GLP-1 Agonists & Psychiatry

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Mason Allen - Disclosure

With respect to the following presentation, in the 24months prior to this declaration there has been no financial relationship of any kind between the party listed above and any ACCME-defined ineligible company which could be considered a conflict of interest.

Outline

- Review action of GLP-1
- Biologic plausibility of GLP-1RA in Psychiatric Disorders
- Target areas in psychiatry:
  - Metabolic side effects
  - Addiction
  - Mood disorders
- Summary
- Questions

Clinical Relevance

- Life expectancy of people with Schizophrenia is 14-20 years shorter
  - -Leading cause of death in people with schizophrenia is cardiovascular disease
- High LDL, blood glucose and low HDL have been associated with an increased risk of depression, anxiety
- Multiple psychiatric medications are associated with increased weight, changes in cholesterol, increased risk of diabetes
- Initial concerns over GLP-1 Receptor Agonists (GLP1-RA) on mood
- Addiction and substance use disorder remain difficult to treat with significant morbidity and mortality

Indications – FDA Approved

Incretin Receptor Agonists

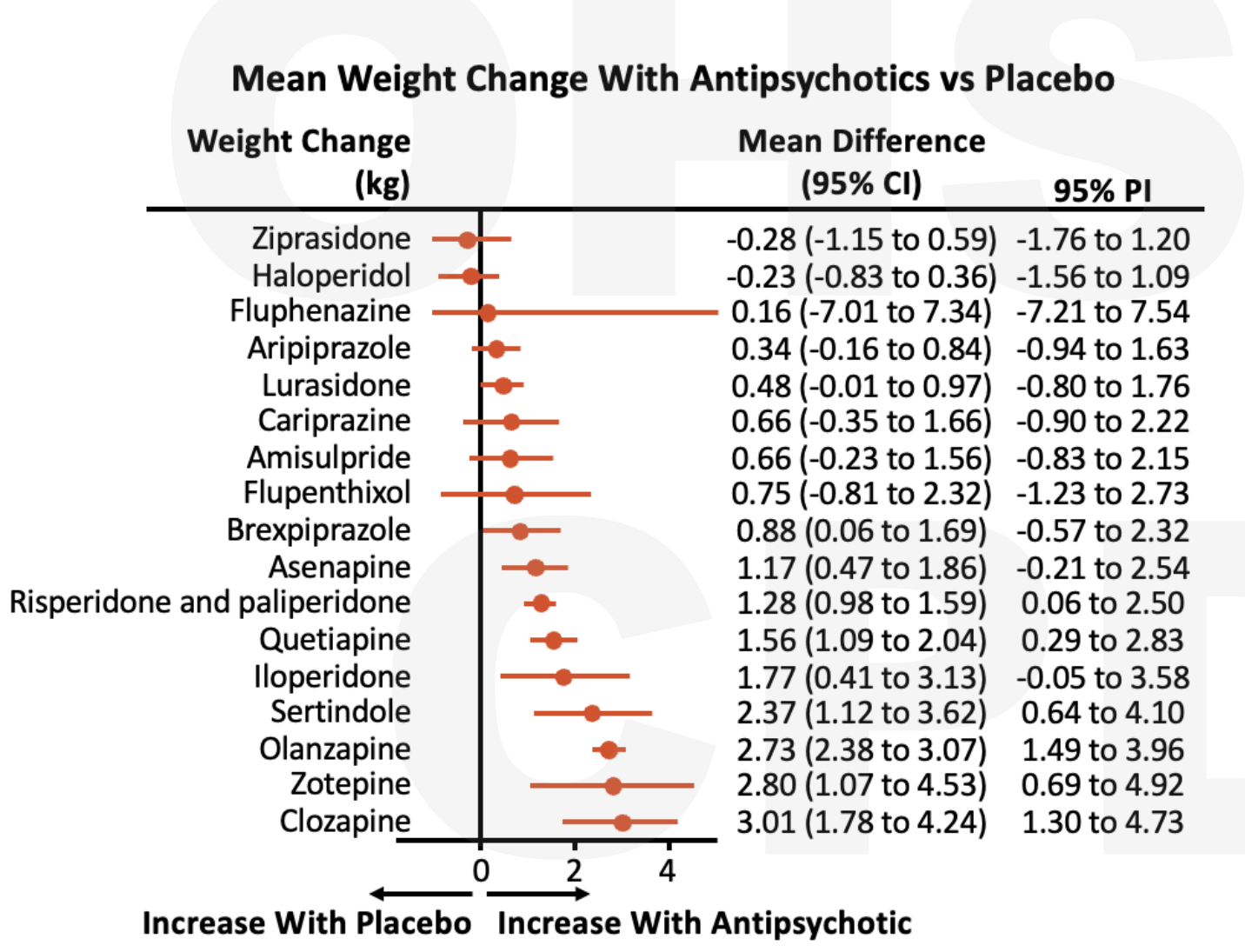
- Reduction of serious cardiac events and stroke in cardiovascular disease in obese/overweight adults
- Reduction of cardiovascular death and worsening kidney function in T2D with CKD
- Metabolic dysfunction–associated steatohepatitis (MASH) in adults with moderate to advanced liver fibrosis
- Type 2 diabetes (T2D)
- Obesity or overweight with comorbidity
- Moderate to severe OSA and obesity

