REVIEW ARTICLE

Glucagon-like Peptide-1 receptor agonists as emerging therapeutics in bipolar disorder: a narrative review of preclinical and clinical evidence

Cristian-Daniel Llach[1,2]✉, Sebastian Badulescu[1,3,4], Aniqa Tabassum[1,3], Hiya Shah[1], Hartej Gill[1,3], Gia Han Le[1,2], Eduard Vieta[5,6,7,8,9], Roger S. McIntyre[2], Joshua D. Rosenblat[1,2,3] and Rodrigo B. Mansur[1,2,3]

Bipolar disorder (BD) is a chronic and disabling psychiatric illness characterized by complex pathophysiological mechanisms. Traditional treatments often fail to address these multidimensional processes, highlighting the need for novel therapeutic strategies. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), widely used for metabolic disorders, have emerged as promising candidates for a range of neuropsychiatric conditions due to their broad neurobiological effects. This narrative review synthesizes preclinical, clinical, and real-world evidence evaluating the therapeutic potential of GLP-1RAs in BD. These agents modulate neurotransmission, reduce neuroinflammation and oxidative stress, enhance mitochondrial and neurotrophic function, and improve insulin sensitivity and hypothalamic-pituitary-adrenal (HPA) axis regulation. These mechanisms are implicated in the neurobiology of BD, and preliminary findings suggest benefits across core psychopathological domains and common comorbidities, including depression, anxiety, mania, cognitive dysfunction, weight gain, and substance use disorders. While human data—particularly in BD populations—remain limited, evidence points to potential adjunctive benefits, especially in individuals with metabolic or cognitive vulnerabilities. Given their pleiotropic actions and established safety profile, GLP-1RAs represent compelling candidates for drug repurposing in BD. Well-powered, controlled trials are needed to confirm efficacy and safety, identify optimal subgroups, and evaluate long-term outcomes.

Molecular Psychiatry; https://doi.org/10.1038/s41380-025-03261-0

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric condition characterized by episodic fluctuations in mood and energy [1]. Even during remission, patients often experience persistent subsyndromal symptoms, such as cognitive dysfunction, reward system alterations, or disturbances in appetite and sleep [2]. BD is among the leading causes of disability worldwide and is frequently comorbid with cardiovascular disease, metabolic syndrome and diabetes, and other psychiatric conditions [3–5].

The etiology of BD is multifactorial, involving genetic, epigenetic, environmental, and neurobiological factors [6]. Genome-wide association studies have linked BD to multiple risk loci related to ion channel regulation, neurotransmitter signaling, neuroplasticity, cellular signaling pathways, and neurodevelopment [2, 7]. Additionally, factors such as inflammation [8], mitochondrial dysfunction [9], hypothalamic-pituitary-adrenal (HPA) axis dysregulation [10] or insulin resistance (IR) [11] have been implicated in BD pathophysiology. Despite available treatments—primarily mood stabilizers and antipsychotics—many patients experience incomplete response and significant side effects [12], underscoring the need for innovative, safe and effective interventions [13].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were developed for glycemic control in type 2 diabetes (T2DM) [14] and are now endorsed by the 2025 American Diabetes Association (ADA) guidelines [15] as an alternative to metformin. They act through GLP-1R, a G-protein-coupled receptor expressed in the pancreas, gastrointestinal tract, and brain [14]. Beyond metabolic benefits, GLP-1RAs exert molecular and cellular effects in several brain regions that may underlie potential therapeutic benefits in neuropsychiatric disorders [16]. While clinical trials are underway in conditions such as Alzheimer's disease [17] or Parkinson's disease [18], their psychiatric applications remain nascent. Increased public and clinical attention, along with growing off-label use, particularly among adolescents and young adults [19], has intensified interest in their broader therapeutic goal.

Given the diverse neurobiological effects of GLP-1RAs, there is growing interest in their potential role in addiction or mood disorders (MD) [20, 21]. Although GLP-1RAs may offer transdiagnostic benefits, BD represents a uniquely promising clinical target.

[1]Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada. [2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada. [3]Institute of Medical Science, University of Toronto, Toronto, ON, Canada. [4]Brain and Cognition Discovery Foundation, Toronto, ON, Canada. [5]Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona, Barcelona, Spain. [6]Institute of Neurosciences (UBNeuro), Barcelona, Spain. [7]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. [8]Biomedical Research Networking Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), University of Barcelona, Barcelona, Spain. [9]Department of Medicine, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain. ✉email: Cristian.llachlopez@utoronto.ca

Received: 24 April 2025 Revised: 15 August 2025 Accepted: 5 September 2025
Published online: 13 September 2025

This is due to its convergence of treatment-resistant mood symptoms, cognitive impairment, high rates of metabolic comorbidity, and progressive neurobiological changes [1]—many of which intersect with the mechanistic effects of GLP-1RAs. In particular, accumulating evidence underscores the strong bidirectional link between psychiatric and metabolic disorders such as diabetes, highlighting at the therapeutic potential of interventions that address both simultaneously. Moreover, BD is associated with markedly long-term functional morbidity [22], emphasizing the need for interventions that go beyond symptoms reduction to address functional recovery and mortality risk. Crucially, GLP-1RAs may offer metabolic safety advantages over current standard treatments. Nonetheless, their application in BD remains unexplored, with only one randomized controlled trial (RCT) [23], one pilot open-label study [24], and a limited number of retrospective studies [25, 26] to date. This narrative review synthesizes current evidence on the potential role of GLP-1RAs in BD—not only as a metabolic intervention with secondary psychiatric benefits, but also as agents that may directly target core pathophysiological processes. Of particular interest is to characterize specific individual profiles within BD that may derive the greatest clinical benefit from GLP-1RA treatment, in terms of both psychiatric outcomes and metabolic parameters. Specifically, we (1) describe the main physiological effects of GLP-1R activation; (2) outline key properties of GLP-1RAs; (3) analyze their role in crucial pathophysiological mechanisms of BD—discussed separately despite their interdependence [27]—and (4) review the available preclinical and clinical evidence across key psychopathological domains and comorbidities, including depression, anxiety, mania and mood regulation, cognition, weight gain and metabolic disturbances, and comorbid substance use disorders. Each of these domains and comorbidities plays a critical role in the disease burden and treatment complexity of BD and will be examined both from a transdiagnostic perspective and within the specific context of BD (Table 1). Finally, we will discuss the safety and tolerability of these agents with a specific focus on neuropsychiatric side effects (Table 2). To improve clarity, human studies are reviewed in decreasing order of evidentiary strength: (1) meta-analyses and RCTs, followed by (2) observational, and (3) real-world studies such as pharmacovigilance analyses. Our aim is to evaluate whether GLP-1RAs may represent a novel therapeutic avenue in BD, bridging biological plausibility with unmet clinical needs.

METHODS

A narrative, non-systematic review approach was chosen due to the broad scope of the topic and the large number of studies exploring BD pathophysiology and its interaction with GLP-1RAs. This analysis did not require ethical approval, and a protocol was not pre-registered. A comprehensive literature search was conducted in PubMed for articles published in English up to March 1st, 2025. using key terms such as “GLP-1”, “GLP-1 receptor agonists”, “bipolar disorder”, “depression”, “mania”, “cognition”, “neurobiology”, and “treatment”. Additional studies were identified through backward citation tracking of relevant reviews and primary sources. We included preclinical, observational and experimental studies reporting on the physiological effects of GLP-1RAs and their relevance to selected pathophysiological mechanisms and core psychopathological domains of BD. We included articles providing original data or high-quality synthesis addressing these dimensions. Studies were included regardless of clinical setting, population demographics, or comparator. Exclusion criteria included non-English publications, conference abstracts without full-texts, preprints, case reports or series, and grey literature. When findings overlapped, more recent, comprehensive, or methodologically rigorous studies were prioritized. Although not a systematic review, efforts were made to minimize selection bias by applying broad search parameters, prioritizing clinical relevance, and including diverse study designs. Our aim was to provide a balanced synthesis that reflects both the current evidence and existing uncertainties.

PHYSIOLOGICAL EFFECTS OF GLP-1R ACTIVATION

GLP-1 is an incretin hormone primarily secreted by enteroendocrine L-cells in the distal small intestine and colon in response to nutrient intake, as well as by certain neurons in the nucleus of the solitary tract (NST) in the brainstem [28]. GLP-1R is a G-protein-coupled receptor widely expressed in both peripheral tissues and the CNS [29]. Upon activation, GLP-1R triggers multiple intracellular signaling pathways, mediating diverse cellular effects that range from metabolic regulation to cytoprotection [28]. Peripherally, GLP-1 enhances insulin secretion, suppresses glucagon release, facilitates peripheral glucose uptake, and delays gastric emptying. Growing evidence also suggests its involvement in modulating inflammation and cardiovascular function [28].

In the CNS, GLP-1Rs are expressed in key regions involved in energy homeostasis, mood, and cognition, including the cortex, hypothalamus, thalamus, hippocampus, caudate-putamen, and globus pallidus [30]. In rodents, GLP-1R have also been characterized in the NTS, nucleus accumbens (NAc), several other nuclei of the hypothalamus, amygdala, and other limbic structures [29, 31, 32]. Through these receptors, GLP-1 influences appetite and body weight, reducing hunger, increasing energy expenditure, and promoting weight loss [33].

UNIQUE PROPERTIES OF GLP-1RAS

GLP-1RAs are pharmacological agents that mimic endogenous GLP-1 and are available in subcutaneous or oral formulations [34]. These drugs cross the blood-brain barrier (BBB) [35] and reach key regions involved in mood regulation such as the hippocampus, amygdala, prefrontal cortex, as well as the brainstem and hypothalamus [36, 37]. They are classified into short-acting (e.g. exenatide, administered twice daily, and lixisenatide, once daily) or long-acting formulations, with the latter being introduced more recently. Long-acting agents, such as liraglutide, semaglutide, dulaglutide, and albiglutide, achieve greater stability through chemical modifications, allowing for less frequent dosing (ranging from daily to weekly). More recently, tirzepatide has emerged as a dual agonist targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. Despite their benefits, GLP-1RAs commonly cause gastrointestinal side effects, including nausea, vomiting, diarrhea, and constipation, which may impact tolerability [38].

TARGETING PATHOPHYSIOLOGICAL MECHANISMS IN BIPOLAR DISORDER: THE POTENTIAL ROLE OF GLP-1RAS

Modulation of neurotransmission

Neurotransmitter dysregulation is a longstanding hypothesis in MD [39]. Mania is associated with excessive dopaminergic and glutamatergic activity, whereas depression involves reductions in these neurotransmitters and in GABAergic signaling. Serotonin and norepinephrine dysregulation further contributes to mood fluctuations, anxiety, cognitive dysfunction, and circadian rhythm disturbances.

GLP-1RAs modulate several neurotransmission systems implicated in BD. For instance, intracerebroventricular GLP-1 reduces hypothalamic serotonin in rodents, while exendin-4—a GLP-1RA derived from the venom of the Gila monster—decreases both serotonin and its metabolite, 5-HIAA [40]. Additionally, exendin-4 transiently increases tonic and synaptic currents mediated by GABA receptors in the hippocampus [41, 42] and laterodorsal tegmental nucleus [43], mitigating neuronal hyperexcitability and potentially stabilizing cognitive and emotional fluctuations associated with BD. GLP-1 increases dopamine turnover in the amygdala via D2 receptor signaling [44], and GLP-1RAs are known

Table 1. Studies assessing GLP-1RA across psychopathological domains and comorbidities in bipolar disorder.

