Metabolism and Mood: Are GLP-1 Receptor Agonists Capable of Preventing and Treating Psychiatric Disorders

X: @rogersmcintyre

Roger S. McIntyre, M.D., FRCPC
Professor of Psychiatry and Pharmacology, University of Toronto, Canada
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada
Board Chair, Depression and Bipolar Support Alliance (DBSA), Chicago, Illinois, USA
Professor and Nanshan Scholar, Guangzhou Medical University, Guangzhou, China
Adjunct Professor College of Medicine, Korea University, Seoul, Republic of Korea
Visiting Professor College of Medicine University of the Philippines
Clinical Professor State University of New York (SUNY) Upstate Medical University, Syracuse, New York, USA
Clinical Professor Department of Psychiatry and Neurosciences University of California School of Medicine, Riverside, California, USA

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Learning Objectives

- To review preclinical, translational, observational and clinical data suggesting that IRAs target substrates subserving the pathophysiology of depressive and disorders (e.g., cognitive function, reward)
- To discuss the rationale for evaluating incretin receptor agonists (IRAs) as therapeutics
- To review safety concerns in the psychiatric population

Should Depressive Syndromes Be Reclassified as Metabolic Syndrome Type II?

Annals of Clinical Psychiatry, 19[4]:257–264, 2007

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Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"?

ROGER S. McINTYRE
Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Toronto, ON, Canada

JOANNA K. SOCZYNSKA and JAKUB Z. KONARSKI
Mood Disorders Psychopharmacology Unit, University Health Network, and Institute of Medical Science, University of Toronto, Toronto, ON, Canada

HANNA O. WOLDEYOHANNES, CANDY W.Y. LAW, and ANDREW MIRANDA
Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

DON FULGOSI
Toronto, Ontario, Canada

SIDNEY H. KENNEDY
Department of Psychiatry and Institute of Medical Science, University of Toronto, and Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

McIntyre RS, et al. Ann. Clin. Psychiatry. 2007. 19(4):257-264.

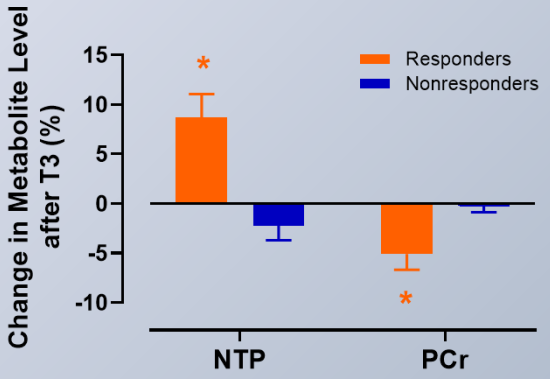
Brain and Cognition
DISCOVERY FOUNDATION

Bipolar depression study data may provide highly valuable scientific and clinical evidence of elunetirom's biologic effects in the depressed brain

Autobahn BP study inspired by precedent human clinical data using ^{31}P-MRS with TH

Potential thyroid hormone effects on brain bioenergetics and cellular energy metabolism

↑ ATP in T3 Responders (MDD)[1]



- **Key Insights & Conclusions**
  - Neurobiology of depression: bioenergetic deficits and mitochondrial dysfunction (↓ beta-ATP in MDD subjects vs. healthy volunteers[2])
  - Thyroid hormone corrects abnormal brain bioenergetic metabolism in depression (↑ cellular ATP and compensatory ↓ PCr)
  - Effect is related to treatment response

- **Key Study Outputs**
  - Enhancement of precedent data with elunetirom
  - Safety and tolerability of elunetirom over 6-weeks of dosing in depressed subjects
  - Potential mechanistic validation on brain bioenergetics, correlated to response
  - Open-label efficacy in bipolar depression, may de-risk readthrough to MDD

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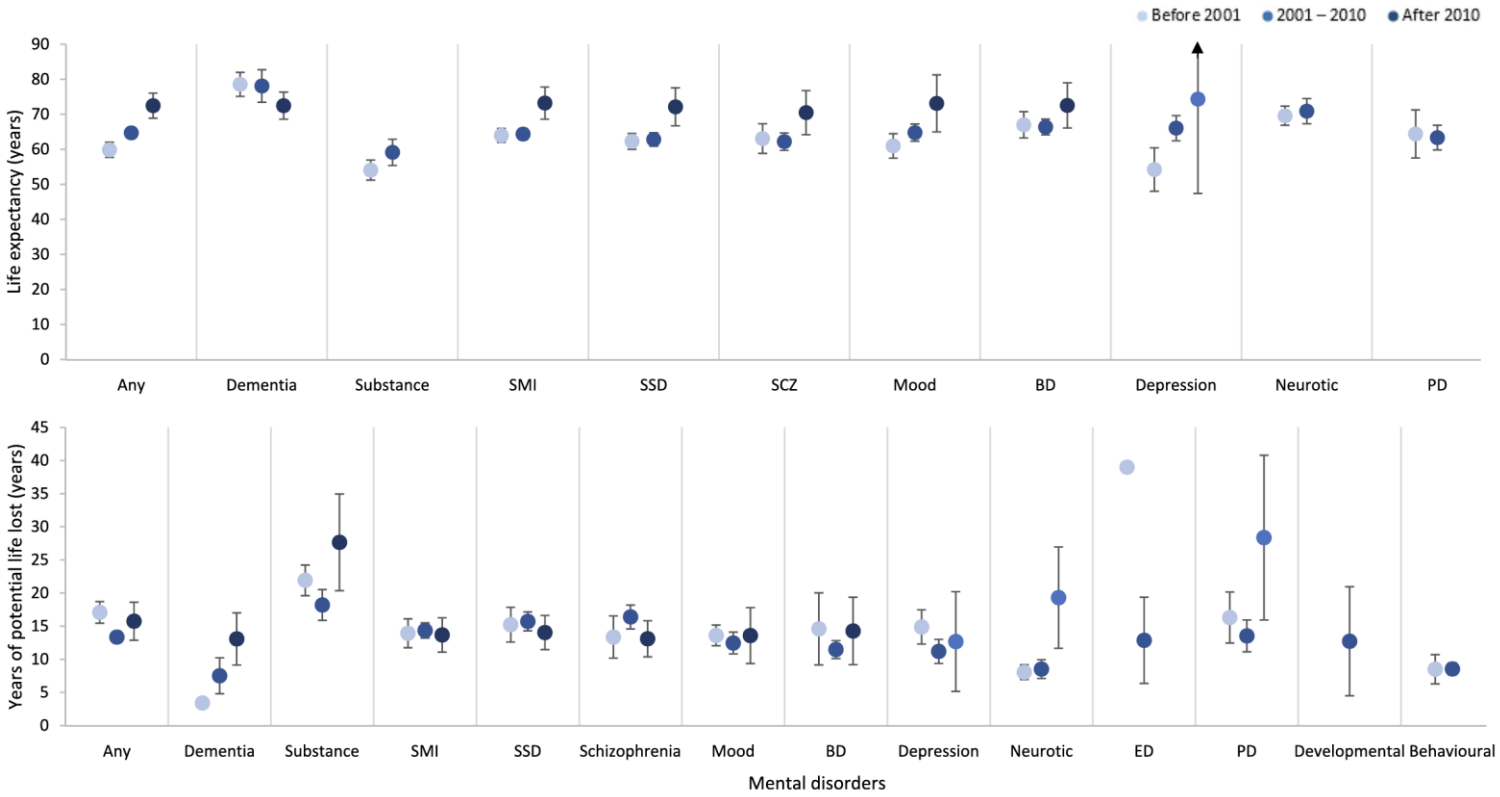
Life Expectancy and Years of Potential Life Lost in People with Mental Disorders: A Systematic Review and Meta-Analysis

Life expectancy and years of potential life lost (YPLL) of people with mental disorders before 2001, in 2001–2010, and after 2010



Abbreviations: Any = any mental disorders; BD = bipolar disorder; ED = eating disorders = PD = personality disorders; SCZ = schizophrenia; SMI = severe mental illness; SSD = schizophrenia-spectrum disorders

Chan et al. Lancet. 2023 Oct. 65:102294

Brain and Cognition DISCOVERY FOUNDATION

Transformation 2.0 - GLP-1 RAs as Psychiatric Medications?

McIntyre RS Psych Times, July 2025

Brain and Cognition DISCOVERY FOUNDATION

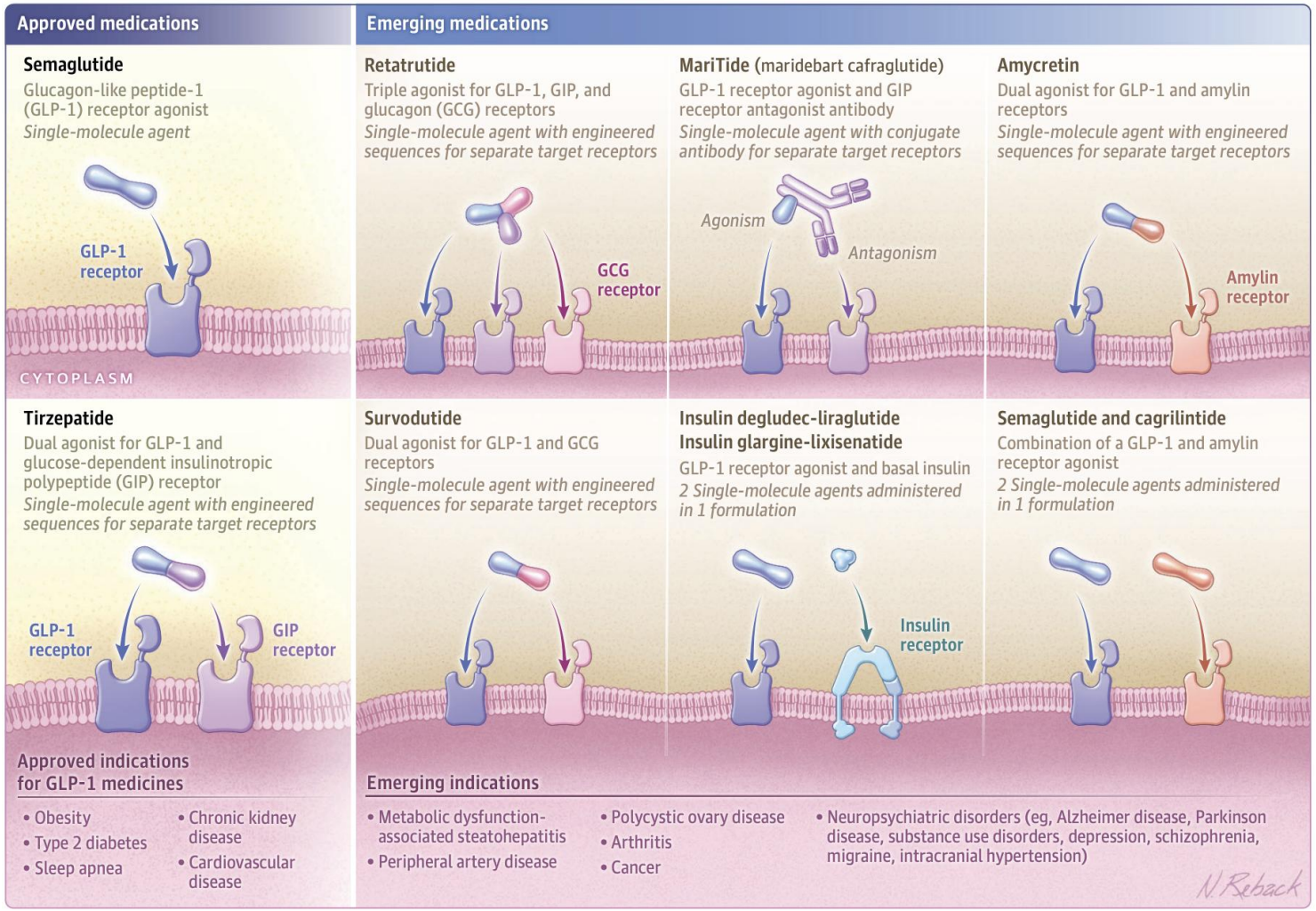
Incretins and Incretin Pharmacology: A History

- 1897: Pavlov pancreatic secretions neurally mediated
- 1902: Secretin coined by Baylis and Starling
- 1921, 1923, 1928: Insulin, Glucagon and Cholecystokinin (CCK) respectively
- 1932: Incretin coined by Jean La Barre
- 1966: DPP-IV discovered by Hopsu-Havu and Glenner
- 1970: Glucose insulinotropic polypeptide (GIP) coined by Pederson and Brown
- 1986: Glucagon-like peptide-1 (GLP-1) discovered by Holst, Habenar, Mojsov, Drucker
- 1992: Exendin-4 (Gila Monster) discovered by Eng
- 2005: FDA approves first GLP-1 receptor agonist Exenatide
- 2025 Incretin receptor agonists in Phase 3 in MDD and BD

