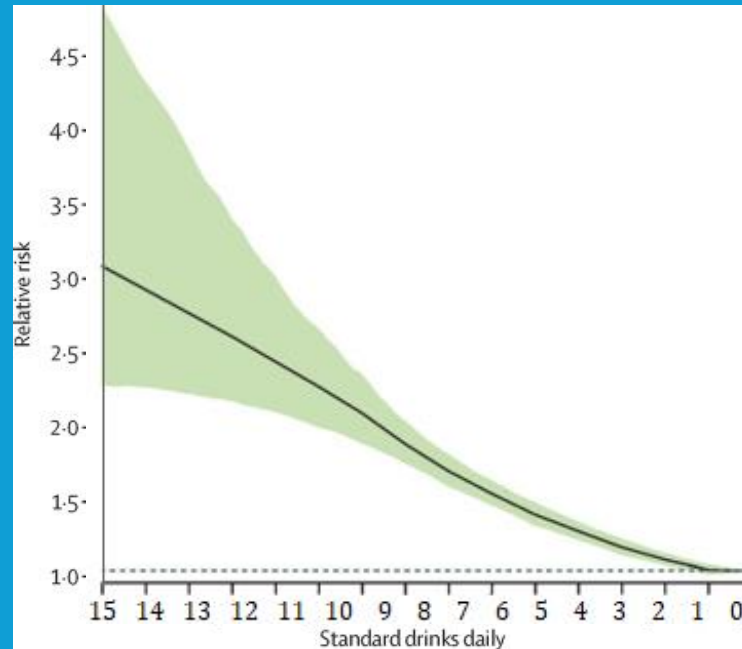
Not being ready to stop using: Is abstinence required?

**ALCOHOL AND DRUGS
HAVE TOXIC EFFECTS ON
THE BODY**



**ABSTINENCE IS
HARM REDUCTION
AND
ACHIEVING
RECOVERY
THROUGH
ABSTINENCE IS
RIGHTLY
CELEBRATED AS A
“SUCCESSFUL”
PATHWAY TO AUD OR
SUD RECOVERY**

**Reductions in use =
Reductions in risk**



**Drinking reductions
- short of abstinence - are
achievable, sustainable,
and associated with
improved health and
function**

Flip the axes on the Global Burden of Disease Risk Factors Collaborators.
2018. Lancet.

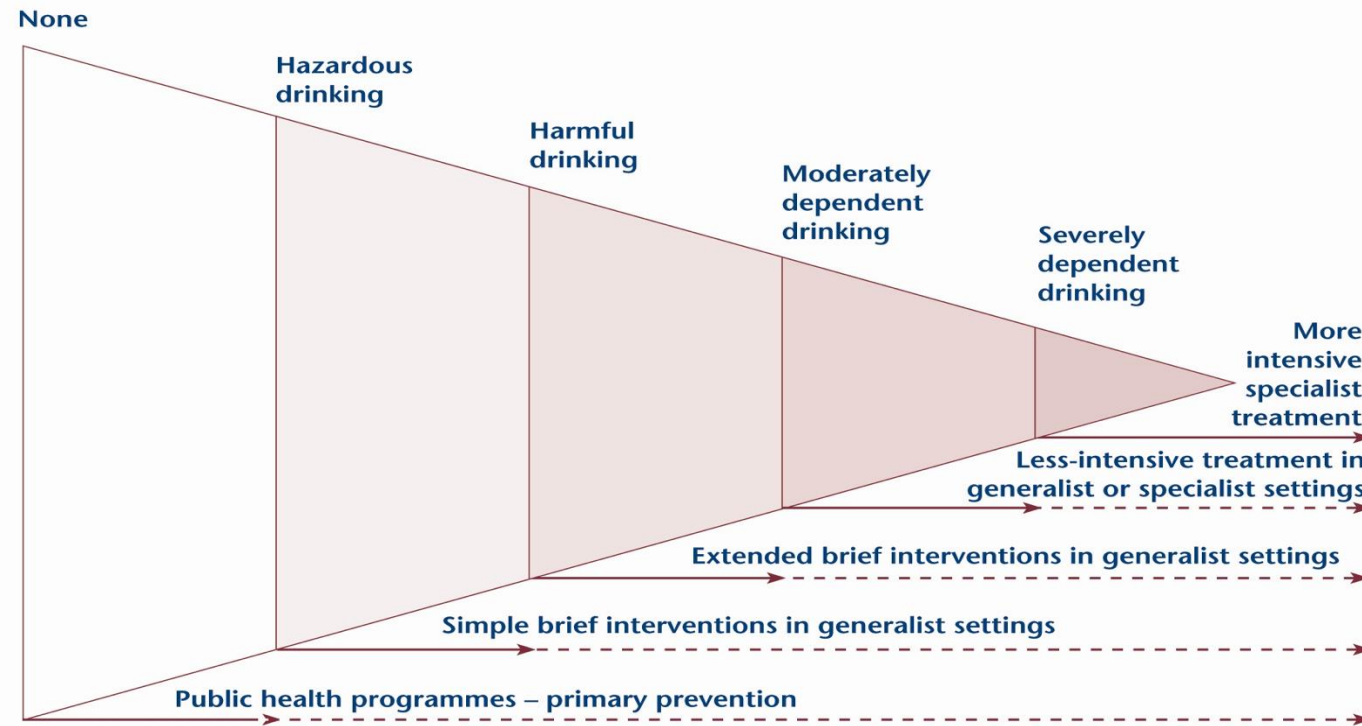
Individuals can reduce their drinking and/or their experience of harm associated with alcohol use, without achieving abstinence

(Wilson et al. 2016; Maisto et al. 2018; Maisto et al. 2021; Pearson et al. 2021; Witkiewitz et al., 2019, 2020, 2021)

Recovery-Oriented Harm Reduction Approach To Treatment

- **Recovery and resiliency focus** – treatment is strengths based, focused on emphasizing client strengths and resilience
- **Client empowerment** – opportunities for involvement in achieving self-determined goals for living, including choice of drinking goals
- **Evidence-based approaches** – targeting individual change via stage model and approaches that have been shown to be effective in supporting change
- **Service integration** – holistic care through more than one approach
- **Continual evaluation** – assess and evaluate needs of client over time
- **De-stigmatization of experience** – normalize the process of reactivity and maintenance of alcohol use disorder

Treatment match to severity and stage of change



Stages of Change	Stages of Treatment	Clinical Focus and Targets
Pre-Contemplation	Engagement	Rapport building, practical support, assessment
Contemplation & Preparation	Enhancing Motivation	Motivational interventions, normalizing ambivalence
Action	Active Treatment	Skill building, social support, evidence-based approaches
Maintenance	Relapse Prevention	Planning, focus on lifestyle, social support

Figure 1 A spectrum of responses to alcohol problems

Source: Rastrick et al. (2006),¹ adapted from Institute of Medicine (1990).²

Evidence-Based Behavioral Treatments

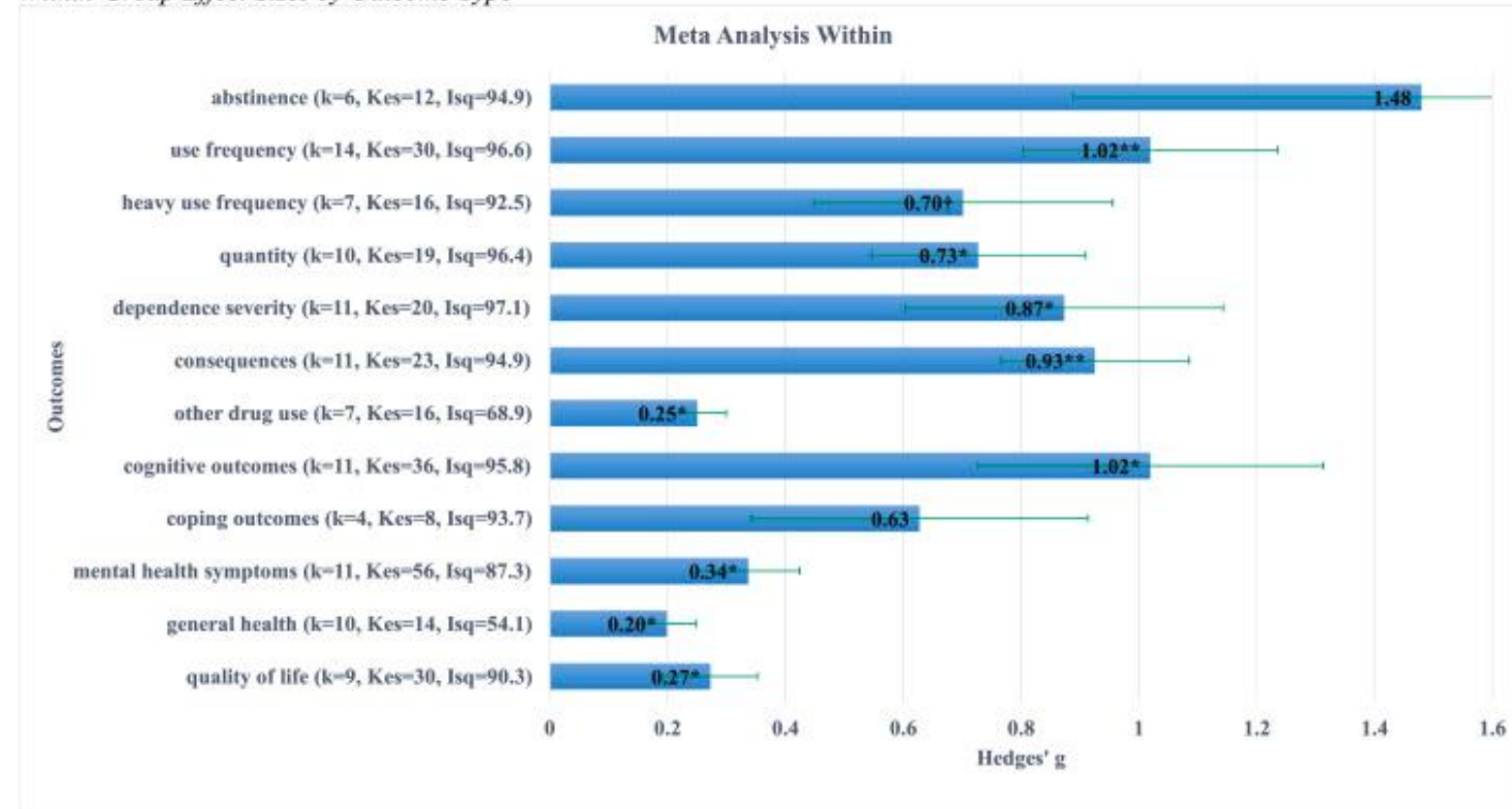
- Cognitive-behavioral treatments (coping skills training, relapse prevention)
- Contingency management
- Community reinforcement
- Twelve-step facilitation
- Mindfulness- and acceptance-based treatments
- Marital and family therapy

NIAAA ALCOHOL TREATMENT
NAVIGATOR
Pointing the way to evidence-based care



CBT for SUD meta-analysis

Within-Group Effect Sizes by Outcome Type



Notes. k = number of studies; Kes = number of effect sizes; Isq = I squared measure of heterogeneity in the pooled estimate. *p*-values are marked to indicate statistical significance: *** <0.0001, ** <0.001, * <0.01, and † <0.05. Binge/peak consumption outcome type not shown due to insufficient number of studies.

Magill et al (2026).

<https://www.sciencedirect.com/science/article/pii/S0005796726001543>



CBT for SUD review of reviews

“A "strong recommendation" was provided for CBT as an empirically supported treatment for SUD, based on effects on substance use, quality of evidence, and consideration of contextual factors (e.g., efficacy in diverse populations).”



[Journal Information](#)
[Journal TOC](#)



APA PsycArticles: Journal Article

An evaluation of cognitive behavioral therapy for substance use disorders: A systematic review and application of the society of clinical psychology criteria for empirically supported treatments.

Boness, C. L., Votaw, V. R., Schwebel, F. J., Moniz-Lewis, D. I. K., McHugh, R. K., & Witkiewitz, K. (2023). An evaluation of cognitive behavioral therapy for substance use disorders: A systematic review and application of the society of clinical psychology criteria for empirically supported treatments. *Clinical Psychology: Science and Practice*, 30(2), 129–142.
<https://doi.org/10.1037/cps0000131>

Mutual Support

- Local AA/NA/SMART or other mutual support meetings
- <https://InTheRooms.com>
- Harm Reduction for Alcohol: <https://hams.cc/>
- SMART Recovery: <https://smartrecovery.org/>
- For family/loved ones:
 - Foundation for Change <https://cmcffc.org/>
 - Family and Friends groups of SMART <https://smartrecovery.org/>

Should treatment content differ, depending on the patient's expressed goal of abstinence vs. reductions?

Abstinence goal



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Reduced harm goal



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Targeting abstinence goals

- Focus on skills to prevent any substance use
 - **Identify high risk situations for substance use**
 - **Avoid people, places, things**
- Prepare for “abstinence violation effect” and reducing harm if a lapse occurs
- Functional analysis and relapse prevention following lapses (shame reduction, re-commitment)
- Increase substance-free activities



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Targeting harm reduction goals

- Focus on setting goals and plans for reductions
 - # of days/week and/or amount used per day
 - Train **protective behavioral strategies**
- Prepare for moderation violation effect
- Functional analysis and prevention of substance use events that exceed limits (shame reduction, re-commitment)
- Increase substance-free or reduced alcohol activities



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Multiple Pathways to Recovery

- Recovery of functioning, well-being, and quality of life is possible among those with alcohol use disorder, and abstinence **may not be required to achieve these recovery outcomes**
- People with alcohol use disorder often have reduction goals, and we also must honor abstinence goals
- Shift attention from targeting individual alcohol use to examining and targeting **the causes and conditions, contextual factors that led to heavy drinking in the first place** (Witkiewitz and Tucker, 2025)



Resources from NIAAA and SAMHSA

Tools: <https://rethinkingdrinking.niaaa.nih.gov/>

Core Resource (free CEs available):

<https://www.niaaa.nih.gov/health-professionals-communities/core-resource-on-alcohol>

Latest SAMHSA TIP on Promoting Recovery:

TIP 65: Counseling Approaches To Promote Recovery From Problematic Substance Use and Related Issues



This Treatment Improvement Protocol (TIP) provides guidance to counselors, administrators, and supervisors about recovery-oriented services, supports, and care, allowing them to better serve individuals in or seeking recovery from problematic substance use.