Obesogenic Medications

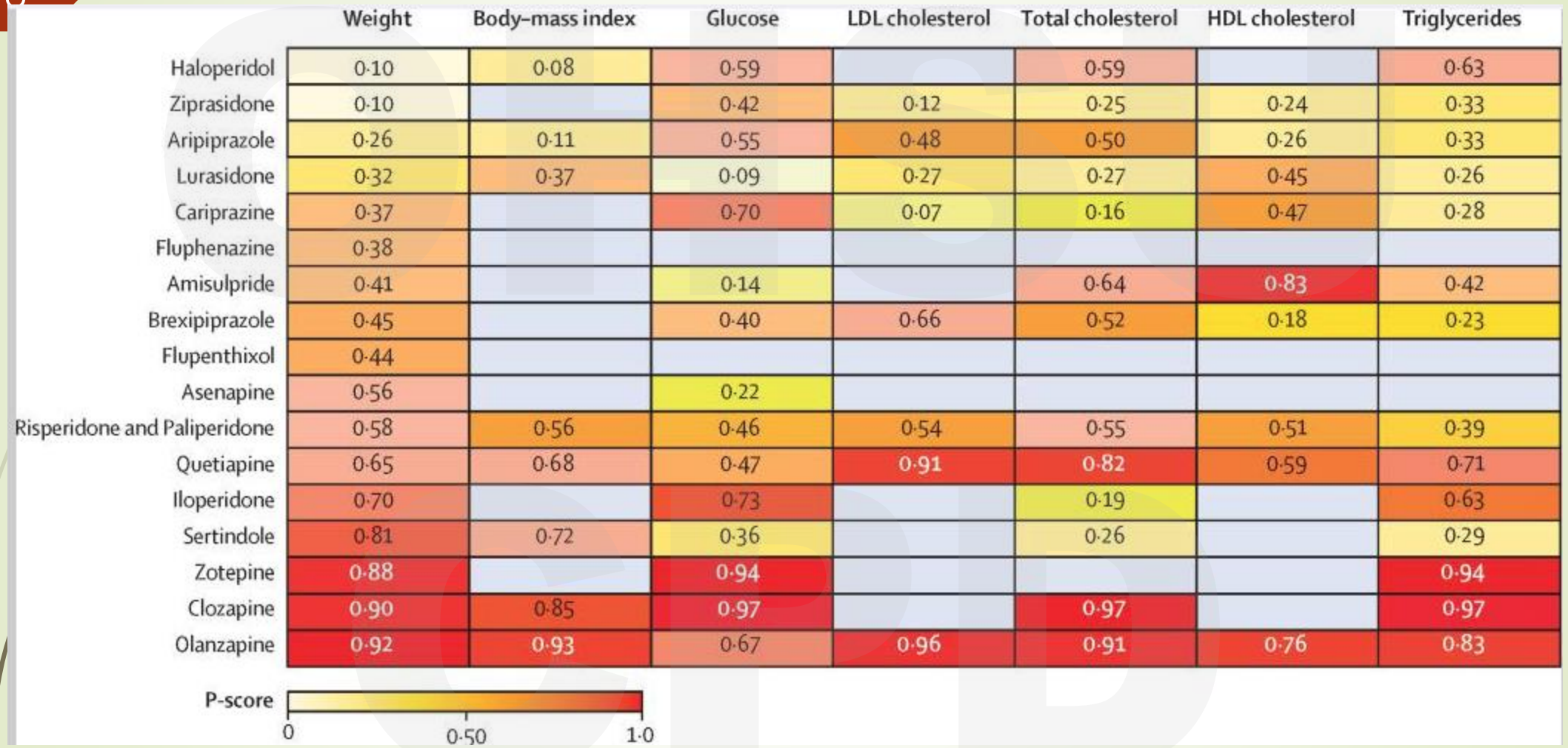
Class of Medication	Medications	Mechanism of Weight Gain
Anticonvulsants/antimigraine/ neuropathic pain	Carbamazepine, gabapentin, pregabalin, valproic acid	Hypothalamic-mediated increase in appetite and decrease in energy expenditure
Antidepressants/antianxiety	Amitriptyline, fluoxetine, mirtazapine, nortriptyline, paroxetine	Appetite increase stimulated via serotonergic pathways
Antihistamines	Cetirizine, diphenhydramine, fexofenadine, hydroxyzine, loratadine	Increased appetite; alters body weight regulation
Antipsychotics	Olanzapine, quetiapine, clozapine, etc	Increased orexigenic and decreased anorexigenic neuropeptide expression in hypothalamus
Contraceptives and hormones	Oral contraceptive pills, medroxyprogesterone	Alters energy intake and expenditure of human body
Corticosteroids	Prednisone	Alters energy intake and expenditure of human body
Hypnotics	Mirtazapine, doxepin	Increased appetite; sleep eating
Opioids	All classes	Decreased metabolic rate and exercise tolerance

Desalermos. Obesity (Silver Spring). 2019;27:716. Mews. Prim Care Companion CNS Disord. 2014;16:PCC.13m01567.
Cassidy. PLoS One. 2017;12:e0187982.

Antipsychotic Weight Gain



Pillinger. Lancet Psychiatry, 2020;7:64. APA Practice Guideline for the Treatment Of Patients With Schizophrenia, 3rd edition. 2020.
He. CNS Drugs. 2013;27:423. Meyer. J Clin Psych. 2009;70:318. Wu. Schizophr Bull. 2022;48:643.



	Weight	Body–mass index	Glucose	LDL cholesterol	Total cholesterol	HDL cholesterol	Triglycerides
Haloperidol	0·10	0·08	0·59		0·59		0·63
Ziprasidone	0·10		0·42	0·12	0·25	0·24	0·33
Aripiprazole	0·26	0·11	0·55	0·48	0·50	0·26	0·33
Lurasidone	0·32	0·37	0·09	0·27	0·27	0·45	0·26
Cariprazine	0·37		0·70	0·07	0·16	0·47	0·28
Fluphenazine	0·38						
Amisulpride	0·41		0·14		0·64	0·83	0·42
Brexipiprazole	0·45		0·40	0·66	0·52	0·18	0·23
Flupenthixol	0·44						
Asenapine	0·56		0·22				
Risperidone and Paliperidone	0·58	0·56	0·46	0·54	0·55	0·51	0·39
Quetiapine	0·65	0·68	0·47	0·91	0·82	0·59	0·71
Iloperidone	0·70		0·73		0·19		0·63
Sertindole	0·81	0·72	0·36		0·26		0·29
Zotepine	0·88		0·94				0·94
Clozapine	0·90	0·85	0·97		0·97		0·97
Olanzapine	0·92	0·93	0·67	0·96	0·91	0·76	0·83

P-score

0 0·50 1·0

GLP-1 (Glucagon Like Peptide) and GIP (gastric Inhibitory Peptide)

- 30-31 AA peptide protein produced in intestinal enteroendocrine L-cells and certain neurons within brain stem
- GLP-1 and GIP are incretins ie enhance the secretion of insulin leading a decrease in blood glucose
- GLP-1 is secreted into hepatic portal system by L-cells (Distal ilium=Colon>Jejunum=duodenum
- Biphasic release – 10-15 minutes PP; 30-60 min
- PRIMARY GOAL: it delays gastric emptying and affects appetite control and satiety