McIntyre RS Psych Times, July 2025

New Molecules and Indications for GLP-1 Medicines

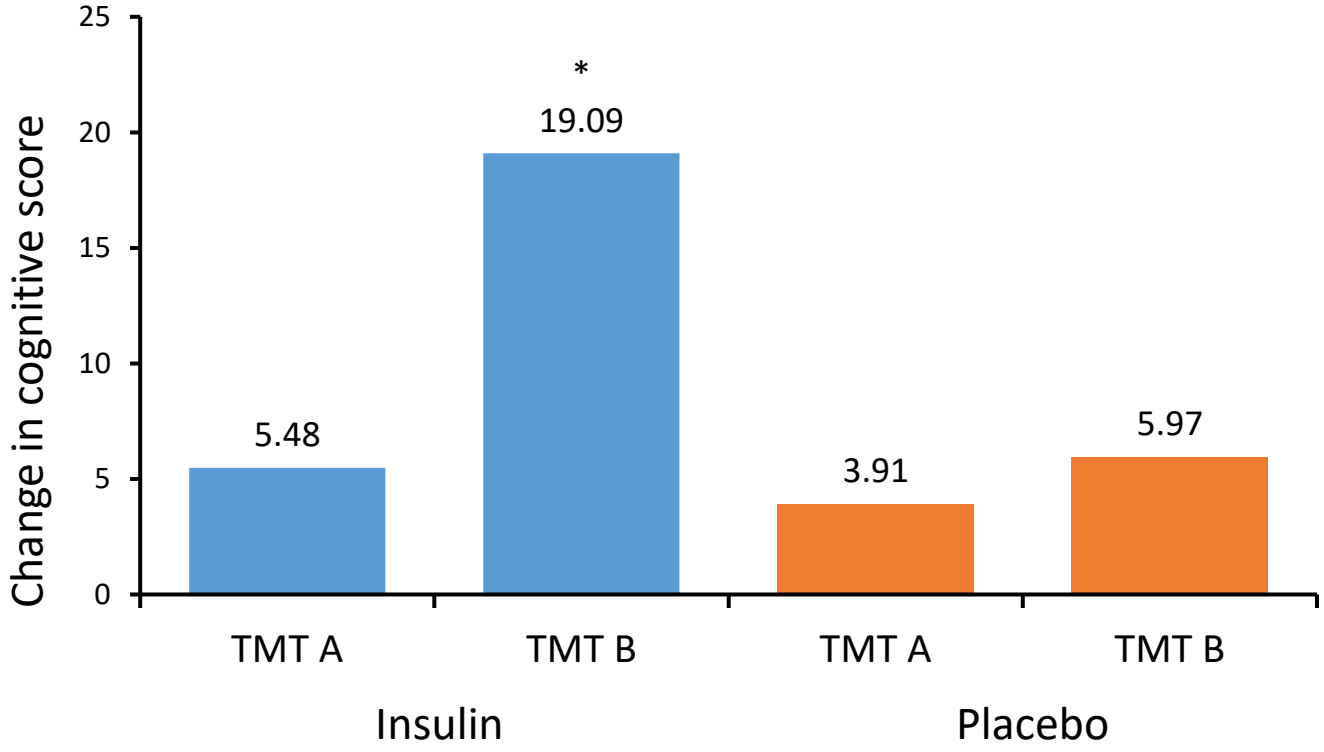
New Molecules and Emerging Indications for GLP-1 Medicines



Brain and Cognition DISCOVERY FOUNDATION

Gonzalez-Rellan MJ et al. JAMA. 2025 Oct 14;334(14):1231-1234

Intranasal Insulin Improves Cognitive Function in Persons Living With Bipolar Disorder



62 adults with bipolar disorder I / II received intranasal insulin (40 IU QID, n=34) or placebo (n=28) for 8 weeks

TMT A: time × treatment interaction, p=0.70

TMT B: time × treatment interaction, *p<0.05

McIntyre RS et al. Bipolar Disord 2012;14:697-706

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Pharmacologic Modulation of Orexin Signaling: Impact on Glucose-Insulin Homeostasis and Potential Mechanism of Antidepressant Action

Evidence Implicating Orexins on Metabolism

The endocrine pancreas produces orexins and expresses orexin receptors
Orexins govern energy expenditure
Orexins influence gluconeogenic activity
Orexins modulate sleep architecture (i.e. REM and non-REM sleep)

McIntyre RS & Wong S. Expert Opin Investig Drugs. 2025. Under Review

Brain and Cognition DISCOVERY FOUNDATION

Multiple Therapeutic Applications for GLP-1 RAs in Persons with Mental Disorders

- If patient has condition wherein GLP-1 is approved (e.g. T2DM, obesity)
- Off-label use for conditions currently under study and/or conditions where preliminary evidence currently exists (e.g. polycystic ovarian syndrome, binge eating disorder)
- To ameliorate psychotropic drug-related weight gain
- Treatment/prevention for lithium-induced nephrotoxicity?

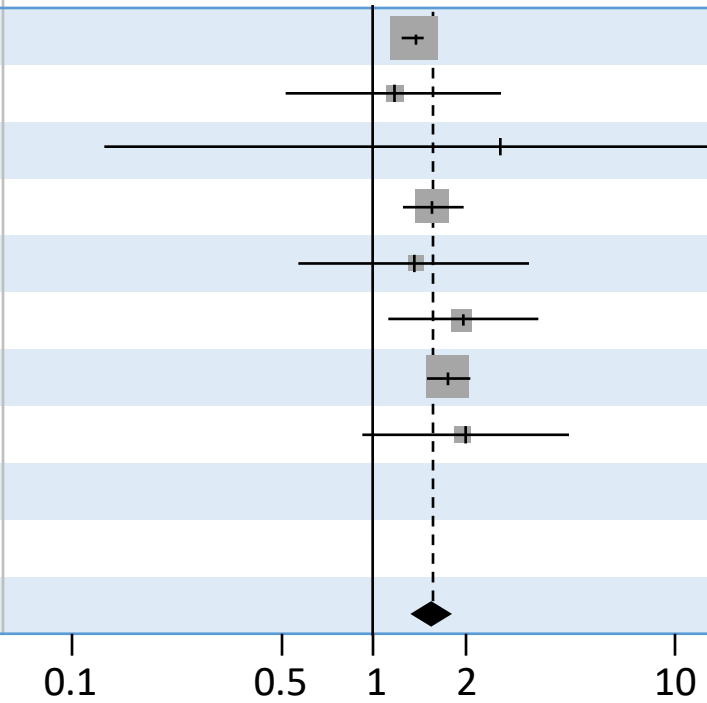
McIntyre RS. Psych Times. July 2025.

Brain and Cognition DISCOVERY FOUNDATION

Prevalence of Type 2 Diabetes and Impaired Fasting Glucose Significantly Increased in Persons with Bipolar Disorder

Relative Risk of Developing Type 2 Diabetes in Bipolar Patients and Age- and Gender-Matched Non-Bipolar Populations

Study	RR	95% CI	Weight
Kessing et al, 2021	1.37	[0.28; 1.48]	36.5%
Kittel-Schneider et al, 2020	4.18	[0.52; 2.66]	2.8%
Coello et al, 2019	2.65	[0.13; 54.74]	0.2%
Schoepf and Heun, 2014	1.57	[1.25; 1.96]	20.2%
Castilla-Puentes et al, 2011	1.37	[0.57; 3.29]	2.4%
Chien et al, 2010 (females)	1.99	[1.14; 3.47]	5.6%
Chien et al, 2010 (males)	1.78	[1.55; 2.05]	29.1%
Tsai et al, 2009	2.00	[0.93; 4.31]	3.1%
			0.0%
			0.0%
Random effects model	**1.57**	**[1.36; 1.81]**	**100.0%**



Heterogeneity: I^2 = 46%, p = 0.07

Brain and Cognition DISCOVERY FOUNDATION

Liu YK, et al. J Affect Disord. 2022; 300:449-61.

The Bidirectional Association of Nonalcoholic Fatty Liver Disease with Depression, Bipolar Disorder and Schizophrenia

CNS Spectrums

www.cambridge.org/cns

The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia

Muhammad Youshay Jawad[1,2], Shakila Meshkat[1], Aniqa Tabassum[1], Andrea Mckenzie[1], Joshua D. Di Vincenzo[1], Ziji Guo[2], Nabiha Batool Musavi[3], Lee Phan[1], Felicia Ceban[1,2], Angela TH Kwan[1,2,4], Ranuk Ramachandra[1,2], Gia Han Le[1,2], Rodrigo B. Mansur[1,5], Joshua D. Rosenblat[1,5], Roger Ho[6,7], Taeho Greg Rhee[8,9,10] and Roger S. McIntyre[1,2,5,11]*

[1]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada, [2]Brain and Cognition Discovery Foundation, Toronto, ON, Canada, [3]Liaquat National Medical College, Karachi, Pakistan, [4]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada, [5]Department of Psychiatry, University of Toronto, Toronto, ON, Canada, [6]Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [7]Institute for Health Innovation and Technology (iHealthtech), National University of Singapore, Singapore, Singapore, [8]Department of Psychiatry, School of Medicine, Yale University, New Haven, CT, USA, [9]VA New England Mental Illness, Research, Education and Clinical Center (MIRECC), VA Connecticut Healthcare System, West Haven, CT, USA, [10]Department of Public Health Sciences, School of Medicine, University of Connecticut, Farmington, CT, USA and [11]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Review

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https://doi.org/10.1017/S1092852922001043

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Key words:
Depression; Bipolar disorder; Mood Disorders; Schizophrenia; NAFLD; NASH; Fatty Liver;

Jawad MY, et al. CNS Spectr. 2023 Oct;28(5):541-560.

Brain and Cognition DISCOVERY FOUNDATION

Screening for Metabolic Dysfunction Associated Steatotic Liver Disease Should be Considered in All Persons Living With SMI With the Fibrosis 4 Index (Fib-4)

- Prevalence of MASLD in the general population: 25%
- OR in MDD = 1.65, BD = 1.76 and SCZ = 2.01
- Risk factors: e.g., obesity, diabetes mellitus, PCOS
- Associated with fibrosis, cirrhosis, hepatocellular and extrahepatic carcinoma
- mRNA levels decreased CYP1A2, CYP2D6 and CYP2E1 mRNA and decreased protein expression of CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4
- Fib-4 Index: age (years) AST (U/L)/[PLT (109/L) ALT ½ (U/L)

McIntyre RS, Le GH, J Clin Psychiatry 86:4, December 2025

Brain and Cognition DISCOVERY FOUNDATION

Psychotropic Drug-Related Weight Gain

Risk of Weight Gain*	Antidepressants	Antipsychotics	Lithium and Anticonvulsants
High	Amitriptyline, citalopram, clomipramine, fluvoxamine, mirtazapine, nortriptyline, paroxetine, phenelzine	Clozapine, olanzapine	Valproate (valproic acid)
Moderate	Desipramine, duloxetine, escitalopram, sertraline, venlafaxine	Chlorpromazine, olanzapine/ samidorphan, paliperidone, quetiapine, risperidone	Lithium
Low	Agomelatine, desvenlafaxine, gepirone, levomilnacipran, moclobemide, selegiline, tranylcypromine, vilazodone, vortioxetine	Amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, haloperidol, iloperidone, ziprasidone	Carbamazepine, gabapentin, oxcarbazepine, pregabalin
Neutral or weight loss	Bupropion, dextromethorphan-bupropion, esketamine, fluoxetine, zuranolone	Lumateperone, lurasidone	Lamotrigine, topiramate

*Risk categorization based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

McIntyre. Am J Psychiatry. 2024;181:26

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Incretin Receptor Agonist Recommended for Psychotropic Drug-Related Weight Gain and Its Treatment

1. Measure patient's weight and BMI; consider waist circumference; use metabolic monitoring and Fibrosis-4 Index (FIB-4) where appropriate
2. Recommend lifestyle behavioral modification, improved diet, and eating pattern
3. Target psychiatric comorbidity associated with weight gain and/or metabolic abnormalities
4. Prioritize psychotropic drugs that are weight-neutral or have low weight gain liability
5. Follow metabolic monitoring guidelines to detect weight gain and allow for earlier intervention
6. When initiating weight-gain-promoting drugs, co-commence metformin if the index agent is an antipsychotic, as part of shared-decision making
7. For established PDWG, consider switching to an agent with lower weight gain liability or adjunctive metformin, and GLP-1 receptor agonists if clinical presentation warrants, as part of shared-decision making.