Publication ID: PEP23-02-01-003

Publication Date: November 2023

Format: [Guides and Manuals](#)

 **Download**

[Counseling Approaches To Promote Recovery From Problematic Substance Use and Related Issues Treatment Improvement Protocol](#)





Thank you!

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Alcohol Use Disorder Part 1: Epidemiology, Evidence-Based Treatments, and Emerging Therapeutics

Lorenzo Leggio, M.D., Ph.D.

lorenzo.leggio@nih.gov

NIDA and NIAAA

September 24, 2026



National Institutes
of Health

Waves in Medication Development for AUD



1st Wave: FDA-approved medications

2nd Wave: medications with evidence of efficacy

3rd Wave: new targets and approaches

1st Wave Pharmacotherapies

Approved Medications

FDA-Approved Pharmacotherapies for Alcohol Dependence

Disulfiram

- Aldehyde dehydrogenase inhibitor
- When taken with alcohol leads to nausea, dizziness, headache, flushing
- Approved by FDA in 1954

Naltrexone

- Opioid antagonist
- Binds to opioid receptors, thus blocking alcohol reward pathways
- Approved by FDA in 1994

Acamprosate

- Glutamate receptor modulator
- Helps maintain complete abstinence during post-acute withdrawal
- Approved by FDA in 2004

SR-Naltrexone

- Sustained-release naltrexone
- Approved by FDA in 2004

NIAAA Clinician Guidelines

“All approved drugs have been shown to be effective adjuncts to the treatment of alcohol dependence. Thus, consider adding medication whenever you are treating someone with active alcohol dependence or someone who has stopped drinking in the past few months but is experiencing problems such as craving or slips.”

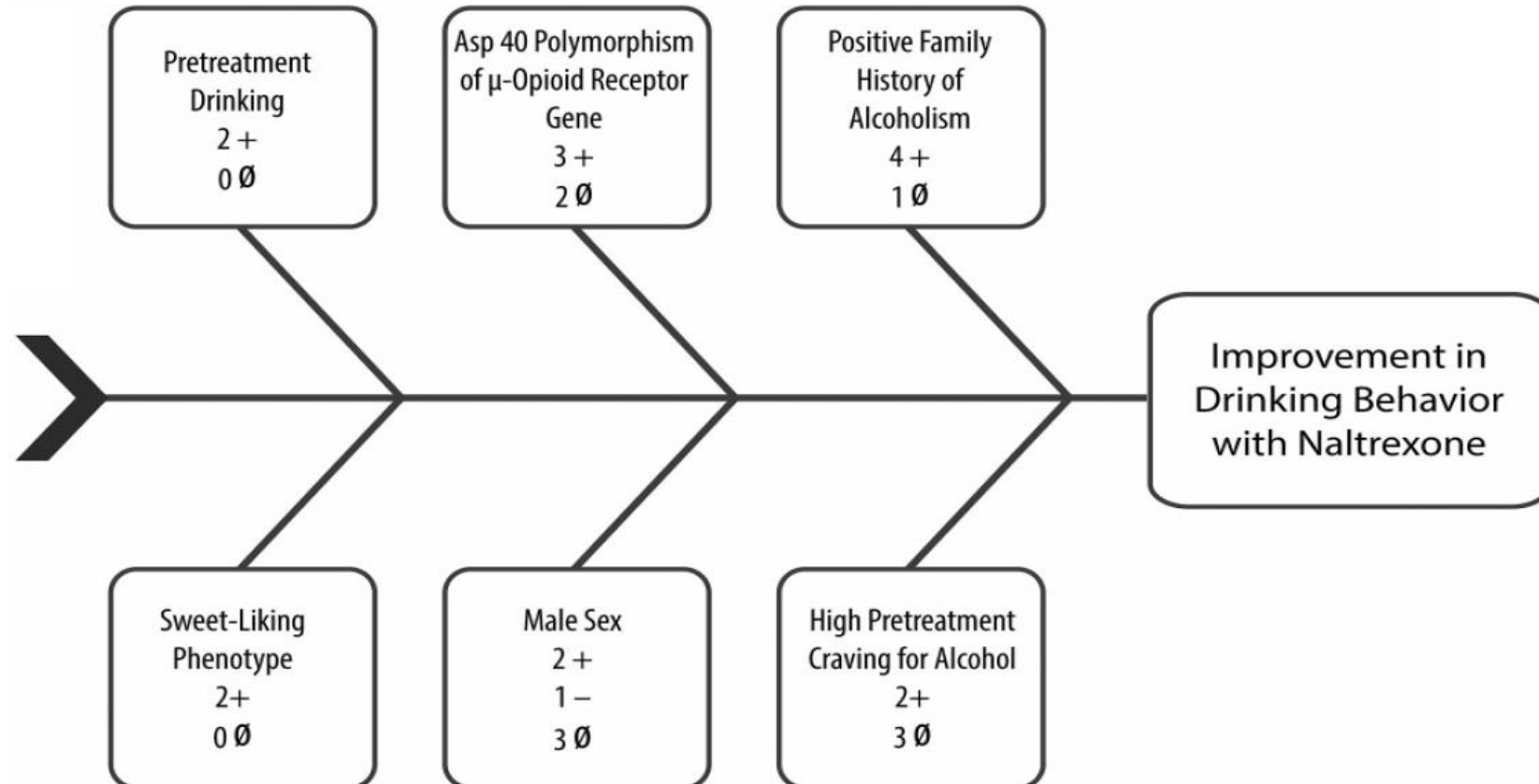
NIAAA NIH Government Publications. *Helping Patients Who Drink Too Much: A Clinician's Guide*. 2005, 2007 Edition. Available at <http://www.niaaa.nih.gov/publications/Practitioner/guide.pdf>.

Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence

**James C. Garbutt¹, Amy M. Greenblatt², Suzanne L. West², Laura C. Morgan²,
Alexei Kampov-Polevoy¹, Harmon S. Jordan² & Georgiy V. Bobashev²**

Department of Psychiatry and Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA¹ and RTI International, Research Triangle Park, NC, USA²

Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence



1st Wave: Approved Medications by the FDA

- Both acamprosate and oral naltrexone were associated with reduction in return to drinking
- There was a small but significant effect for both medications on several alcohol drinking outcomes
- Their efficacy is comparable to beta-blockers to prevent hospitalizations in people with CHF and SSRIs in people with depression, yet they are dramatically under utilized

Maisel et al., Addiction 2013
Jonas et al., JAMA 2014
Heilig & Leggio, Prog Brain Res 2016
McPheeters et al., JAMA 2023

June 16, 2021

Use of Medications for Alcohol Use Disorder in the US

Results From the 2019 National Survey on Drug Use and Health

Beth Han, MD, PhD, MPH¹; Christopher M. Jones, PharmD, DrPH, MPH²; Emily B. Einstein, PhD¹; Patricia A. Powell, PhD³; Wilson M. Compton, MD, MPE¹

Among an estimated 14.1 million adults with past-year AUD in 2019, only 1.6% used an FDA-approved evidence-based medication for AUD

2nd Wave Pharmacotherapies



Promising Medications
(non-approved by the FDA)

Evidence of efficacy and
possible off-label use

Promising Medications (not approved by the FDA) for AUD

Topiramate

- Increases GABAA-facilitated neuronal activity and simultaneously antagonizes AMPA and kainite glutamate receptor
- Approved by FDA for epilepsy, migraine and obesity

Ondansetron

- 5-HT₃ receptor antagonist
- Approved by the FDA for nausea and vomiting

Gabapentin

- GABA analog whose activity may involve interaction with voltage-gated calcium channels
- approved by the FDA for epilepsy and postherpetic neuralgia

Varenicline

- Nicotinic receptor partial agonist
- Approved by the FDA for smoking cessation

Baclofen

- GABA_B receptor agonist
- approved by the FDA for muscle spasticity

Prazosin/ Doxazosin

- α_1 -blocker
- approved by the FDA for hypertension (HTN) and benign prostatic hyperplasia (BPH)

Gabapentin and Topiramate for AUD

The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder

Victor I. Reus, M.D., Laura J. Fochtmann, M.D., M.B.I., Oscar Bukstein, M.D., M.P.H., A. Evan Eyler, M.D., M.P.H., Donald M. Hilty, M.D., Marcela Horvitz-Lennon, M.D., M.P.H., Jane Mahoney, Ph.D., R.N., PMHCNS-B.C., Jagoda Pasic, M.D., Ph.D., Michael Weaver, M.D., Cheryl D. Wills, M.D., Jack McIntyre, M.D. (Consultant), Jeremy Kidd, M.D. (Consultant), Joel Yager, M.D. (Systematic Review), Seung-Hee Hong (Systematic Review)

APA suggests that gabapentin and topiramate be offered to patients with moderate to severe AUD who:

- Have a goal of reducing alcohol consumption or achieving abstinence
- Prefer topiramate or gabapentin
- Are intolerant to or have not responded to naltrexone and acamprosate
- Have no contradictions to the use of these medications

Waves in Medication Development for AUD

1st Wave: FDA-approved medications

2nd Wave: medications with evidence of efficacy

3rd Wave: new targets and approaches

Baclofen for the treatment of alcohol use disorder: the Cagliari Statement

THE LANCET
Psychiatry

**Roberta Agabio, Julia MA Sinclair, Giovanni Addolorato, Henri-Jean Aubin, Esther M Beraha, Fabio Caputo, Jonathan D Chick, Patrick de La Selle, Nicolas Franchitto, James C Garbutt, Paul S Haber, Mathis Heydtmann, Philippe Jaury, Anne R Lingford-Hughes, Kirsten C Morley, Christian A Müller, Lynn Owens, Adam Pastor, Louise M Paterson, Fanny Pélissier, Benjamin Rolland, Amanda Stafford, Andrew Thompson, Wim van den Brink, Renaud de Beaurepaire, Lorenzo Leggio*

- Approved for AUD in France
- Endorsed by AASLD and ACG for AUD in patients with ALD