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Antidepressant effects					
Pozzi et al. [118]	Systematic review and meta-analysis of longitudinal interventional and observational studies	Adults with T2DM or obesity from 1 post-hoc analysis of an RCT, 2 RCTs, 1 extension non-controlled trial, 1 sequential-treatment trial, and 3 prospective cohort studies; one study included patients with PCOS but was not included in the meta-analysis	GLP-1RAs (liraglutide, exenatide, others) vs placebo or other antidiabetic treatments (glimepride, insulin)	Changes in depression rating scales (BDI, GDS, PHQ-9, HADS, HRQoL)	Y. GLP-1RAs were associated with a larger reduction in depression scores vs Controls (SMD = −0.57; 95%CI [−0.66, −0.49])
Chen et al. [21]	Systematic review and meta-analysis of longitudinal interventional and observational studies	Adults with T2DM or Parkinson´s disease obesity from 5 RCTs and 1 prospective cohort study (n = 2071, average age 57.81)	GLP-1RAs (liraglutide, exenatide) vs placebo or other antidiabetic treatments (pioglitazone, glimepride, insulin)	Changes in depression rating scales (MADRS, BDI, HADS, HRQoL)	Y. GLP-1RAs were associated with a larger reduction in depression scores vs Controls (SMD = −0.12; 95% CI [− 0.21, −0.03])
Athauda et al. [128]	RCT	Adults with Parkinson's disease (n = 60)	Exenatide 2 mg (n = 31, mean age = 61.6 (8.2), 29% females) vs placebo (n = 29, mean age = 57.8 (8.0), 24% females) sc once weekly	Changes in adjusted difference in the MDS-UPDRS motor subscale (part 3) in the practically defined off-medication state at 60 weeks	N. No significant difference in depressive symptoms (MADRS, p = 0.15)
Gonzalez et al. [132]	Open-label randomized trial	Adults with early T2DM; mean age = 58 (10.72)	Liraglutide vs basal insulin (glargine)	Changes in diabetes distress and depressive symptoms (PHQ-8) at 1 year	N. No significant difference in depressive symptoms (p = 0.135)
Mansur et al. [24]	Open-label trial	Adults with MDD (n = 13) or BD (n = 6) and impairment in executive function (mean age = 38.71, 57.9% female)	Liraglutide 1.8 mg/day as adjunct to existing pharmacotherapy	Changes in cognition (Trail Making Test-B) after 4 weeks	Y. Liraglutide was associated with a significant decrease in the HAM-D (mean = 12.18; SD 4.82 vs 8.41; SD 6.12, Cohen's d 0.68, p = 0.022) after 4 weeks
Kahal et al. [122]	Case-control study	Women with PCOS (n = 19, mean age = 33.9(6.7)) and controls (n = 17, mean age = 33.5(7.1))	Liraglutide 1.8 mg/day	Changes in quality of life and depression scores (CES-D scale) at 6 months	N. No significant difference in depressive symptoms (p = 0.42)
Tsai et al. [134]	Retrospective cohort study	Adults with T2DM, drawn from insurance claims data (NHIRD, Taiwan)	GLP-1RAs (n = 10,690, mean age = 53.33 (13.04), 45.06% females) vs propensity score-matched non-GLP-1RA-users (n = 42,766, mean age = 54 (12.91), 44.08% females).	Incidence, HR and 95% CI of depression and/or anxiety	N/Y. Incidence of depression was not significantly reduced by GLP-1RA as a group. However, risk of incident depression was reduced particularly with dulaglutide (aHR of 0.45 (95%CI = [0.26, 0.79])
Battini et al. [133]	Nested case/non-case study using pharmacovigilan ce databases (FAERS and WHO VigiBase)	FAERS: Cases (depressed patients experiencing therapy failure; n = 121,368; 59.16% females) and non-cases (depressed patients experiencing any other adverse event; n = 423,943; 58.38% females); VigiBase: Cases (n = 85,267, 60.61% females) and non-cases (n = 562,041; 62.51% females)	GLP-1RAs (several)	ROR for cases vs non-cases	Y. Analyses in both databases reported a lower reporting of cases associated to GLP-1RA (ROR = 0.546; 95% CI [0.450, 0.662] in FAERS; ROR = 0.717; 95% CI [0.559, 0.921]

Table 1. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Effects on anxiety					
Miras et al. [129]	RCT	Patients with persistent or recurrent T2DM after metabolic surgery (n = 70)	Liraglutide 1.8 mg (n = 53, median age 55 (50–61), 62% females) vs placebo (n = 27, median age 57 (52–64), 52% females) sc for 26 weeks	Change in HbA1c (glycemic control)	N. No significant difference in anxiety symptoms (HADS-A)
Strawn et al. [140]	Single-blind challenge study	Patients with panic disorder (n = 7, mean age 38 (17), 4 females) and healthy controls (n = 9, mean age 47 (8), 4 females)	IV GLP-1 infusion	Number of panic attacks and anxiety reduction (API scale)	N. GLP-1 infusion did not induce panic attacks or increase anxiety scores (API scale) in either group
Miller et al. [142]	Retrospective cohort study	Adults with and without T2DM (n ≈ 4 million), drawn from EPIC EHR databases.	1) T2DM (n = 3,081,254): initiation of GLP-1RA vs No GLP-1RA and HbA1c documented; 2) non-T2DM (n = 929,174): initiation of GLP-1RA vs other weight management medication	Rates of anxiety and depression diagnoses	Y. GLP-1RAs associated with lower odds of new anxiety diagnoses in T2DM and tirzepatide showed the largest effect (60% reduction). In non-T2DM, semaglutide reduced risk by 31% while liraglutide showed no significant effect
Tsai et al. [134]	Retrospective cohort study	Adults with T2DM, drawn from insurance claims data (NHIRD, Taiwan)	GLP-1RAs (n = 10,690, mean age = 53.33 (13.04), 45.06% females) vs propensity score-matched non-GLP-1RA-users (n = 42,766, mean age = 54 (12.91), 44.08% females).	Incidence, hazard ratios (HR) and 95% CI of depression and/or anxiety	Y. Incidence of anxiety reduced to 2.93 per 1000 person-years, with an aHR of 0.41 (95%CI = [0.27, 0.61], driven by the use of dulaglutide (aHR = 0.32; 95% CI [0.21, 0.45])
Eren-Yazicioglu et al. [141]	Observational cross-sectional study	Adults with T2DM (n = 43, mean age = 53.47(8.74))	Exenatide (n = 23) vs no exenatide (n = 20)	Several questionnaires and laboratory-based measures	Y/N. Exenatide was associated with increased perceived stress (p = 0.004) mediating an increase of depressive symptoms
Cognitive effects					
Nørgaard et al. [163]	Systematic review and meta-analysis of longitudinal interventional and observational studies	Adults with T2DM from 3 RCTs (n = 15,820) and a nationwide registry (Danish National Prescription Register) (n = 120,054; dementia cases n = 4849, 52.6% females; controls n = 48,506, 52.6% females)	RCT: GLP-1RAs (various, n = 7907, mean age 64.6 (7.2), 35.4% females) vs Placebo (n = 7913, mean age 64.8 (7.3), 35.9% females); nationwide registry: GLP-1RA vs other second-line diabetes treatments	Rates of subsequent diagnosis of dementia	Y. Dementia rate was lower both in patients randomized to GLP-1RAs vs Placebo (HR = 0.47 (95% CI [0.25, 0.86] and in the nationwide cohort (HR = 0.89; 95% CI [0.86, 0.93] with yearly increased exposure to GLP-1RAs)
Luan et al. [162]	Systematic review and meta-analysis of longitudinal interventional and observational studies	Adults with T2DM from 3 RCTs and 2 prospective cohort studies (n = 7732)	GLP-1RAs (several) vs Placebo or active controls	Cognitive function (several domains)	N. GLP-1RAs were not associated with significant effects on the general cognitive functioning (SMD = 0.33, 95% CI [−0.03, 0.69]). Subgroup analyses showed a significant effect in patients younger than 65 years (SMD = 1.04; 95% CI [−0.61, 1.47]) or those without cardio-cerebrovascular diseases (SMD = 1.04; 95% CI [−0.61, 1.47])

Table 1. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Tang et al. [164]	Systematic review and meta-analysis of longitudinal observational studies	Adults with T2DM from 10 prospective cohort studies (n = 819,511, mean age = 68, 56% females)	DPP4I (7 studies), GLP-1RAs (5 studies), and SGLT2I (3 studies) vs Placebo or active controls	Rates of subsequent diagnosis of dementia	Y. Five studies found that users vs nonusers of GLP-1RAs were associated with a significant reduction in the risk of all-cause dementia (RR = 0.72; 95% CI [0.54, 0.97])
Gejl et al. 2016 [17]	RCT	Adults with Alzheimer's disease (n = 38)	Liraglutide 1.8 mg/day (n = 14, mean age = 63.1 (1.3), 57% females) vs Placebo (n = 20, mean age = 66.6 (1.8), 25% females)	Ab load in brain with tracer [11 C] PIB, glucose metabolism (CMRglc with [18 F] FDG), and cognition with the WMS-IV after 26 weeks	Y/N. GLP-1RA prevented the decline of CMRglc that signifies cognitive impairment, synaptic dysfunction, and disease evolution. Ab load and cognitive measures did not differ between the groups; however, the study was underpowered for cognitive outcomes
Ishøy et al. [166]	RCT	Adults with Schizophrenia Spectrum Disorder (n = 40)	Exenatide (n = 23, mean age 37.1 (10.6), 12 females) vs Placebo (n = 22, mean age 34.5 (10.1), 12 females) once weekly	Change in cognition (BACS)	N. No significant between-group effects on cognition were detected (p = 0.77)
Athauda et al. [128]	RCT	Adults with Parkinson's disease (n = 60)	Exenatide 2 mg (n = 31, mean age = 61.6 (8.2), 29% females) vs placebo (n = 29, mean age = 57.8 (8.0), 24% females) sc once weekly	Changes in adjusted difference in the MDS-UPDRS motor subscale (part 3) in the practically defined off-medication state at 60 weeks	N. No significant difference in cognitive symptoms (MDRS, p = 0.32)
Watson et al. [85]	RCT	Cognitively normal (MMSE > 27) middle-aged individuals with subjective cognitive complaints (n = 43)	Liraglutide 1.8 mg/day, mean age = 61.4 (6.1), 14 females) vs Placebo (n = 21, mean age = 60.3 (5.4), 14 females)	Resting-state functional connectivity	Y/N. Liraglutide improved intrinsic connectivity within default mode network. There were no cognitive differences between groups
Dei Cas et al. [165]	RCT	Adults with Mild Cognitive Impairment (n = 32, mean age 73 (5), 50% females)	Slow release exenatide 2 mg (n = 17, mean age 74 (4), 53% females) vs Placebo (n = 72 (6), 47% females) sc once weekly	Change in cognition (ADAS-Cog11 cognitive test score) at 32 weeks	N. No significant between-group effects on cognition were detected
Mansur et al. [24]	Open-label trial	Adults with MDD (n = 13) or BD (n = 6) and impairment in executive function (mean age = 38.71, 57.9% female)	Liraglutide 1.8 mg/day as adjunct to existing pharmacotherapy	Changes in cognition (TMTB) after 4 weeks	Y. Liraglutide was associated with a significant increase in the TMTB standard score (mean = 53.18; SD = 9.36 vs 646.41; SD 11.71, p = 0.009), as well as in the DSST, RAVLT, Stroop congruent and incongruent, patient-rated PDQ and composite Z-score after 4 weeks
Effects on reward and motivation					
Hanssen et al. [177]	Single-blind, randomized, controlled, crossover fMRI study	Insulin-resistant (n = 20) and insulin-sensitive (n = 23) healthy participants	Single 0.6 mg dose of liraglutide vs Placebo	fMRI response to reward-predictive cues; behavioral learning	Y. GLP-1RA normalizes associative learning in insulin-resistant individuals by modulating prediction error signals within the mesoaccumbens pathway. Findings suggest that dopamine-driven learning processes depend on metabolic state

Table 1. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Treatment of substance abuse					
Yammine et al. [174]	RCT	Adult smokers with prediabetes and/or overweight, n = 82, mean age = 51.1 (9.2), 30% females)	Exenatide 2 mg (n = 41, mean age=51 (9.1), 31.7% females)) vs Placebo (n = 41, mean age = 51.2 (9.4), 29.3% females) sc once weekly in addition to nicotine replacement therapy and brief smoking cessation counseling	Seven-day point prevalence abstinence (expired CO level ≤5 ppm), craving, withdrawal, and post-cessation body weight at 6 weeks	Y. Higher abstinence rate (46.3% and 26.8%, respectively; RR = 1.70; 95% CI [0.96, 3.27])
Klausen et al. [196]	RCT	Adults seeking treatment for AUD (n = 127)	Exenatide (2 mg sc, n = 62, mean age 52.1 (10.8), 40.3% females)) vs Placebo (n = 65, mean age 52.5 (10), 40% females) once weekly in addition to standard cognitive-behavioral therapy	Reduction in number of heavy drinking days at 26 weeks	N. Although exenatide did not reduce the number of heavy drinking days, it attenuated fMRI alcohol cue reactivity in the ventral striatum and septal area. In an exploratory analysis, exenatide reduced heavy drinking days and total alcohol intake in a subgroup of obese patients (BMI > 30 kg/m2)
Angarita et al. [197]	RCT with a cross-over, within-subject design	Adults with non-treatment-seeking cocaine use disorder (n = 13, mean age 45 (7), 1 female)	Acute administration of a single dose of exenatide (5 mcg; subcutaneously) vs placebo	Infusions of cocaine and visual analog scale self-ratings of euphoria and wanting cocaine at 3 h post-intervention	N. Exenatide did not change cocaine infusions vs placebo (8.5 (1.2) vs 9.1 (1.2); p = 0.39), self-reported euphoria (4.4 (0.8) vs 4.1 (0.8); p = 0.21), or wanting of cocaine (5.6 (0.9) vs 5.4 (0.9); p = 0.46)
Lengsfeld et al. [198]	RCT	Adult smokers with at least moderate cigarette dependence who wanted to quit (n = 255, mean age = 43.2 (13.1), 60.8% females)	Dulaglutide 1.5 mg (n = 127, mean age = 42.7 (13.8), 65.4% females) vs Placebo (n = 128, mean age = 43.2 (13.1), 56.3% females) sc once weekly in addition to standard of care including behavioural counselling and oral varenicline 2 mg/day	Self-reported and biochemically confirmed point prevalence abstinence rate at week 12	N. No differences in abstinence rates (63% (80/127) and 65% (83/128) respectively; difference in proportions = −1.9% [95% CI [−10.7, 14.4])
Probst et al. [195]	Secondary analysis of a RCT	Adults in smoking cessation trial who consumed alcohol (n = 151, mean age 42 (33–53), 60.9% females)	Dulaglutide (0.75 mg/0.5 mL for 1 week, then 1.5 mg/0.5 mL, n = 76, mean age = 41 (33–54.2), 67.1% females) vs Placebo (n = 75, mean age = 43 (33–51.5), 54.7 females)	Differences in alcohol consumption (glasses per week)	Y. Participants in the dulaglutide group drank 29% less (baseline alcohol intake adjusted relative effect = 0.71; 95% CI [0.52, 0.97], P = 0.04)
Wang et al. [199]	Retrospective cohort study of electronic health records	Adults with obesity (n = 83,825) or T2DM (n = 598,803) with or without a prior history of AUD	Treatment with semaglutide vs Propensity score-matched comparison cohorts	Incident or recurrent diagnosis of AUD occurring within the 12-month, 2 year and 3-year time window after starting treatment	Y. Semaglutide was associated with lower risk of both recurrent (HR = 0.50; 95% CI [0.39, 0.63]) and incident (HR = 0.44; 95% CI [0.32, 0.61]) AUD diagnoses in individuals with obesity and a prior history of AUD. Similar associations were observed in patients with type 2 diabetes mellitus (T2DM), with reduced risk of recurrent (HR = 0.61; 95% CI [0.50, 0.75] and incident (HR = 0.56; 95% CI [0.43, 0.74] AUD diagnoses

