Teaching an Old Disorder New Tricks: Endocrine Pharmacotherapies for Alcohol Use Disorder

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Disclosure Information

- Presenter 1: Rani Richardson, B.A.
  - No Disclosures
- Presenter 2: Stephanie T. Weiss, M.D., Ph.D.
  - No Disclosures
- Presenter 3: Andras Leko, M.D., Ph.D.
  - No Disclosures
- Presenter 4: Mehdi Farokhnia, M.D., M.P.H.
  - No Disclosures

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Learning Objectives

- Review AUD treatments currently used in the U.S.
- Describe ongoing, cutting-edge translational and clinical research to develop novel AUD therapies
- Illustrate the early-phase clinical trial process using case examples
- Identify barriers and complexities in the AUD medication development process

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Current Therapies for AUD

4

Alcohol Use Disorder (AUD)

- 15 million American adults living with AUD
- High burden of morbidity and mortality, comorbidities
- Only 3 FDA-approved treatments for AUD
  - Heterogeneity in the AUD population

Litten RZ, Handb Exp Pharmacol 2018, Grant BF, JAMA Psychiatry 2015; National Survey on Drug Use and Health; Koob GF, Pharmacol Rev 2021; The Healthcare Professional's Core Resource on Alcohol (NIAAA)

5

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.

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FDA-Approved AUD Pharmacotherapies

- **Disulfiram**
  - Aldehyde dehydrogenase inhibitor
  - Causes nausea, dizziness, headache, flushing when taken with alcohol
  - Approved by FDA in 1948
- **Naltrexone**
  - Opioid antagonist
  - Binds to opioid receptors, thus blocking alcohol reward pathways
  - Approved by FDA in 1994
- **SR-Naltrexone**
  - Sustained-release naltrexone
  - Approved by FDA in 2006
- **Acamprosate**
  - Glutamate receptor modulator (?)
  - Helps maintain complete abstinence during post-acute withdrawal
  - Approved by FDA in 2004

Zindel LR, JSAD, 2014
Kranzler HR, JAMA 2018

7

Acamprosate

- Abstinence, relapse prevention
- Drug metabolism
- Compliance

Anton RF, JAMA 2006; Mann K, Addict Biol 2013; Cheng HY, Bmj. 2020; Maisel NC, Addiction 2013; Jonas DE, JAMA 2014

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Naltrexone

- Multiple outcomes
  - Craving
  - Number of heavy drinking days
  - Return to drinking
  - Binge drinking

Anton RF, JAMA 2006; Mann K, Addict Biol. 2013; Cheng HY, BMJ. 2020; Maisel NC, Addiction 2013; Jonas DE, JAMA 2014

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Disulfiram

- Complete abstinence, not drinking reduction
- Supervised administration
- Difficulty in study design
- Liver considerations

Jørgensen CH, Alcohol Clin Exp Res 2011; Skinner MD, PLoS One 2014

10

Promising Medications for AUD (not approved by the FDA)

Topiramate
- Increases GABA-A activity
- Approved by FDA for epilepsy, migraine and obesity

Gabapentin
- GABA analog, voltage-gated calcium channels
- Approved by FDA for epilepsy and postherpetic neuralgia

Baclofen
- GABA-B receptor agonist
- Approved by FDA for muscle spasticity

Morley KC, Expert Opinion on Pharmacotherapy, 2021

11

Topiramate

- Reduction of craving
- Reduction of heavy drinking days, drinks per day

Miranda R, Jr. Addict Biol 2016; Johnson BA, JAMA 2007; Johnson BA, Lancet 2003, Palpacuer C, Addiction, 2018; Wetherill RR, Neuropsychopharmacology 2021; Kranzler HR, Addict Biol. 2022

12

Gabapentin

- Heavy drinking days
- Responders: withdrawal symptoms

Furieri FA, J Clin Psychiatry; Karam-Hage M, Am J Psychiatry; Myrick H, Am J Psychiatry. 1998; Karam-Hage M, 2003; Mason BJ, JAMA Intern Med, 2014; Anton RF, JAMA Intern Med 2020; Falk DE, ACER 2019

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Baclofen

- Craving, abstinence, time to relapse
- High drinking individuals
- Comorbid liver disease

Addolorato G, Lancet 2007; Leggio L, CNS Neurol Disord Drug Targets 2010; Agabio R, Lancet Psychiatry 2018; Rombouts SA, Alcohol Alcohol 2019; Garbutt JC, Neuropsychopharmacology 2021cc