GLP-1 In the brain

- Quite complex, research is ongoing but broadly GLP-1 is involved in homeostatic systems related to satiety, metabolism, energy expenditure and maintenance.
- Produced in the Nucleus of the solitary tract (Medulla) and ventrolateral medulla
- Project to Hindbrain & Hypothalamus, Parietal Cortex, Paraventricular Nucleus (PVN), Dorsal Medial Nucleus, Arcuate nucleus
- A study of 22 (18 included in analysis) patients w/ DMII on Liraglutide (RCT, Placebo, x-over) studied neurocognitive changes with fMRI, as well as metabolic changes
- fMRI performed after 3 days at 1.8 mg dose (3mg not yet approved) (7)
- Liraglutide led to decreased activation of parietal cortex, insula, and putamen when shown highly desirable food on fMRI

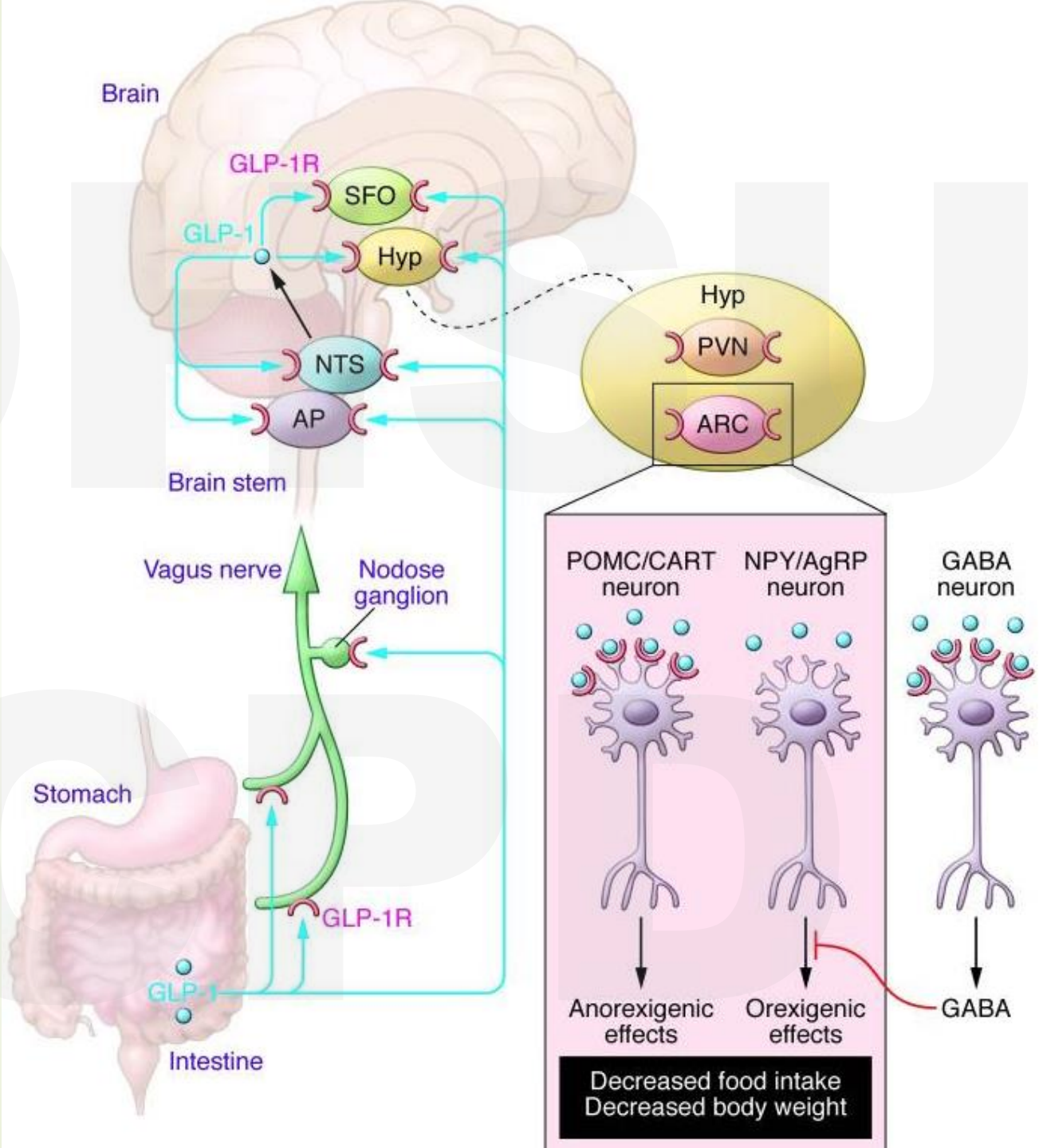
Farr OM, Sofopoulos M, Tsoukas MA, Dincer F, Thakkar B, Sahin-Efe A, Filippaios A, Bowers J, Srnka A, Gavrieli A, Ko BJ, Liakou C, Kanyuch N, Tseleni-Balafouta S, Mantzoros CS. GLP-1 receptors exist in the parietal cortex, hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. Diabetologia. 2016 May;59(5):954-65. doi: 10.1007/s00125-016-3874-y. Epub 2016 Feb 1. PMID: 26831302; PMCID: PMC4826792.