Table 1. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Lähteenvuo et al. [200]	Retrospective cohort study of a nationwide registry in Sweden (National Patient registry)	Adults with a prior history of AUD (n = 227,866, mean age = 40 (15.7), 36.5% females)	GLP-1RA (exenatide, liraglutide, dulaglutide, and semaglutide) vs nonuse of GLP-1RA	AUD hospitalization analyzed in a Cox regression within-individual model.	Y. Semaglutide (4321 users) was associated with the lowest risk (aHR = 0.64; 95% CI [0.50, 0.83], and use of liraglutide (2509 users) with the second lowest risk (aHR = 0.72; 95% CI [0.57, 0.92], of AUD hospitalization
Wang et al. [201]	Retrospective cohort study of electronic health records	Adults with obesity (n = 83,189) or T2DM (n = 587,849) with or without a prior history of cannabis use disorder	Treatment with semaglutide vs Propensity score-matched comparison cohorts	Incident or recurrent diagnosis of cannabis use disorder occurring within the 12-month, 2 year and 3-year time window after starting treatment	Y. Semaglutide was associated with a lower risk of both recurrent (HR = 0.62; 95% CI [0.46, 0.84]) and incident (HR = 0.56; 95% CI [0.42, 0.75]) cannabis use disorder diagnoses in individuals with obesity and a prior history of cannabis use disorder. Similar associations were observed in patients with type 2 diabetes mellitus (T2DM), with reduced risk of recurrent (HR = 0.66; 95% CI [0.42, 1.03]) and incident (HR = 0.40; 95% CI [0.29, 0.56) cannabis use disorder diagnoses
Effects on weight gain					
Ishøy et al. [166]	RCT	Adults with schizophrenia spectrum disorders and obesity, without diabetes, treated with antipsychotics (n = 45)	Exenatide (n = 23, mean age 37.1 (10.6), 12 females) vs Placebo (n = 22, mean age 34.5 (10.1), 12 females) once weekly	Body weight reduction at 3 months	N. No significant difference between groups (p = 0.98)

ADAS (Alzheimer's disease assessment scale), AUD (alcohol use disorder), BACS (brief assessment of cognition in schizophrenia), BD (BD), BDI (beck depression inventory), BMI (body mass index), CES-D (centre for epidemiologic studies depression scale), CI (confidence intervals), CMRglc (cerebral metabolic rate of glucose), DSST (digit symbol substitution test), DPP4I (dipeptidyl peptidase 4 inhibitors), EHR (electronic health records), FAERS (FDA adverse event reporting system), FDG (fluorodeoxyglucose), fMRI (functional magnetic resonance imaging), GDS (geriatric depression scale), GLP-1RA (Glucagon-like Peptide-1 receptor agonist), HADS (hospital anxiety and depression scale), HbA1c (glycated hemoglobin), HR (hazard ratio), HRQoL (Health-related quality of life), IV (intravenous administration), MADRS (Montgomery-asberg depression rating scale), MDRS (Mattis-dementia rating scale), MDS-UPDRS (movement disorders society unified Parkinson's disease rating scale), MMSE (mini mental status exam), PCOS (polycystic ovary syndrome), PDQ (perceived deficits questionnaire), PIB (pittsburgh compound B), PHQ-9 (patient health questionnaire-9), RAVLT (rey auditory verbal learning test), RCT (randomized controlled trial), ROR (reporting odds ratio), RR (risk ratio), sc (subcutaneous), SGLT2I (Sodium-glucose cotransporter 2 inhibitors), SD (standard deviation) SMD (standardized mean differences), TMTB (trail making Test-B), T2DM (Type 2 diabetes mellitus), WHO (world health organization), WMS-IV (wechsler memory Scale-IV).

Table 2. Studies evaluating neuropsychiatric safety of GLP-1 receptor agonists.

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
O'Neil et al. [121]	Meta-analysis of RCTs (SCALE trials, n = 5)	Adults with BMI ≥ 30 or ≥27 kg/m^2 with weight-related comorbidities (n = 5325) without T2DM	Liraglutide 3 mg (n = 3384, mean age = 46.6 (12.2), 72.4% females) vs Placebo (n = 1941, mean age = 46.6 (11.8), 70.8% females) sc once daily, both with a 500 kcal/d deficit diet, plus exercise	Incidence rates of suicidal ideation or behavior	N. In the pooled analysis, 9 (0.3%) individuals receiving liraglutide and 2 (0.1%) receiving placebo reported adverse events of suicidal ideation or behaviour. In phase 3a trials, 34/3291 individuals (1.0%) receiving liraglutide vs 19/1843 (1.0%) receiving placebo reported suicidal ideation on the Columbia-Suicide Severity Rating Scale
Silverii et al. [213]	Meta-analysis of RCTs with at least one case of psychiatric disorder reported as an adverse event (n = 31)	Adults with T2DM or obesity (n = 84,713)	GLP-1RA vs Placebo or active comparators	Incidence rates of suicidal ideation or behavior	N. No significant difference in psychiatric adverse events was observed between GLP-1RA and placebo [MH-OR = 0.97; 95% CI [0.83, 1.15]). The GLP-1RA treatment was not associated with a significant difference in the risk for overall suicidal episodes [MH-OR = 0.86; 95% CI [0.47, 1.56])
McElroy et al. [23]	RCT	Adults with stable bipolar disorder and obesity	Liraglutide up to 3 mg (n = 29, mean age 43.9 (11), 82.8% females) vs Placebo (n = 31, mean age = 41.4 (12.3), 77.4% females) sc daily	Body weight reduction at 40 weeks	N. No significant association between liraglutide and increased risk of suicidal ideation or behavior
Mansur et al. [24]	Open-label trial	Adults with MDD (n = 13) or BD (n = 6) and impairment in executive function (mean age = 38.71, 57.9% females)	Liraglutide 1.8 mg/day as adjunct to existing pharmacotherapy	Changes in cognition (Trail Making Test-B) after 4 weeks	N. No significant association between liraglutide and increased risk of suicidal ideation or behavior
Gamble et al. [218]	Retrospective propensity score-matched cohort study of the UK-based Clinical Practice Research Datalink (CPRD)	Adults with T2DM or a prescription for any glucose-lowering therapy	GLP-1RA (n = 488, mean age = 49.7 (11.2), 40.6% females) vs sulfonylureas (n = 488, mean age = 49.2 (12.6), 35.7% females)	Incidence rates of depression or self-harm	N. GLP-1RAs were not associated with an increased or decreased incidence of depression or self-harm compared with sulfonylureas (adjusted HR = 1.25; 95%CI [0.63, 2.50])
De Giorgi et al. [220]	Retrospective propensity score-matched cohort study EHR from TriNetX US Collaborative Network	Adults with T2DM	Semaglutide vs sitagliptin (n = 23,386, mean age = 56.7 (12.2) vs 56.6 (13.3), 48.8% vs 48.4% females), semaglutide vs empaglifozin (n = 22,584, mean age = 57.6 (12.3) vs 57.6 (12.4), 49% vs 48.8% females), semaglutide vs glipizide (n = 19,206, mean age = 56.4 (12.4) vs 56.2 (13.6), 49.2% vs 49.4% females)	Incidence rates of depression or suicidality	N. Semaglutide was not associated with an increased incidence of depression or suicidality for sitagliptin (HR = 0.75; 95% CI [0.52–1.07]), for empaglifozin (HR = 0.96; 95% CI [0.66, 1.40], or for glipizide (HR = 0.54; 95% CI [0.36–0.83]

Table 2. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Hurtado et al. [216]	Retrospective propensity score-matched cohort study of several population-wide databases from Spain	Adults with obesity who initiated GLP-1RA or SGLT2I for T2DM (n = 14,667)	GLP-1RA (liraglutide or semaglutide, n = 3040, 44.41% females)) vs SGLT2I (n = 11,627, 44.17% females)	Incidence rates of suicidal ideation and self-injury	N. No evidence that GLP-1RA increased the incidence of suicidal ideation and self-injury (HR 1.04; 95% CI [0.35, 3.14])
Kornelius et al. [222]	Retrospective propensity score-matched cohort study EHR from TriNetX US Collaborative Network	Adults with obesity (n = 9,265,469) without prior anti-obesity mediation, recent diagnosis of severe mental illness or recent suicidal ideation or attempt (<1 year)	GLP-1RA (semaglutide, liraglutide, n = 162,253, mean age = 52.4 (13.5), 55.6% females) vs non-GLP-1RA (n = 162,253, mean age = 52.5 (13.5), 55.6% females))	Incidence rates of suicidal ideation or attempts	Y. The incidences of suicidal ideation or attempt were higher in the GLP-1RA group (HR = 2.06; 95% CI [1.92, 2.21])
Kerem et al. [225]	Retrospective propensity score-matched cohort study EHR from TriNetX US Collaborative Network	Adolescents (12–18 years) with a diagnosis of obesity	GLP-1RA (n = 4506) vs lifestyle intervention without GLP-1RA (n = 50,112)	Incidence rates of suicidal ideation or attempts	N. Prescription of GLP1R was associated with a 33% reduced risk for suicidal ideation or attempts over 12 months of follow-up (1.45% vs 2.26%; HR = 0.67; 95% CI [0.47, 0.95])
Nassar et al. [226]	Retrospective propensity score-matched cohort study EHR from TriNetX US Collaborative Network	Adults with T2DM	GLP-1RA (n = 373,218, mean age = 65.1 (11.1), 58.89% females) vs DPP4I (n = 373,218, mean age = 64.8 (11.5), 58.36% females)	Incidence rates of suicide attempts	N. People with T2D treated with GLP-1RA consistently exhibited a lower risk of suicide attempts compared to those treated with DPP4I (OR = 0.461; 95% CI [0.366, 0.58]). This was particularly significant in people with a history of depression or suicide attempts (OR = 0.377; 95% CI [0.285, 0.499])
Tang et al. [217]	Retrospective propensity score-matched cohort study of Medicare administrative claims data	Older adults (>65 years) with T2DM, no record of suicidal ideation or behaviours	GLP-1RA vs SGLT2I (n = 21,906, mean age = 73(5.5) vs 73 (5.4), 50.7% vs 50.6 females) and GLP-1RA vs DPP4I (n = 21,402, mean age = 73.4 (5.6) vs 73.6 (5.8), 54.3% vs 54.5% females)	Incidence rates of suicidal ideation and behaviors	N. GLP-1RAs were not associated with an increased risk relative to SGLT2Is (HR = 1.07; 95% CI [0.80, 1.45]) or relative to DPP4Is (0.94; 95% CI [0.71 to 1.24]
Ueda et al. [215]	Retrospective propensity score-matched cohort study of a nationwide registry in Sweden and Denmark	Adults who initiated treatment with GLP-1RA or comparators (n = 298,553)	Sweden: GLP-1RA (n = 77,495, mean age = 60.3 (12.6), 43.2% females) vs SGLT2I (n = 77,495, mean age = 60.2 (10.5), 43.4% females) / Denmark: GLP-1RA (n = 47,022, mean age = 58.4 (13.1), 47.3% females) vs SGLT2I (n = 77,495, mean age = 58.8 (108), 46.2% females)	Incidence rates of suicide death	N. No significant association between GLP-1RA and increased risk of suicide death or self-harm (HR = 0.83; 95% CI [0.70, 0.97)
Wang et al. [224]	Retrospective propensity score-matched cohort study EHR from TriNetX US Collaborative Network	Adults with overweight or obesity (n = 26,566) and adults with T2DM (n = 27,276) without previous history of suicidal ideation	Obesity: Semaglutide (mean age = 50 (13.4), 72.6% females vs non-GLP-1RA anti-obesity medications (mean age = 50.3 (15.1), 72.5% females); T2DM: Semaglutide (mean age = 57.5 (12.5), 48.8% females vs non-GLP-1RA anti-obesity medications (mean age = 57.4 (14.4), 49.5% females)	Rates of incident or recurrent suicidal ideation	N. In patients with overweight or obesity, semaglutide was associated with lower risk for incident (HR = 0.27; 95% CI [0.20, 0.36) and recurrent (HR = 0.44; 95% CI [0.32–0.60]) suicidal ideation. Similar findings were replicated in patients with T2DM