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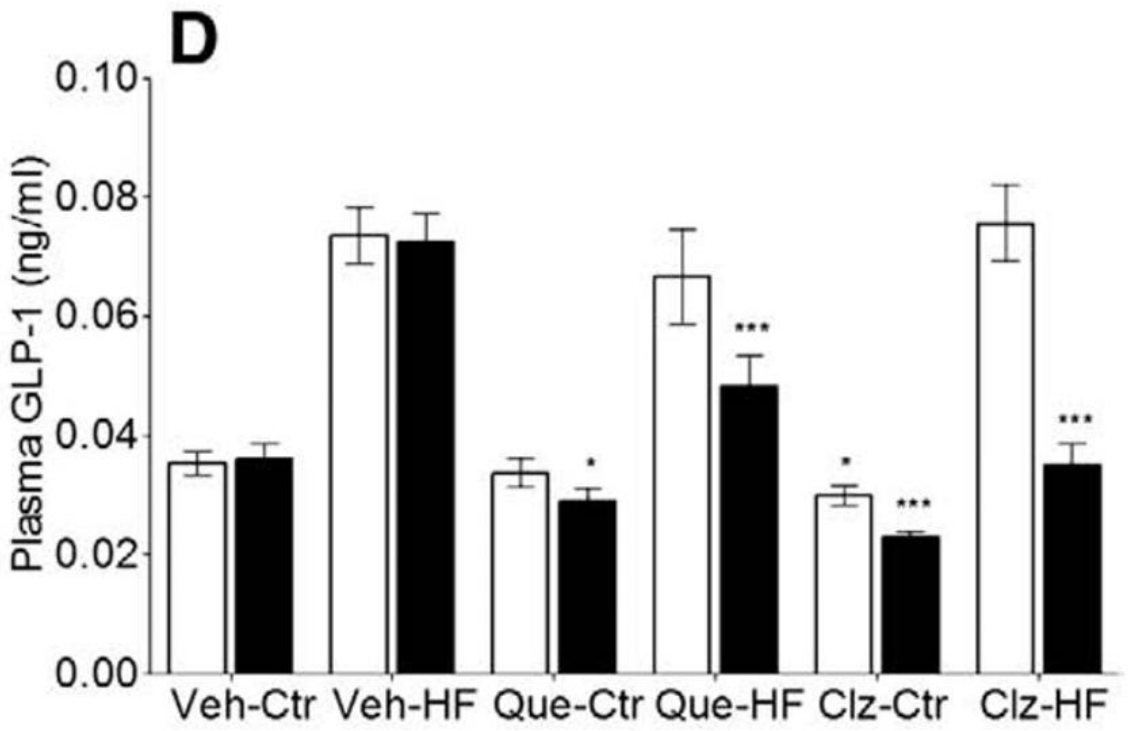
McIntyre. Am J Psychiatry. 2024;181:1

Quetiapine and Clozapine Suppress the Release of GLP 1

The effect of antipsychotic drugs on plasma endocrine measurements chronic (42 days) exposure on chow and high fat/high sugar diets



Plasma GLP-1 Active Before (0 h; white box) and After (1 h; black box) Drug Exposure
Abbreviations: Ctr = Chow. HF = High fat/high sugar. Veh = Vehicle. Que = Quetiapine. Clz = Clozapine
*p<0.05, **p<0.01, ***p<0.001 (determined by one-way ANOVA for each of the groups)

Smith et al. Schizophr Res. 2009 Aug.

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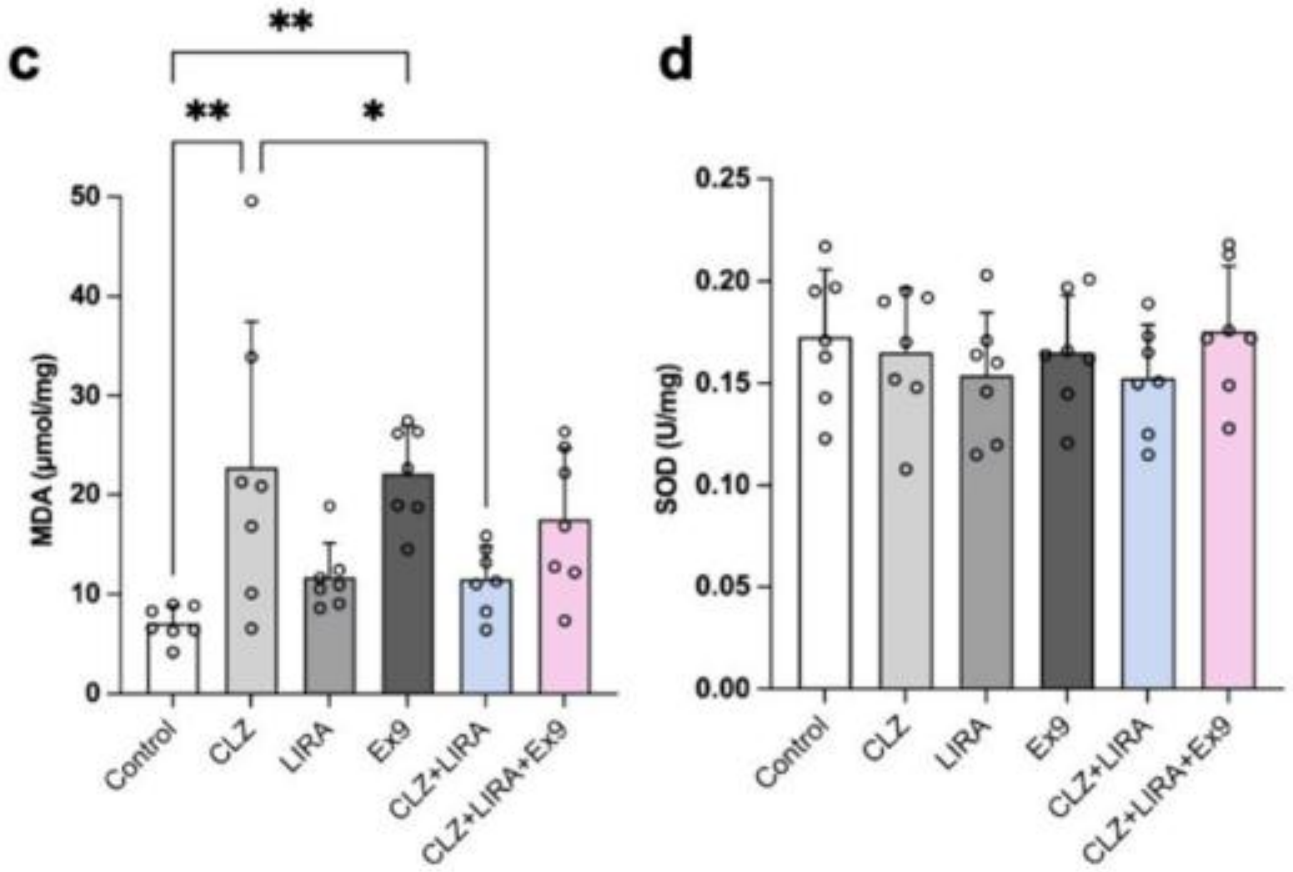
Liraglutide Attenuates Clozapine-Induced Mitochondrial Dysfunction and Improves Energy Metabolism in the Brain of Rats

Assessment of mitochondrial morphology and oxidative stress - LIRA treatment improved the mitochondrial conditions

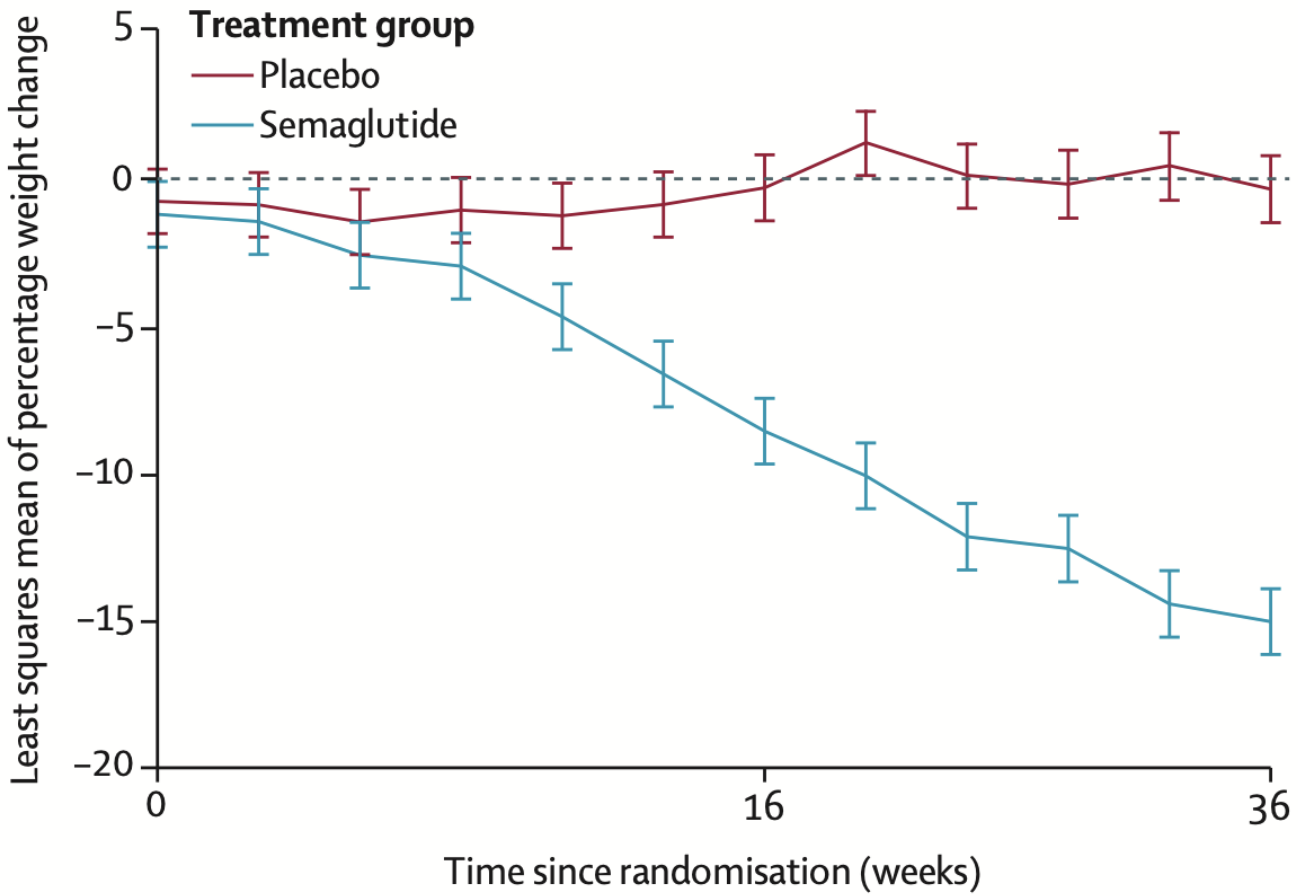


He Y., et al. Biochem Pharmacol. 2025 Jun 28;240:117091.

Brain and Cognition DISCOVERY FOUNDATION

Efficacy and Safety of Semaglutide Versus Placebo for People with Schizophrenia on Clozapine with Obesity (COaST): A Phase 2, Multi-Centre, Participant and Investigator- Blinded, Randomised Controlled Trial in Australia

Percentage weight change in participants up to 36 weeks



Siskind D, et al. *Lancet Psychiatry*. 2025;12(7):493-503.

Brain and Cognition DISCOVERY FOUNDATION

Potential Protective Role of GLP-1 Receptor Agonists in Lithium-Induced Nephrotoxicity?

Forest plots of RORs for lithium, semaglutide, and their combination across key renal adverse events.

McIntyre RS & Kwan ATH. Expert Opin Drug Saf. 2025. Under Review.

Brain and Cognition DISCOVERY FOUNDATION

Mental Disorders Wherein Incretin-Based Pharmacologic Agents are Under Investigation:

- Major Depressive Disorder, Bipolar Disorder , Schizophrenia: relapse prevention, negative symptoms, general cognitive impairment
- Parkinson's Disease
- Early-Stage Alzheimer's Disease
- Opioid Use Disorder/ Tobacco Use Disorder/Alcohol Use Disorder

McIntyre RS. Psych Times. July 2025.