-AP: area postrema

-NTS: solitary nucleus

-Hyp: Hypothalamus
-PVN: Paraventricular nucleus
-ARC: acuate nucleus

-SFO: Subfornical Organ



GLP-1 Receptor Agonism

GIP Receptor Agonism

- GIP receptor agonism
- GLP-1 receptor agonism
- Indirect action

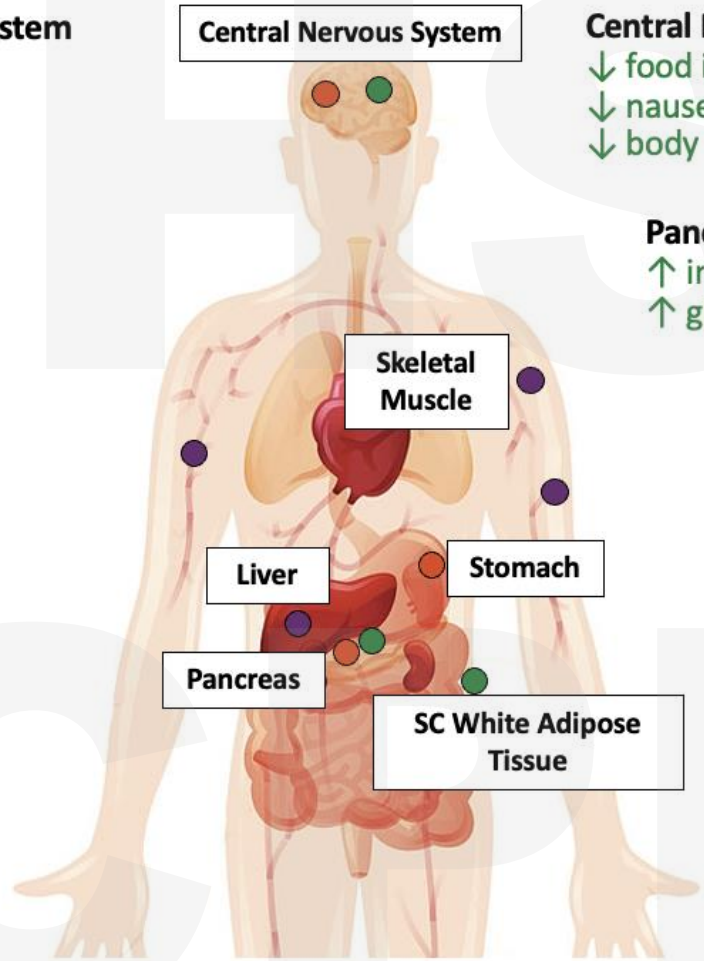
Central Nervous System
↑ satiety
↓ food intake
↑ nausea
↓ body weight

Pancreas
↑ insulin
↓ glucagon

Stomach
↓ gastric emptying

Systemic
↓ hyperglycemia

Liver
↑ insulin sensitivity
↓ hepatic glucose production
↓ ectopic lipid accumulation



Central Nervous System
↓ food intake
↓ nausea
↓ body weight

Pancreas
↑ insulin
↑ glucagon

SC White Adipose Tissue
↑ insulin sensitivity
↑ lipid buffering capacity
↑ blood flow
↑ storage capacity
↓ proinflammatory immune cell infiltration

Systemic
↓ hyperglycemia
↓ dietary triglyceride

Skeletal Muscle
↑ insulin sensitivity
↑ metabolic flexibility
↓ ectopic lipid accumulation

Table 2. Comparative overview of efficacy and adverse effects of mainstream GLP-1RA medications

	CV benefit	Renal benefit	Weight loss	Patient adherence	HbA1c reduction	HbA1c problem	Injection reactions	GI side effects	Antibody issues
Exenatide					+	−−	−−	−	−−
Lixisenatide					+	−−	−−	−	−
Oral Semaglutide	++				+	−−		−−	
Dulaglutide	++	+		++	++	−−−			
Liraglutide		+	++	++	++	−−		−−	
Exenatide (ER)				++	++	−			−
Semaglutide (S.C)	+++	+++	+++	++	++			−	

CV cardiovascular, *GI* gastrointestinal, *RE* extended-release, *SC* subcutaneous administration
The "+" and "−" symbols indicate the efficacy profile or adverse effect profile of each parameter, with more symbols meaning greater strength or severity. More "+" signs indicate a greater benefit. More "−" signs indicate more severe side effect issues

Zheng, Z., Zong, Y., Ma, Y. *et al.* Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. *Sig Transduct Target Ther* **9**, 234 (2024). https://doi.org/10.1038/s41392-024-01931-z

GLP1-RA and antipsychotic Weight gain

- Meta-analysis of 3 studies: Exenatide 1x weekly (2), Liraglutide qday (1)
- N=164, Age=40 +/- 11.1 yrs, Weight=105.8 kg +/- 11.8 kg , 16.2 +/- 4 weeks of treatment
- Average loss of ~3.5 kg weight loss (2.44-4.99 kg), NNT for >5% of body weight loss 3.8
- Weight loss: Olanzapine/Clozaril > other antipsychotics
- Other outcomes: BMI, waist circumference, A1c, FBG all showed benefit only in Olanzapine/Clozaril patients

Siskind D, Hahn M, Correll CU, et al. Glucagon-like peptide-1 receptor agonists for antipsychotic-associated cardio-metabolic risk factors: A systematic review and individual participant data meta-analysis. *Diabetes Obes Metab*. 2019; 21: 293–302. **https://doi.org/10.1111/dom.13522**

Semaglutide Weight loss

Case series of 12 patients, failed metformin. On various antipsychotics including some on LAI. Most on multiple medications. Dx included MDD, Bipolar, Schizophrenia; Semaglutide dosed up to 2mg/wk

- Weight loss outcome:
  - - 3 mo: 4.56 kg +/- 3.15 kg (P< .001)
  - - 6 mo: 5.16 kg +/- 6.27 kg (P< .04)
  - - 12 mo: 8.67 kg +/- 9 kg (P< .04)

Another non-randomized, open label study assessed Oral Semaglutide vs Metformin for AIWG

- Followed for 16 weeks, criteria BMI >27.5, 15 yo+,
- Mean weight loss for semaglutide 4.5 kg, 2.5 kg for metformin
- Also showed some benefit in waist circumfrence and BMI
- No benefit in lipids, A1c, fasting glucose
- BUT some small benefit in symptoms as measured on the BPRS

Effect of GLP-1RA on Cardio-metabolic risk factors among overweight/obese individuals treated with Antipsychotics: a systematic review of RCTs

-142 trials --> 4 eligible RCTs: 2 were Liraglutide vs SOC; 2 were exenatide vs SOC

-3x trials were double blinded, both liraglutide and one exenatide, the other study was open label. Total of 199 patients completed the study