Table 2. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Chen et al. [219]	Retrospective disproportionate analysis using post-marketing data from the FAERS	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	GLP-1RA (n = 534, 53.18% females) vs Other drugs (case/non-case approach; 53.4% females) from 2005 Q2 to 2023 Q2	Spontaneous ROR of suicide/self-injury cases	N. GLP-1RA did not cause a disproportionate increase in overall suicidal and self-injurious cases (ROR = 0.16; 95% CI [0.15, 0.18]; EBGM05 = 0.15)
McIntyre et al. [229]	Retrospective disproportionate analysis using post-marketing data from the FAERS	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	GLP-1RA vs. Other glucose-lowering agents (metformin, insulin) from 2005 to October 2023	Spontaneous ROR of suicidal ideation, behavior, attempts, or completed suicide	Y. Disproportionate reporting of suicidal ideation and "depression/suicidal" was observed with semaglutide and liraglutide. Disproportionate reporting of suicidal behavior, suicide attempts, and completed suicide was not observed for any of the FDA-approved GLP-1 RAs
Nakhla et al. [214]	Retrospective disproportionate analysis using post-marketing data from 4 databases: the FAERS, the DAEN, the European Medicines Agency's (EudraVigilance), and the WHO-VigiBase	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	GLP-1RA (n = 634, 377 females) vs DPP4Is (n = 221, 102 females), SGLT2Is (n = 211, 53 females) and other glucose-lowering agents from 2003 Q4 to 2023 Q3	Spontaneous RRR, PRR, ROR, and chi-squared ($\chi 2$) for suicidal events. Positive signal considered if PRR > 2 and $\chi 2 > 4$ for any drug-event pair	N. No positive signals were observed between GLP1-RAs and suicide risk. Semaglutide (ROR = 0.60; CI 95% [0.51, 0.71]) and liraglutide (ROR = 0.28; CI 95% [0.23, 0.35]) had higher suicidal events than DPP4Is and SGLT2Is
Ruggiero et al. 2024 [223]	Retrospective disproportionate analysis using post-marketing data from the European Pharmacovigilance database	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	Semaglutide (n = 84, 57.1% females) vs liraglutide (n = 88, 68.2% females) vs exenatide (n = 16, 43.8% females) vs dulaglutide (n = 37, 48.6% females) from 1 January 2018 to 10 July 2023	Spontaneous ROR of suicidal events.	Y. Suicidal events were mostly reported with semaglutide and liraglutide. There was a higher ROR for semaglutide than dulaglutide (ROR = 2.05; 95% CI [1.40, 3.01]) and exenatide (ROR = 1.81; 95% CI [1.08, 3.05]). Liraglutide was associated with a higher ROR than dulaglutide (ROR = 3.98; 95% CI [2.73, 5.82) and exenatide (ROR = 3.52; 95% CI [2.10, 5.92). A lower ROR was found for semaglutide than liraglutide (ROR = 0.51; 95% CI [0.38, 0.69])
Schoretsanitis et al. [235]	Retrospective disproportionate analysis using post-marketing data from the WHO global database of suspected ADR	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	Semaglutide (n = 107, median age = 48 (40–56), 55.1% females) and liraglutide (n = 162, median age = 47 (38–60), 61.7% females) vs. Other active comparators (dapagliflozin, metformin, orlistat) from inception to August 2023	Spontaneous ROR of suicidal or self-injurious ADRs	Y. Significant disproportionality detected only for semaglutide-associated suicidal ideation (ROR = 1.45; 95% CI [1.18, 1.77])

Table 2. continued

Author/Year	Study design	Population	Intervention	Primary outcomes	Positive? (Y/N). Main findings of interest
Zhou et al. [234]	Retrospective disproportionate analysis using post-marketing data from the FAERS	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	GLP-1RA (n = 204, 64.22% females) vs. Empagliflozin and orlistat (negative controls) and venlafaxine (positive control) from 2018 Q1 to 2022 Q4	Spontaneous ROR of SSIBs	N. No significant disproportionate reporting of SSIB was observed with any GLP-1RA. No single mechanism (tolerance effect/accumulation effect) explains the temporal association of onset between GLP-1RAs and SSIBs
McIntyre et al. [236]	Retrospective disproportionate analysis using post-marketing data from the WHO global database of suspected ADR (VigiBase)	Clinical patients experiencing an ADR suspectedly attributable to GLP-1RA	GLP-1RA vs. Other glucose-lowering agents (metformin) from inception to January 2024	Spontaneous ROR of depression/suicidal, suicidal ideation, behavior, attempts, or completed suicide	Y. Increased RORs for suicidal ideation (semaglutide 5.82, liraglutide 4.03, tirzepatide 2.25); "depression/suicidal" (semaglutide 14.74, liraglutide 5.86); suicidal behavior (semaglutide 6.52, liraglutide 3.90). Decreased RORs for suicide attempts (semaglutide 0.11, dulaglutide 0.075, exenatide 0.047, liraglutide 0.15) and completed suicides (semaglutide 0.01, dulaglutide 0.003, exenatide 0.002, liraglutide 0.008)

ADR (adverse drug reaction), BMI (body mass index), CI (confidence intervals), DAEN (australian database of adverse event notifications), DPP4I (dipeptidyl peptidase 4 (DPP-4) inhibitors), EHR (electronic health records), FAERS (FDA adverse event reporting system), GLP-1RA (Glucagon-like Peptide-1 receptor agonist), HR (hazard ratio), PRR (proportional reporting ratio), RCT (randomized controlled trial), ROR (reporting odds ratio), RRR (relative reporting ratio), SGLT2I (Sodium-glucose cotransporter 2 inhibitors), sc (subcutaneous), SSIB (suicidal or self-injurious behaviors), T2DM (Type 2 diabetes mellitus), WHO (world health organization).

to influence mesolimbic dopaminergic activity [45–47]. Furthermore, GLP-1RAs modulate glutamate transmission by reducing AMPA receptor expression and excitatory postsynaptic currents in ventral tegmental area (VTA) dopamine neurons [48], weakening excitatory strength in reward circuits.

Anti-inflammatory effects

The neuroinflammatory hypothesis of BD suggests that CNS inflammation plays a key role in its pathophysiology [49, 50]. Elevated levels of proinflammatory cytokines (e.g. C-reactive protein, IL-1, IL-4, IL-6, IL-1β, and tumor necrosis factor-alpha (TNF-α)) and microglial activation have been observed in BD. These inflammatory processes can disrupt neurotransmitter metabolism, influence kynurenine pathway metabolites, impair neurogenesis and synaptic plasticity, alter mitochondrial function, and increase BBB permeability—ultimately establishing a vicious cycle that drives disease progression [49].

GLP-1RAs exhibit immunomodulatory effects that could mitigate neuroinflammatory burden in BD. Exendin-4 reduces TNF-α levels induced by multiple Toll-like receptor (TLR) agonists [51], while semaglutide decreases bacterial load and systemic inflammation [51]. GLP-1RAs further suppress inflammation by inhibiting NF-κB activation [52], attenuating microglial activation [53, 54], reducing proinflammatory cytokines (IL-6, TNF-α, and IL-1β), and enhancing anti-inflammatory cytokine (IL-10 [55]) production. [57]Clinically, these agents show promise in reducing systemic inflammation in cardiovascular diseases, neurodegenerative diseases [54], and inflammatory bowel disease [55]. However, their role in MD-related inflammation remains unclear. In animal models of depression, exendin-4 prevented lipopolysaccharide (LPS)-induced depression-like behaviors but did not significantly alter proinflammatory cytokine levels [56]. These discrepancies suggest that GLP-1RAs may differentially influence neuroinflammatory pathways depending on the model and context.

Effects on mitochondrial function and oxidative stress

Mitochondrial dysfunction and oxidative stress are critical components of BD pathophysiology. Abnormalities include altered mitochondrial morphology and intracellular distribution, disrupted oxidative phosphorylation, reduced ATP production, a shift toward glycolysis, and increased oxidative stress markers [9, 57–59]. Insufficient ATP levels in the brain can impair Na+/K+-ATPase activity, resting membrane potential, and neurotransmitter release, potentially triggering mood episodes [60]. These dysfunctions compromise neuronal activity and long-term potentiation (LTP), contributing to emotional dysregulation, cognitive deficits, and neurodegeneration [61].

GLP-1 signaling appears essential for mitochondrial integrity. Astrocytic GLP-1R loss has been shown to disrupt mitochondrial structure [62] and increases the production of fibroblast growth factor 21 (FGF21), a key stress response factor involved in mitigating mitochondrial dysfunction [63]. Conversely, GLP-1RA activate cytoprotective pathways, protects neurons from oxidative stress and promotes β-oxidation in astrocytes [64]. In epilepsy models, liraglutide prevented mitochondrial stress and inflammation [65], while in focal cortical ischemia, it restored Krebs cycle enzyme activity, reduced reactive oxygen species (ROS) production, stabilized mitochondrial membrane potential, enhanced mitochondrial complex I activity, and increased ATP levels [66]. Liraglutide also activates the nuclear factor erythroid 2-related factor (Nrf2) pathway, that upregulates key antioxidant genes [67]. Altogether, GLP-1RAs may counteract BD-associated mitochondrial dysfunction and oxidative stress by enhancing mitochondrial integrity and antioxidant pathways.

Neurotrophic, neuroplastic and brain connectivity effects

Neurotrophins, including brain-derived neurotrophic factor (BDNF), regulate neuronal survival, growth, and synapse formation, playing a critical role in neuroplasticity and cognitive processes. Reduced levels of BDNF, its receptor TrkB, and other neurotrophins have been observed in both peripheral and central samples from BD patients [68, 69]. Furthermore, certain BDNF polymorphisms have been repeatedly associated with the disorder [70]. Preclinical BD models show decreased BDNF in association to depressive and manic behaviors [71–73]. Conversely, chronic lithium or valproate administration increases BDNF expression [74].

GLP-1RAs enhance BDNF and other neurotrophin expression across models of aging [75], diabetes [76], and neurodegeneration [77]. They also neurogenesis markers such as BrdU, Ki67, and DCX in the hippocampus, olfactory bulb, and medial striatum [37], modulate apoptotic and survival pathways (e.g., PI3K, CREB, Wnt/β-catenin), and restore dendritic spine density via mTOR1 activation [78]. Furthermore, GLP-1RAs promote neural stem/progenitor cell proliferation, a crucial process in neurogenesis [79], by 100–150% in some rodent models [54, 80].

Closely related to neuroplasticity is brain connectivity, which is known to be altered in individuals with BD—particularly in the hippocampus, amygdala and cortical regions [81–83]. In this context, GLP-1RAs modulate several large-scale brain networks implicated in BD psychopathology, including the default mode, salience, and frontoparietal network [84]. Some agents, such as liraglutide and exenatide, also increase connectivity in subcortical regions such as the hippocampus, hypothalamus, and NTS [85]. These findings further support the potential neuroplastic effects of GLP-1RAs in BD.

Modulation of the stress response

The HPA axis is the primary mediator of the biological stress response and is frequently dysregulated in BD [10], with heightened activity during manic episodes and inter-episodic periods [10]. Additionally, prolonged exposure to elevated cortisol contributes to hippocampal atrophy, emotional dysregulation and long-term cognitive decline seen in BD [86, 87].

GLP-1 is produced by preproglucagon neurons in the NST and projects to the hypothalamus and brainstem, influencing autonomic function and stress adaptation [88]. Acute hypothalamic GLP-1R activation stimulates corticotropin-releasing factor (CRF) release and elevates adrenocorticotropic hormone (ACTH) and corticosterone levels in both rodents and humans [89]. However, the effects of GLP-1RAs on the HPA axis appears complex and context-dependent. In rodents, subacute or prolonged administration of short-acting GLP-1RAs like exendin-4 and liraglutide (7–14 days) induces HPA axis hyperactivity, disrupts circadian glucocorticoid secretion, causes adrenal hypertrophy, and dysregulates the hypothalamic-adrenal stress response [90]. In contrast, a RCT of weekly dulaglutide over three weeks in healthy humans showed no significant effects on HPA function [91], suggesting that long-acting GLP-1RAs may have a more neutral neuroendocrine profile.

Insulin resistance

Over 50% of BD patients show impaired glucose metabolism [11]. Co-occurring T2DM is associated with a more severe illness course [92] and a poorer treatment response [93]. Additionally, BD patients with IR or T2DM exhibit reduced hippocampal and cortical volumes compared to both euglycemic BD and non-psychiatric controls [94]. Pre-treatment levels of neural-derived extracellular vesicle pS312-IRS-1, a marker of IR, were associated with cognitive dysfunction and reduced ventromedial prefrontal cortex volume, highlighting a potential link between insulin dysregulation, neurostructural changes, and cognitive impairment in BD [95]. Mechanistically, insulin plays a key role in hippocampal neuroplasticity [96], and IR disrupts neuronal function and synaptic plasticity, potentially contributing to cognitive decline. IR is also bidirectionally linked to inflammation, oxidative stress, lipid peroxidation [97], and endothelial dysfunction [98].

GLP-1RAs may reduce brain insulin resistance [99, 100]. Liraglutide has been shown to improve hippocampal insulin sensitivity in individuals with mild cognitive impairment [101]. Additional studies have reported increased cerebral metabolic activity following GLP-1 administration [102]. These insulin-sensitizing effects suggest a therapeutic avenue by which GLP-1RAs may benefit neuroplasticity and cognition in BD.