Waves in Medication Development for AUD

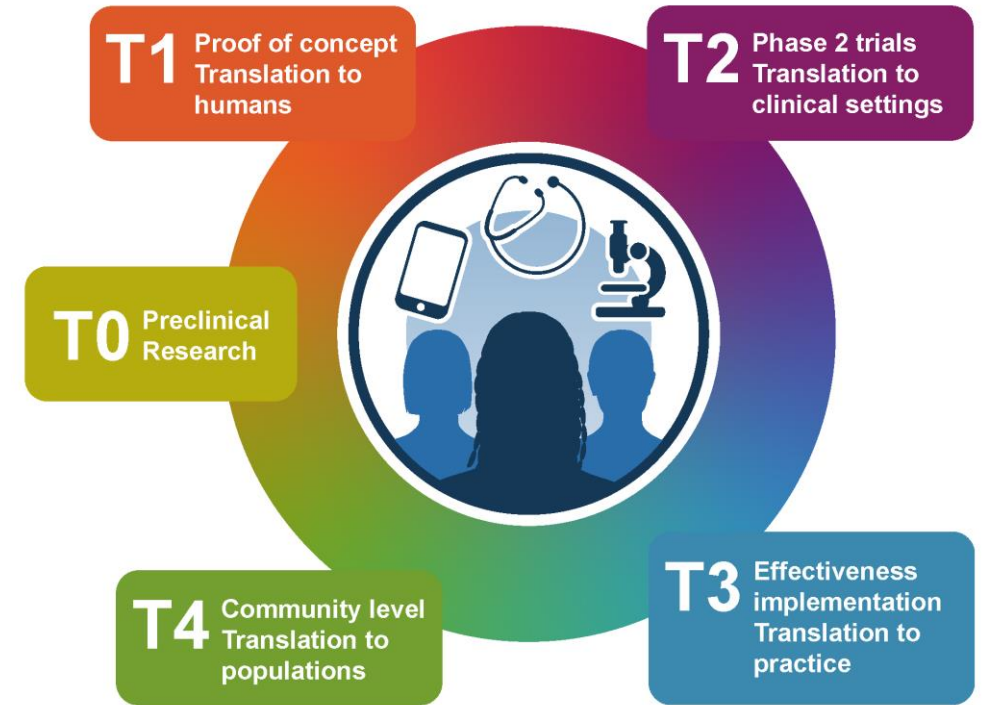


1st Wave: FDA-approved medications

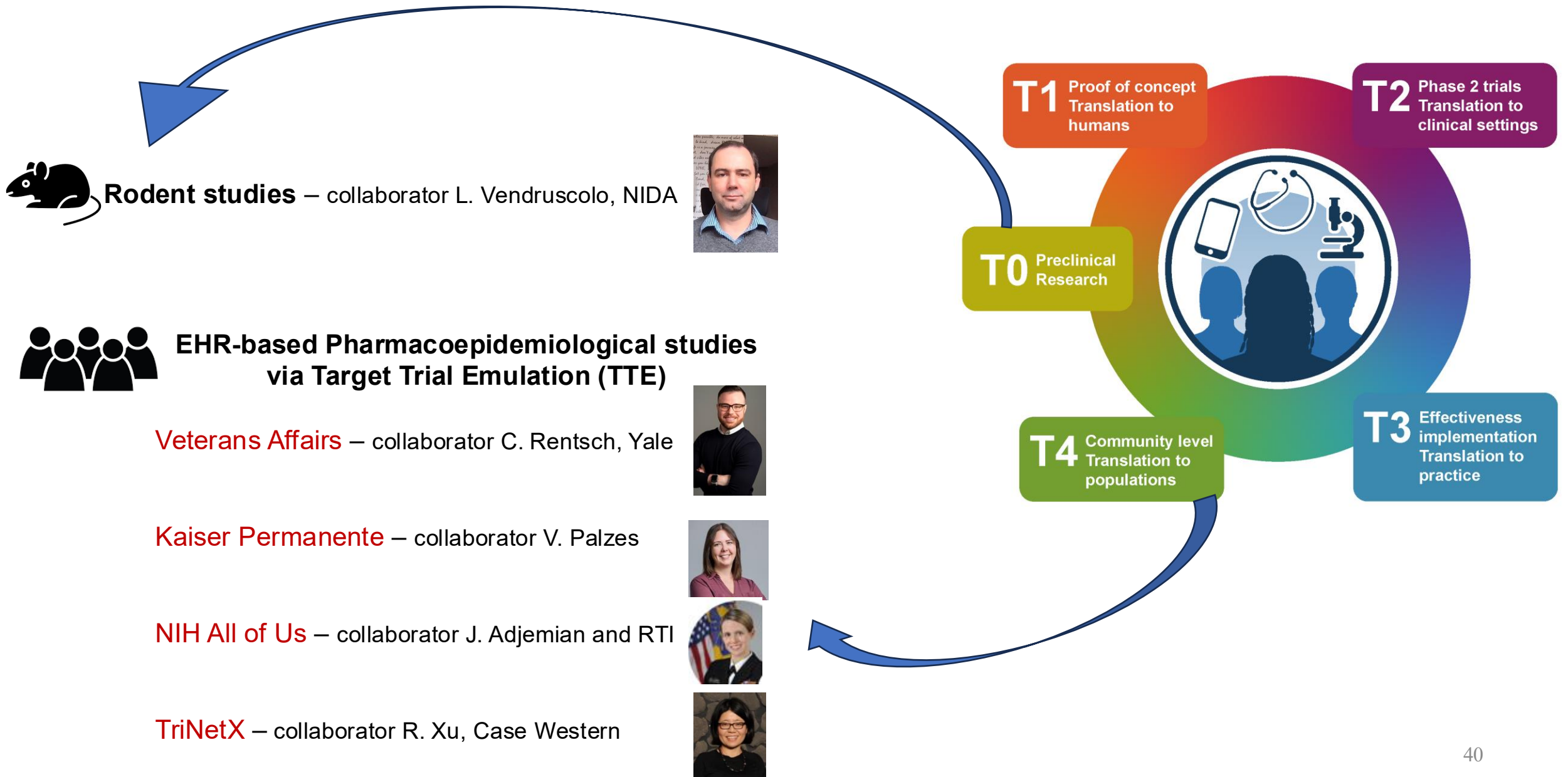
2nd Wave: medications with evidence of efficacy

3rd Wave: new targets and approaches

Translational Multidisciplinary Collaborative Approach



Translational Multidisciplinary Collaborative Approach



Addiction: A Brain Disease

FRONTIERS IN NEUROSCIENCE: THE SCIENCE OF SUBSTANCE ABUSE

1997

Addiction Is a Brain Disease, and It Matters

Alan I. Leshner

Science

The NEW ENGLAND JOURNAL of MEDICINE

2016

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Neurobiologic Advances from the Brain Disease Model of Addiction

Nora D. Volkow, M.D., George F. Koob, Ph.D., and A. Thomas McLellan, Ph.D.

Neuropsychopharmacology

2021

REVIEW ARTICLE **OPEN**

Addiction as a brain disease revised: why it still matters, and the need for consilience

Markus Heilig¹, James MacKillop^{2,3}, Diana Martinez⁴, Jürgen Rehm^{5,6,7,8}, Lorenzo Leggio⁹ and Louk J. M. J. Vanderschuren¹⁰

Personal View

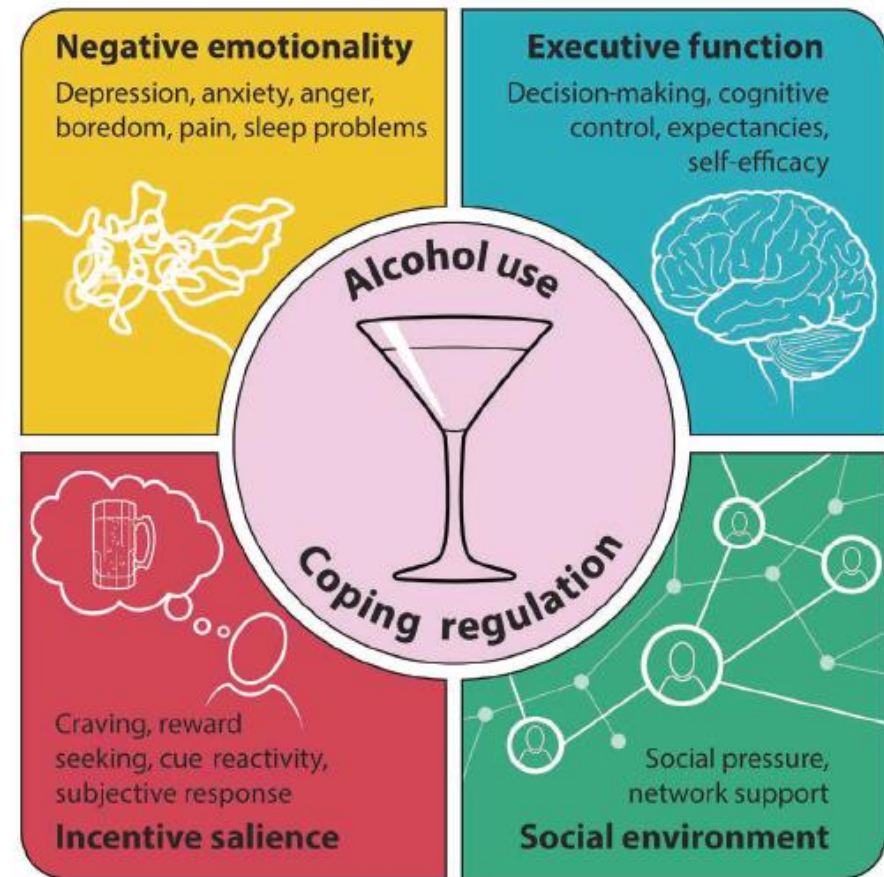
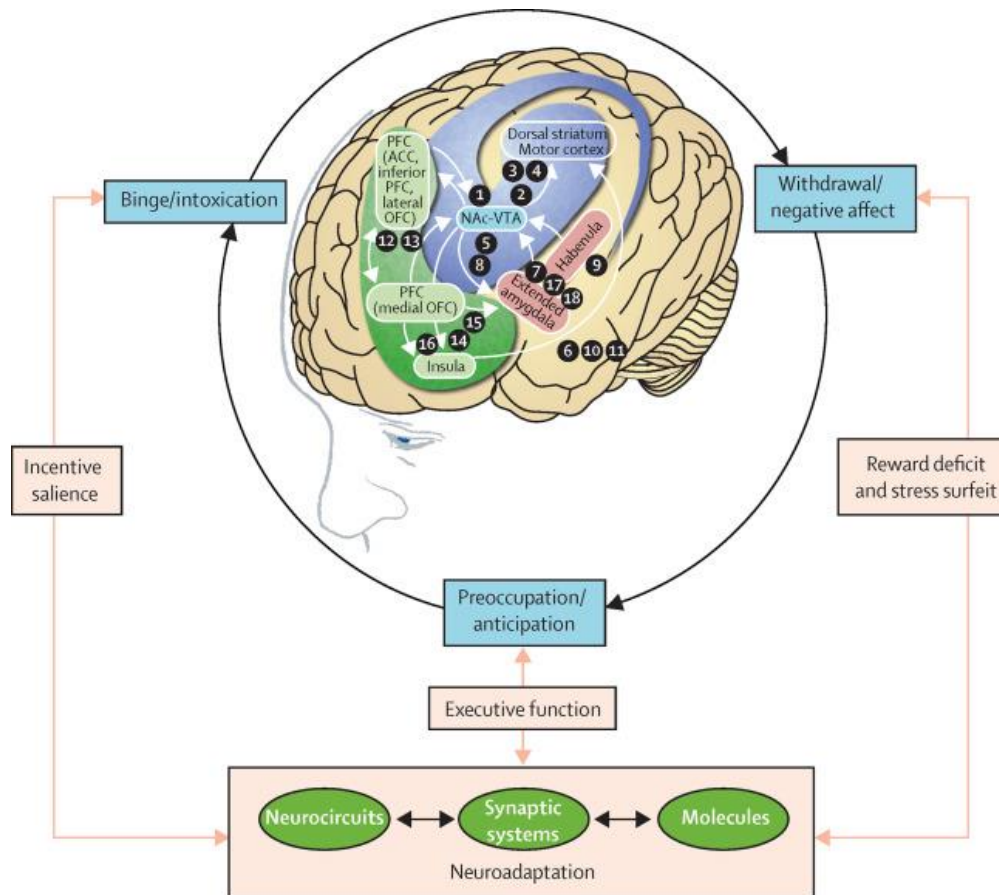
Reevaluating the brain disease model of addiction

Chrysanthi Blithikioti, Eiko I Fried, Emiliano Albanese, Matt Field, Ioana A Cristea



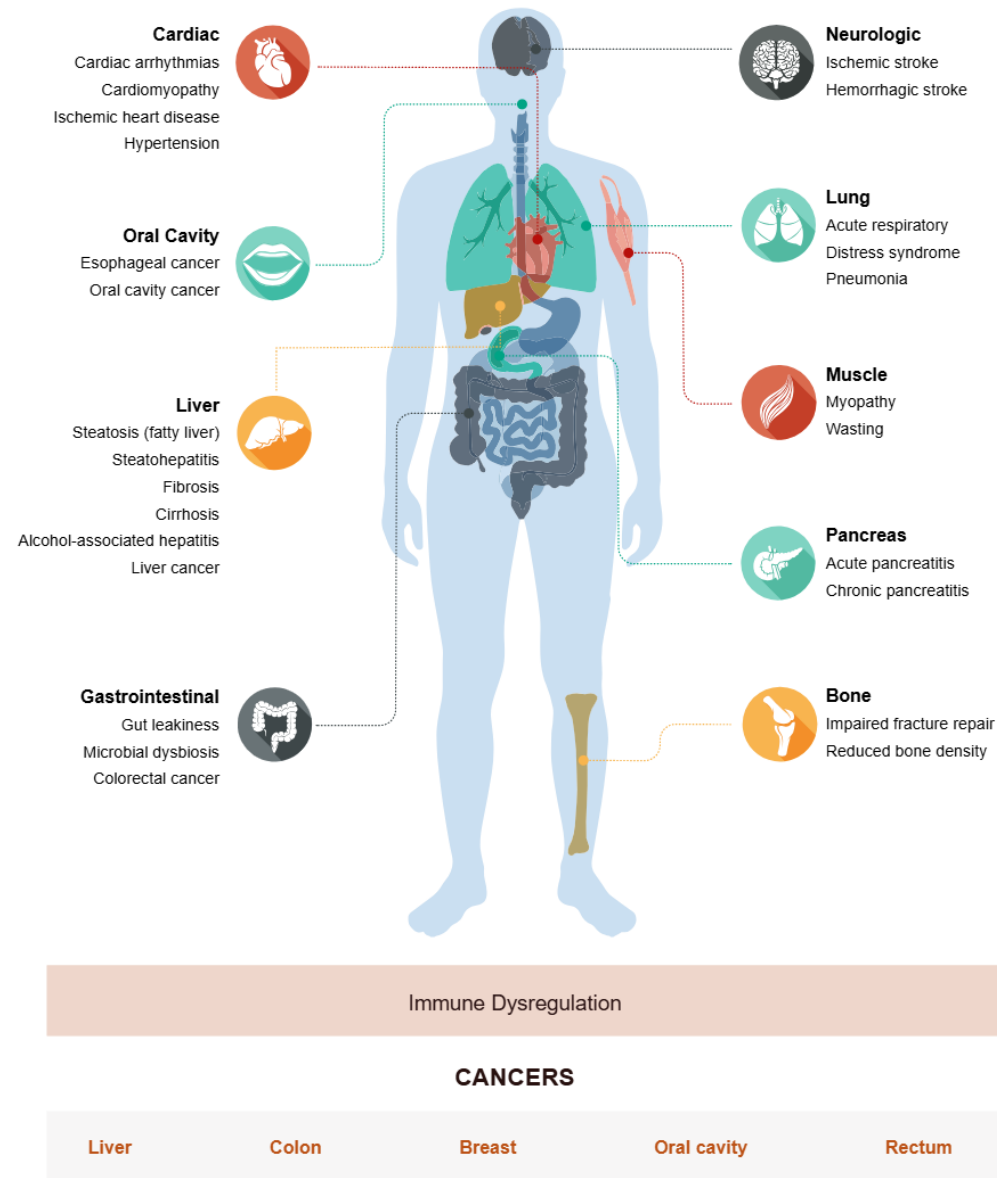
The brain disease model of addiction has dominated public and scientific discourse on addiction (termed substance *Lancet Psychiatry* 2025)

A Complex Multifactorial Medical Disease



AUD: A Whole-Body Disease

Alcohol-Associated Organ Damage



Thinking Outside the Box? Targeting Outside the Brain

Addiction is a brain disorder ...
and the connections between the periphery and the brain matter