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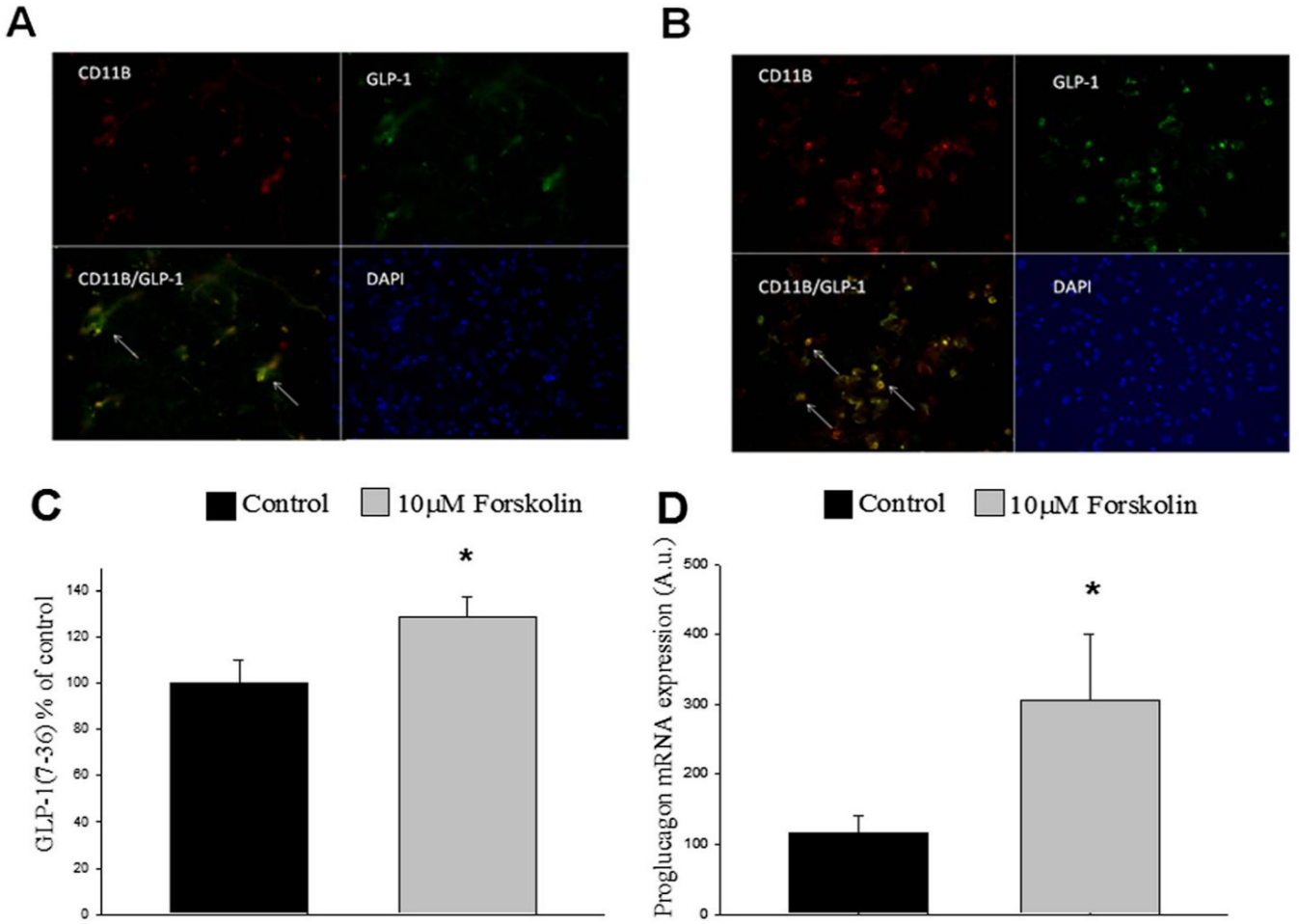
GLP-1 Secretion By Microglial Cells and Decreased CNS Expression In Obesity

Microglia express proglucagon mRNA and express and secrete GLP-1

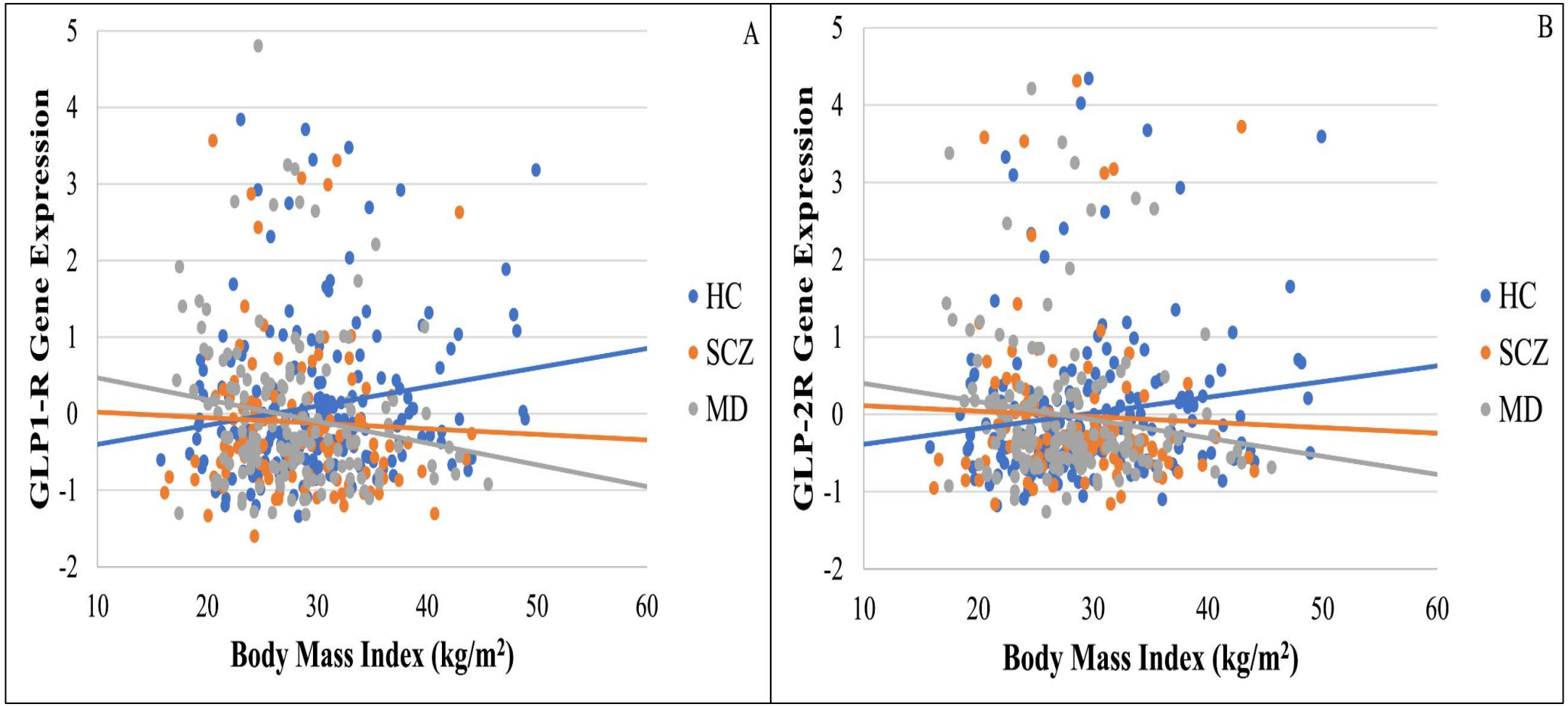


Kappe C, et al. J Neuroinflammation. 2012 Dec:9:276.

Brain and Cognition DISCOVERY FOUNDATION

Glucagon-Like Peptide Receptor Gene Expression is Reduced in Individuals with Mood and Psychotic Disorders

Associations between body mass index and (A) GLP-1R and (B) GLP-2R gene expression, according to diagnosis, in the dorsolateral prefrontal cortex

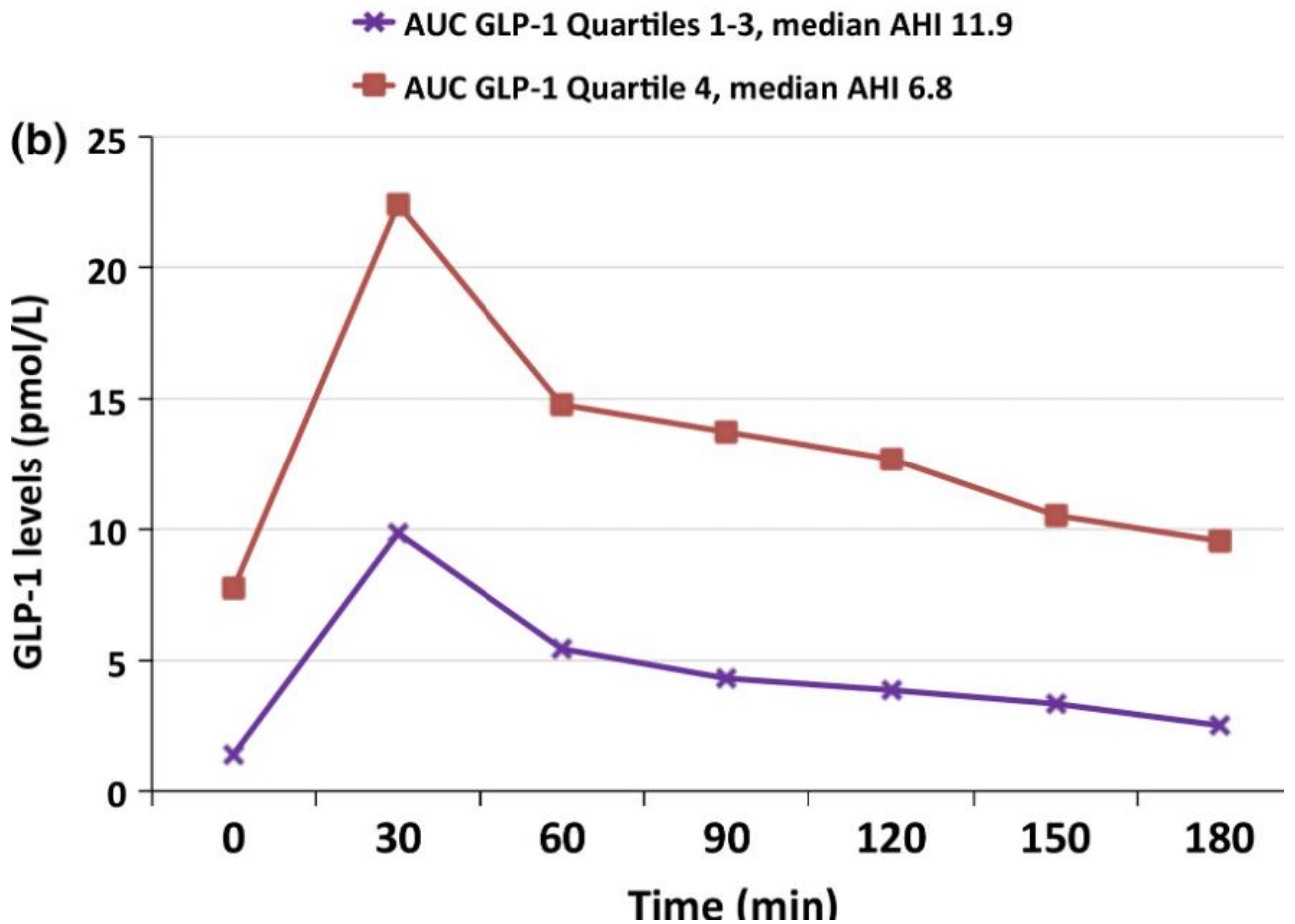


Mansur RB, et al. Eur Neuropsychopharmacol. 2019 Jan;29(1):137-146.

Brain and Cognition DISCOVERY FOUNDATION

The relationship between sleep and glucagon-like peptide 1 in patients with abnormal glucose tolerance

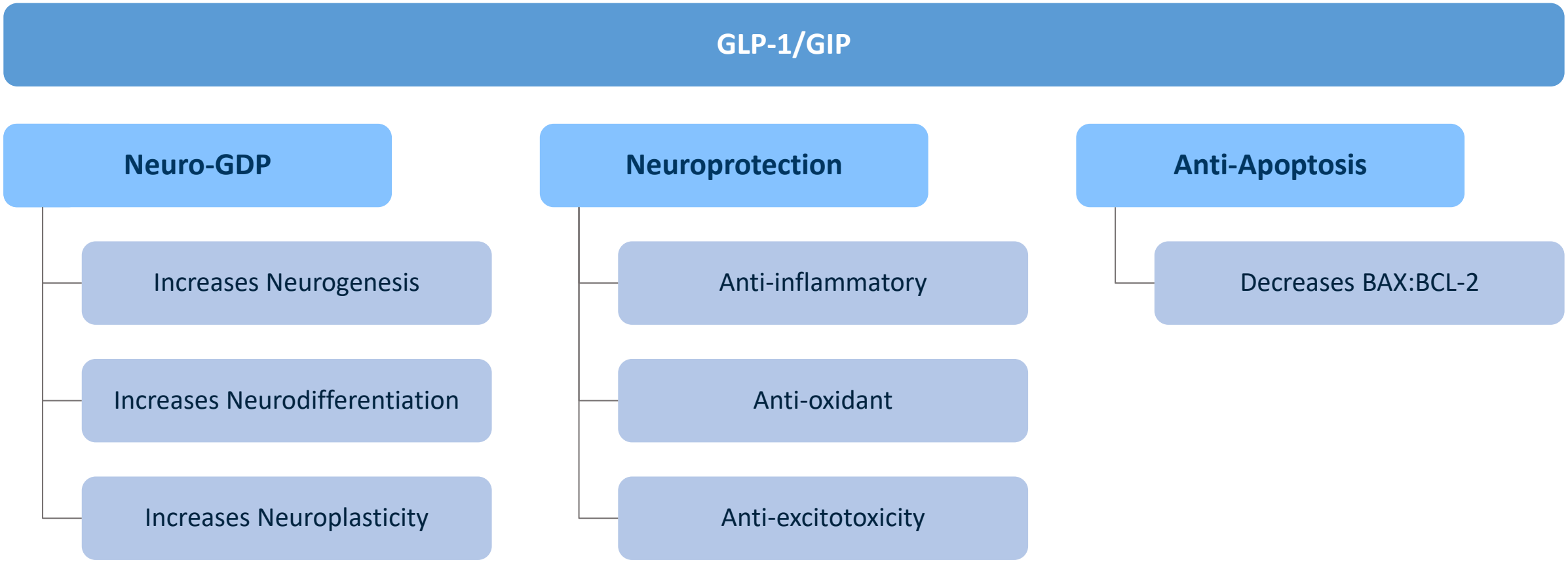
Median GLP-1 levels after 75-g glucose challenge tests per quartiles 1–3 and quartile 4 of area under the curve (AUC) GLP-1.