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Varenicline

- Craving
- Heavy Drinking Days
- Comorbid smokers (nicotine)

Litten RZ, J Addict Med. 2013; Falk DE, J Addict Med. 2015; Donato S Alcohol Clin Exp Res. 2021; de Bejczy A, Alcohol Clin Exp Res. 2015; Gandhi KD, J Clin Psychiatry. 2020

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Drug	Advantages	Considerations	References
Acamprosate	Abstinence, relapse prevention, no hepatic metabolism	3x daily admin (compliance)	Anton RF, JAMA 2006; Mann K, Addict Biol 2013; Cheng HY, Bmj. 2020; Maisel NC, Addiction 2013; Jonas DE, JAMA 2014
Naltrexone	Craving, # heavy drinking days, binge drinking, return to drinking	Requires abstinence from opioids prior to initiation	Anton RF, JAMA 2006; Mann K, Addict Biol. 2013; Cheng HY, BMJ. 2020; Maisel NC, Addiction 2013; Jonas DE, JAMA 2014
Disulfiram	Complete abstinence, not reduction	Supervised admin, study design difficult, potential hepatotoxicity	Jørgensen CH, Alcohol Clin Exp Res 2011;Skinner MD,PLoS One 2014
Topiramate	Craving, heavy drinking days, drinks per day	Potential cognitive dysfunction	Miranda R, Jr. Addict Biol 2016; Johnson BA, JAMA 2007; Johnson BA, Lancet 2003, Palpacuer C, Addiction, 2018; Wethenill RR, Neuropsychopharmacology 2021; Kranzler HR, Addict Biol 2022
Gabapentin	Withdrawal symptoms (responders), heavy drinking days	Potential sedation, drowsiness	Furieri FA, J Clin Psychiatry; Karam-Hage M, Am J Psychiatry; Myrick H, Am J Psychiatry. 1998; Karam-Hage M, 2003; Mason BJ, JAMA Intern Med, 2014; Anton RF, JAMA Intern Med 2020; Falk DE, ACER 2019
Baclofen	Time to relapse, high drinking, comorbid liver disease, dose dependent	Potential sedation, drowsiness	Addolorato G, Alcohol Alcohol 2002; Leggio L, CNS Neurol Disord Drug Targets 2010; Agabio R, 2018; Pierce M, Eur Neuropsychopharmacol 2018; Rombouts SA, Alcohol Alcohol 2019; Reynaud M, Alcohol Alcohol 2017
Varenicline	Craving, heavy drinking days, comorbid nicotine		Litten RZ, J Addict Med. 2013; Falk DE, J Addict Med. 2015; Donato S, Alcohol Clin Exp Res. 2021; de Bejczy A, Alcohol Clin Exp Res. 2015; Gandhi KD, J Clin Psychiatry. 2020

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Development of the GLWL-01 Investigational New Drug

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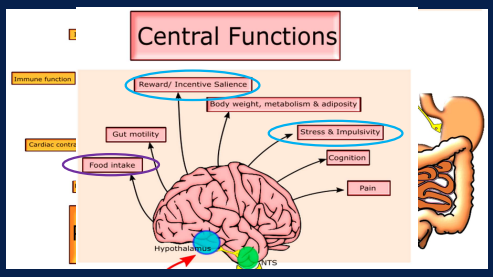
Ghrelin Functions



Howick, K., Griffin, B.T., Cryan, J.F. and Schellekens, H., 2017. From belly to brain: targeting the ghrelin receptor in appetite and food intake regulation. *International journal of molecular sciences*, *18*(2), p.273.

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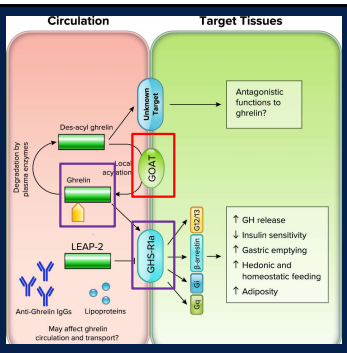
Overview of Ghrelin Physiology



Deschaine, S.L. and Leggio, L., 2022. From "hunger hormone" to "it's complicated": ghrelin beyond feeding control. *Physiology*, *37*(1), pp.5-15.