-2 trials excluded DMII, the other two trials had low rates of baseline DMII

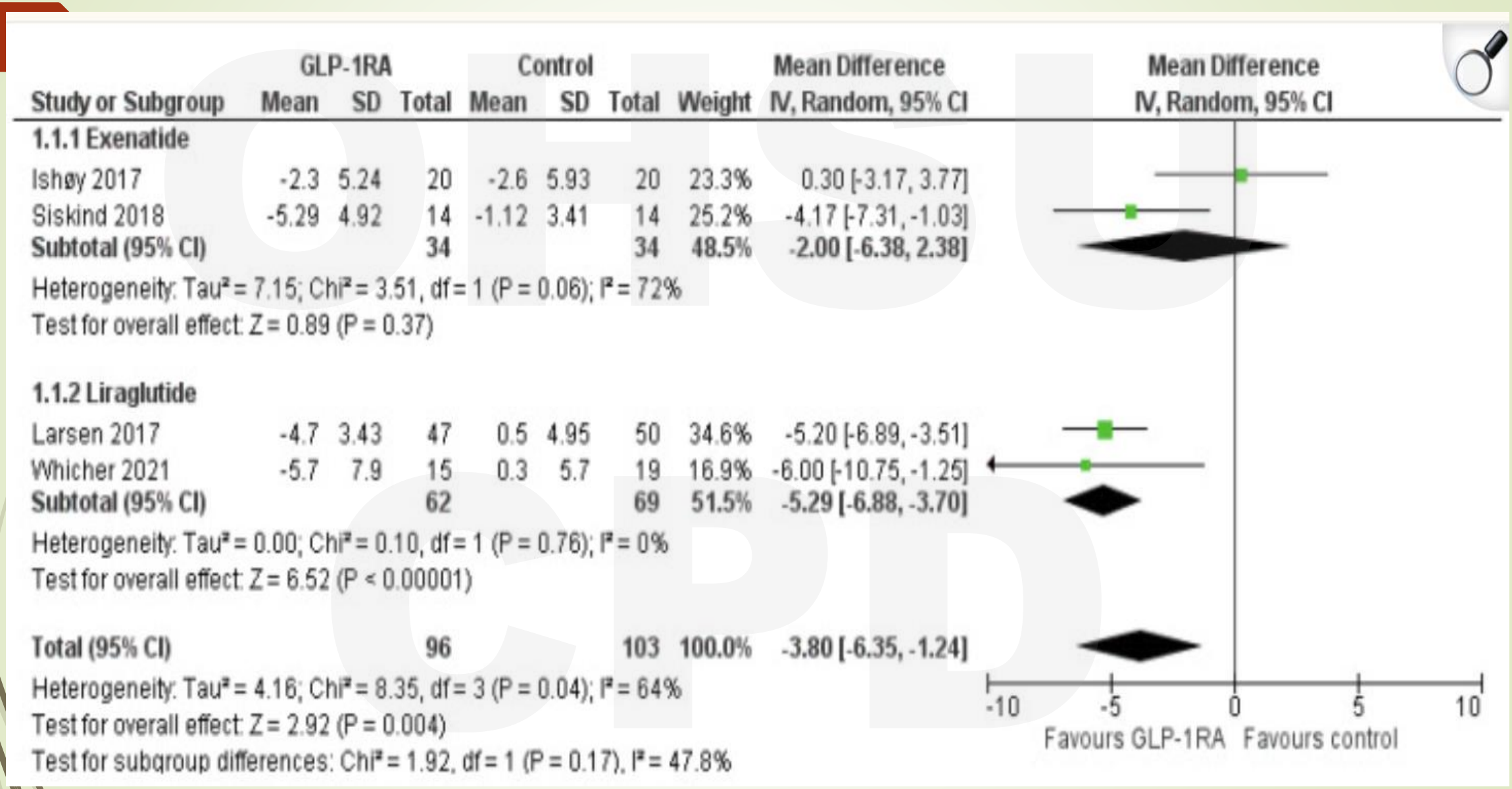
-Most common dx was Schizophrenia, then Schizoaffetive.

-GLP-1RA treatment, compared to control, resulted in a significant decrease in body weight by 3.8 kg

-Subgroup analysis demonstrated only benefit with Liraglutide (5.8 kg loss ave) and Exenetide did not demonstrate improvement vs control

-GLP-1RA demonstrated a significant improvement in lipid and glycemic profiles as well

Patoulias D, Michailidis T, Dimosiari A, Fragakis N, Tse G, Rizzo M. Effect of Glucagon-like Peptide-1 Receptor Agonists on Cardio-Metabolic Risk Factors among Obese/Overweight Individuals Treated with Antipsychotic Drug Classes: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biomedicines. 2023 Feb 22;11(3):669. doi: 10.3390/biomedicines11030669. PMID: 36979648; PMCID: PMC10045529.


GLP-1RA
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Exenatide
Ishøy 2017 -2.3 5.24 20 -2.6 5.93 20 23.3% 0.30 [-3.17, 3.77]
Siskind 2018 -5.29 4.92 14 -1.12 3.41 14 25.2% -4.17 [-7.31, -1.03]
Subtotal (95% CI) 34 34 48.5% -2.00 [-6.38, 2.38]
Heterogeneity: Tau² = 7.15; Chi² = 3.51, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.89 (P = 0.37)
1.1.2 Liraglutide
Larsen 2017 -4.7 3.43 47 0.5 4.95 50 34.6% -5.20 [-6.89, -3.51]
Whicher 2021 -5.7 7.9 15 0.3 5.7 19 16.9% -6.00 [-10.75, -1.25]
Subtotal (95% CI) 62 69 51.5% -5.29 [-6.88, -3.70]
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 6.52 (P < 0.00001)
Total (95% CI) 96 103 100.0% -3.80 [-6.35, -1.24]
Heterogeneity: Tau² = 4.16; Chi² = 8.35, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.92 (P = 0.004)
Test for subgroup differences: Chi² = 1.92, df = 1 (P = 0.17), I² = 47.8%
-10
-5
0
5
10
Favours GLP-1RA
Favours control

Semaglutide In Schizophrenia – Emerging Data

Data from recent RCT - Sep 3 2025

Semaglutide in schizophrenia

Semaglutide 1 mg weekly in a sample with schizophrenia, treated with SGA, who also have prediabetes and obesity vs the placebo group
- baseline to 30 weeks:

Results

- Semaglutide reduced HBA1C to less than 5.7% in 81% of the study group compared to 19% in the placebo group.
- Semaglutide group had significant body weight reduction compared to placebo
- Semaglutide group had significant improvement in physical QoL
- Semaglutide group did not negatively impact PNSS-6

Relevance

Semaglutide at a lower dose was effective in reducing glucose tolerance, body weight and improving physical QoL without affecting psychiatric symptoms in patients with schizophrenia treated with antipsychotics

GLP-1RA and substance use disorders

- WHO estimates that worldwide 280 million people have an alcohol use disorder
- Alcohol is estimated to cause about 5.3% of deaths annually worldwide
- In 2019 nearly a billion men and 190 million women were estimated to be smoking cigarettes
- Findings regarding benefit from GLP-1RA have been slowly increasing, a significant portion of evidence is anecdotal or small case reports/series
- Effects are thought to be mediated through GLP-1 receptors in reward pathway including in areas like the VTA, Habenula

Case series demonstrating improvements in Alcohol use in pts on semaglutide

- Retrospective case series of 6 patients showed 100% improvement (AUDIT score decrease 9.5 pts) in patients on semaglutide.

Potential Role of GLP-1 RA in SUD: systematic review of randomized trials

- Systematic review of 5 studies, 3 demonstrated benefit from exenatide or dulaglutide on smoking and alcohol:
- Study 1 demonstrated increased abstinence from cigarettes (46% vs 26% placebo) f/u 6 weeks with Exenatide. Another study showed no benefit from Dulaglutide on smoking
- 2 studies (one Exenatide and one dulaglutide) demonstrated decrease in alcohol use

Silvia Martinelli, Alessandro Mazzotta, Mattia Longaroni, Niccolò Petrucciani, Potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in substance use disorder: A systematic review of randomized trials,

SEMAGLUTIDE & liraglutide FOR Alcohol Use Disorder (AUD)

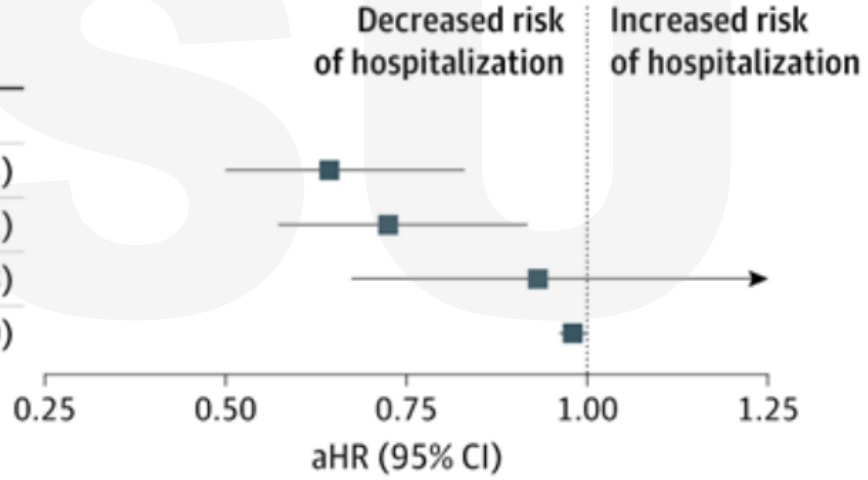
- Cohort + observation study in Sweden from 2006 – 2023 of people with AUD 227866
- Primary out was hospitalization d/t AUD, 2ndary: hospitalization due to SUD, Somatic disorder, suicide attempt
- 63.5% M, 36.5% F mean age 40, 133210 were hospitalized for AUD during this time
- Semaglutide (4321) associated w/ lowest risk (HR 0.64, 0.68 for any SUD)
- Liraglutide (2509) HR 0.72, 0.78 for any SUD
- Both Liraglutide and Semaglutide reduced risk of somatic hospitalization but not suicide attempts
- Of note in this study AUD medications in general were not associated with a decreased risk of hospitalization for either AUD or SUD, though individually naltrexone was

Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder. *JAMA Psychiatry.* 2025;82(1):94–98. doi:10.1001/jamapsychiatry.2024.3599

Figure 1. Risk of Hospitalization Due to Alcohol Use Disorder (AUD) and Substance Use Disorder (SUD)

A Risk of hospitalization due to AUD associated with use of GLP-1 agonists and AUD medications in within-individual model of persons with AUD

Drug	No. Users	Events	PYs	aHR (95% CI)
GLP-1 agonists				
Semaglutide	4321	222	4677	0.64 (0.50-0.83)
Liraglutide	2509	212	3076	0.72 (0.57-0.92)
Dulaglutide	1118	139	1443	0.93 (0.68-1.28)
AUD medications	75454	30198	73222	0.98 (0.96-1.00)



B Risk of hospitalization due to substance use disorder associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

Drug	No. Users	Events	PYs	aHR (95% CI)
GLP-1 agonists				
Semaglutide	4321	281	4667	0.68 (0.54-0.85)
Exenatide	98	13	167	0.73 (0.34-1.55)
Liraglutide	2509	262	3076	0.78 (0.64-0.97)
Dulaglutide	1118	172	1443	0.96 (0.71-1.28)
AUD medications	75454	32543	73222	0.98 (0.97-1.00)