Reutrakul S, et al. J Sleep Res. 2017 Dec;26(6):756-763

Brain and Cognition DISCOVERY FOUNDATION

GLP/GIP Targets Molecular and Cellular Systems Implicated in the Pathophysiology of Mental Disorders



BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; GIP, glucose dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; Neuro-GDP, neuro-genesis, -differentiation, -plasticity

McIntyre RS, et al. CNS Spectrums 2025:1–7.

Brain and Cognition DISCOVERY FOUNDATION

Glucagon-like Peptide-1 (GLP-1) Increases Neurogenesis

Effect of GLP-1 Agonists on Neurogenesis

GLP-1 Agonist	Effects on Neurogenesis	*P*-value	Regions of interest
Exenatide	**Increased**: • DCX-positive neuroblasts • BrdU-positive mature neurons	 < 0.01 < 0.01	 • Increased number of neuroblasts identified in the medial striatum. • Increased neuronal proliferation in the subventricular zone.
Dulaglutide	N/A	N/A	N/A
Geniposide	**Increased**: • DCX-positive neuroblasts • DCX-positive dendrites	 < 0.05 < 0.05	N/A
Liraglutide	**Increased**: • BrdU-positive mature neurons • DCX-positive neuroblasts • Ki67-postive immature neurons No statistically significant changes in gliogenesis or astrocyte proliferation were observed.	 < 0.05 < 0.05 < 0.05	 • Increased number of mature neurons in the dentate gyrus. • Increased number of neuroblasts in the subventricular zone. • Increased number of immature neurons in the dentate gyrus.
Lixisenatide	**Increased**: • BrdU-positive mature neurons • DCX-positive immature neurons	 < 0.01 < 0.05	• Increased number of mature neurons in the olfactory bulb and the hippocampus. • Increased number of immature neurons in the olfactory bulb and the hippocampus.
Semaglutide	**Increased**: • DCX-positive immature neurons	 < 0.01	N/A

Abbreviations: DCX = Doublecortin, BrdU = Bromodeoxyuridine, Ki67 = Antigen Kiel67

Au et al. Acta Neuropsychiatr. 2025 Feb; 1-25

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The Effect of GLP-1 Receptor Agonists on Autophagy: Implications for the Treatment of Neurodegenerative and Other Mental Disorders

In Vivo Studies

Study	Beclin-1	LC3-II/ LC3-I	p62 (SQSTM1)	ATG7	ATG3	LAMP1
Zhang et al. (2018)	↑	↑	↑	↑	NR	NR
Lin et al. (2021)	NR	↑	↓	NR	NR	NR
Zhang et al. (2020)	↑	↑	↑	NR	NR	NR
Zhang et al. (2023)	NR	↑	↓	NR	NR	NR
Bu et al. (2021)	NR	↑	NR	NR	NR	NR
Zhang et al. (2021)	↑	NR	No difference	NR	NR	NR
Wu et al. (2022)	↑	↑	↓	NR	NR	NR
Elbadawy et al. (2025)	↑	↑	NR	NR	NR	NR

Assessment:

- ↑ = *reported increase in expression of autophagy-specific marker by GLP-1RA(s)*
- ↓ = *reported decrease in expression of autophagy-specific marker by GLP-1RA(s)*
- *NR = Not Reported*

Sioufi, M.C. Dri C et al, 2025 Under Revciew

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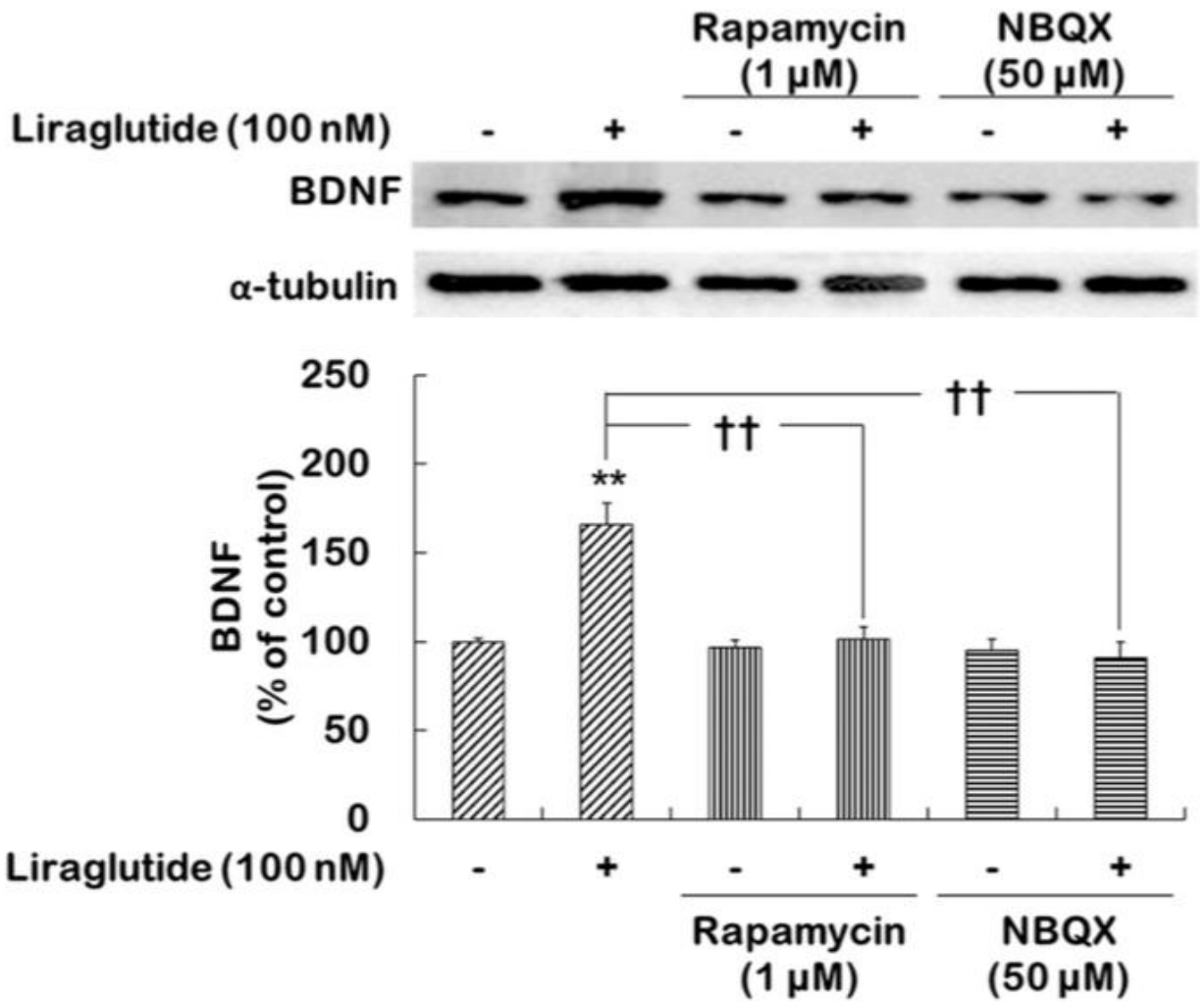
Liraglutide-Induced BDNF Expression and Interactions With Glutamate Systems



Park SW et al., Front Neurosci. 2018; 12:756

Brain and Cognition DISCOVERY FOUNDATION

Effects of Glucagon-like Peptide-1 (GLP-1) Monoagonists Restore Functional Connectivity

Effect of GLP-1 Agonists on Brain Functional Connectivity

GLP-1 Agonist	Effects on functional connectivity	*P*-value	Z-score	Regions of interest
Exenatide	**Increased**: • Within the hypothalamus. • Between the left hypothalamus and left NTS. • Between the left NTS and left thalamus. • Between the right NTS and left thalamus.† • Between the left NTS and right thalamus.†	 < 0.0001 0.026 0.028 0.054 0.140	 - 3.38 4.86 3.79 3.47	• Affected rsFC in the hypothalamus may affect integration of emotional and bodily sensations. • Dysconnectivity of thalamus attributed to emotional and cognitive impairments. • Affected rsFC of the NTS may be implicated in MDD.
Liraglutide	**Increased**: • Within the bilateral hippocampus.	 < 0.05	 -	• Reduced functional connectivity of bilateral hippocampus observed in persons with BD.
Dulaglutide	No statistically significant changes in functional connectivity reported.	-	-	
Lixisenatide	N/A	N/A	N/A	N/A
Semaglutide	N/A	N/A	N/A	N/A
Tirzepatide	N/A	N/A	N/A	N/A

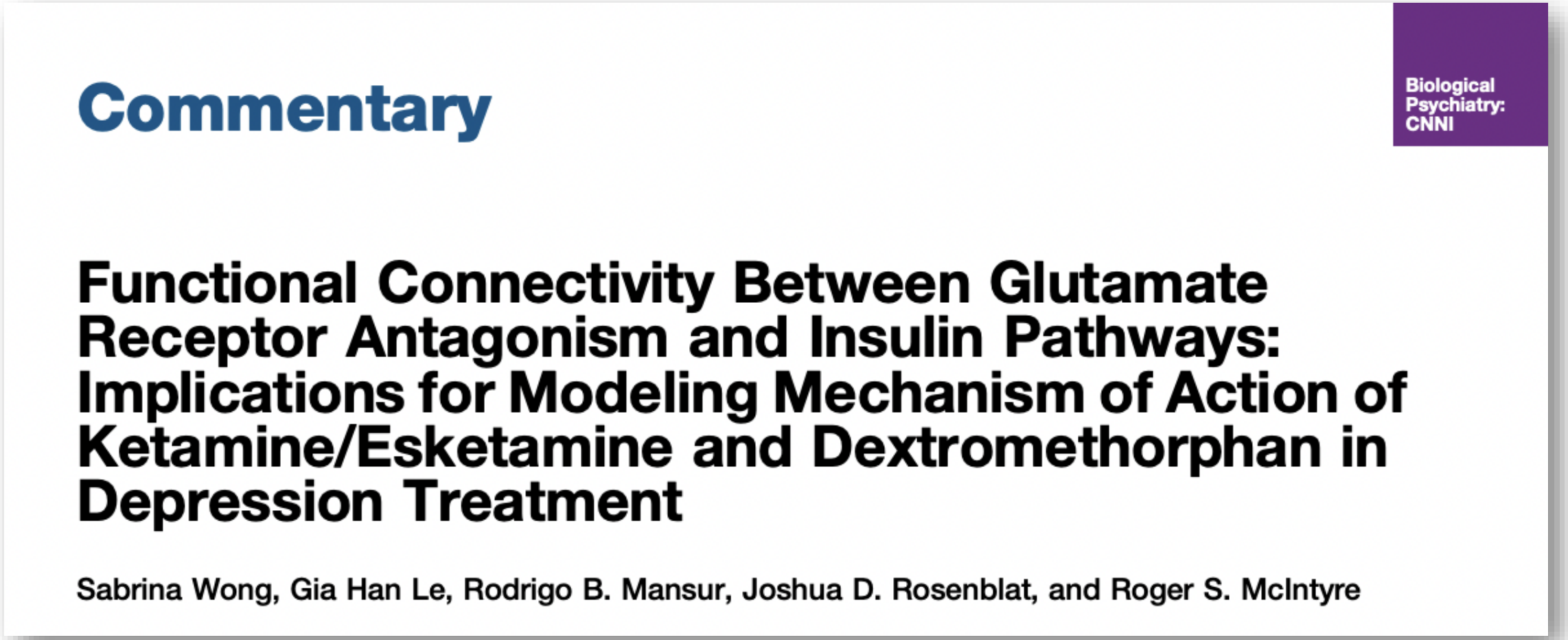
Abbreviations: rsFC = Resting-State Functional Connectivity, MDD = Major Depressive Disorder, BD = Bipolar Disorder, NTS = Nucleus tractus solitarius, N/A- not available

†Results not significant under the P < 0.05 threshold.

Au et al. J Affect Disorders. 2025 Feb; 370:321-327.