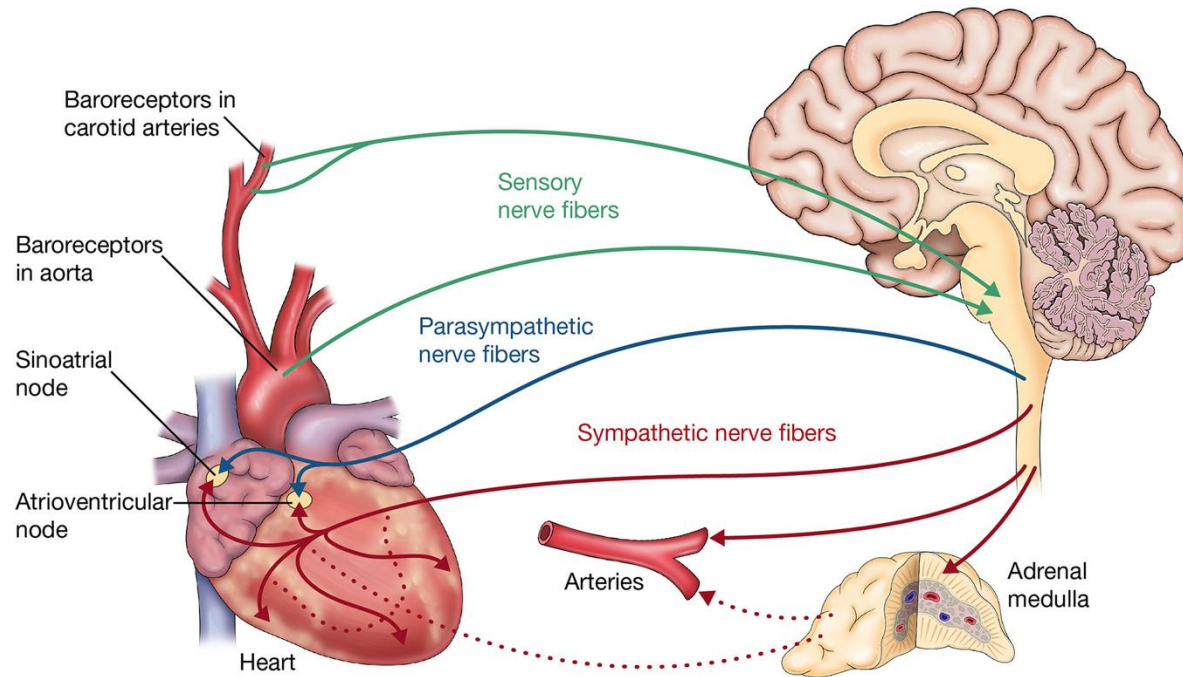


Figure from: Eddie et al., Addict Biol 2022

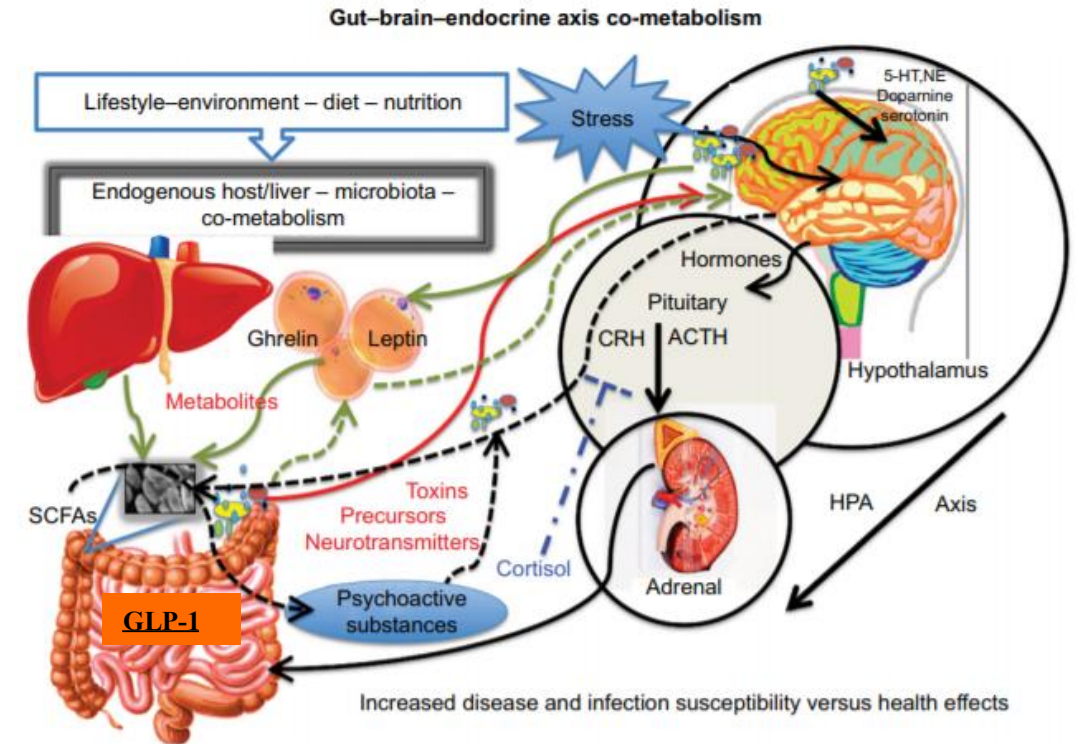


Figure from: Obrenovic et al., Pathol Lab Med Int 2017

Thinking Outside the Box? Targeting Outside the Brain

Addiction is a brain disorder ...
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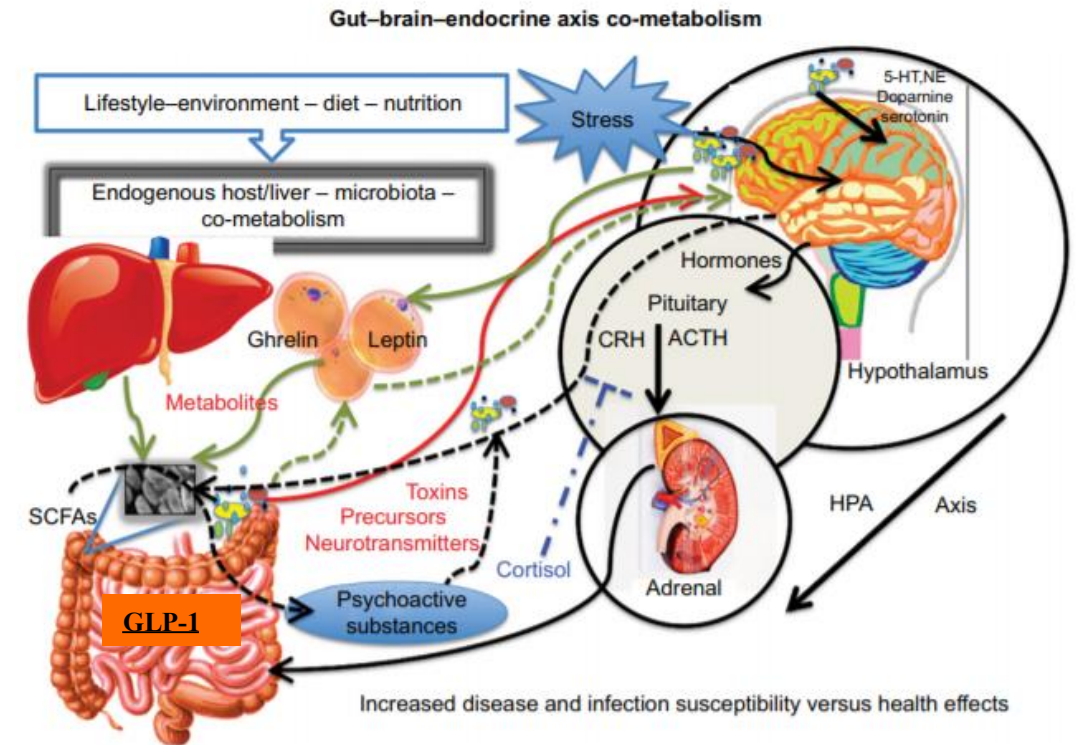
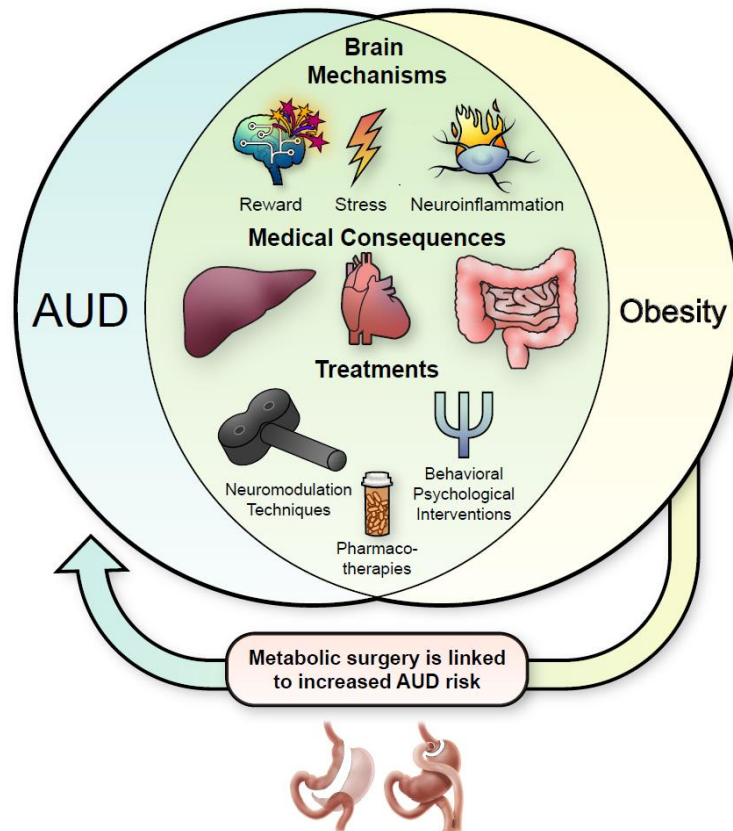


Figure from: Leggio et al., Mol Psychiatry 2025

Figure from: Obrenovic et al., Pathol Lab Med Int 2017

Gut-Brain, Heart-Brain and other Body-Brain Connections

Ghrelin

PHYSIOLOGY

PHYSIOLOGY 37: 5–15, 2022. First published December 29, 2021; doi:10.1152/physiol.00024.2021

REVIEW

From “Hunger Hormone” to “It’s Complicated”: Ghrelin Beyond Feeding Control

Sara L. Deschaine¹ and
Lorenzo Leggio^{1,2,3,4,5}

¹Clinical Psychoneuroendocrinology and
Neuropsychopharmacology Section, Translational Addiction
Medicine Branch, National Institute on Drug Abuse and National
Institute on Alcohol Abuse and Alcoholism, National Institutes of
Health, Baltimore and Bethesda, Maryland; ²Medication

Aldosterone / MR



Role of aldosterone and mineralocorticoid receptor (MR) in addiction: A scoping review

Claire L. Pince^{a,b,c,1}, Kimberly E. Whiting^{a,b,1}, Tammy Wang^{a,1}, Andr s H. L   ^{a,d,1},
Lisa A. Farinelli^a, Diane Cooper^c, Mehdi Farokhnia^a, Leandro F. Vendruscolo^{c,1,2},
Lorenzo Leggio^{a,*,2}

Inflammatory /
Immune Pathways

Received: 24 January 2023 | Accepted: 28 February 2023
DOI: 10.1111/acer.15049

COMMENTARY



The vicious cycle between (neuro)inflammation and alcohol use disorder: An opportunity to develop new medications?

Andr s H. L   ^{1,2} | Lara A. Ray³ | Lorenzo Leggio^{1,4,5,6}

Oxytocin

CNS Drugs (2016) 30:109–123
DOI 10.1007/s40263-016-0313-z



LEADING ARTICLE

Targeting the Oxytocin System to Treat Addictive Disorders: Rationale and Progress to Date

Mary R. Lee¹ · Matthew C. H. Rohn¹ · Gianluigi Tanda² · Lorenzo Leggio^{1,3}

Journal of the Endocrine Society, 2025, 9, bvaf141
https://doi.org/10.1210/endo/bvaf141
Advance access publication 9 October 2025
Expert Endocrine Consult



GLP-1

GLP-1 Therapeutics and Their Emerging Role in Alcohol and Substance Use Disorders: An Endocrinology Primer

Nirupam M. Srinivasan,¹ Mehdi Farokhnia,^{2,3} Lisa A. Farinelli,⁴ Anna Ferrulli,^{5,6}
and Lorenzo Leggio^{2,4,6,7,8,9}