GLP-1RAS IN BD KEY PSYCHOPATHOLOGICAL DOMAINS AND COMORBIDITIES

Antidepressant effects

Bipolar depression is the leading cause of morbidity in BD, and a major contributor to its high suicide risk, functional impairment, and reduced quality of life [103].

Emerging evidence suggests that GLP-1RAs may exert antidepressant effects via mechanisms relevant to BD, including modulation of neurotransmission and neuroinflammation, enhancement of BDNF signaling, promotion of hippocampal neurogenesis, and restoration of mitochondrial function in brain regions involved in mood regulation [20]. In this context, preclinical studies have yielded mixed findings [104]. While some reported no behavioral effects [105, 106], most support antidepressant-like properties [107–113], often accompanied by hippocampal neuroprotection or cognitive improvement. In comorbid models, exendin-4 worsened depressive behavior and increased seizure frequency in rodents with epilepsy [114], whereas liraglutide reduced depression-like symptoms in a similar context [115]. In diabetic depression models, exendin-4 showed antidepressant-like effects, possibly through microglial modulation [116]. Supporting translational relevance, a postmortem human study by our group [117] found reduced GLP-1R gene expression in the dorsolateral prefrontal cortex and hippocampus of individuals with MD—a pattern not observed in schizophrenia. While heterogeneity exists, the bulk of preclinical data suggests a potential antidepressant effect of GLP-1RAs.

Two meta-analyses—mostly involving patients with T2DM—further support this hypothesis. The first [118] included two RCTs [119, 120], a post-hoc analysis of five trials [121], one exploratory [122] and one extension [123] non-controlled trials, a sequential-treatment trial [124], and three observational studies [125–127]. It reported a significant antidepressant effect of GLP-1RAs versus controls (SMD = −1.28, 95% CI [−2.34, −0.21], $p = 0.02$), with even larger effects in studies not excluding depressed patients (SMD = −2.09, 95% CI [−2.28, −1.91], $p < 0.00001$). A second meta-analysis [21], which included five RCTs [119, 120, 128–130] and one prospective cohort study [131] supported these findings (SMD = −0.12, 95% CI [−0.21, −0.03], $p < 0.01$). Subgroup analyses suggested that liraglutide, but not exenatide, was associated with mood improvements, though direct comparisons were inconclusive. Notably, effect sizes varied depending on study design, duration, measurement tools, agents, and population. One large-scale clinical trial [132] published after these meta-analyses compared metformin to other glucose-lowering agents in 5047 adults with T2DM. Among 450 participants assigned to liraglutide, no significant differences in depressive symptoms were observed. Observational studies have yielded mixed results: a pharmacovigilance analysis found lower reporting of depression-related adverse events with GLP-1RA [133], while a Taiwanese insurance database study reported significant antidepressant effects only for dulaglutide ($p < 0.001$) [134]. However, these studies carry a lower evidentiary weight and should be considered hypothesis-generating.

A key limitation of existing literature is the focus on T2DM populations rather than individuals with primary MD. Improved cerebral perfusion and reduced microvascular dysfunction may confound mood outcomes in these cases. Similar mood improvements observed with other glucose-lowering medications, such as pioglitazone, reinforces this concern [135]. Additionally, negative findings have been reported in non-metabolic populations, including individuals with Parkinson's disease [128] and polycystic ovary syndrome [122].

In an open-label trial by our group [24], we evaluated liraglutide in individuals with major depressive disorder (MDD) and BD. After four weeks, we observed a significant reduction in Hamilton Depression Rating Scale (HAM-D) scores across both populations (baseline = 12.18 (4.82) vs. post-treatment = 8.41 (6.12), Cohen's $d = 0.68$, $p = 0.022$). Although exploratory and limited by its uncontrolled design, this study provides preliminary clinical support for liraglutide's antidepressant potential in BD. We found no ongoing RCTs focusing on depressive symptoms as the primary outcome in MD populations treated with GLP-1RAs. However, two trials are underway assessing mood as a secondary outcome: one in BD (NCT06331286, liraglutide) and another in MDD (NCT0446635, semaglutide).

Effects on anxiety

Anxiety is a common comorbidity in BD, affecting up to 50% of individuals and often complicating its course and management [136]. The presence of co-occurring anxiety disorders is associated with greater symptom severity, functional impairment, and higher suicide risk in BD [136].

The relationship between GLP-1R signaling and anxiety is complex. In rodent models, peripheral administration of GLP-1RAs has shown anxiolytic effects in some studies [137], while GLP-1R knockout mice exhibit either unchanged or increased anxiety-like behaviors [138]. However, other studies report opposing results: acute administration of GLP-1 and exendin-4—either intraperitoneally or directly into the dorsal raphe nucleus—induced anxiety-like behaviors, along with increased serotonergic activity in the amygdala [109]. Interestingly, subchronic central injections of exendin over nine days normalized anxiety symptoms and produced antidepressant effects [109]. This biphasic pattern—initial anxiogenesis followed by longer-term anxiolysis—resembles early treatment responses seen with selective serotonin reuptake inhibitors [139]. Variability in outcomes may stem from differences in agents, drug administration routes, dosing regimen, rat strains, and behavioral testing protocols.

In humans, evidence remains limited. One large RCT including 80 individuals with T2DM and obesity post-bariatric surgery found no significant differences in anxiety symptoms between liraglutide and placebo after 26 weeks. Similarly, an intravenous GLP-1 challenge study in anxiety-prone individuals found no anxiogenic/panicogenic effects [140]. However, a small cross-sectional study [141] of 43 patients with T2DM and obesity reported an association between exenatide use and increased perceived stress, which mediated worsening depressive symptoms. In contrast, real-world studies—defined as analyses based on data collected outside the context of RCTs (e.g., electronic health records, insurance databases, or large observational cohorts)—in T2DM populations suggest potential anxiolytic benefits, even after adjusting for key variables such as demographics, body mass index (BMI), comorbidities, and concurrent medications [134]. Tirzepatide, in particular, showed the strongest effects, with a 60% lower likelihood of developing anxiety compared to non-GLP-1RA users [142]. In summary, while findings are mixed, emerging evidence suggests that GLP-1RAs may influence anxiety-related pathways. Given the high prevalence and clinical impact of anxiety in BD, further investigation into the potential anxiolytic effects of GLP-1RAs in this population is warranted. Notably, no ongoing RCTs currently target anxiety as a primary outcome.

Antimanic and mood-stabilizing effects

Manic and hypomanic episodes are hallmark features of BD. The neurobiology of mania involves dysregulation across multiple systems, including oxidative stress [143], mitochondrial

dysfunction inflammation, and neurotransmitter imbalances [39]. Current mood-stabilizing treatments are believed to act through these pathways. Lithium, in particular, reduces oxidative stress [144], and modulates glycogen synthase kinase-3 beta (GSK-3β) [145, 146], a key signaling enzyme involved in inflammation, mitochondrial function, and ion channel activity in BD [147].

Preclinical models suggest that GLP-1RAs may exert mood-stabilizing effects. In the amphetamine-induced mania model, liraglutide significantly attenuated hyperlocomotion and cognitive deficits but did not reverse impulsivity-related behaviors [148]. However, when combined with lithium, liraglutide mitigated the majority of amphetamine-induced behaviors and outperformed lithium monotherapy. Neurobiologically, liraglutide exerted antioxidant and neurotrophic effects primarily in the hippocampus, whereas lithium's actions were more pronounced in the prefrontal cortex and amygdala. Importantly, the combination reversed deficits across all examined regions.

In a separate ouabain-induced mania model, liraglutide reduced hyperlocomotion, anxiety- and depression-like behaviors, and modulated GSK-3β expression while alleviating oxidative stress. These effects were reflected in an increased serum total antioxidant status/total oxidant status ratio, reduced lipid peroxidation in brain tissue, and restoration of antioxidant enzyme activity [149]. Liraglutide's efficacy was comparable to that of valproate, a widely used mood stabilizer.

Collectively, these findings support the hypothesis that GLP-1RAs may confer mood-stabilizing effects by modulating oxidative stress, BDNF and GSK-3β signaling in BD. However, all evidence to date derives exclusively from animal models and have not been replicated in human studies. As such, they should be interpreted only within a strict hypothesis-generating framework. At present, no clinical data support the antimanic effects of GLP-1RAs, and no ongoing RCTs specifically address this domain, highlighting an important gap in translational research.

Cognitive effects

Cognitive dysfunction is a core domain in BD, affecting at least 30% of patients and exceeding rates observed in MDD [150]. Cognitive dysfunction contributes substantially to disability and social burden, independently of concurrent mood episodes [150], and remains inadequately addressed by current treatments [151]. Importantly, obesity and related metabolic abnormalities may exacerbate cognitive impairment in BD [152].

Emerging evidence implicates GLP-1R signaling in the regulation of cognitive function. GLP-1R knockout mice exhibit impaired associative learning, which is reversed by hippocampal GLP-1R gene transfer [153]. Similarly, intracerebroventricular GLP-1 administration enhances associative and spatial learning, effects abolished by GLP-1R antagonists [154]. In stress-induced depression models, liraglutide improves synaptic plasticity and mitigates LTP inhibition in the hippocampus [54, 155]—key processes underlying learning and memory [107]. Additional preclinical studies support these findings [156–158], pointing to multiple converging mechanisms [159, 160]: attenuation of neuroinflammation, restoration of oxidative and endoplasmic reticulum function, improved insulin signaling in neurons [161], and increased synthesis of neurotrophic factors. GLP-1R activation has also been linked to enhanced autophagy, reduced apoptosis, neurogenesis, improved cerebrovascular function and BBB integrity [159].

Human data are more mixed. A recent meta-analysis of five RCTs involving over 7700 patients with T2DM reported no overall cognitive benefit from GLP-1RA treatment [162]. However, subgroup analyses suggested potential advantages in individuals under 65 years or without cardiovascular disease. Another meta-analysis of three long-term RCTs (n = 15,820) reported a reduced risk of dementia with semaglutide and liraglutide compared to placebo in T2DM [163], findings further supported by a subsequent meta-analysis incorporating observational studies [164]. Five clinical trials have evaluated cognitive outcomes with GLP-1RA in neuropsychiatric populations, though none found significant cognitive improvements. These include (1) a 6-month trial of liraglutide in Alzheimer's disease (AD) [17], which showed no cognitive or amyloid changes, but suggested preservation of cerebral metabolic rate of glucose (CMRglc), a surrogate of disease progression; and (2) a study showing increased default mode network intrinsic connectivity in individuals at risk for AD [85]. Importantly, these two studies were underpowered for cognitive outcomes. The other three trials trialed exenatide in (3) Parkinson's disease [128], (4) mild cognitive impairment [165], and (5) antipsychotic-treated patients with schizophrenia and obesity [166]. A major limitation of these studies [85, 128, 165, 166] is the lack of enrichment for cognitive dysfunction, which reduced the power to detect treatment effects. Heterogeneity in sample composition (e.g., elderly vs. younger adults), agents used, and cognitive measures may also explain inconsistent results.

In contrast, our group conducted a 4-week open-label study of liraglutide in patients with BD and MDD, selectively enrolling those with preexisting executive dysfunction. Participants showed significant improvements in executive function and a composite cognitive index [24]. Structural brain changes were also observed and correlated with both reductions in BMI and cognitive gains [167]. However, these findings are preliminary and limited by the study's open-label design, small sample size, and absence of a control group. Further well-controlled trials are needed to clarify the cognitive effects of GLP-1RAs in MD and to identify subgroups most likely to benefit. In this regard, an open-label study (NCT06331286) is underway, comparing 24 weeks of dulaglutide to lifestyle guidance in 60 patients with BD and obesity. Additional trials are exploring GLP-1RAs in other high-risk groups: NCT04466345 investigates semaglutide's effects on executive function in MDD with cognitive dysfunction; NCT06072963 examines semaglutide plus intranasal insulin in older adults with metabolic syndrome and MCI; NCT05313529 evaluates liraglutide in T2DM with MCI; and NCT06720246 investigates liraglutide and bariatric surgery on cognitive-behavioral markers of long-term weight loss.

Effects on reward and motivation

Dysfunction in reward processing and motivation is increasingly recognized as a core feature of BD, regardless of subtypes and mood states [168–171]. Interestingly, Jiménez et al. identified an euthymic BD cognitive subtype with impaired decision-making and reduced reward sensitivity, despite intact general cognition [171]—supporting reward dysfunction as an independent domain in BD.

GLP-1Rs are expressed in mesocorticolimbic regions involved in reward valuation, salience attribution, and reinforcement learning [172]. GLP-1RAs attenuate neuronal activation [50] in response to high-reward stimuli—especially food-related cues—by decreasing excitatory input from VTA dopaminergic neurons to the NAc [48]. They also reduce caloric intake, appetite, and cravings, while shifting preference toward low-fat or sweet foods [173, 174]. These effects likely involve not only enhanced satiety but also diminished reward valuation [175, 176], pointing to broader neuromodulatory mechanisms.