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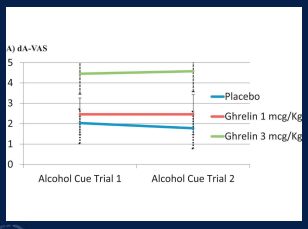
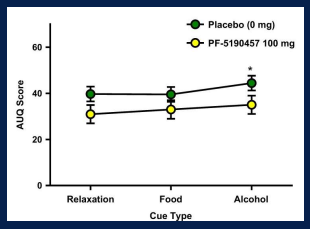
Ghrelin as a Target for AUD

Ghrelin Effect on Alcohol Urge



Alcohol Craving in Cue Reactivity



Leggio, L., et al., 2014. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. *Biological psychiatry*, *76*(9), pp.734-741.; Lee, M.R., et al., 2020. The novel ghrelin receptor inverse agonist PF-5190457 administered with alcohol: preclinical safety experiments and a phase 1b human laboratory study. *Molecular psychiatry*, *25*(2), pp.461-475..

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Manipulating Ghrelin Signaling Via GOAT Inhibition in Alcohol Use Disorder

- Objectives:
  - Evaluate the safety of the IND GLWL-01 in people with AUD
  - Provide preliminary evidence of its efficacy to decrease drinking
  - Evaluate its effect on food choices
- Population:
  - People ages 18-70 with AUD (34 completers)
  - Not physically dependent on alcohol/benzodiazepines
  - No other health conditions that would make participation unsafe

https://clinicaltrials.gov/ct2/show/NCT03896516

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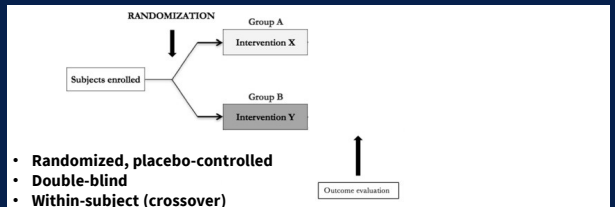
Study Design



- **Randomized, placebo-controlled**
- **Double-blind**
- **Within-subject (crossover)**
- **Counterbalanced**

Dinu, M., Pounis, G. and Sofi, F., 2019. Study design in experimental settings. In *Analysis in Nutrition Research* (pp. 23-41). Academic Press.

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GOAT Study Schedule

DAY 1
Enrollment

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Study Procedures

Virtual Reality Buffett

Cue Reactivity in the Mock Bar

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Known Unknowns

- "Surprising" side effects?
  - Green poop!
  - Decreased tobacco smoking in some patients

https://www.google.com/aclk?sa=l&ai=DChcSEwinzbzd_4H9AhWC5HcKHVdHBfoYABAFGgJlZg&sig=AOD64_1ivFBtaTaNtOVtnVMXaVnktzwuVg&adurl&ctype=5&ved=2ahUKEwj0zLLd_4H9AhVun_0HHf5aD2EQvhd6BAgBEDU

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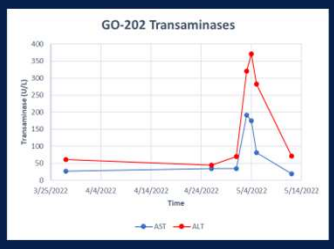
Known Unknowns

- Hepatic Toxicity?
  - Stricter enrollment criteria (LFTs <1.5x ULN)
  - Liver fibrosis risk calculation (FIB-4)



Shah, Amy G., et al. "Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease." *Clinical gastroenterology and hepatology* 7.10 (2009): 1104-1112.

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Unknown Unknowns

- Drug withdrawal
  - Caffeine
  - Cannabis/THC

Supplement Facts

Serving Size 8.0 fl oz. (240 mL)

Servings Per Container: 2

Amount Per Serving		% Daily Value
Calories	**100**	
Total Carb	**27g**	**9%***
Sugars	27g	†
Riboflavin Vit B2	1.7mg	100%
Niacin Vit B3	20mg	100%
Vitamin B6	2mg	100%
Vitamin B12	6mcg	100%
Sodium	180mg	8%
Taurine	1000mg	†
Panax Ginseng	200mg	†
Energy Blend	2500mg	†

L-Carnitine, Glucose, Caffeine, Guarana, Inositol, Glucuronolactone, Maltodextrin

*Percent Daily Values are based on a 2000 calorie diet. † Daily Value not established.

https://shop.mypricechopper.com/product/monster-energy-drink-ultra-paradise-16-oz-00070847033080

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Unknown Unknowns

- Clinically normal protocol-based patient withdrawal
  - Threshold QTcF: <470 ms
  - Baseline QTcF: 377 ms
  - Post-Dosing QTcF: 439 ms

- 3a. Criteria for individual subject withdrawal:
  - .....If there is prolongation of the QTcF interval to >500 ms or >60 ms over that on Day 1 ECG....