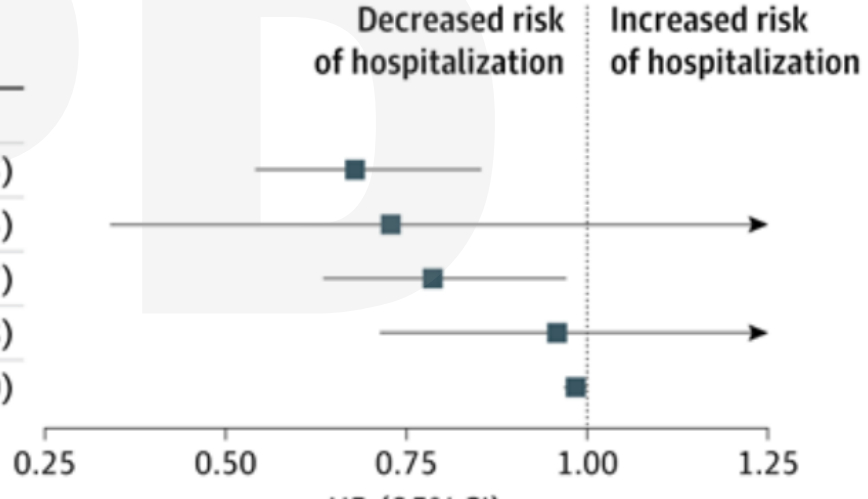
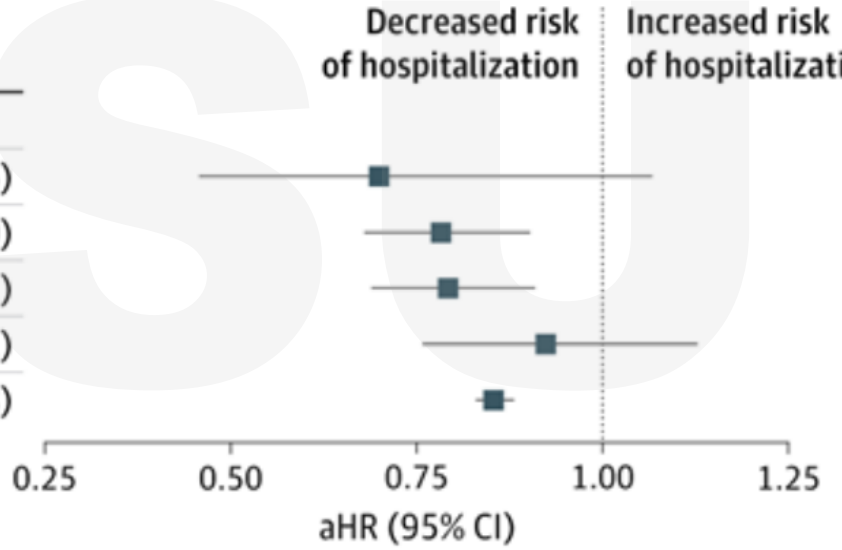


Figure 2. Risk of Hospitalization Due to Somatic Reasons and Suicide Attempt

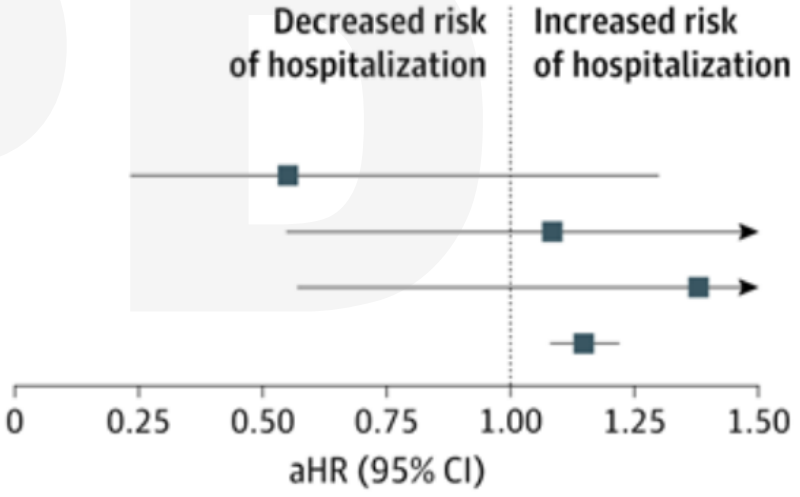
A Risk of somatic hospitalization associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

Drug	No. Users	Events	PYs	aHR (95% CI)
GLP-1 agonists				
Exenatide	98	50	167	0.70 (0.46-1.06)
Semaglutide	4321	708	4677	0.78 (0.68-0.90)
Liraglutide	2509	613	3076	0.79 (0.69-0.91)
Dulaglutide	1118	362	1443	0.92 (0.76-1.12)
AUD medications	75454	9995	73222	0.85 (0.83-0.88)



B Risk of suicide attempt associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

Drug	No. Users	Events	PYs	aHR (95% CI)
GLP-1 agonists				
Semaglutide	4321	32	4677	0.55 (0.23-1.30)
Liraglutide	2509	28	3076	1.08 (0.55-2.15)
Dulaglutide	1118	19	1443	1.38 (0.57-3.34)
AUD medications	75454	3265	73222	1.15 (1.08-1.22)



GLP-1ra AND ALCOHOL RELEATED EVENTS: COHORT STUDY

- Nationwide study in Denmark of new GLP-1RA medications and DDP4 medications 2009-2018
- Followed for hospitalization for AUD or buying medications to treat AUD
- Follow up time of 4.1 years median, 0.7% of people had an event
- GLP1-RA were associated with lower risk of alcohol related event (HR 0.46) vs DDP4 medications

)Wium-Andersen IK, Wium-Andersen MK, Fink-Jensen A, Rungby J, Jørgensen MB, Osler M. Use of GLP-1 receptor agonists and subsequent risk of alcohol-related events. A nationwide register-based cohort and self-controlled case series study. Basic Clin Pharmacol Toxicol. 2022 Nov;131(5):372-379. doi: 10.1111/bcpt.13776. Epub 2022 Aug 30. PMID: 35968738; PMCID: PMC9804689.

Cannabis Use disorder

- In US estimated to be 45 million cannabis users, 1/3 w/ CUD
- Currently there are no FDA approved treatments for CUD
- US used TriNetX to look at 105 million patients in 61 large health systems
- Study design to determine semaglutide effects on cannabis use compared to non-semaglutide users in both obese patients and patients with DMII
- Study took place between (incident event) 6/2021 - 12/2022 for obese patients 6/2017 - 12/2022 for pts with DMII
- Then followed for 12 months: f/u ended 12/2023

Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study. Mol Psychiatry. 2024 Aug;29(8):2587-2598. doi: 10.1038/s41380-024-02498-5. Epub 2024 Mar 14. PMID: 38486046; PMCID: PMC11412894

26

83,189 pts w/ dx of obesity
-no dx of CUD
-1+ dx obesity related dx

45,445 rx semaglutide

37744 rx for other weight loss meds*

Obesity Cohorts

2034 pts w/ dx of obesity
-Dx CUD
-1+ dx obesity related dx

688 rx semaglutide

1346 rx for other weight loss meds

587849 pts w/ dx of DMII
-no CUD dx
-1+ dx obesity related dx

25843 rx for semaglutide

562006 rx for other DMII meds*

Diabetes II Cohorts

8196 pts w/ dx of DMII
-Dx CUD
-1+ dx obesity related dx

254 rx for semaglutide

7942 rx for other DMII meds

Obese, **no prior CUD dx**
RESULTS:
-Semaglutide cohort significantly lower risk of incident CUD vs non-Semaglutide cohort
.28% vs .48%