GLP-1RAs also enhance motivation and adaptive learning. In obese, insulin-resistant individuals, liraglutide restored impaired associative learning by normalizing behavioral updating in response to predictive cues and increasing activation in dopaminergic targets such as the ventral striatum and NAc [177]. These effects align with modulation of dopamine-mediated prediction error signaling, a key mechanism for flexible, goal-directed behavior. Although direct effects on dopamine signaling appears context-dependent, improved insulin sensitivity and reduced neuroinflammation may contribute to restored dopaminergic tone and motivational drive—suggesting possible benefit in BD.

NCT06363487 is investigating the acute effects of semaglutide versus placebo on reward sensitivity in healthy volunteers. Secondary outcomes include emotional processing, impulsivity, memory, and energy levels. We found no ongoing RCTs specifically addressing reward processing or motivation in BD, underscoring an important area for future investigation.

Treatment of comorbid substance use

BD and substance use disorders (SUDs) share one of the highest comorbidity rates among all psychiatric conditions [178, 179]. Substance use worsens the clinical course of BD and complicates its treatment [180, 181], leading to higher relapse rates, slower recovery from mood episodes, greater need for hospitalization, and overall worse functioning [182]. While pharmacological options exist for SUD treatment, their effectiveness remains limited, and sustained remission is uncommon [183], highlighting the need for novel interventions.

GLP-1RAs may influence addiction vulnerability through several converging neurobiological mechanisms [184, 185]. GLP-1Rs are expressed in mesolimbic dopaminergic regions—including the VTA and NAc [29], where they modulate drug-induced dopamine release and reinforcement learning [186]. For instance, GLP-1R activation attenuates cocaine-evoked dopamine surges in the NAc and decreases drug-seeking behaviors [187]; Other regions, such as the medial habenula, may mediate aversive responses to nicotine: GLP-1R optogenetic stimulation in this area appears to convert nicotine's effects into aversive signals, thereby reducing intake, while GLP-1RA knockout mice display increased consumption of multiple addictive substances [188]. Semaglutide, liraglutide, and tirzepatide, have been shown to reduce alcohol intake in rodents [189], while liraglutide had similar effects in non-human primates [190]. One study reported that exenatide blocked amphetamine-conditioned place preference and alcohol consumption in mice with intact GLP-1Rs but not in those with GLP-1R deletion [191]. GLP-1RAs may also buffer stress-induced relapse—a major driver of substance use—by modulating reward-related responses to stress, as observed in models of stress-related overeating [192]. Moreover, GLP-1RAs may exert anti-addictive effects by mitigating neuroinflammation—a recognized contributor to both BD and SUD [193]—via opioid receptor-related pathways [51]. Overall, preclinical evidence is robust: a recent review reported over 24 studies on the beneficial effects of GLP-1RAs on alcohol use, 8 in opioids, 16 on stimulants, and 4 on nicotine [104].

Clinical data are emerging. A recent systematic review [194] analyzed five RCTs evaluating GLP-1RAs for reducing substance use. Two trials found reductions in alcohol [195] and nicotine [174] consumption following GLP-1RA treatment; another found no significant effect on alcohol consumption but did report benefits in obese subgroups [196]. Conversely, two trials found no significant impact on subjective cocaine effects or consumption [197], or smoking cessation rates with dulaglutide [198]. Large retrospective cohort studies have reported associations between GLP-1RA use and reduced alcohol consumption [199, 200] and decreased cannabis use disorder risk [201].

While these findings are promising, the limited number of studies and heterogeneity in methodology, patient characteristics and specific agents necessitate cautious interpretation. Ongoing RCTs are exploring this therapeutic avenue. NCT06015893, NCT05895643, and NCT05892432 are assessing semaglutide's safety and efficacy in alcohol use disorder (AUD). Tirzepatide is also being studied for alcohol consumption in NCT06994338, NCT06939088, and NCT06727331. For nicotine use, GLP-1RAs are being investigated in NCT05530577, NCT03712098, and NCT05610800. In opioid use disorder, semaglutide and tirzepatide are under investigation in NCT06548490, NCT06639464, and NCT06651177. Despite this growing interest, no ongoing RCTs are investigating SUD outcomes in individuals with MD.

Effects on iatrogenic and non-iatrogenic weight gain

Individuals with BD are at an increased risk of weight gain and metabolic syndrome, driven by both intrinsic disease-related factors—such as insulin resistance, hormonal imbalances, motivational deficits, and socioeconomic disparities [202], and iatrogenic causes, particularly psychotropic-drug-related weight gain (PDWG) [13]. These effects not only exacerbate metabolic burden but also undermine treatment adherence [203], worsen long-term disease control [204], and increase the risk of cardiovascular, endocrine, and psychiatric comorbidities—ultimately reducing quality of life and increasing healthcare utilization [205].

GLP-1RAs have emerged as promising agents for managing weight gain in psychiatric populations. A systematic review [206] identified five RCTs evaluating GLP-1RA for PDWG, most of which reported positive outcomes [23, 207–210], with only one showing no significant results [210]. Overall, GLP-1RAs were associated with average weight reductions of 3.5 to 6 kg compared to placebo, alongside improvements in lipid profiles. Reflecting this evidence, GLP-1RAs are increasingly recommended for the treatment of obesity and PDWG, especially in patients with cardiometabolic risk [13].

In BD, McElroy et al. [23] conducted a 40-week, randomized, placebo-controlled trial assessing liraglutide in patients with comorbid overweight or obesity. Liraglutide led to a significant reduction in body weight percentage, along with improvements in BMI, HbA1c levels, hunger perception, and binge-eating frequency. These findings align with those from a retrospective study examining GLP-1As in BD and schizophrenia patients treated with antipsychotics [26], as well as another study evaluating patients with MDD and BD [25].

NEUROPSYCHIATRIC SAFETY

Randomized controlled trials

GLP-1RAs are generally well-tolerated and safe medications [211, 212]. Two post-hoc analysis of pooled RCT data from obese, diabetic populations—including one involving 5325 participants treated with liraglutide [121] and another with GLP-1 [213]—reported no significant differences in suicidal ideation or behavior (SIB) compared to placebo. However, these trials systematically excluded individuals with severe psychiatric disorders or a history of suicidality, limiting their generalizability to BD. Importantly, one RCT in BD [23] and one open-label trial including patients with MDD and BD [24] reported no increase in neuropsychiatric adverse events.

Observational studies and risk quantification

Most cohort studies, though primarily focused on T2DM or obesity, have not found an association between GLP-1RA use and suicidality [214–221]. A few studies have reported positive associations [222, 223], but these findings are often limited by residual confounding and lack of psychiatric stratification. Conversely, other observational data suggest a possible protective effect of GLP-1RAs on SIB risk in these populations [224–226].

Pharmacovigilance and signal detection

Both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) have received reports of SIB associated with GLP-1RA use, particularly with liraglutide and semaglutide [227, 228]. An analysis of the FDA Adverse Event Reporting System (FAERS) revealed an increased number of reports of depression and suicidal ideation in GLP-1RA users [229]. However, such findings are hypothesis-generating and represent signal detection, not risk quantification. Signal detection refers to the identification of unexpected or disproportionate reporting patterns in pharmacovigilance systems. While it serves as a valuable early-warning tool, it is subject to reporting bias, lack of denominator data, and inability to adjust for key confounders. In contrast, risk quantification relies on structured data—typically from RCTs—that enable

statistical comparison between exposed and unexposed groups under controlled conditions. It is important to consider that individuals with T2DM have a 1.5- to 2-fold higher risk of developing MDD [230], a pattern similarly observed in obesity [231]. As such, these pharmacovigilance signals do not establish causality [232, 233]. In the aforementioned study, no association was found between GLP-1RA use and suicide attempts or completed suicides. A second FAERS analysis also yielded negative results [234]. Other studies using the World Health Organization's VigiBase also reported a higher rate of suicidal ideation reports [235], but found reduced risk for suicide attempts or completed suicides [236].

Vulnerable populations and biological considerations

Patients with a history of psychiatric disorders may be more vulnerable to SIB, even if the overall incidence remains rare in the general population, and particularly in response to rapid weight loss. Rapid weight reduction can trigger increased psychosocial [237] and biological stress, due to heightened allostatic load from cortisol and norepinephrine [238], which have been implicated in psychiatric disturbances and suicidality [239, 240]. Notably, in a post-bariatric surgery cohort, 93% of SIB events occurred in individuals with pre-existing psychiatric conditions [241]. Furthermore, the frustration of unmet weight loss expectations may also contribute to increased SIB, as observed in patients who fail other weight loss interventions [242]. These considerations are particularly relevant for patients with BD [243], where suicide rates are up to 20–30 times higher than in the general population [244]. Nevertheless, the two clinical trials evaluating GLP-1RA use in BD reported no increased risk of SIB [23, 24]. Taken together, while pharmacovigilance signals warrant attention, current data are insufficient to establish a causal relationship between GLP-1RA use and neuropsychiatric harm.

DISCUSSION

According to the principle of the "Five Ws and One H", a comprehensive analysis should answer the questions of what, why, who, how, when, and where. In this regard, and in the first place, *what* have we explored in this review? We have examined the possible applications of GLP-1RAs in BD, synthesizing evidence from preclinical, clinical, and real-world studies.

Why should GLP-1RAs be considered in BD? Biological rationale and clinical evidence (Fig. 1)

GLP-1RAs warrant consideration in BD due to their pleiotropic effects on biological systems implicated in the disorder, including neurotransmitter regulation, neuroinflammation, mitochondrial dysfunction and oxidative stress, neurotrophic signaling, and insulin-glucose metabolism. Preliminary evidence suggests potential therapeutic benefits across multiple domains relevant to BD: (1) meta-analyses in populations with T2DM report antidepressant effects, and one open-label trial in MDD and BD observed symptom improvement after four weeks of liraglutide treatment [24]; (2) preclinical and real-world studies suggest anxiolytic properties, though clinical data remain sparce; (3) in animal models, liraglutide exhibits mood-stabilizing effects [245], particularly when combined with lithium [148], but these findings await replication in humans; (4) emerging evidence suggests cognitive benefits in MD [24], especially in individuals with baseline executive dysfunction, though results across different neuropsychiatric populations remain inconsistent [17, 165, 166]; (5) GLP-1RAs mitigate weight gain and metabolic disturbances in BD—an especially relevant outcome for those patients exposed to antipsychotics or/and mood stabilizers; and 6) preclinical and retrospective studies suggest potential benefits for SUD, with some RCTs showing efficacy in nicotine [174] and alcohol use disorders [195].

How should GLP-1RAs be incorporated into BD treatment? Opportunities, risks, and practical challenges for the clinician

Managing BD extends beyond acute symptom control, emphasizing long-term functional recovery and metabolic health. GLP-1RAs may provide a rare opportunity to target both psychiatric and somatic dimensions of BD simultaneously, supporting sustained recovery through improvements in cognition, motivation, and cardiometabolic regulation. They could serve as adjunctive agents to existing mood stabilizers or antipsychotics, mitigating their metabolic side effects while potentially enhancing neuroprotection. Potential synergy with lithium deserves further investigation, as both compounds complimentarily influence oxidative stress, neurotrophic signaling, and mitochondrial function. Given their properties, GLP-1RAs appear better suited for symptom prevention and disease course modification rather than acute mood episode treatment [246].

However, several limitations and risks must be acknowledged. Although most studies do not show increased risk of SIB, pharmacovigilance signals have emerged. Special caution and monitoring are advised for individuals with a personal or family history of suicidality [244], rapid weight changes, or significant weight loss expectations. Another important concern is the absence of studies evaluating potential drug interactions. GLP-1RAs are known to delay gastric emptying [247], which could theoretically affect the absorption of co-administered medications. Although not yet demonstrated clinically, this may be particularly relevant for drugs with narrow therapeutic windows such as lithium. Furthermore, gastrointestinal side effects associated to GLP-1RA may be exacerbated in patients already taking SSRI, SNRI, or tricyclic antidepressants, all of which have overlapping side effect profiles. The potential for additive or synergistic gastrointestinal burden deserves greater attention, as it may impact both tolerability and adherence. Further studies should assess these interactions directly, especially in patients receiving polypharmacy regimens typical of real-world psychiatric care.

Who might benefit the most from GLP-1RAs? Key patient profiles

Psychiatric disorders such as BD are highly heterogeneous, both in clinical presentation, neurobiology, and treatment response. While high-quality RCTs in BD are lacking, certain subgroups of patients seem more likely to benefit. These include patients with established executive dysfunction [24], elevated BMI [196], metabolic syndrome, cardiovascular disease, or comorbid alcohol [196] or nicotine use disorders [174]. Additionally, individuals at higher risk for neuroprogression [248, 249] such as those with a greater number of mood episodes (particularly manic episodes) [250]; a history of trauma [250], biomarkers indicative of increased peripheral inflammation [251] or neuroanatomical changes [251]—could also derive significant benefits, given the role of GLP-1RAs on inflammatory, oxidative, mitochondrial, and neuroplastic pathways, which are thought to underlie BD progression [252]. Emerging evidence also points to greater cognitive benefits among younger individuals [162].

When (and *where*) should GLP-1RAs be considered for BD management? Practical challenges for the patient

The growing public interest in GLP-1RAs—largely fueled by media coverage of their weight loss benefits—presents an opportunity to challenge the stigma surrounding psychiatric treatments. BD has traditionally been a late-stage indication for novel pharmacotherapies, often following trials in schizophrenia, epilepsy, or unipolar depression, leading to missed opportunities for millions of individuals. Given that many GLP-1RAs are already commercially available with well-established safety profiles, launching expedited clinical trials seems feasible.