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Unknown Unknowns

- Other logistics
  - Food issues
  - Managing patient expectations

https://easybudgetrecipes.com/ground-turkey-chili/

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Repurposing of Spironolactone

A new indication for a "good old drug"?

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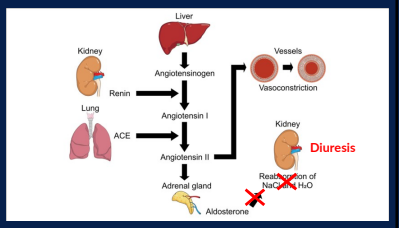
What is spironolactone?

cortisol
aldosterone
spironolactone
MR



Vargas-Rodriguez JR et al., Front Med, 2022

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What is spironolactone?

cortisol
aldosterone
spironolactone
MR

FDA approved in 1960
Hypertension: 25-100 mg/day
Heart failure: 25-50 mg/day
Edema due to cirrhosis: 25-200 mg/day
Hyperaldosteronism: 100-400 mg/day

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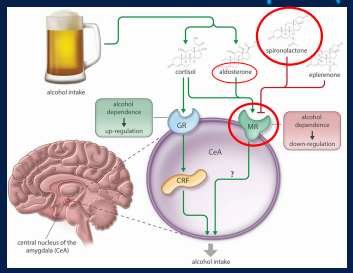
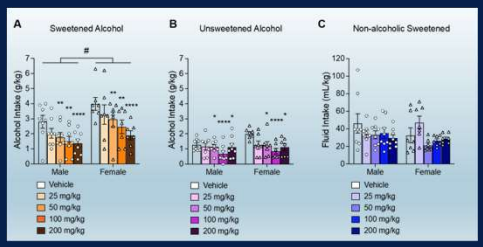
Why Spironolactone and the Mineralocorticoid Receptor (MR)?



Lékó AH et al., ACS Chem Neurosci, 2022
Leggio L et al., Alcohol, 2008
Aoun et al., Mol Psychiatry, 2018

33

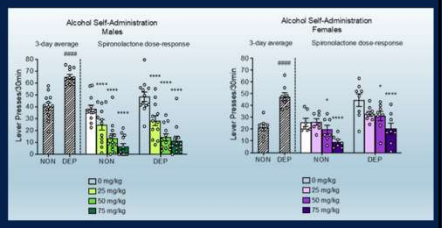
Spironolactone affects alcohol intake



Farokhnia, Rentsch, Chuong, McGinn et al., Mol Psychiatry, 2022

34

Spironolactone affects alcohol intake



Farokhnia, Rentsch, Chuong, McGinn et al., Mol Psychiatry, 2022

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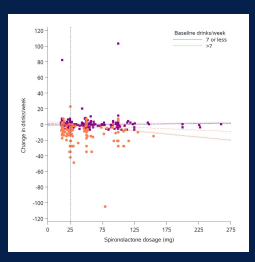
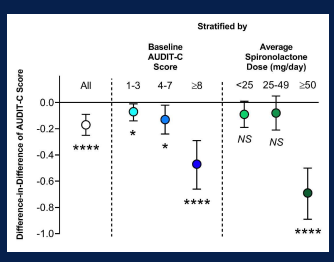
OK, but what about humans?





Palzes et al, Neuropsychopharmacology, 2021

Farokhnia, Rentsch, Chuong, McGinn et al., Mol Psychiatry, 2022

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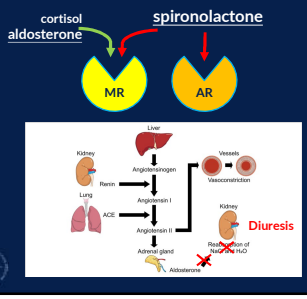
Spironolactone – side effects



- Hyperkalemia
- Gynecomastia
- Hypotension
- Worsening renal function
- Hyponatremia
- Hypomagnesemia
- Hypocalcemia
- Hypochloremic alkalosis
- Hyperglycemia
- Hyperuricemia (asymptomatic)

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Spironolactone in Alcohol Use Disorder (SAUD)