Brain and Cognition DISCOVERY FOUNDATION

Functional Connectivity Between Glutamate Receptor Antagonism and Insulin Pathways: Implications for Modeling Mechanism of Action of Ketamine/Esketamine and Dextromethorphan in Depression Treatment

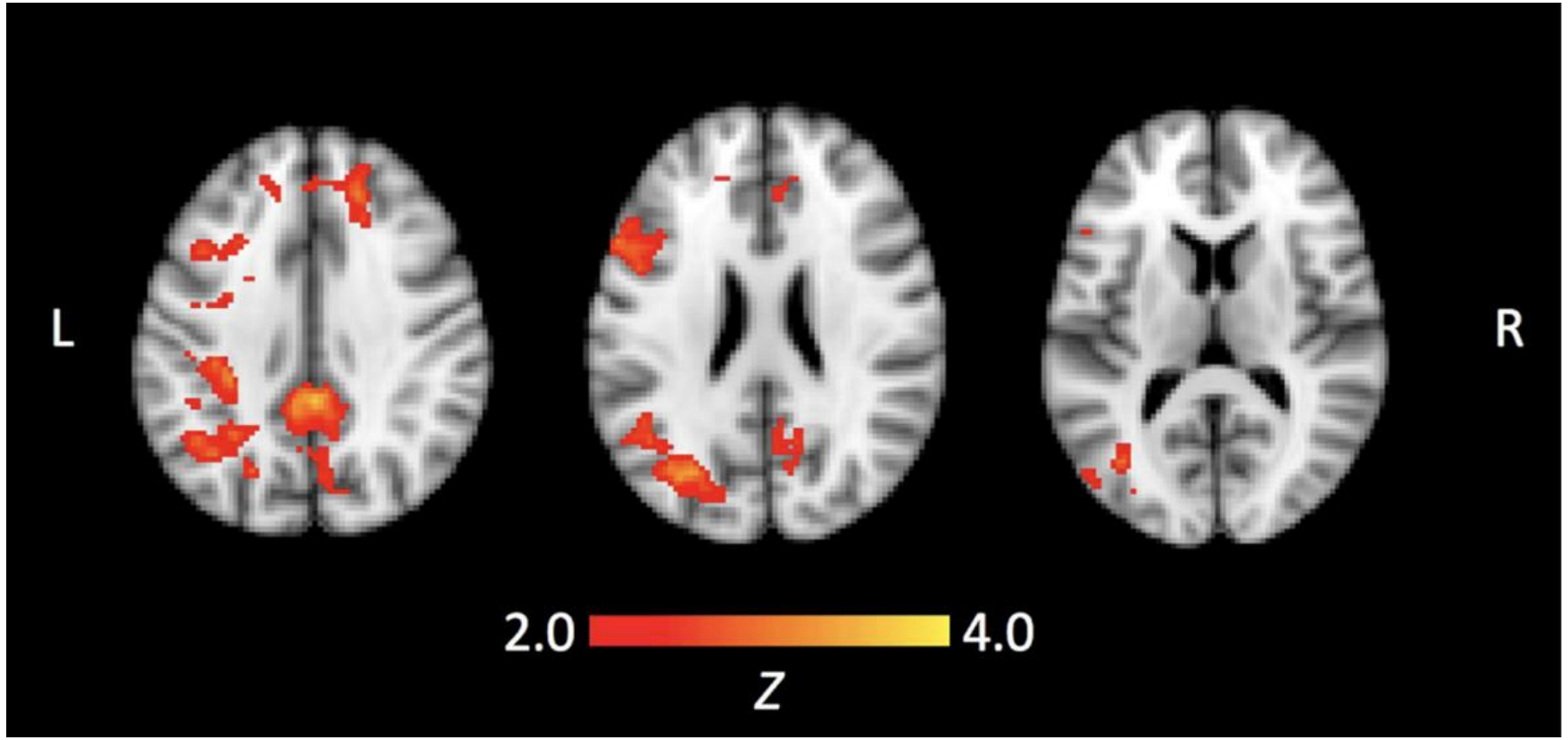


Wong S, et al. Biol Psychiatry Cogn Neurosci Neuroimaging. 2025 Mar;10(3):241-243.

Brain and Cognition DISCOVERY FOUNDATION

Liraglutide Normalizes Circuit Connectivity in Persons at Risk for Alzheimer's Disease

Brain regions showing increased connectivity with the bilateral hippocampus in the treatment group relative to the placebo group at Time Point 2



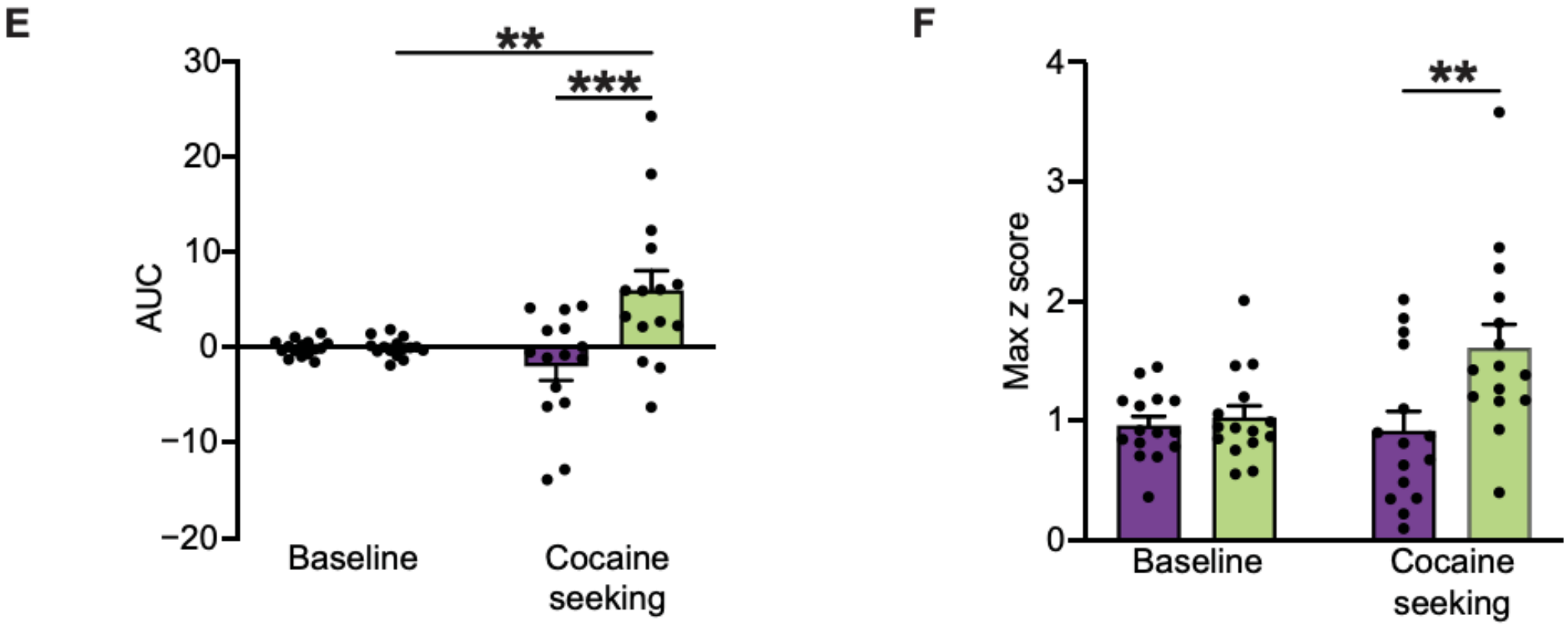
Statistical maps are thresholded using a cluster Z threshold > 2.0 and p < 0.05 (corrected). Slices taken from the following z coordinate locations: 36 (left), 24(middle), 12 (right).

Watson KT, et al. Behav Brain Res. 2019 Jan 1:356:271-278.

Brain and Cognition DISCOVERY FOUNDATION

An Endogenous GLP-1 Circuit Engages VTA GABA Neurons to Regulate Mesolimbic Dopamine Neurons and Attenuate Cocaine Seeking

Systemic GLP-1R agonist pharmacotherapy increases VTA GABA neuron activity and decreases cocaine seeking

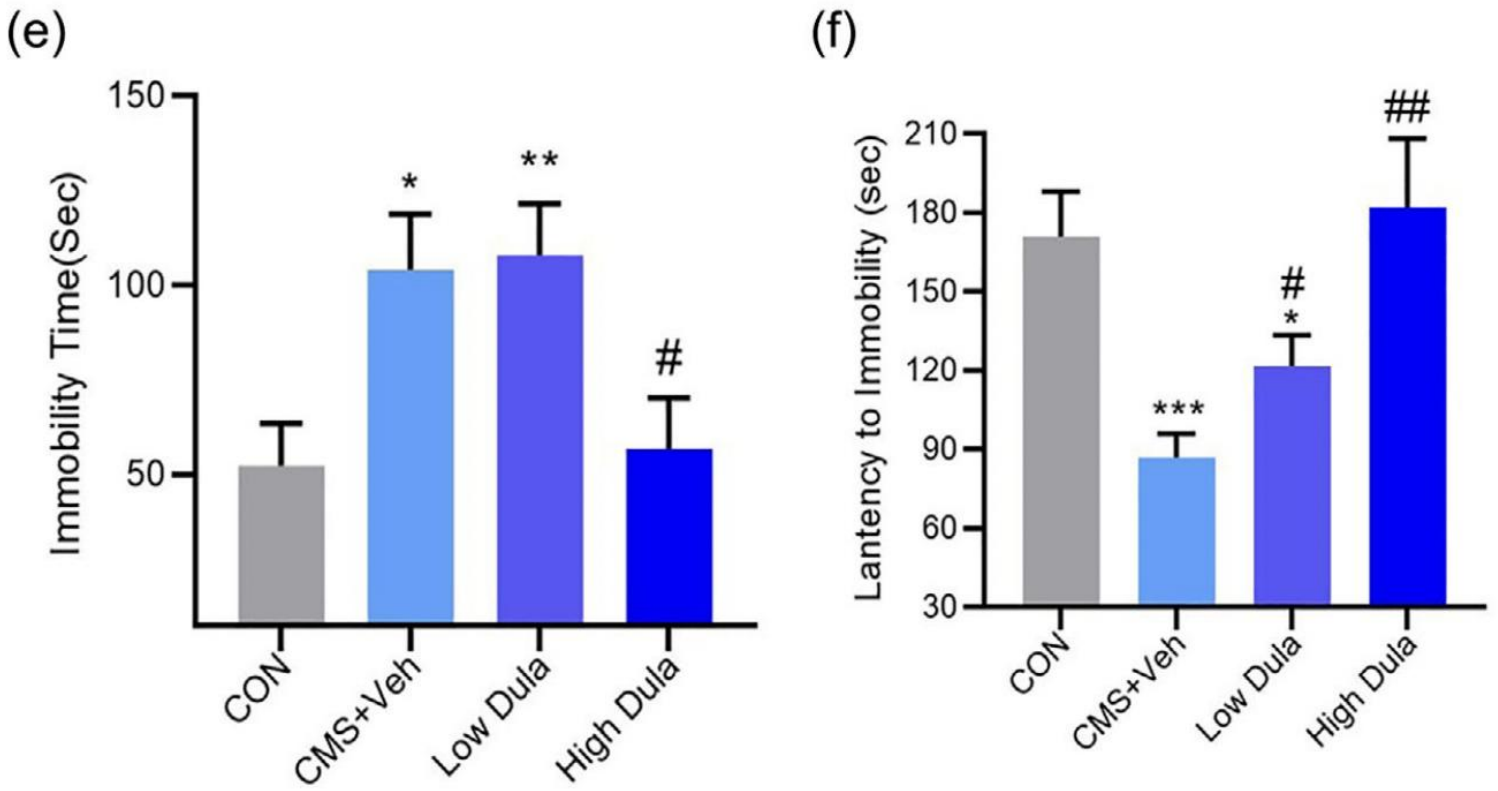


Merkel R, et al. *Sci Adv*. 2025;11(9):eadr5051.

Brain and Cognition DISCOVERY FOUNDATION

Dulaglutide treatment reverses depression-like behavior and hippocampal metabolomic homeostasis in mice exposed to chronic mild stress

Immobility time (e) and latency to immobility (f) in the tail suspension test (TST) after dulaglutide treatment (n = 13–15).



Jin M, et al. Brain Behav. 2024 Mar;14(3):e3448.

Glucagon-like Peptide 1 (GLP-1) Receptor Agonists as a Protective Factor for Incident Depression in Patients with Diabetes Mellitus: A Systematic Review

Journal of Psychiatric Research 164 (2023) 80–89

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Check for updates

Glucagon-like peptide 1 (GLP-1) receptor agonists as a protective factor for incident depression in patients with diabetes mellitus: A systematic review

Daniel H. Cooper [a], Ranuk Ramachandra [a,b], Felicia Ceban [a,b], Joshua D. Di Vincenzo [a,b], Taeho Greg Rhee [e,f,g], Rodrigo B. Mansur [a,d,k], Kayla M. Teopiz [b], Hartej Gill [a,k], Roger Ho [h,i], Bing Cao [j], Leanna M.W. Lui [a,b,k], Muhammad Youshay Jawad [a], Juliet Arsenault [a,b], Gia Han Le [a,b], Diluk Ramachandra [a], Ziji Guo [b,c], Roger S. McIntyre [a,b,c,d,*]

Cooper DH et al., J Psychiatr Res. 2023 Aug;164:80-89. Epub 2023 Jun 5.

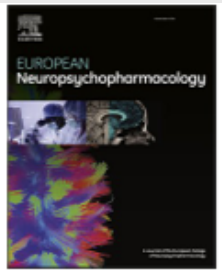
Brain and Cognition DISCOVERY FOUNDATION

Repurposing Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists for the Treatment of Depression: A Systematic Review of Preclinical, Observational and Clinical Investigations

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology



Check for updates

Repurposing glucagon-like peptide-1 (GLP-1) receptor agonists for the treatment of depression: A systematic review of preclinical, observational and clinical investigations

Sophie Li [a,1], Sami George Sabbah [a,1], Angela T.H. Kwan [a,b], Roger S. McIntyre [c,d,*]

[a] Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[b] Brain and Cognition Discovery Foundation, Toronto, ON, Canada
[c] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[d] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

Li S, et al. Eur. Neuropsychopharmacol. Oct 2025. 99, 56-67.