Several barriers, however, may impede their broader psychiatric use. Chief among these remains cost. In the United States, annual

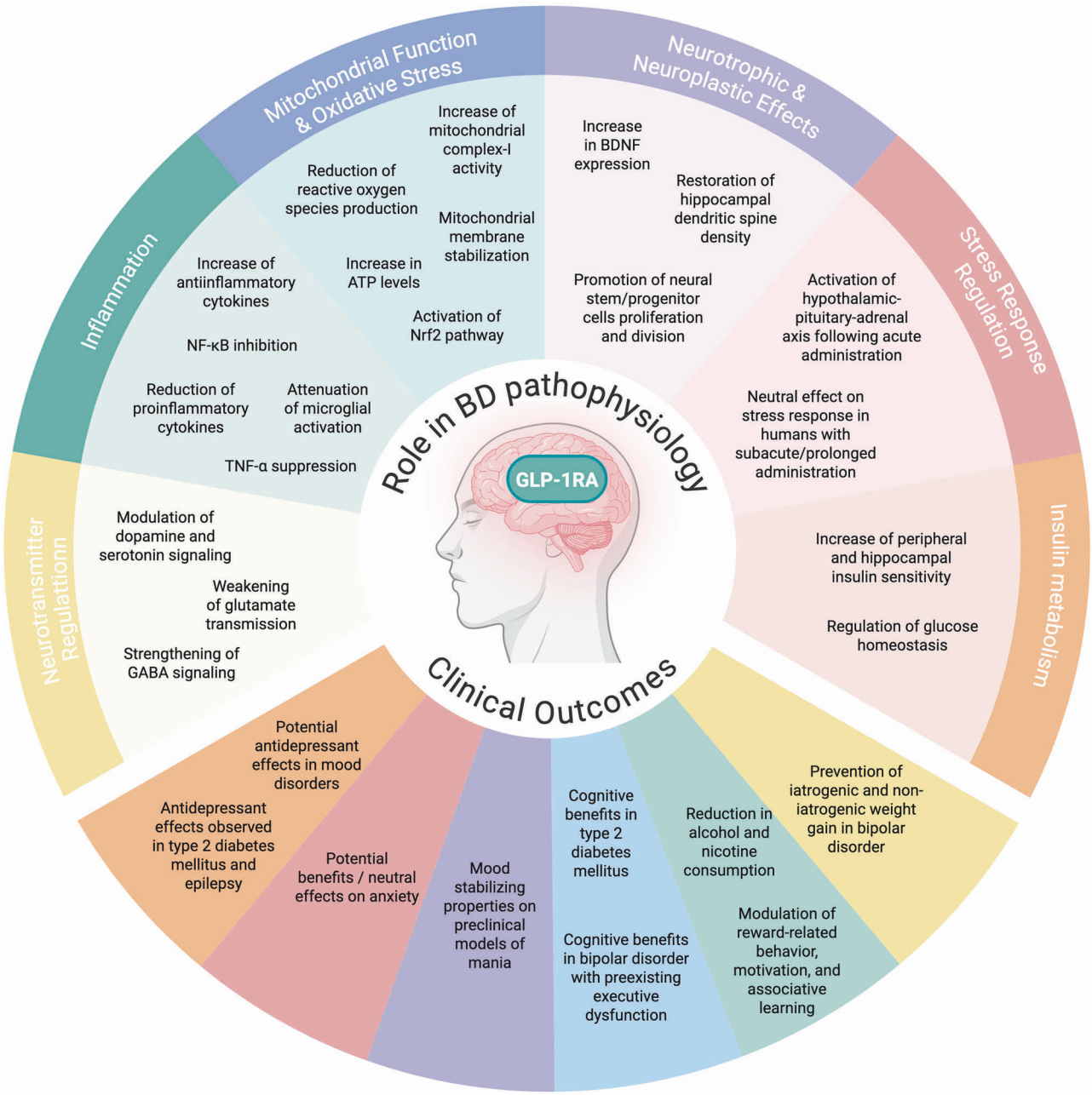

Fig. 1 Proposed mechanisms of action and clinical outcomes of GLP-1RAs in BD. Created in BioRender. Llach, C. (2025) https://BioRender.com/8z4cla5.

treatment expenses can exceed $16,000, with insurance coverage varying widely across states and plans. Financial constraints are one the most commonly cited reasons for discontinuation, reported by 50% of users [253–255]. Even in countries with lower prices, such as the UK, prescribing restrictions confine access to patients with severe obesity or comorbid conditions [255]. These constraints may hinder broader application of GLP-1RAs, especially for patients who fall outside standard metabolic indications but may still benefit from treatment. Beyond financial and regulatory hurdles, other challenges include limited prescriber familiarity with GLP-1RAs in psychiatric settings, a lack of long-term safety data in psychiatric populations, and insufficient exploration of potential drug interactions. Patient-related barriers may also arise from stigma, a persistent underrecognition of cognitive and subthreshold depressive symptoms as features of MDD or BD, or a reluctance to conceptualize metabolic and mental illness as interconnected. Overcoming these challenges would require coordinated efforts across regulatory agencies, insurers, clinicians, and advocacy organizations to improve education, reduce stigma, and ensure equitable access to promising metabolic-psychiatric treatments.

Future directions and conclusions

While current evidence remains preliminary, heterogenous, and mostly derived from T2DM populations, additional well-powered, BD-focused studies are urgently needed. Future research should examine differential responses across BD subtypes and clinical subgroups, prioritizing individuals with treatment-resistant depression and comorbid metabolic conditions; early-stage BD patients with high risk of neuroprogression, and those with cognitive impairment. Trials should evaluate both psychiatric and somatic outcomes and aim to determine treatment duration, long-term side

effects, and combination strategies—including co-administration with lithium, psychotherapy, or cognitive [256] or functional remediation [257]. Longer follow-up periods will be essential to assess sustained effects on cognition and functional recovery. Practical considerations should guide compound selection. Oral formulations like oral semaglutide may be preferable in psychiatric populations, where injectable treatments often face adherence barriers [258]. Newer multi-agonists, including tirzepatide, retatutride, and orfoglipron, warrant evaluation given their broader metabolic and neurobiological actions [259]. Whether the anticipated transformative potential of GLP-1RAs in medicine and society will extend to individuals with BD remains unclear. However, the opportunity to fully explore their potential—while maintaining appropriate caution and scientific skepticism—should not be overlooked.

REFERENCES

1. McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. Lancet. 2020;396:1841–56.
2. Oliva V, Fico G, De Prisco M, Gonda X, Rosa AR, Vieta E. Bipolar disorders: an update on critical aspects. Lancet Reg Health Eur. 2024;48:101135.
3. Léda-Rêgo G, Studart-Bottó P, Abbade P, Rabelo-Da-Ponte FD, Casqueiro JS, Sarmento S, et al. Lifetime prevalence of psychiatric comorbidities in patients with bipolar disorder: a systematic review and meta-analysis. Psychiatry Res. 2024;337:115953.
4. Liu YK, Ling S, Lui LMW, Ceban F, Vinberg M, Kessing LV, et al. Prevalence of type 2 diabetes mellitus, impaired fasting glucose, general obesity, and abdominal obesity in patients with bipolar disorder: a systematic review and meta-analysis. J Affect Disord. 2022;300:449–61.
5. Jawad MY, Meshkat S, Tabassum A, McKenzie A, Di Vincenzo JD, Guo Z, et al. The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia. CNS Spectr. 2023;28:541–60.
6. McIntyre RS, Alda M, Baldessarini RJ, Bauer M, Berk M, Correll CU, et al. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry. 2022;21:364–87.
7. Robinson N, Bergen SE. Environmental risk factors for schizophrenia and bipolar disorder and their relationship to genetic risk: current knowledge and future directions. Front Genet. 2021;12:686666.
8. Poletti S, Mazza MG, Benedetti F. Inflammatory mediators in major depression and bipolar disorder. Transl Psychiatry. 2024;14:247.
9. Giménez-Palomo A, Guitart-Mampel M, Meseguer A, Borràs R, García-García FJ, Tobías E, et al. Reduced mitochondrial respiratory capacity in patients with acute episodes of bipolar disorder: could bipolar disorder be a state-dependent mitochondrial disease? Acta Psychiatr Scand. 2024;149:52–64.
10. Belvederi Murri M, Prestia D, Mondelli V, Pariante C, Patti S, Olivieri B, et al. The HPA axis in bipolar disorder: systematic review and meta-analysis. Psychoneuroendocrinology. 2016;63:327–42.
11. Calkin CV. Insulin resistance takes center stage: a new paradigm in the progression of bipolar disorder. Ann Med. 2019;51:281.
12. Nierenberg AA, Agustini B, Köhler-Forsberg O, Cusin C, Katz D, Sylvia LG, et al. Diagnosis and treatment of bipolar disorder: a review. JAMA. 2023;330:1370–80.
13. McIntyre RS, Kwan ATH, Rosenblat JD, Teopiz KM, Mansur RB. Psychotropic drug–related weight gain and its treatment. Am J Psychiatry. 2024;181:26–38. https://doi.org/10.1176/appi.ajp.20230922.
14. Drucker DJ. The GLP-1 journey: from discovery science to therapeutic impact. J Clin Invest. 2024;134:e175634.
15. Committee ADAPP, ElSayed NA, McCoy RG, Aleppo G, Bajaj M, Balapattabi K, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2025. Diabetes Care. 2025;48:S181–S206.
16. McIntyre RS, Rasgon N, Goldberg JF, Wong S, Le GH, Mansur RB, et al. The effect of glucagon-like peptide-1 and glucose dependent insulinotropic polypeptide receptor agonists on neurogenesis, differentiation, and plasticity (Neuro-GDP): potential mechanistically informed therapeutics in the treatment and prevention of mental disorders. CNS Spectr. 2025;30:e23.
17. Gejl M, Gjedde A, Egefjord L, Møller A, Hansen SB, Vang K, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci. 2016;8:108.
18. Javed D, Jajja FA, Javed A. GLP-1 receptor agonists: a revolution in the treatment of Parkinson's disease? Eur Neuropsychopharmacol. 2024;86:11–12.
19. Lee JM, Sharifi M, Oshman L, Griauzde DH, Chua KP. Dispensing of glucagon-like Peptide-1 receptor agonists to adolescents and young adults, 2020–2023. JAMA. 2024;331:2041–3.
20. Detka J, Głombik K. Insights into a possible role of glucagon-like peptide-1 receptor agonists in the treatment of depression. Pharmacol Rep. 2021;73:1020–32.
21. Chen X, Zhao P, Wang W, Guo L, Pan Q. The antidepressant effects of GLP-1 receptor agonists: a systematic review and meta-analysis. Am J Geriatr Psychiatry. 2024;32:117–27.
22. Levy B, Manove E. Functional outcome in bipolar disorder: the big picture. Depress Res Treat. 2012;2012:12.
23. Mcelroy SL, Guerdjikova AI, Blom TJ, Mori N, Romo-Nava F. Liraglutide in obese or overweight individuals with stable bipolar disorder. J Clin Psychopharmacol. 2024;44:89–95.
24. Mansur RB, Ahmed J, Cha DS, Woldeyohannes HO, Subramaniapillai M, Lovshin J, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: a pilot, open-label study. J Affect Disord. 2017;207:114–20.
25. Cuomo A, Bolognesi S, Goracci A, Ciuoli C, Crescenzi BB, Maina G, et al. Feasibility, adherence and efficacy of liraglutide treatment in a sample of individuals with mood disorders and obesity. Front Psychiatry. 2019;10:432154.
26. Lee SE, Lee NY, Kim SH, Kim KA, Kim YS. Effect of liraglutide 3.0 mg treatment on weight reduction in obese antipsychotic-treated patients. Psychiatry Res. 2021;299:113830.
27. Magioncalda P, Martino M. A unified model of the pathophysiology of bipolar disorder. Mol Psychiatry. 2021;27:202–11.
28. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role ofglucagon and GLP-1 in health and disease. Physiol Rev. 2015;95:513–48.
29. Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. Mol Metab. 2015;4:718–31.
30. Alvarez E, Martínez MD, Roncero I, Chowen JA, García-Cuartero B, Gispert JD, et al. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. J Neurochem. 2005;92:798–806.
31. Hsu TM, Hahn JD, Konanur VR, Lam A, Kanoski SE. Hippocampal GLP-1 receptors influence food intake, meal size, and effort-based responding for food through volume transmission. Neuropsychopharmacology. 2014;40:327.
32. Zeng N, Cutts EJ, Lopez CB, Kaur S, Duran M, Virkus SA, et al. Anatomical and functional characterization of central amygdala Glucagon-like peptide 1 receptor expressing neurons. Front Behav Neurosci. 2021;15:724030.
33. van Bloemendaal L, ten Kulve JS, La Fleur SE, Ijzerman RG, Diamant M. Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. J Endocrinol. 2014;221:T1–T16.
34. Kalra S, Bhattacharya S, Kapoor N. Contemporary classification of Glucagon-like peptide 1 receptor agonists (GLP1RAs). Diabetes Ther. 2021;12:2133.
35. West J, Li M, Wong S, Le GH, Teopiz KM, Valentino K, et al. Are Glucagon-like peptide-1 (GLP-1) receptor agonists Central Nervous System (CNS) penetrant: a narrative review. Neurol Ther. 2025;14:1157–66. https://doi.org/10.1007/S40120-025-00724-Y.
36. Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. BMC Neurosci. 2012;13:33.
37. Au HCT, Zheng YJ, Le GH, Wong S, Teopiz KM, Kwan ATH, et al. Association of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and neurogenesis: a systematic review. Acta Neuropsychiatr. 2025;37:e50.
38. Trujillo PharmD J, Jennifer Trujillo C. Safety and tolerability of once-weekly GLP-1 receptor agonists in type 2 diabetes. J Clin Pharm Ther. 2020;45:43–60.
39. Lee JG, Woo YS, Park SW, Seog DH, Seo MK, Bahk WM. Neuromolecular etiology of bipolar disorder: possible therapeutic targets of mood stabilizers. Clin Psychopharmacol Neurosci. 2022;20:228.
40. Owji AA, Khoshdel Z, Sanea F, Panjehshahin MR, Shojaee Fard M, Smith DM, et al. Effects of intracerebroventricular injection of glucagon like peptide-1 and its related peptides on serotonin metabolism and on levels of amino acids in the rat hypothalamus. Brain Res. 2002;929:70–75.
41. Korol SV, Jin Z, Babateen O, Birnir B. GLP-1 and exendin-4 transiently enhance GABAA receptor–mediated synaptic and tonic currents in rat hippocampal CA3 pyramidal neurons. Diabetes. 2015;64:79–89.
42. Rebosio C, Balbi M, Passalacqua M, Ricciarelli R, Fedele E. Presynaptic GLP-1 receptors enhance the depolarization-evoked release of glutamate and GABA in the mouse cortex and hippocampus. Biofactors. 2018;44:148–57.
43. Hernandez NS, Weir VR, Ragnini K, Merkel R, Zhang Y, Mace K, et al. GLP-1 receptor signaling in the laterodorsal tegmental nucleus attenuates cocaine seeking by activating GABAergic circuits that project to the VTA. Mol Psychiatry. 2021;26:4394–408.
44. Anderberg RH, Anefors C, Bergquist F, Nissbrandt H, Skibicka KP. Dopamine signaling in the amygdala, increased by food ingestion and GLP-1, regulates feeding behavior. Physiol Behav. 2014;136:135–44.