Phase 1b study under review

- Features
  - Inpatient, within-subject, double-blind, placebo-controlled
  - Heavy-drinking individuals with AUD (N=12)
  - Day 6: Spironolactone + Alcohol
- Outcomes:
  - Spironolactone Pharmacokinetics
  - Safety/tolerability
  - Alcohol Pharmacokinetics
  - Subjective and cognitive effects of alcohol

- Visit 1: Day 2-6; placebo
- 3+ days washout
- Visit 2: Day 2-6; 2x50 mg spironolactone
- 3+ days washout
- Visit 3: Day 2-6; 2x100 mg spironolactone
- 3+ days washout
- Visit 4: Day 2-6; 2x200 mg spironolactone
- Discharge from the study

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"Alcohol Challenge"

- Day 6: morning dose (spironolactone/placebo)
- 90 min
- Oral alcohol 0.5 g / kg fat-free mass (based on DXA scan)
- BAC 0.08%
- Spironolactone PK
  Alcohol PK (BAC)
  Subjective and cognitive effects of alcohol

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GLP-1 Analogues for AUD: Bench-to-Bedside and Back

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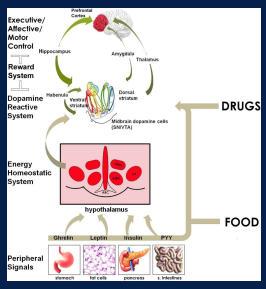
Feeding/Metabolic Neuropeptides



GLP-1

Volkow ND, et. al. The addictive dimensionality of obesity. Biol Psychiatry 2013

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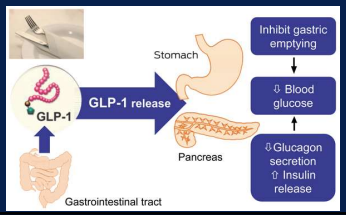
Glucagon-Like Peptide-1 (GLP-1)

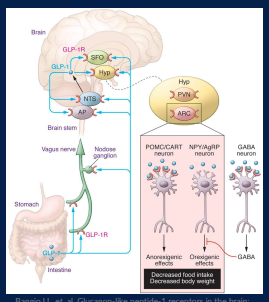
- A peptide with 30 amino acids
- Produced in the intestinal mucosa and pancreas
- Regulates blood glucose and food intake



Cohen ND, et. al. The rationale for combining GLP-1 receptor agonists with basal insulin. Med J Aust 2013

42

GLP-1 is also a Neuropeptide



Baggio LL, et. al. Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight. J Clin Invest 2014

Reward Processing — *e.g., hedonic food intake*

Alcohol Seeking and Use

Stress Regulation — *e.g., interaction with cortisol*

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GLP-1 and Alcohol

- GLP-1 receptor gene variants impact AUD risk and brain activity/connectivity
- Acute alcohol intake reduces circulating GLP-1 levels
- Chronic alcohol intake increases GLP-1 receptor gene expression in AUD-related brain regions

The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: evidence from human genetic association studies and a mouse model of alcohol dependence

Differential association between the GLP1R gene variants and brain functional connectivity according to the severity of alcohol use

The glucagon-like peptide-1 system is modulated by acute and chronic alcohol exposure: Findings from human laboratory experiments and a post-mortem brain study

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Alcohol intake/dependence modulates the GLP-1 system

GLP-1 system as a pharmacotherapeutic target for AUD?

- FDA-approved GLP-1 analogues:

Exenatide, Lixisenatide, Albiglutide, Dulaglutide, Liraglutide, Semaglutide

Zhang Z, et. al. Overcoming cancer therapeutic bottleneck by drug repurposing. Signal Transduct Target Ther 2020

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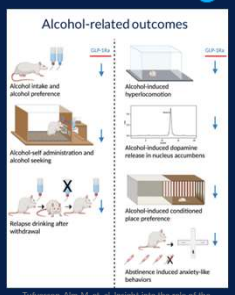
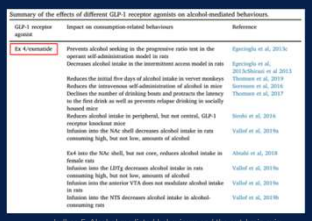
GLP-1 Analogues and Alcohol Use



Tufvesson-Alm M, et. al. Insight into the role of the gut-brain axis in alcohol-related responses: Emphasis on GLP-1, amylin, and ghrelin. Front Psychiatry 2023



Summary of the effects of different GLP-1 receptor agonists on alcohol-mediated behaviours.