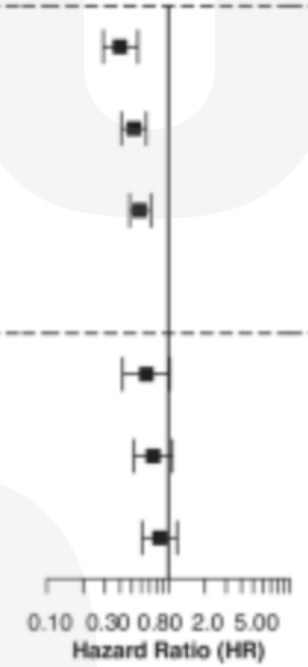
***Obese,* prior dx CUD**
RESULTS:
-Semaglutide cohort lower risk vs non-semaglutide cohort
13% vs 20%

DMII, **no prior CUD dx**
RESULTS:
-Semaglutide cohort lower risk vs non-semaglutide cohort
.21% vs .48%

DMII, **prior dx CUD**
RESULTS:
Semaglutide cohort lower risk vs non-semaglutide cohort
13.7% vs 19.2%

Outcomes in patients with type 2 diabetes at different follow–up

Follow–up	Semaglutide cohort	Non–GLP1R agonist anti–diabetes medications cohort	HR (95% CI)
No prior history of CUD (n=25,820/cohort)			
1–year	0.21% (54)	0.48% (123)	0.40 (0.29–0.56)
2–year	0.41% (105)	0.72% (185)	0.52 (0.41–0.66)
3–year	0.57% (148)	0.91% (235)	0.58 (0.48–0.72)
Prior history of CUD (n=241/cohort)			
1–year	13.7% (33)	19.1% (46)	0.66 (0.42–1.03)
2–year	22.4% (54)	26.6% (64)	0.75 (0.52–1.08)
3–year	29.0% (70)	30.7% (74)	0.85 (0.61–1.18)



Only DMII cohorts were followed at 2 and 3 years. Effect attenuated over time

Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study. Mol Psychiatry. 2024 Aug;29(8):2587-2598. doi: 10.1038/s41380-024-02498-5. Epub 2024 Mar 14. PMID: 38486046; PMCID: PMC11412894.

GLP-1RA depression, Suicide, self-harm

- Studies have not directly investigated GLP1RA for treatment of primary mood disorders, but concerns were initially raised about worsening depression in patients

A 2024 study examining association between SI, completed suicides, self-harm and GLP-1RA

- 209,354 ADRs reported for GLP1RA, 5378 psychiatric, 383 "serious" 2005-2023
- SI reported in 236 patients, 13 completed suicides, thus no causal link is inferred

In a JAMA psychiatry systematic Review and Meta-Analysis pub 5/14/2025

- Eighty randomized clinical trials involving 107 860 patient
- In patients with overweight/obese and/or diabetes GLP-1RA tx **is not associated with increased risk of adverse events or worsening depressive symptoms**
- Is associated with improvements in QOL, restrained eating, emotional eating

A Guirguis, S Chiappini, GD Papanti P, R. Vickers-Smith, D Harris, JM Corkery, D Arillotta, G. Floresta, G Martinotti, F Schifano, Exploring the association between suicidal thoughts, self-injury, and GLP-1 receptor agonists in weight loss treatments: Insights from pharmacovigilance measures and unmasking analysis, European Neuropsychopharmacology, Volume 82, 2024, Pages 82-91, ISSN 0924-977X, https://doi.org/10.1016/j.euroneuro.2024.02.003

GLP1-RA in Parkinson's and other CNS disorders

Mehan, S. et al. Potential roles of glucagon-like peptide-1 and its analogues in dementia targeting impaired insulin secretion and neurodegeneration. Degener. Neurol. Neuromuscul. Dis. 12, 31–59 (2022) - demonstrated some improvement in cognitive tasks, seemed to minimize injury to astrocytes especially

Anti-diabetic drug use and reduced risk of Parkinson's disease: cohort study of >80,000 pts, GLP-1RA and SGLT2 inhibitors were associated with lower risk of PD

Another study using 1x weekly exenatide did not show benefit in disease symptoms or progression in patients with PD

Violetta Rozani, Miri Glikshtein Bezimianski, Joseph Azuri, Michal Bitan, Chava Peretz, Anti-diabetic drug use and reduced risk of Parkinson's disease: A community-based cohort study, Parkinsonism & Related Disorders,Volume 128, 2024, 107132, ISSN 1253-8020

Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial Vijiaratnam, Nirosen et al. The Lancet, Volume 405, Issue 10479, 627 – 636

GLP-1RA and other benefits

Animal studies (mostly) have demonstrated benefits in a huge variety of areas including

-Improvements in OA via effects on osteoblasts and osteoclasts

-Increased muscle mass and fiber size, enhancements in exercise endurance**

-Inflammatory myopathies

-Reduction of cardiac ischemia-reperfusion injury

-Improvement in sepsis

-Improvement of Hypertension via effects on Carotid body

-Reduced risk of GI cancers, pancreatic cancer, Hepatocellular carcinoma

** study done in humans

Barrera JG, Sandoval DA, D'Alessio DA, Seeley RJ. GLP-1 and energy balance: an integrated model of short-term and long-term control. Nat Rev Endocrinol. 2011 Jun 7;7(9):507-16. doi: 10.1038/nrendo.2011.77. PMID: 21647189; PMCID: PMC4231434

Conclusions

- GLP-1RA seem to be effective against weight gain as well as other markers of metabolic disease in patients on antipsychotics
- Evidence continues to mount that these medications can be helpful in treating AUD and other SUD including cannabis
- Based on the current data then newer GLP-1RA (Semaglutide, Liraglutide) seem to be better for AUD/SUD than older medications
- GLP-1RA do not seem to be associated with increased risk of SI, suicide or self harm.

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