Brain and Cognition DISCOVERY FOUNDATION

Dulaglutide Slows the Progression of Cognitive Impairment in Type 2 Diabetes: An Exploratory Analysis of the REWIND Trial

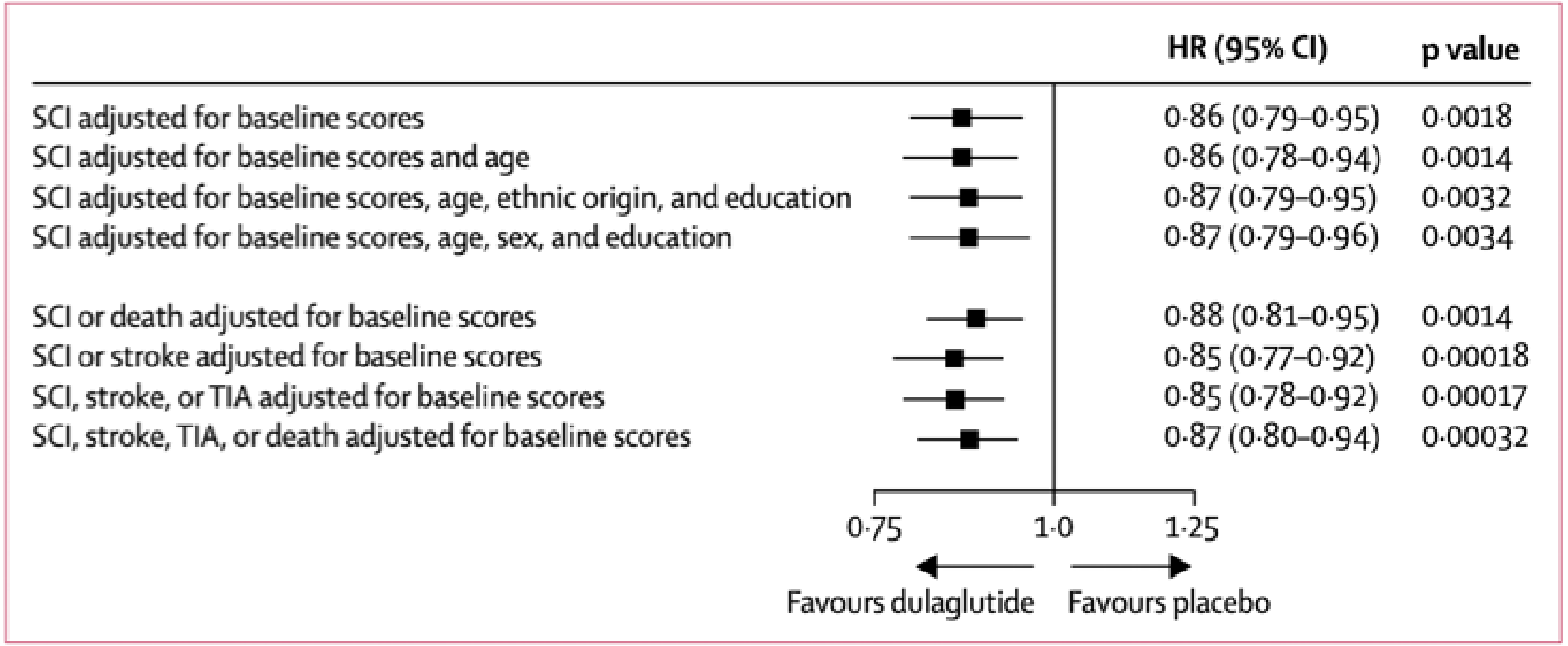
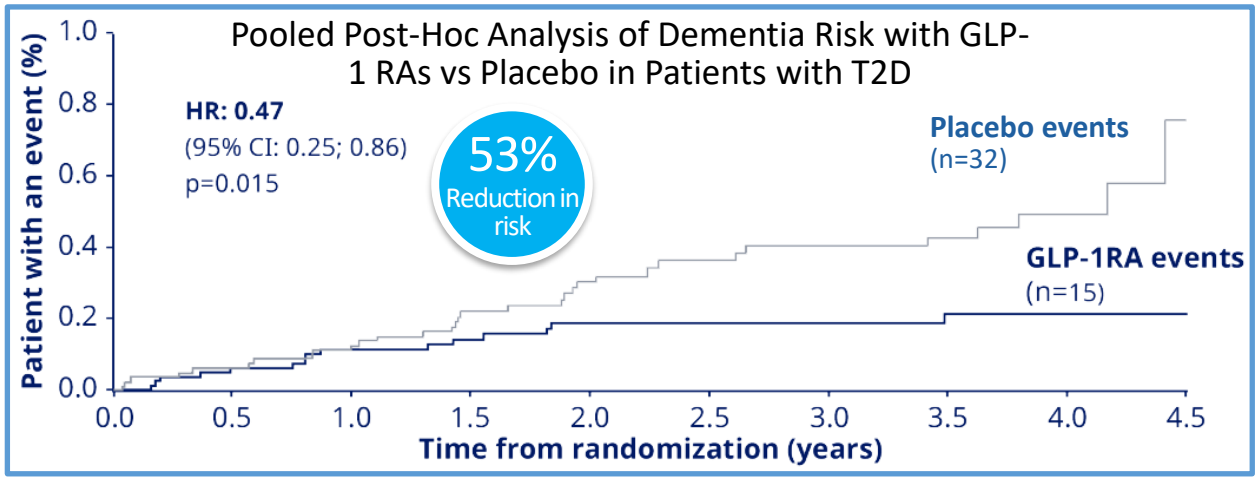


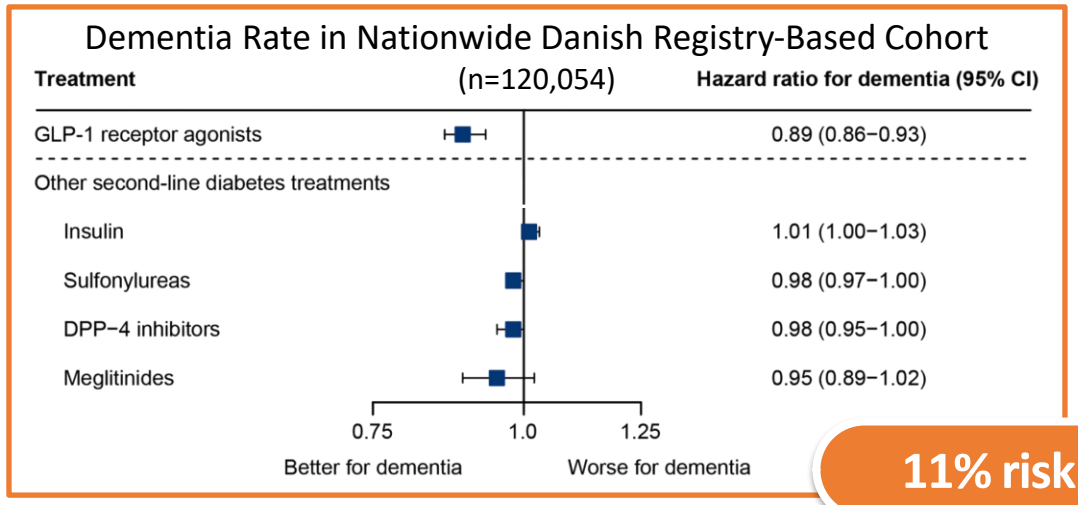
Figure 1: **Risk of SCI, adjusted for baseline standardised MoCA and DSST scores**

Cukierman-Yaffe, C et al. Lancet Neurol. 2020;(7):582-590.

Brain and Cognition DISCOVERY FOUNDATION

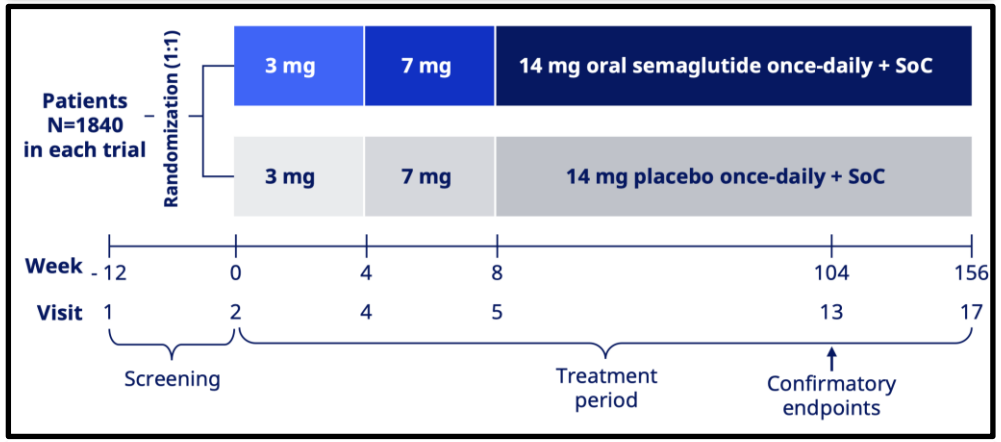
Treatment with GLP-1 RAs Are Associated with Reduced Incidence of Dementia





11% risk reduction

These potential signals for preventing progression in early Alzheimer's prompted initiation of two large clinical trials in in a nondiabetic general population



Primary outcome is change in CDR-SB over 2 years (impact of cognitive decline on daily function)

The trials began in 2021, with likely results in 2026

RA = receptor agonist; CDR-SB = Clinical Dementia Rating-Sum of Boxes.

Nørgaard CH, et al. *Alzheimers Dement (N Y)*. 2022;8(1):e12268. Atri, A, et al. Alzheimer's & Dementia. 2022;18(S10):e062415.

Brain and Cognition DISCOVERY FOUNDATION

Glucagon-like Peptide 1 Receptor Agonists (GLP-1 RAs) as Treatment for Nicotine Cessation in Psychiatric Populations: A Systematic Review

Lee *et al. Annals of General Psychiatry* (2024) 23:45
https://doi.org/10.1186/s12991-024-00527-9

Annals of General Psychiatry

REVIEW

Open Access

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) as treatment for nicotine cessation in psychiatric populations: a systematic review

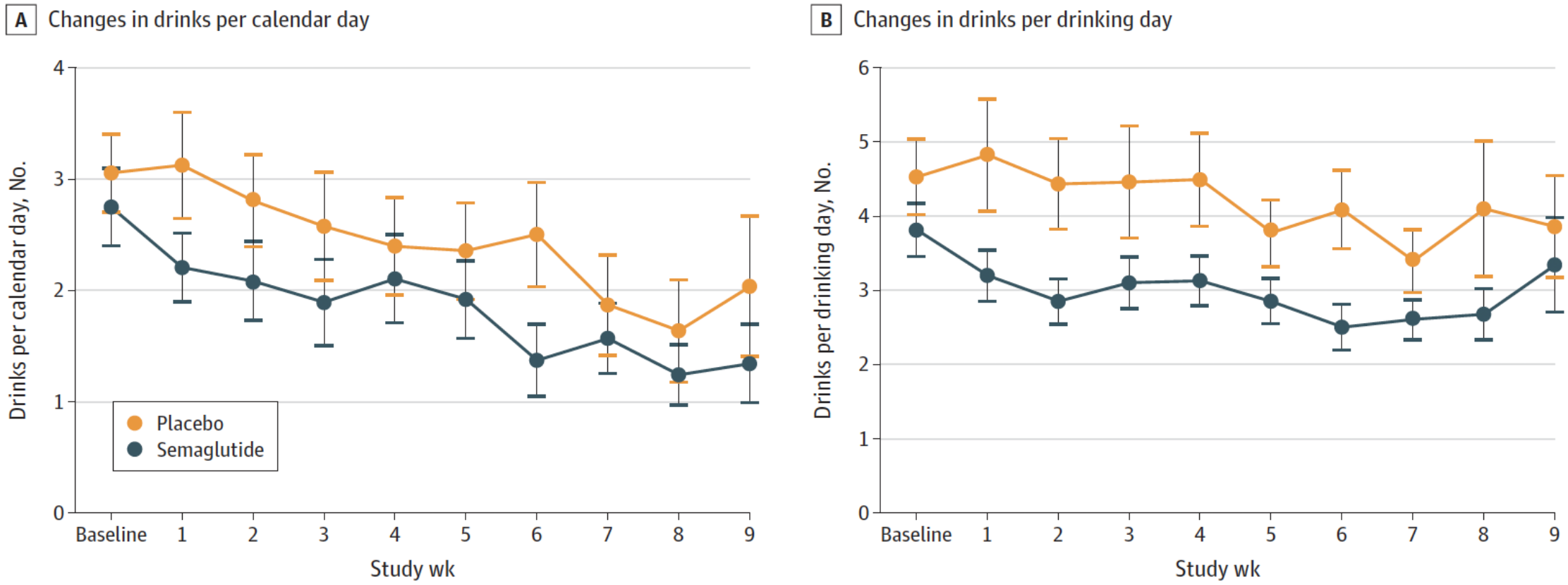
Serene Lee[1,5†], Maggie Li[1†], Gia Han Le[1,2,3], Kayla M. Teopiz[1], Maj Vinberg[10,11], Roger Ho[7,8,9], Hezekiah C. T. Au[1], Sabrina Wong[1,2,4], Kyle Valentino[1,4], Angela T. H. Kwan[1,6], Joshua D. Rosenblat[2,3,4,12] and Roger S. McIntyre[1,4,12*]

Lee, S. et al. Ann Gen Psychiatry. 2024 Nov 11;23(1):45.