FGF-21

iScience

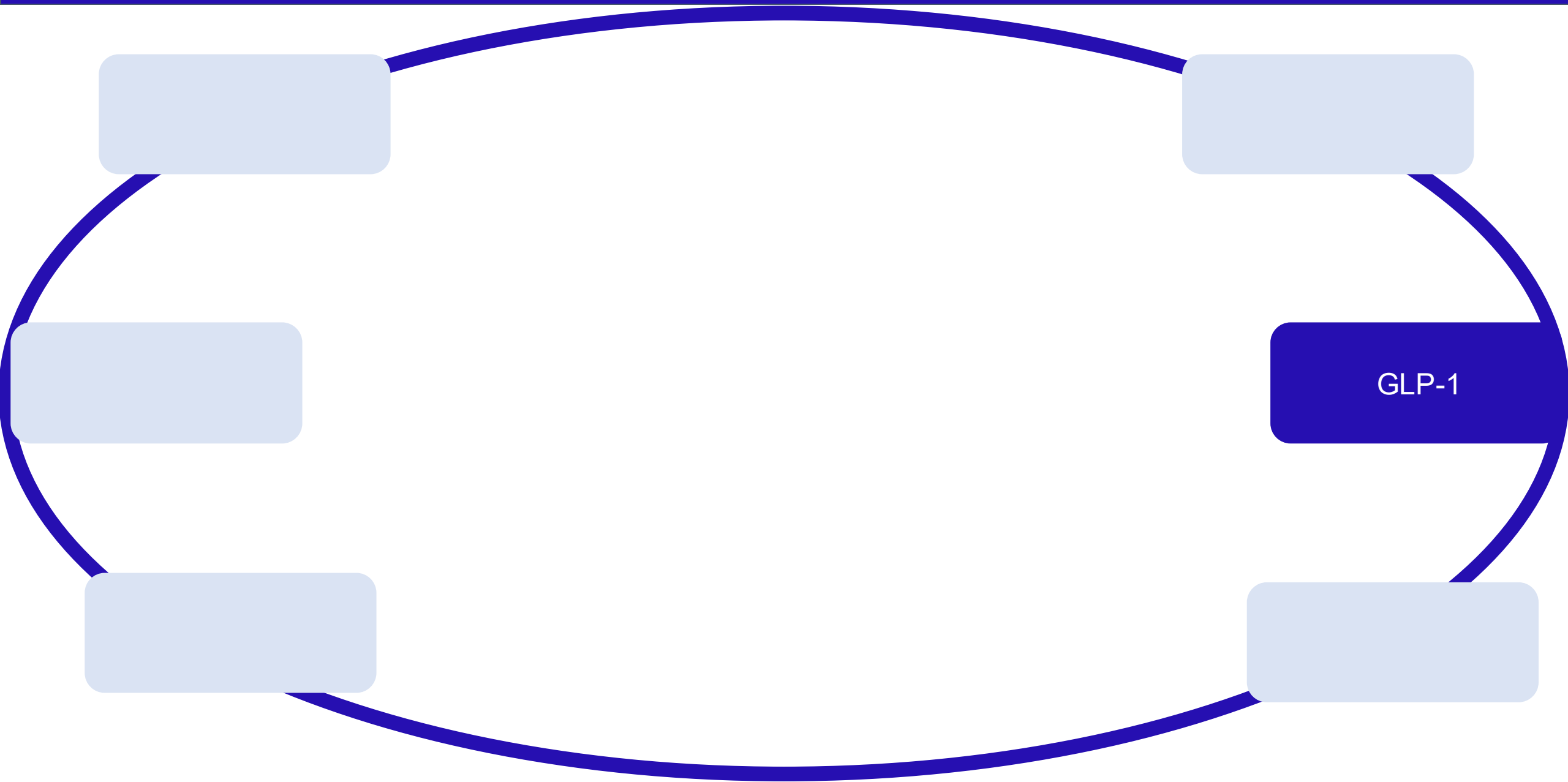


Review

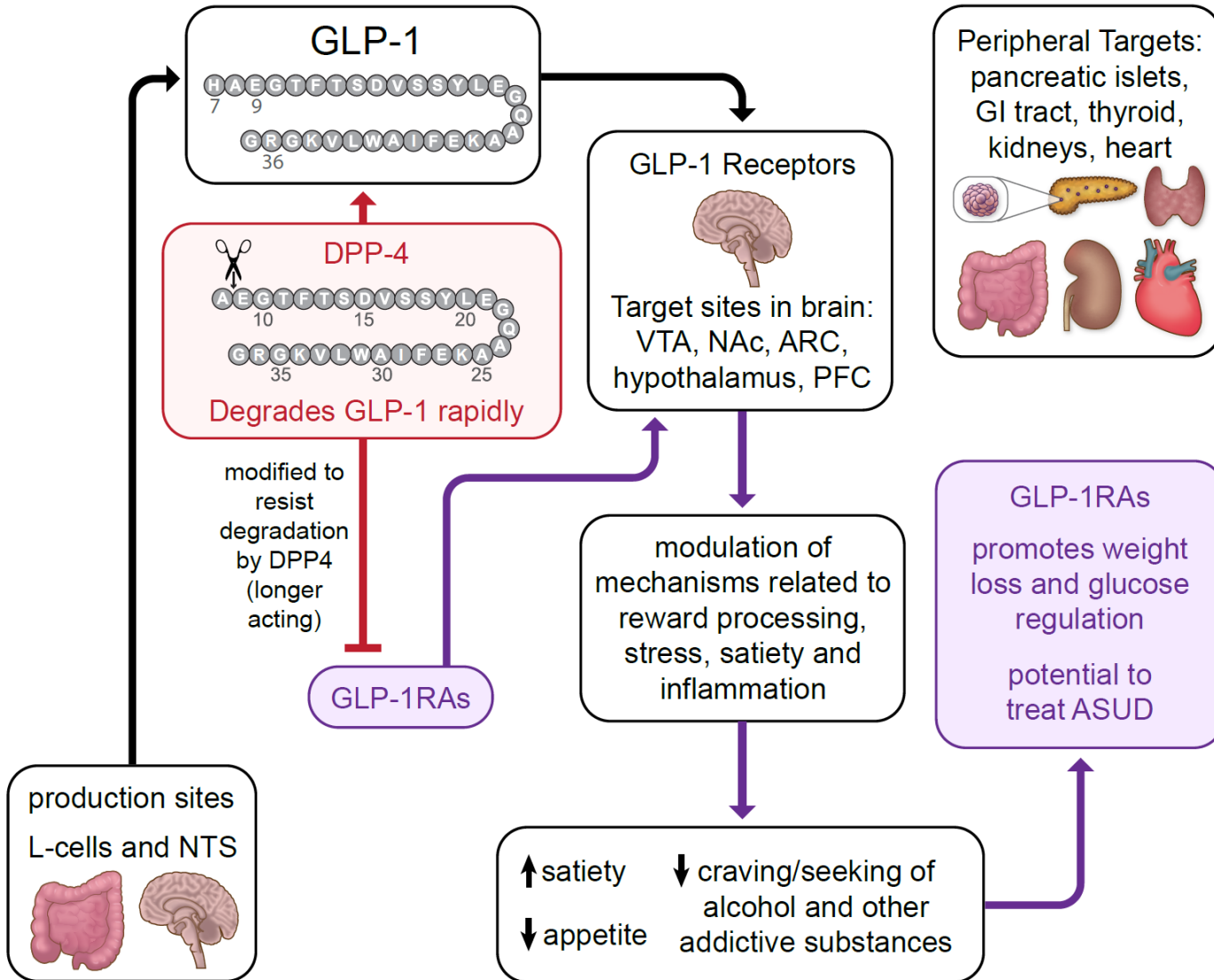
The crosstalk between fibroblast growth factor 21 (FGF21) system and substance use

Tammy Wang,^{1,2,5} Ryan E. Tyler,^{1,5} Oyenike Ilaka,^{1,3} Diane Cooper,⁴ Mehdi Farokhnia,^{1,6} and Lorenzo Leggio^{1,6,*}

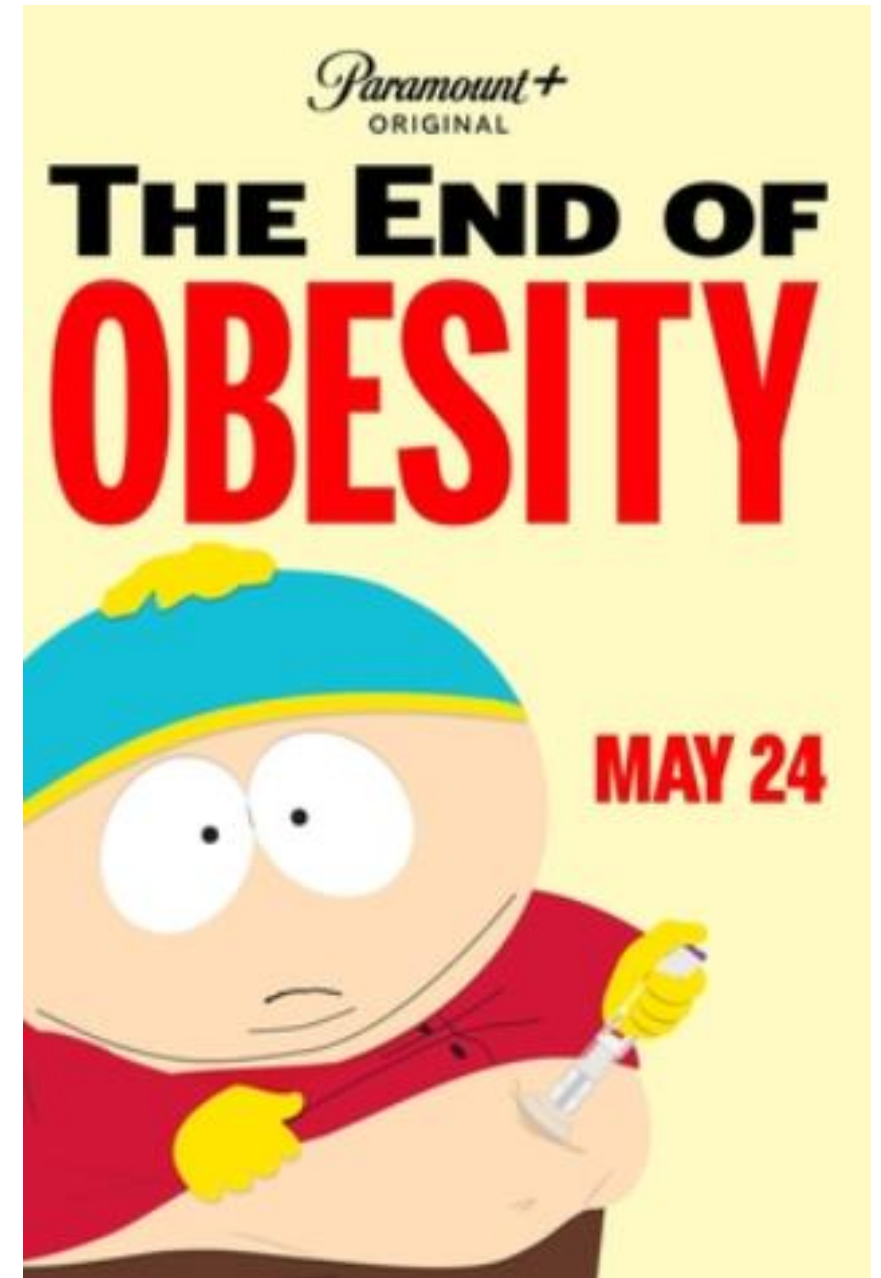
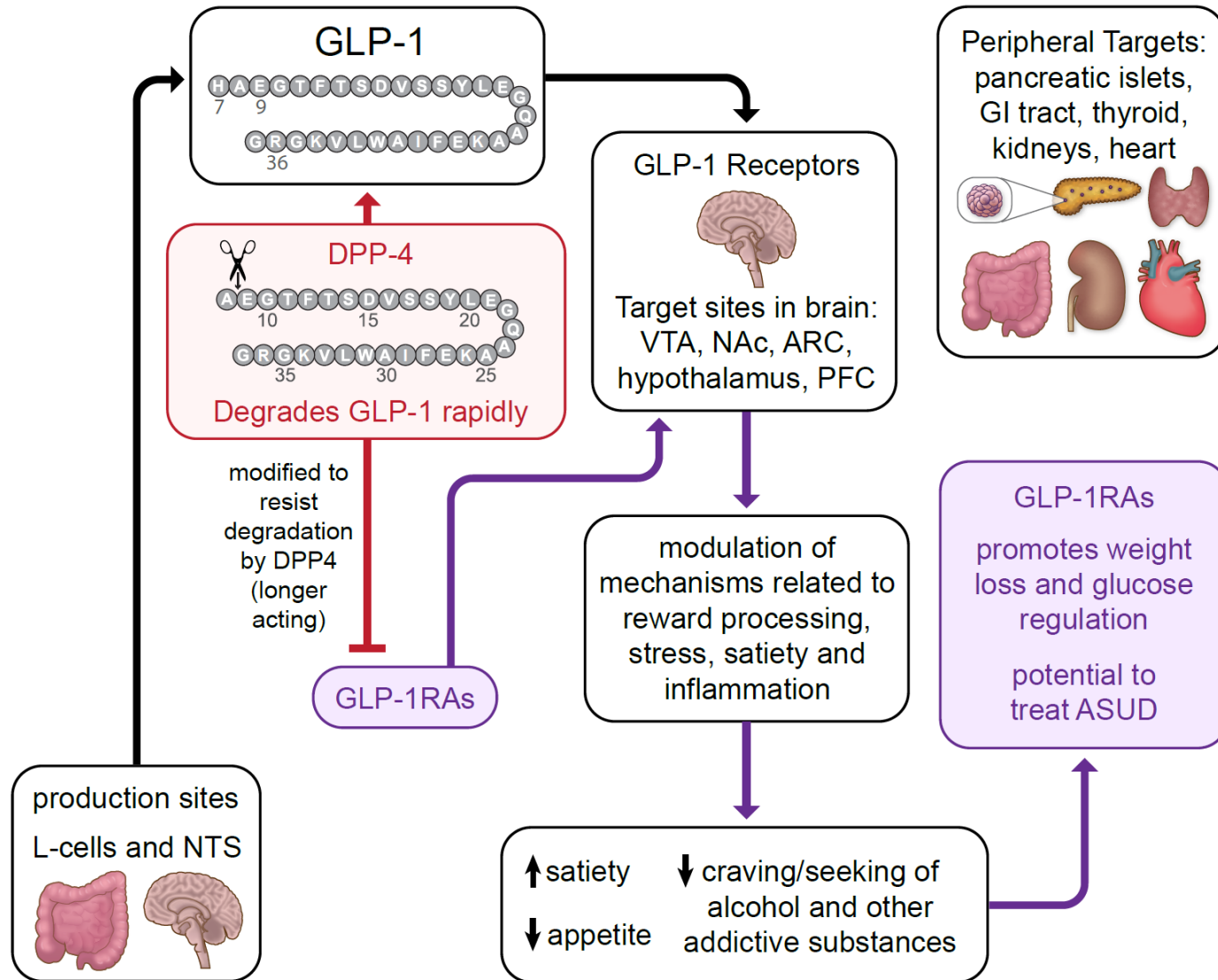
Gut-Brain, Heart-Brain and other Body-Brain Connections



GLP-1: Key Concepts



GLP-1: Key Concepts



Preclinical Evidence

Role of GLP-1 in AUD

Administration of GLP-1R agonists (GLP-1RAs) in rodents and NHP reduces:

- Alcohol conditioned place preference (CPP)
- Operant self-administration of alcohol
- 2-bottle free-choice
- Alcohol's discriminative interoceptive effects

Egecioglu et al., Psychoneuroendocrinology 2013

Shirazi et al., PLoS One 2013

Suchankova et al., Transl Psychiatry 2015

Vallof et al., Addict Biol 2016

Sorensen et al., Alcohol Clin Exp Res 2016

Sirohi et al., Physiol Behav 2016

Thomsen et al., Pharmacol Biochem Behav 2017

Marty*, Farokhnia* et al., Front Neurosci 2020

Chuong*, Farokhnia*, Khom*, et al., JCI Insight 2023

Aranäs et al., eBioMedicine 2023

Windram et al., Psychopharmacology 2025

See also recent reviews from our lab:

Bruns et al., Pharmacol Res 2024

Guo et al., J Neurosci 2025

Srinivasan et al., J Endocr Soc 2025

Farokhnia & Leggio, JAMA Psychiatry 2026

Preclinical Evidence

Role of GLP-1 in AUD

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- Alcohol conditioned place preference (CPP)
- Operant self-administration of alcohol
- 2-bottle free-choice
- Alcohol's discriminative interoceptive effects

INVITED REVIEW

Addiction Biology

SSA

WILEY

The future of translational research on alcohol use disorder

Lara A. Ray¹  | Erica N. Grodin¹ | Lorenzo Leggio²  | Anita J. Bechtholt³ |
Howard Becker⁴ | Sarah W. Feldstein Ewing⁵ | James David Jentsch⁶ |
Andrea C. King⁷ | Barbara J. Mason⁸ | Stephanie O'Malley⁹ |
James MacKillop¹⁰  | Markus Heilig¹¹ | George F. Koob¹²

Translational Psychiatry

www.nature.com/tp

SYSTEMATIC REVIEW **OPEN**

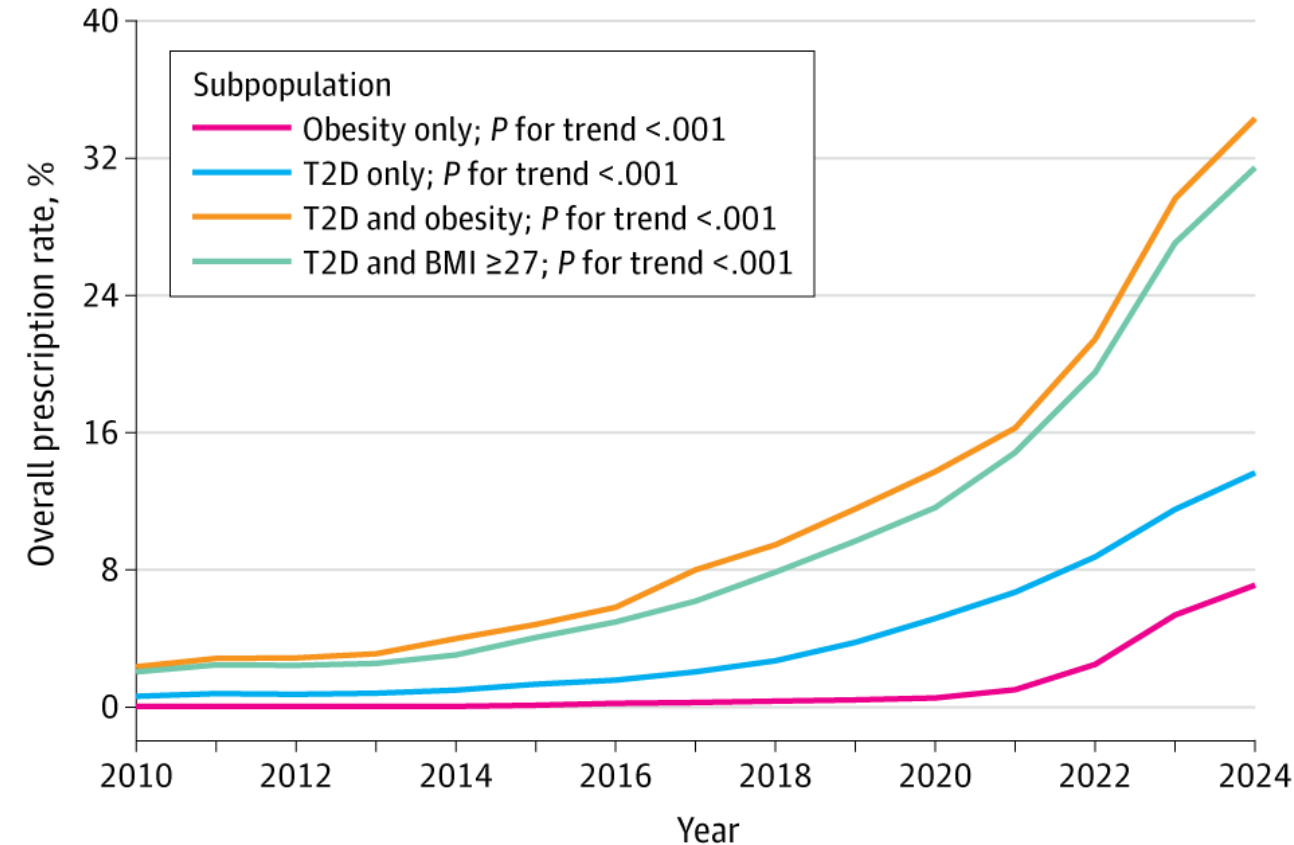
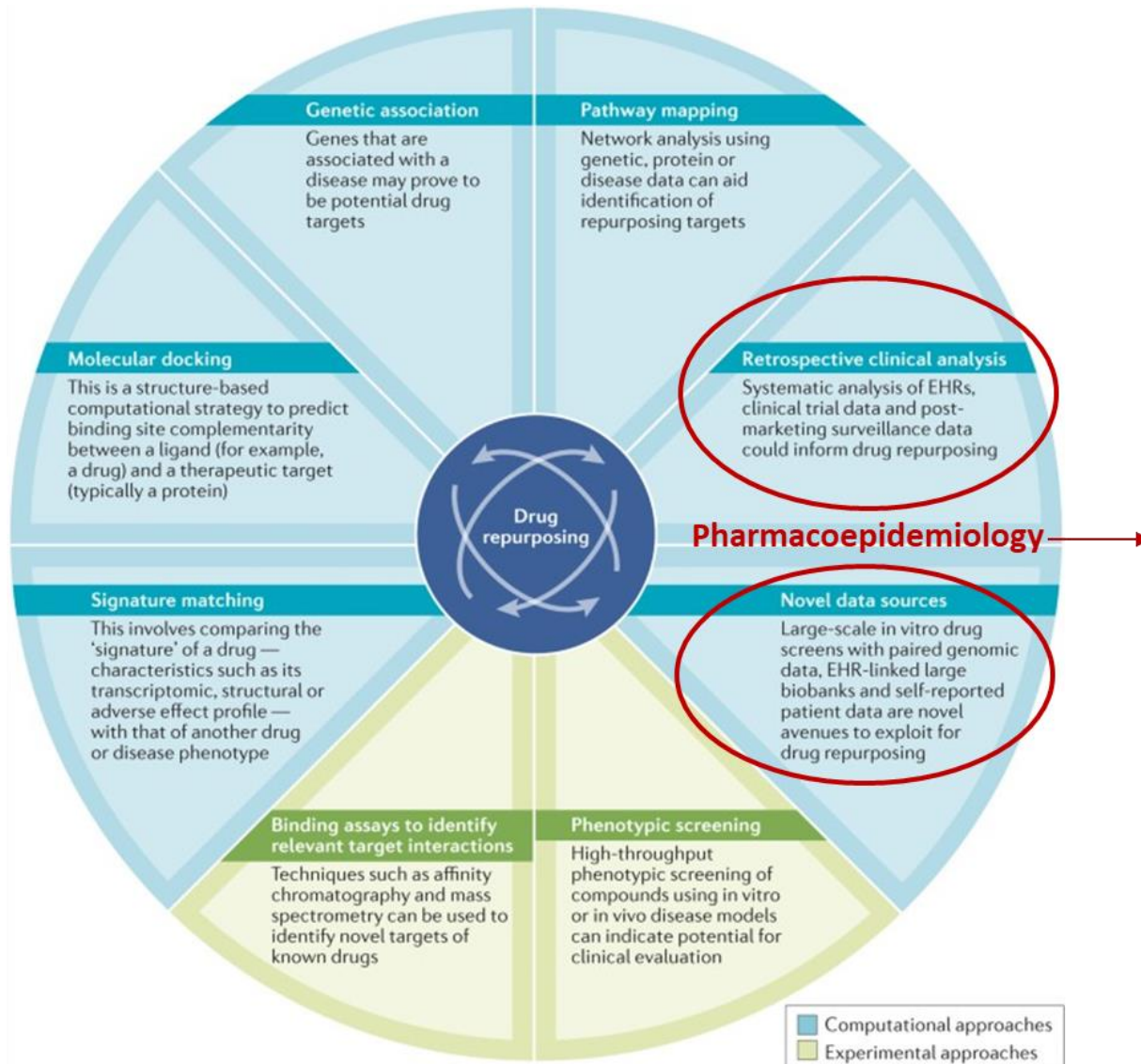
 Check for updates

Translating medication effects for alcohol use disorder across preclinical, human laboratory, and clinical trial outcomes using meta-analysis

Steven J. Nieto ^{1,2} ², Suzanna Donato¹, Han Du¹, Lindsay R. Meredith ¹, Wave-Ananda Baskerville¹, Kaitlin R. McManus ¹, Molly Magill³, Marcelo F. Lopez ⁴, Howard C. Becker ⁴ and Lara A. Ray ^{1,5}

Drug Repurposing via Real-World EHR data

Pharmacoepidemiological TTE Approaches



Received: 7 May 2022 | Revised: 20 July 2022 | Accepted: 9 August 2022
DOI: 10.1111/bcpt.13776

ORIGINAL ARTICLE



Use of GLP-1 receptor agonists and subsequent risk of alcohol-related events. A nationwide register-based cohort and self-controlled case series study

Ida Kim Wium-Andersen^{1,2} | Marie Kim Wium-Andersen² | Anders Fink-Jensen¹ | Jørgen Rungby^{3,4} | Martin Balslev Jørgensen¹ | Merete Osler^{2,5}

RESEARCH REPORT

ADDICTION **SSA**

The association between glucose-dependent insulinotropic polypeptide and/or glucagon-like peptide-1 receptor agonist prescriptions and substance-related outcomes in patients with opioid and alcohol use disorders: A real-world data analysis

Fares Qeadan | Ashlie McCunn | Benjamin Tingey

Genetically modeled GLP1R and GIPR agonism reduce binge drinking and alcohol-associated phenotypes: a multi-ancestry drug-target Mendelian randomization study

Joshua Reitz ^{1,4}, Daniel B. Rosoff^{1,2,4}, Tyler Perlstein¹, Alexandra Wagner ¹, Jeesun Jung ¹, Josephin Wagner ¹, Benjamin C. Reiner ¹ and Falk W. Lohoff ^{1,5}

Molecular Psychiatry

Communications Medicine

<https://doi.org/10.1038/s43856-026-01685-5>

Article in Press

Exploratory associations between co-occurring opioid and alcohol use disorders and GIP/GLP-1 receptor agonist treatment

Received: 21 October 2025 | Fares Qeadan, Ashlie McCunn, Benjamin Tingey & Phillip J. Kroth

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

William Wang¹, Nora D. Volkow² , Nathan A. Berger³, Pamela B. Davis³, David C. Kaelber⁴ & Rong Xu⁵

Accepted: 8 May 2024

JAMA Psychiatry | Brief Report

Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder

Markku Lähteenvuuo, MD, PhD; Jari Tiihonen, MD, PhD; Anssi Solismaa, MD, PhD; Antti Tanskanen, PhD; Ellenor Mittendorf-Rutz, PhD; Heidi Taipale, PhD

GLP-1 Receptor Agonists and Substance Use Disorders in Older Adults With Type 2 Diabetes: A Target Trial Emulation

Hao Dai¹ | Rotana M. Radwan² | Grant D. Scheffele² | Huilin Tang³ | Amy Sheer⁴ | Hsin-Yueh Lin² | Pengyue Zhang¹ | Darlene Adirika⁵ | Kate Luong⁵ | Jiang Bian^{1,6,7} | Jingchuan Guo²

WILEY



Obesity

Association of GLP-1 receptor agonists with alcohol use disorder-related and substance use disorder-related hospital admissions during treatment and after discontinuation: a Swedish register-based within-individual observational study

Patrick Bach, Johan Franck, Jonas Hallgren, Hårie Widing, Mika Gissler, Jeanette Westman

Lancet Psychiatry 2026; 13: 669-77

nature medicine

Article

<https://doi.org/10.1038/s41591-024-03412-w>

Mapping the effectiveness and risks of GLP-1 receptor agonists

Received: 14 June 2024

Yan Xie ^{1,2,3,4}, Taeyoung Choi^{1,2} & Ziyad Al-Aly ^{1,2,5,6,7}

BMJ Open Association between GLP-1 receptor agonists and alcohol-related hospitalisations among adults with alcohol use disorder: multi-target trial emulation study

Patricia J Rodriguez ¹, Jay B Lusk^{2,3}, Hemalkumar B Mehta ^{1,4}, Joseph F Levy⁵, Andreas P Kalogeropoulos⁵, Samir Soneji⁷, Duy Do¹, Emma Holler¹, Emily Webber¹, Ty Gluckman⁸, Nicholas Stucky ¹

Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes: cohort study

Miao Cai^{1,2}, Taeyoung Choi^{1,2,3}, Yan Xie^{1,2,3,4}, Ziyad Al-Aly^{1,2,5,6,7}



Alcohol Use Following GLP-1 Receptor Agonist Therapy in the Cooper Center Longitudinal Study

Tamanna Basri, MD, Stephanie J. Shea, MD, Adam Brantley, MD, Rahul Tharoor, MD, Julia Chavez, MD, Mehvish Khan, MD, William G. Burton, MD, David Leonard, PhD, Carolyn E. Barlow, PhD, Kerem Shuval, PhD, Laura F. DeFina, MD, E. Sherwood Brown, MD, PhD



Drug Repurposing via Real-World EHR data Pharmacoepidemiological / TTE Approaches

- We have contributed to this field through three distinct but complementary EHR-based studies examining real-world alcohol consumption.
- The innovative, unique, and clinically impactful aspect of our studies, vis-à-vis other EHR-based studies, is the focus on alcohol **quantity** which is the basis of FDA-accepted outcomes.