GLP-1 receptor agonist	Impact on consumption-related behaviours	Reference
Ex 4/exenatide	Prevents alcohol seeking in the progressive ratio test in the operant self-administration model in rats	Egecioglu et al, 2013c
	Decreases alcohol intake in the intermittent access model in rats	Egecioglu et al., 2013; Ishikawa et al 2013
	Reduces the initial five days of alcohol intake in vervet monkeys	Thomsen et al, 2019
	Reduces the intravenous self-administration of alcohol in mice	Suremen et al, 2016
	Declines the number of drinking bouts and protracts the latency to the first drink as well as prevents relapse drinking in socially housed mice	Thomsen et al, 2017
	Reduces alcohol intake in peripheral, but not central, GLP-1 receptor knockout mice	Sirohi et al, 2016
	Infusion into the NAc shell decreases alcohol intake in rats consuming high, but not low, amounts of alcohol	Vallof et al, 2019a
	Ex4 into the NAc shell, but not core, reduces alcohol intake in female rats	Alvaki et al, 2018
	Infusion into the LDTg decreases alcohol intake in rats consuming high, but not low, amounts of alcohol	Vallof et al, 2019a
	Infusion into the anterior VTA does not modulate alcohol intake in rats	Vallof et al, 2019a
	Infusion into the NTS decreases alcohol intake in alcohol-consuming rats	Vallof et al, 2019b

Jerlhag E. Alcohol-mediated behaviours and the gut-brain axis: with focus on glucagon-like peptide-1. Brain Res 2020

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Novel GLP-1 Analogues

- Longer half-life → less frequent injections
- Higher affinity for the GLP-1R
- More effective in ↓ HbA1c and weight

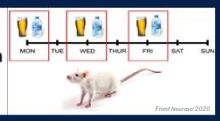
The Discovery and Development of Liraglutide and Semaglutide

Lotte Bjerre Knudsen[1] and Jesper Lau[2]*

Front Endocrinol 2019

Long-Acting Glucagon-Like Peptide-1 Receptor Agonists Suppress Voluntary Alcohol Intake in Male Wistar Rats

Vincent N. Marty[1†], Mehdi Farokhnia[1,3,4†], Joseph J. Munier[1], Yatendra Mulpuri[1], Lorenzo Leggio[1,3,5,6,7] and Igor Spigelman[1]**



Front Neurosci 2020

- Semaglutide and liraglutide reduced alcohol intake
- Semaglutide's effects were more specific for alcohol

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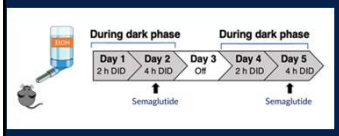
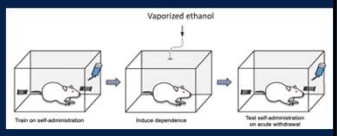
Semaglutide for Alcohol Use in Rodents (unpublished)





Semaglutide dose-dependently reduced binge-like alcohol drinking in male and female mice

Semaglutide dose-dependently reduced alcohol self-administration in male and female rats

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Semaglutide for Clinical Use

Ozempic
FDA-approved for diabetes

Wegovy
FDA-approved for obesity

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Semaglutide for Alcohol Use in Humans
(RCT under development)

- Outpatient, between-subject, double-blind, placebo-controlled
- Heavy-drinking individuals with AUD (N = 52 completers)
- Weekly injection of semaglutide/placebo up to 2.4 mg/week
- Outcomes:
  - Safety and tolerability
  - Alcohol use (drinks/week, etc.)
  - Three experimental procedures

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Visit / Week # →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Follow up
Study Drug or Placebo (mg)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Take Control	x			x			x			x			x			x			x		

Assessments:
- Alcohol intake, side effects (co-primary outcome)
- Clinical assessments and labs
- Measures of craving, mood, anxiety, sleep, anhedonia, etc.

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Take-Home Points

- Current AUD medications are helpful but not sufficient
- Endocrine pathways (ghrelin, mineralocorticoids, GLP-1) are promising targets for AUD drug discovery
- Multiple drug discovery techniques are being pursued by the TAMB at the NIDA IRP
  - Testing of Investigational New Drugs (e.g., GLWL-01)
  - Repurposing of existing drugs (e.g., spironolactone, semaglutide)

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