Brain and Cognition DISCOVERY FOUNDATION

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

Prospective Changes in Weekly Alcohol Outcomes



Hendershot. C.S. et al. JAMA Psychiatry. 2025 Feb 12.

Brain and Cognition DISCOVERY FOUNDATION

Intersection of Cardiovascular Risk and Suicide Risk in Youth with Bipolar Disorder

High Cardiovascular Risk Factors

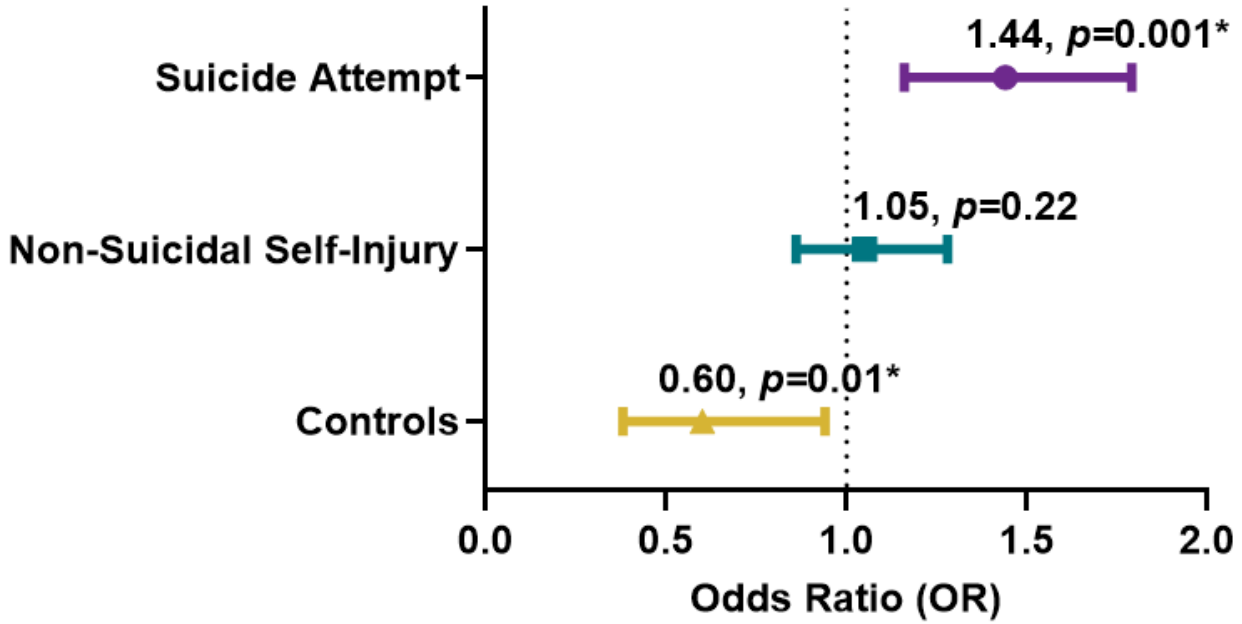
High Prevalence of Suicide Risk

- Suicidal ideation: **~64%**
- Non-suicidal self-injury: **~55%**
- Suicide attempt: **~25%**

Cardiovascular risk factors associated with non-suicidal self-injury and suicide attempt in young individuals with bipolar disorder

Esposito-Smythers *J Affect Disord* 2010; Goldstein *Am J Addict* 2010; García-Jiménez *Front Psychiatry* 2023; Goldstein *Bipolar Disord* 2020; Khoubaeva *Eur Child Adolesc Psychiatry* 2020; Naiberg *Acta Psychiatr Scand* 2016; Naiberg *J Psychiatr Res* 2016; Serra *J Affect Disord* 2022; Wu *Front Public Health* 2024; Zhong *Psychol Med* 2020

Higher Cardiovascular Risk Score Associated with Suicide Attempt



Cardiovascular risk score: blood pressure, BMI, and cigarette smoking
Covariates: age, sex, race, SES, mood disorder subtype, anxiety, adversity, substance use disorder, medications
Reference group: mood disorder without self-injury/suicide attempt

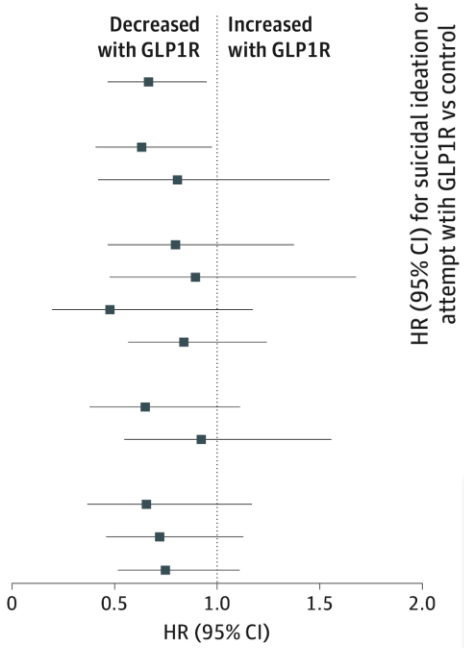
Esposito-Smythers J Affect Disord 2010; Goldstein Am J Addict 2010; García-Jiménez Front Psychiatry 2023; Goldstein Bipolar Disord 2020; Khoubaeva Eur Child Adolesc Psychiatry 2020; Naiberg Acta Psychiatr Scand 2016; Naiberg J Psychiatr Res 2016; Serra J Affect Disord 2022; Wu Front Public Health 2024; Zhong Psychol Med 2020

GLP-1 RAs are Associated with a Reduction in the Risk of Suicidality in Adolescents With Obesity

A retrospective cohort study of 4052 adolescents with obesity prescribed a GLP1-RA compared to a propensity score–matched cohort of 50,112 treated with lifestyle intervention.

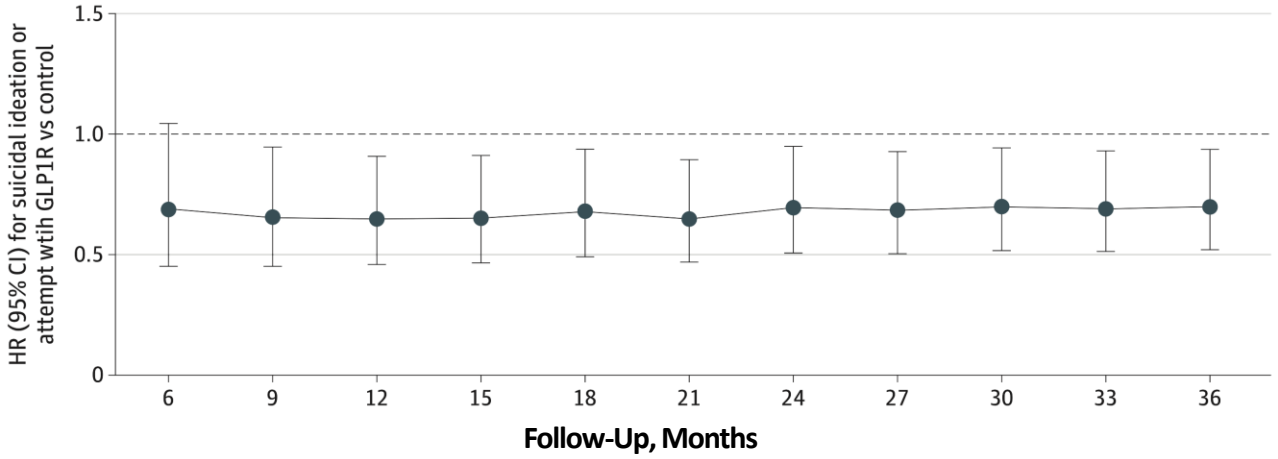
Risk for Suicidal Ideation or Attempts in Adolescents With Obesity Prescribed GLP1-RA vs Propensity Score Matched Controls

Subgroup (No./cohort)	No. (%) GLP1R	No. (%) Control	HR (95% CI)
Overall (3456)	50 (1.5)	78 (2.3)	0.67 (0.47-0.95)
Sex			
Female (2064)	33 (1.6)	54 (2.6)	0.63 (0.41-0.98)
Male (1323)	16 (1.2)	21 (1.6)	0.81 (0.42-1.16)
Race and ethnicity			
White (1621)	23 (1.4)	30 (1.9)	0.80 (0.46-1.38)
Black (770)	18 (2.3)	21 (2.7)	0.89 (0.48-1.68)
Hispanic (764)	10 (1.3)	15 (2.0)	0.48 (0.20-1.18)
Non-Hispanic (2190)	45 (2.1)	56 (2.6)	0.84 (0.57-1.24)
GLP1R			
Liraglutide (1602)	22 (1.4)	34 (2.1)	0.65 (0.38-1.11)
Semaglutide (1553)	26 (1.7)	31 (2.0)	0.92 (0.55-1.56)
Diabetes status			
Diabetes (1191)	19 (1.6)	29 (2.4)	0.66 (0.37-1.17)
No diabetes (2215)	32 (1.4)	48 (2.2)	0.72 (0.46-1.13)
No bariatric surgery (3235)	49 (1.5)	68 (2.1)	0.75 (0.52-1.08)



GLP-1=Glucagon-Like Peptide; RA=Receptor Agonist

Risk for Suicidal Ideation or Attempts by Follow-up Time



Prescription of GLP1-RA was associated with a **33% reduced risk** for suicidal ideation or attempts over 12 months of follow-up

(1.45% vs 2.26%; hazard ratio [HR], 0.67; 95% CI, 0.47-0.95; P=.02)

Kerem, L, and J Stokar. JAMA pediatrics (2024). doi:10.1001/jamapediatrics.2024.3812
Published online October 14, 2024.

Brain and Cognition DISCOVERY FOUNDATION

GLP-1 Associated with Suicidality But No BHC Causality Established

EXPERT OPINION ON DRUG SAFETY
2024, VOL. 23, NO. 1, 47–55
https://doi.org/10.1080/14740338.2023.2295397

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ORIGINAL RESEARCH

The association between glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: reports to the Food and Drug Administration Adverse Event Reporting System (FAERS)

Roger S. McIntyre [a,b,c], Rodrigo B. Mansur[a,d], Joshua D. Rosenblat[a,d] and Angela T.H. Kwan [c,e]

[a]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [b]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada; [c]Brain and Cognition Discovery Foundation, Toronto, Ontario, Canada; [d]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada; [e]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

McIntyre RS, et al., Expert Opin Drug Saf. 2024 Jan;23(1):47-55. Epub 2023 Dec 19.

Brain and Cognition
DISCOVERY FOUNDATION

Glucagon-Like Peptide-1 Receptor Agonists and Suicidality: Association Versus Causation and the Need for Ongoing Surveillance

COMMENTARY

Glucagon-Like Peptide-1 Receptor Agonists and Suicidality: Association Versus Causation and the Need for Ongoing Surveillance

Roger S. McIntyre, M.D.[1]

McIntyre RS. Am J Psychiatry. 2025 Aug 27:appiajp20241087.

Brain and Cognition
DISCOVERY FOUNDATION

Treatments Reported to Be Efficacious Across the Various Phases of Bipolar Disorder

ACUTE BIPOLAR DEPRESSION

Treatments APPROVED by the FDA

- Cariprazine
- Lumateperone
- Lurasidone
- Quetiapine
- Olanzapine/fluoxetine†

Treatments not approved by the FDA

- Lithium
- Lamotrigine
- Antidepressants
- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation (rTMS)

ACUTE MANIA

Treatments APPROVED by the FDA

- Lithium
- Divalproex
- Carbamazepine
- Aripiprazole
- Asenapine
- Cariprazine
- Haloperidol
- Olanzapine
- Olanzapine-Samidorphan
- Quetiapine
- Risperidone
- Ziprasidone
- Combination of aripiprazole, asenapine, olanzapine, quetiapine,† or risperidone + lithium or divalproex
- Iloperidone

MAINTENANCE

Treatments APPROVED by the FDA

- Lithium
- Aripiprazole (oral and long-acting injectable)
- Asenapine
- Lamotrigine†
- Quetiapine (adjunctive)†
- Olanzapine
- Olanzapine-Samidorphan
- Risperidone (long-acting injectable)
- Incretin Receptor Agonists???

McIntyre RS, et al. Lancet. 2020;396:1841-56.

Brain and Cognition DISCOVERY FOUNDATION

Metabolism and Mood: Are GLP-1 Receptor Agonists Capable of Preventing and Treating Psychiatric Disorders

X: @rogersmcintyre

Roger S. McIntyre, M.D., FRCPC
Professor of Psychiatry and Pharmacology, University of Toronto, Canada
Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada
Board Chair, Depression and Bipolar Support Alliance (DBSA), Chicago, Illinois, USA
Professor and Nanshan Scholar, Guangzhou Medical University, Guangzhou, China
Adjunct Professor College of Medicine, Korea University, Seoul, Republic of Korea
Visiting Professor College of Medicine University of the Philippines
Clinical Professor State University of New York (SUNY) Upstate Medical University, Syracuse, New York, USA
Clinical Professor Department of Psychiatry and Neurosciences University of California School of Medicine, Riverside, California, USA