Qualification Statement

Qualification of the 2-level Reduction of the World Health Organization (WHO) Risk Drinking Levels (RDL) of Alcohol Consumption, an Efficacy Endpoint in Pivotal Clinical Trials with Adults Diagnosed with Alcohol Use Disorder (AUD)

Date: January 14, 2025



GLP-1RAs, but not DPP-4 inhibitors, reduce alcohol intake



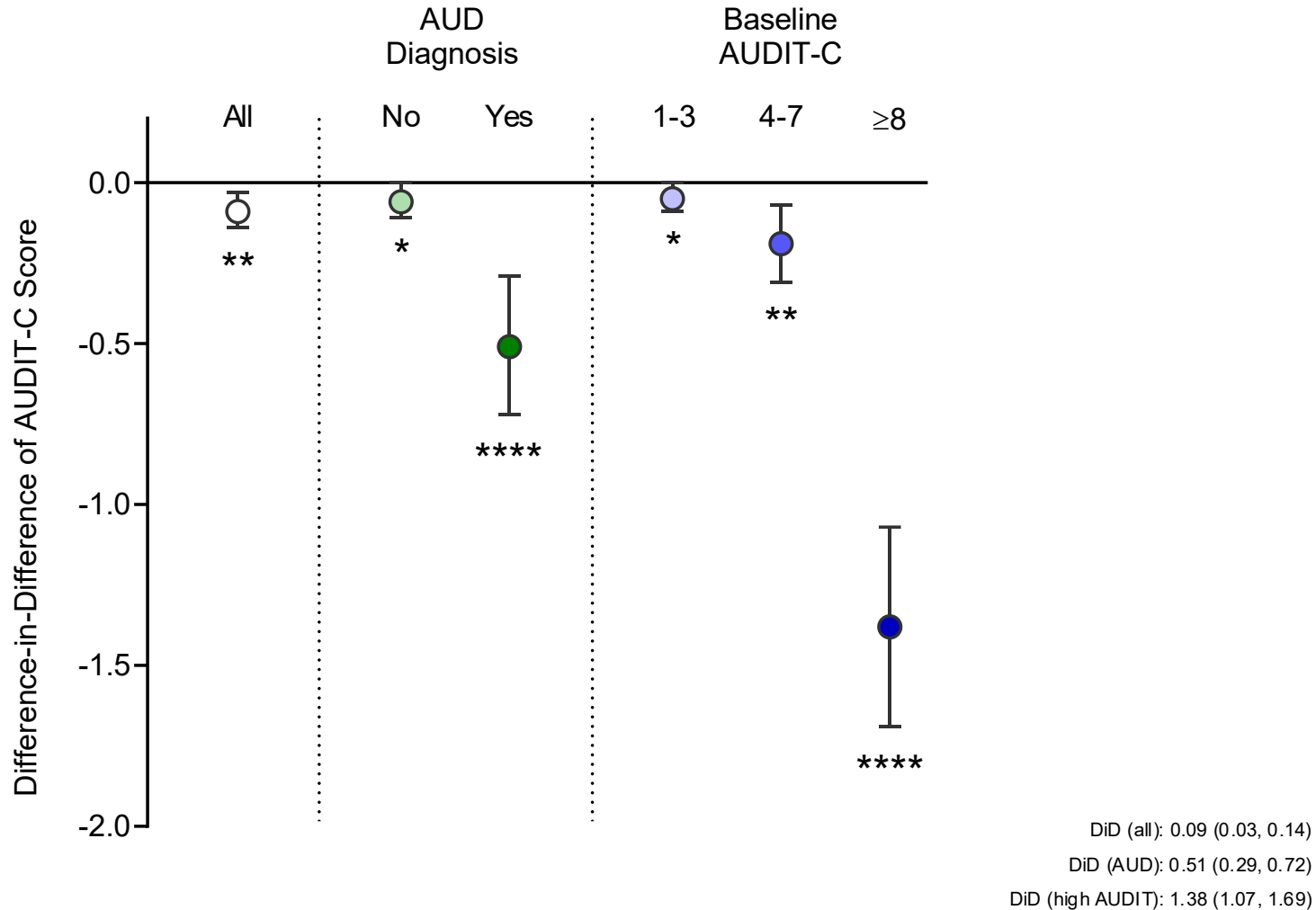
- ~13.5 million veterans ever received care in the Department of Veterans Affairs, the largest integrated healthcare system in the US
- All VA patients receive an annual alcohol screening via the AUDIT-C score

Collaborators: Leandro Vendruscolo (NIDA IRP) and Chris Rentsch (Yale)

Farokhnia et al., JCI 2025

GLP-1RAs, but not DPP-4 inhibitors, reduce alcohol intake

Receipt of GLP-1RAs, compared to unexposed, was associated with decreased AUDIT-C score, especially among those with AUD and hazardous alcohol use



Drug Repurposing via Real-World EHR data Pharmacoepidemiological TTE Approaches

We have recently replicated the association between GLP-1RA prescription and reduction in **quantity** of alcohol drinking via two additional independent pharmacoepidemiological human studies with Kaiser Permanente and NIH All of US

Archival Report

Biological
Psychiatry:
GOS



Glucagon-Like Peptide-1 Receptor Agonists and Alcohol Use: A Real-World Observational Study in a Large, Integrated Health Care System

Vanessa A. Palzes, Brianna Costales, Stacy Sterling, Andrea Kline-Simon, Lorenzo Leggio, and Mehdi Farokhnia

Kaiser Permanente
Research

Alcohol: Clinical and Experimental Research



RESEARCH ARTICLE OPEN ACCESS

Behavior, Treatment and Prevention

Association of GLP-1 Receptor Agonist Prescriptions and Alcohol Consumption in the National Institutes of Health's *All of Us* Cohort

Benjamin Tyndall¹ | Angela Gasdaska¹ | M. Daniel Brannock¹ | Ed Preble¹ | Melissa McPheeters¹ | Laura Marcial¹ | Ariba Huda¹ | Josephine Egan² | Tamara R. Litwin² | Jennifer Adjemian² | Chandan Sastry² | Mehdi Farokhnia² | Lorenzo Leggio²

NIH National Institutes of Health



Are GLP-1 Receptor Agonists a New Treatment for AUD (and SUD)?

Comment

nature medicine

Addictive disorders

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

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

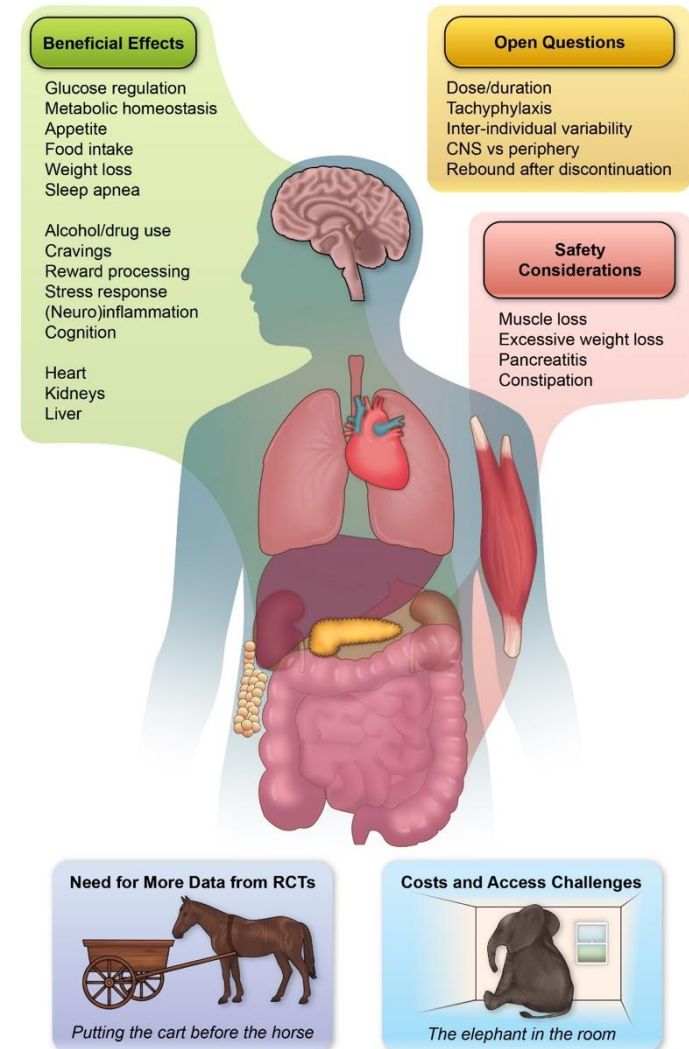
Lorenzo Leggio, Christian S. Hendershot, Mehdi Farokhnia, Anders Fink-Jensen, Mette Kruse Klausen, Joseph P. Schacht & W. Kyle Simmons

 Check for updates

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

Initial evidence from animal and human studies

Preclinical work on the effects of GLP-1RAs on use of alcohols 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 mouse



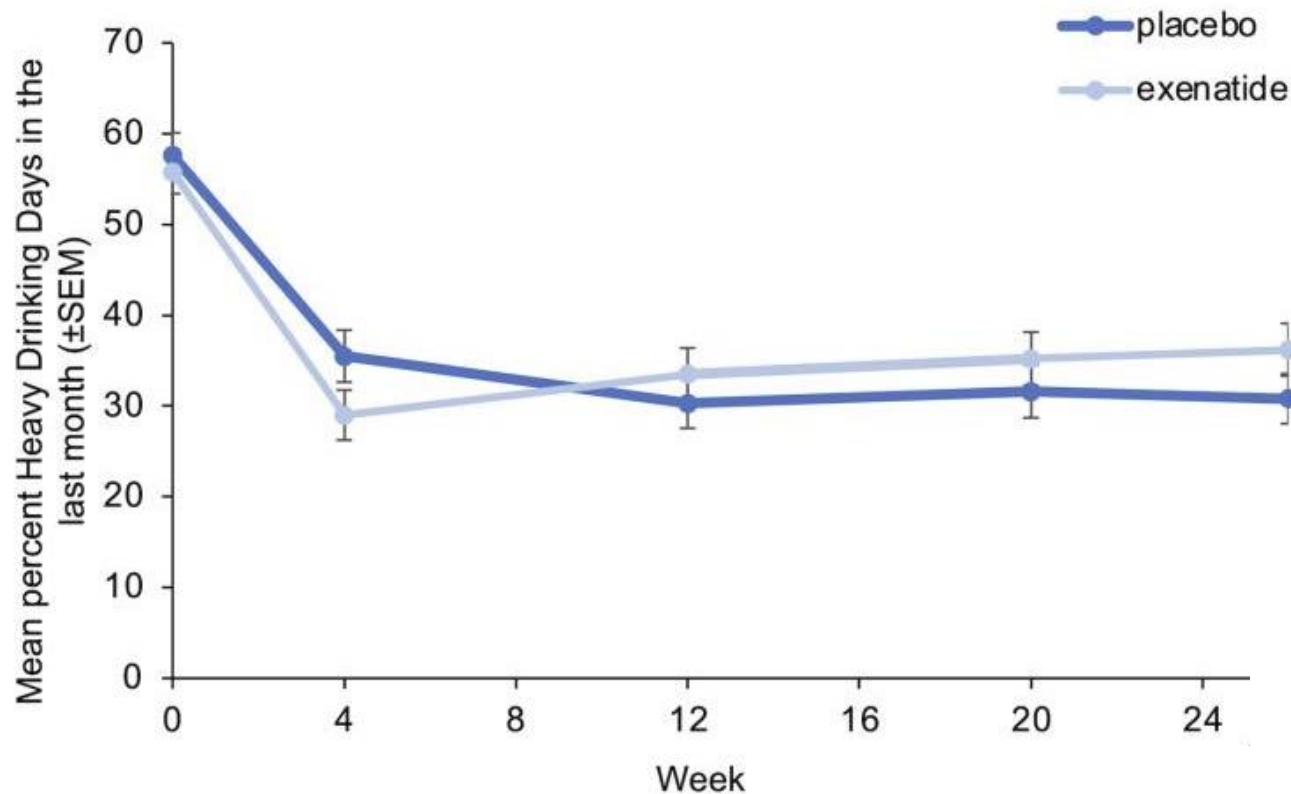
The GLP-1RA Exenatide did not reduce alcohol drinking in a RCT

JCI insight

CLINICAL MEDICINE

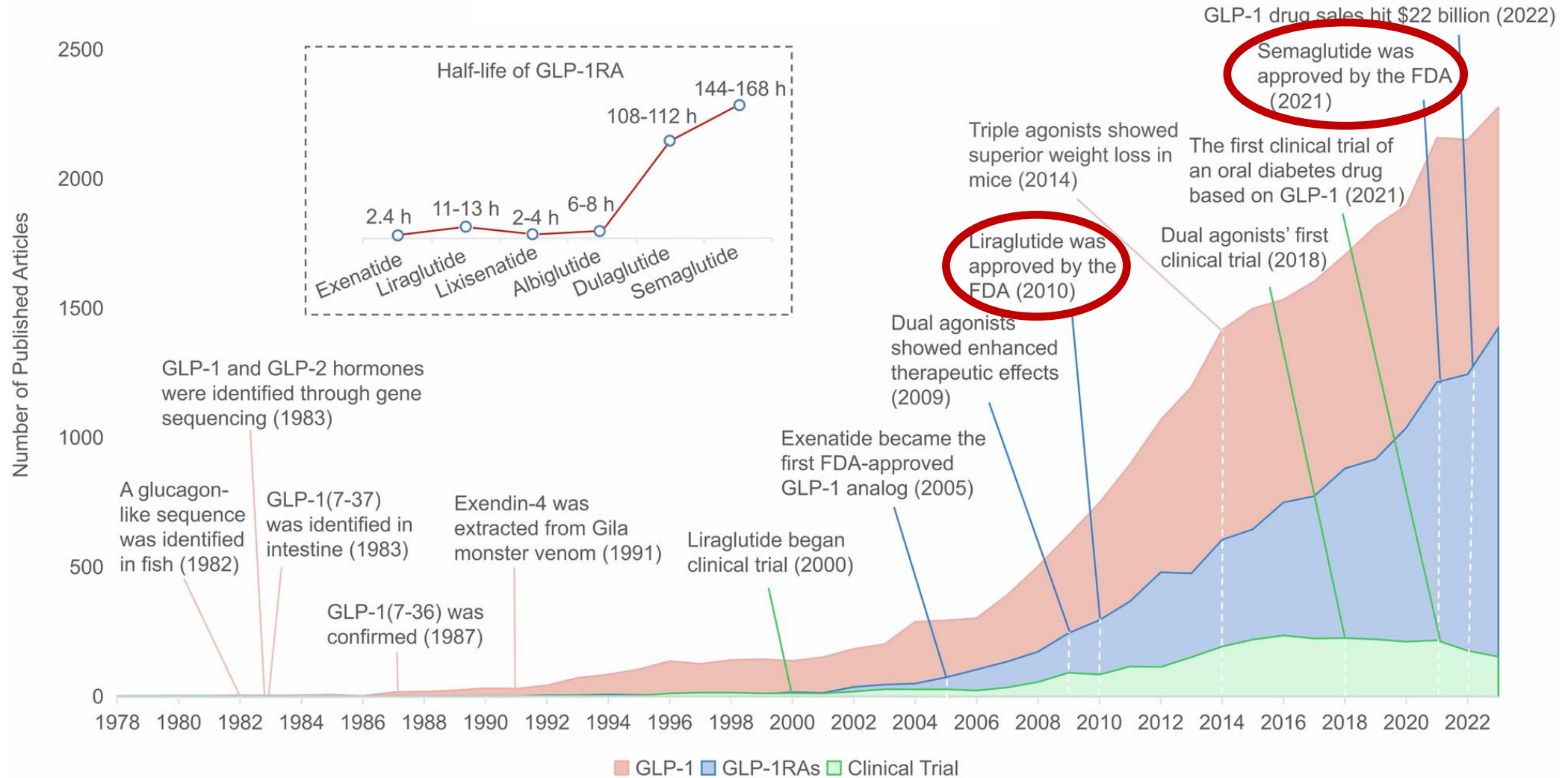
Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial

Mette Kruse Klausen,^{1,2} Mathias Ebbesen Jensen,^{1,2} Marco Möller,¹ Nina Le Dous,¹ Anne-Marie Østergaard Jensen,¹ Victoria Alberte Zeeman,¹ Claas-Frederik Johannsen,¹ Alycia Lee,^{3,4} Gerda Krog Thomsen,⁵ Julian Macoveanu,¹ Patrick MacDonald Fisher,⁵ Matthew Paul Gillum,⁶ Niklas Rye Jørgensen,^{2,7} Marianne Lerbæk Bergmann,⁸ Henrik Enghusen Poulsen,^{2,9} Ulrik Becker,¹⁰ Jens Juul Holst,^{2,6} Helene Benveniste,¹¹ Nora D. Volkow,¹² Sabine Vollstädt-Klein,^{3,4} Kamilla Woznica Miskowiak,^{1,2,13} Claus Thorn Ekstrøm,¹⁴ Gitte Moos Knudsen,^{2,5} Tina Vilsbøll,^{2,15} and Anders Fink-Jensen^{1,2}



Primary endpoint: Reduction in Heavy drinking days (n = 127)

Growth and Timescale of GLP-1 Medical Publications



Several RCTs on AUD and SUD are ongoing across NIH, Academia, and Industry

ClinicalTrials.gov

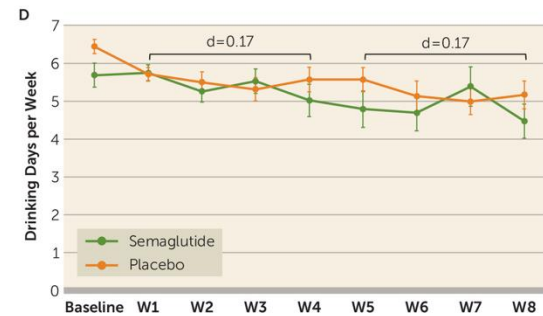
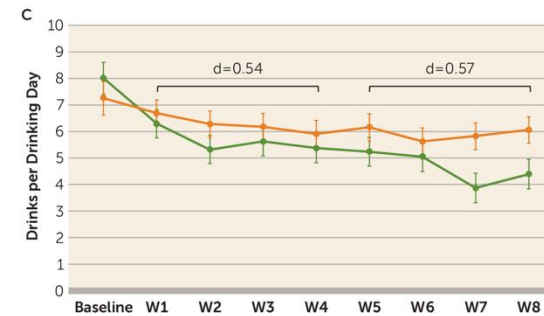
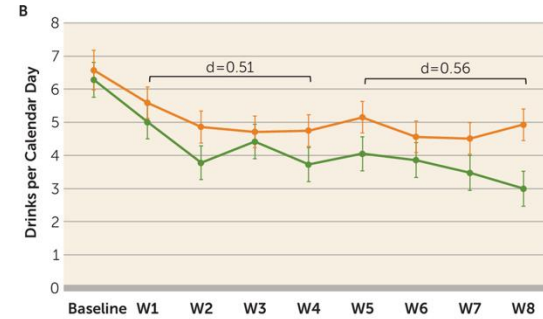
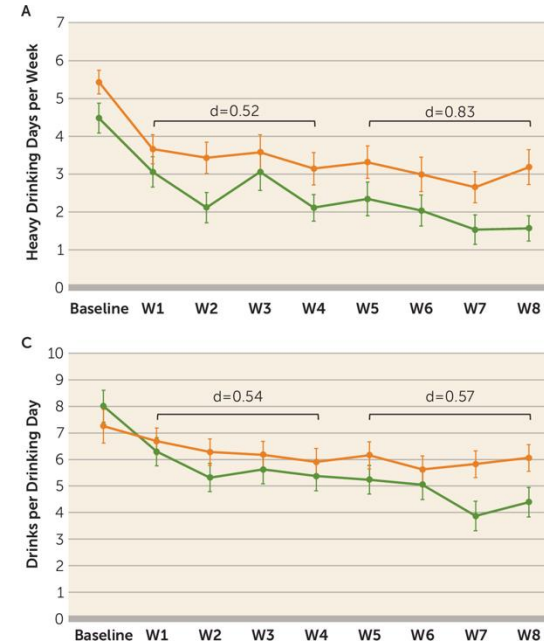
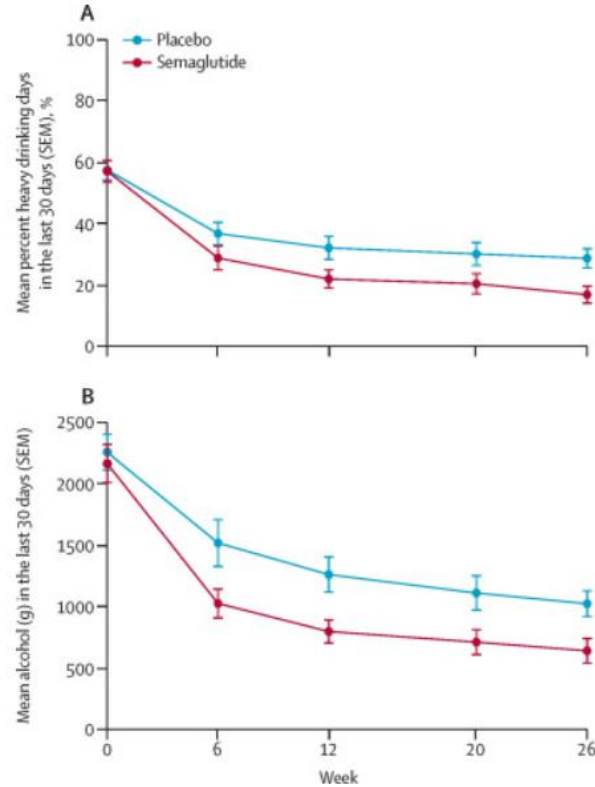
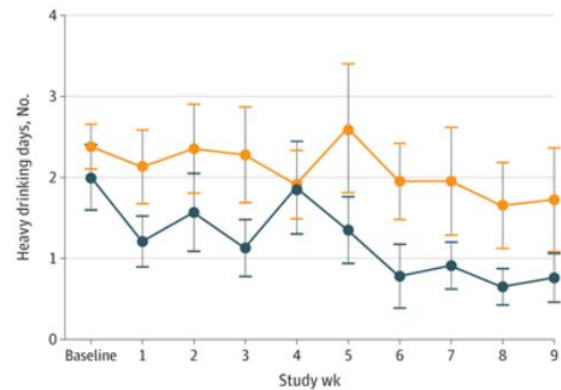
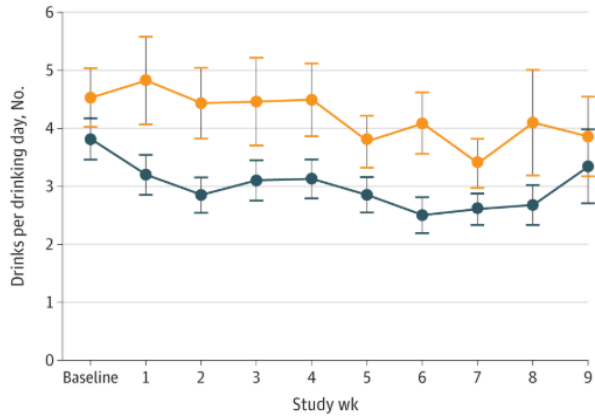
A service of the U.S. National Institutes of Health



"Why are these test subjects so adverse to taking a simple placebo?"

Several RCTs on AUD and SUD are ongoing across NIH, Academia, and Industry

Recent readouts from three RCTs support semaglutide's efficacy in patients with AUD



Hendershot et al., JAMA Psychiatry 2025

Klausen et al., Lancet 2026

Schacht et al., Am J Psychiatry 2026

Our ongoing RCT

Semaglutide Therapy for Alcohol Reduction – Baltimore (STAR–B)

- A 5-month RCT with outpatients with AUD
- Efficacy: Drinks/week, risk drinking levels, phosphatidylethanol (PEth)
- Safety/tolerability
- Experimental medicine procedures
 - Cue-Reactivity (CR) craving in the bar-lab
 - Food choices in the VR buffet-like cafeteria
 - fMRI outcomes: alcohol/food cue task, MID task, amygdala reactivity task



Our ongoing RCT testing Semaglutide in AUD The STAR-B Study

Two Harmonized RCTs: STAR-B and STAR-T

NIH/NIDA IRP – Baltimore



Oklahoma State University – Tulsa



STAR-T PI: Kyle Simmons, Ph.D.

Novel medications for problematic alcohol use

Markus Heilig,¹ Katie Witkiewitz,² Lara A. Ray,³ and Lorenzo Leggio⁴

¹Center for Social and Affective Neuroscience, Linköping University, and Department of Psychiatry, Linköping University Hospital, Linköping, Sweden. ²Department of Psychology and Center on Alcohol, Substance Use and Addictions, University of New Mexico, Albuquerque, New Mexico, USA. ³Department of Psychology, UCLA, Los Angeles, California, USA. ⁴Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, National Institute on Drug Abuse Intramural Research Program and National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, NIH, Baltimore and Bethesda, Maryland, USA.

Alcohol-related harm, a major cause of disease burden globally, affects people along a spectrum of use. When a harmful pattern of drinking is present in the absence of significant behavioral pathology, low-intensity brief interventions that provide information about health consequences of continued use provide large health benefits. At the other end of the spectrum, profound behavioral pathology, including continued use despite knowledge of potentially fatal consequences, warrants a medical diagnosis, and treatment is strongly indicated. Available behavioral and pharmacological treatments are supported by scientific evidence but are vastly underutilized. Discovery of additional medications, with a favorable balance of efficacy versus safety and tolerability can improve clinical uptake of treatment, allow personalized treatment, and improve outcomes. Here, we delineate the clinical conditions when pharmacotherapy should be considered in relation to the main diagnostic systems in use and discuss clinical endpoints that represent meaningful clinical benefits. We then review specific developments in three categories of targets that show promise for expanding the treatment toolkit. GPCRs remain the largest category of successful drug targets across contemporary medicine, and several GPCR targets are currently pursued for alcohol-related indications. Endocrine systems are another established category, and several promising targets have emerged for alcohol indications. Finally, immune modulators have revolutionized treatment of multiple medical conditions, and they may also hold potential to produce benefits in patients with alcohol problems.

With Deep Gratitude Our Teams at NIH

- All current and former lab members
- All Collaborators across the NIH, Academia, and private sector
- Lisa Farinelli, Steph Weiss, all PAs, Nurses, and OCD Staff
- Our Cores/Programs, Administrative, Pharmacy and Animal Care Staff



National Institute
on Drug Abuse



National Institute
on Alcohol Abuse
and Alcoholism



Alcohol Use Disorder Part 1: Epidemiology, Evidence-Based Treatments, and Emerging Therapeutics

Lorenzo Leggio, M.D., Ph.D.

lorenzo.leggio@nih.gov

NIDA and NIAAA

September 24, 2026



National Institutes
of Health