45. Reddy IA, Pino JA, Weikop P, Osses N, Sørensen G, Bering T, et al. Glucagon-like peptide 1 receptor activation regulates cocaine actions and dopamine homeostasis in the lateral septum by decreasing arachidonic acid levels. Transl Psychiatry. 2016;6:809.
46. Fortin SM, Roitman MF. Central GLP-1 receptor activation modulates cocaine-evoked phasic dopamine signaling in the nucleus accumbens core. Physiol Behav. 2017;176:17–25.
47. Hayes MR, Schmidt HD. GLP-1 influences food and drug reward. Curr Opin Behav Sci. 2016;9:66–70.
48. Wang XF, Liu JJ, Xia J, Liu J, Mirabella V, Pang ZP. Endogenous glucagon-like peptide-1 suppresses high-fat food intake by reducing synaptic drive onto mesolimbic dopamine neurons. Cell Rep. 2015;12:726–33.
49. Rosenblat JD, McIntyre RS. Bipolar disorder and immune dysfunction: epidemiological findings, proposed pathophysiology and clinical implications. Brain Sci. 2017;7:144.
50. Sayana P, Colpo GD, Simões LR, Giridharan VV, Teixeira AL, Quevedo J, et al. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. J Psychiatr Res. 2017;92:160–82.
51. Wong CK, McLean BA, Baggio LL, Koehler JA, Hammoud R, Rittig N, et al. Central glucagon-like peptide 1 receptor activation inhibits toll-like receptor agonist-induced inflammation. Cell Metab. 2024;36:130–143.e5.
52. Velmurugan K, Balamurugan AN, Loganathan G, Ahmad A, Hering BJ, Pugazhenthi S. Antiapoptotic actions of Exendin-4 against hypoxia and cytokines are augmented by CREB. Endocrinology. 2012;153:1116–28.
53. Yoon G, Kim YK, Song J. Glucagon-like peptide-1 suppresses neuroinflammation and improves neural structure. Pharmacol Res. 2020;152:104615.
54. Mcclean PL, Parthsarathy V, Faivre E, Holscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci. 2011;31:6587–94.
55. Alharbi SH. Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. Ther Adv Endocrinol Metab. 2024;15:20420188231222370.
56. Ventorp F, Bay-Richter C, Nagendra AS, Janelidze S, Matsson VS, Lipton J, et al. Exendin-4 treatment improves LPS-induced depressive-like behavior without affecting pro-inflammatory cytokines. J Parkinsons Dis. 2017;7:263–73.
57. Andreazza AC, Duong A, Young LT. Bipolar disorder as a mitochondrial disease. Biol Psychiatry. 2018;83:720–1.
58. Morris G, Walder K, Mcgee SL, Dean OM, Tye SJ, Maes M, et al. A model of the mitochondrial basis of bipolar disorder. Neurosci Biobehav Rev. 2017;74:1–20.
59. Andreazza AC, Kauer-Sant'Anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008;111:135–44.
60. Lichtstein D, Ilani A, Rosen H, Horesh N, Singh SV, Buzaglo N, et al. Na+, K +-ATPase signaling and bipolar disorder. Int J Mol Sci. 2018;19:2314.
61. Todorova V, Blokland A. Mitochondria and synaptic plasticity in the mature and aging nervous system. Curr Neuropharmacol. 2016;15:166–73.
62. González-García I, Gruber T, García-Cáceres C. Insulin action on astrocytes: from energy homeostasis to behaviour. J Neuroendocrinol. 2021;33:e12953.
63. Reiner DJ, Mietlicki-Baase EG, McGrath LE, Zimmer DJ, Bence KK, Sousa GL, et al. Astrocytes regulate GLP-1 receptor-mediated effects on energy balance. J Neurosci. 2016;36:3531–40.
64. Timper K, del Río-Martín A, Cremer AL, Bremser S, Alber J, Giavalisco P, et al. GLP-1 Receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. Cell Metab. 2020;31:1189–1205.e13.
65. Wang RF, Xue GF, Hölscher C, Tian MJ, Feng P, Zheng JY, et al. Post-treatment with the GLP-1 analogue liraglutide alleviate chronic inflammation and mitochondrial stress induced by status epilepticus. Epilepsy Res. 2018;142:45–52.
66. He W, Wang H, Zhao C, Tian X, Li L, Wang H. Role of liraglutide in brain repair promotion through Sirt1-mediated mitochondrial improvement in stroke. J Cell Physiol. 2020;235:2986–3001.
67. Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci. 2014;39:199–218.
68. Thompson Ray M, Cynthia, Weickert S, Wyatt E, Webster MJ, Ray T, et al. Decreased BDNF, trkB-TK+ and GAD67 mRNA expression in the hippocampus of individuals with schizophrenia and mood disorders. J Psychiatry Neurosci. 2011;36:195–203.
69. Huang TL, Hung YY, Te Lee C, Chen RF. Serum protein levels of brain-derived neurotrophic factor and tropomyosin-related Kinase B in bipolar disorder: effects of mood stabilizers. Neuropsychobiology. 2012;65:65–69.
70. Craddock N, O'Donovan MC, Owen MJ. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. J Med Genet. 2005;42:193.
71. Valvassori SS, Resende WR, Budni J, Dal-Pont GC, Bavaresco DV, Reus GZ, et al. Sodium butyrate, a histone deacetylase inhibitor, reverses behavioral and mitochondrial alterations in animal models of depression induced by Early- or Late-life stress. Curr Neurovasc Res. 2015;12:312–20.
72. Jornada LK, Moretti M, Valvassori SS, Ferreira CL, Padilha PT, Arent CO, et al. Effects of mood stabilizers on hippocampus and amygdala BDNF levels in an animal model of mania induced by ouabain. J Psychiatr Res. 2010;44:506–10.
73. Valvassori SS, Mariot E, Varela RB, Bavaresco DV, Dal-Pont GC, Ferreira CL, et al. The role of neurotrophic factors in manic-, anxious- and depressive-like behaviors induced by amphetamine sensitization: implications to the animal model of bipolar disorder. J Affect Disord. 2019;245:1106–13.
74. Varela RB, Valvassori SS, Lopes-Borges J, Mariot E, Dal-Pont GC, Amboni RT, et al. Sodium butyrate and mood stabilizers block ouabain-induced hyperlocomotion and increase BDNF, NGF and GDNF levels in brain of Wistar rats. J Psychiatr Res. 2015;61:114–21.
75. Bomba M, Granzotto A, Castelli V, Massetti N, Silvestri E, Canzoniero LMT, et al. Exenatide exerts cognitive effects by modulating the BDNF-TrkB neurotrophic axis in adult mice. Neurobiol Aging. 2018;64:33–43.
76. Gumuslu E, Mutlu O, Celikyurt IK, Ulak G, Akar F, Erden F, et al. Exenatide enhances cognitive performance and upregulates neurotrophic factor gene expression levels in diabetic mice. Fundam Clin Pharmacol. 2016;30:376–84.
77. Ji C, Xue GF, Lijun C, Feng P, Li D, Li L, et al. A novel dual GLP-1 and GIP receptor agonist is neuroprotective in the MPTP mouse model of Parkinson's disease by increasing expression of BNDF. Brain Res. 2016;1634:1–11.
78. Park SW, Mansur RB, Lee Y, Lee JH, Seo MK, Choi AJ, et al. Liraglutide activates mTORC1 signaling and AMPA receptors in rat hippocampal neurons under toxic conditions. Front Neurosci. 2018;12:417341.
79. Bertilsson G, Patrone C, Zachrisson O, Andersson A, Dannaeus K, Heidrich J, et al. Peptide hormone exendin-4 stimulates subventricular zone neurogenesis in the adult rodent brain and induces recovery in an animal model of parkinson's disease. J Neurosci Res. 2008;86:326–38.
80. Hamilton A, Patterson S, Porter D, Gault VA, Holscher C. Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. J Neurosci Res. 2011;89:481–9.
81. Song Y, Yang J, Chang M, Wei Y, Yin Z, Zhu Y, et al. Shared and distinct functional connectivity of hippocampal subregions in schizophrenia, bipolar disorder, and major depressive disorder. Front Psychiatry. 2022;13:993356.
82. Perry A, Roberts G, Mitchell PB, Breakspear M. Connectomics of bipolar disorder: a critical review, and evidence for dynamic instabilities within interoceptive networks. Mol Psychiatry. 2019;24:1296–318.
83. Syan SK, Smith M, Frey BN, Remtulla R, Kapczinski F, Hall GBC, et al. Resting-state functional connectivity in individuals with bipolar disorder during clinical remission: a systematic review. J Psychiatry Neurosci. 2018;43:298.
84. Au HCT, Zheng YJ, Le GH, Wong S, Phan L, Teopiz KM, et al. A systematic review in effects of glucagon-like peptide-1 (GLP-1) mono-agonists on functional connectivity: target engagement and rationale for the development in mental disorders. J Affect Disord. 2025;370:321–7.
85. Watson KT, Wroolie TE, Tong G, Foland-Ross LC, Frangou S, Singh M, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. Behav Brain Res. 2019;356:271–8.
86. Juruena MF, Cleare AJ, Young AH. Neuroendocrine stress system in bipolar disorder. Curr Top Behav Neurosci. 2021;48:149–71.
87. Daban C, Vieta E, Mackin P, Young AH. Hypothalamic-pituitary-adrenal axis and bipolar disorder. Psychiatr Clin North Am. 2005;28:469–80.
88. Diz-Chaves Y, Mastoor Z, Spuch C, González-Matías LC, Mallo F. Anti-inflammatory effects of GLP-1 receptor activation in the brain in neurodegenerative diseases. Int J Mol Sci. 2022;23:9583.
89. Gil-Lozano M, Pérez-Tilve D, Alvarez-Crespo M, Martís A, Fernandez AM, Catalina PAF, et al. GLP-1(7-36)-amide and Exendin-4 stimulate the HPA axis in rodents and humans. Endocrinology. 2010;151:2629–40.
90. Gil-Lozano M, Romaní-Pérez M, Outeiriño-Iglesias V, Vigo E, González-Matías LC, Brubaker PL, et al. Corticotropin-releasing hormone and the sympathoadrenal system are major mediators in the effects of peripherally administered Exendin-4 on the Hypothalamic-Pituitary-Adrenal axis of male rats. Endocrinology. 2014;155:2511–23.
91. Winzeler B, Da Conceição I, Refardt J, Sailer CO, Dutilh G, Christ-Crain M. Effects of Glucagon-like peptide-1 receptor agonists on Hypothalamic-Pituitary-Adrenal axis in healthy volunteers. J Clin Endocrinol Metab. 2019;104:202–8.
92. Charles EF, Lambert CG, Kerner B. Bipolar disorder and diabetes mellitus: evidence for disease-modifying effects and treatment implications. Int J Bipolar Disord. 2016;4:13.
93. Steardo L, Fabrazzo M, Sampogna G, Monteleone AM, D'Agostino G, Monteleone P, et al. Impaired glucose metabolism in bipolar patients and response to mood stabilizer treatments. J Affect Disord. 2019;245:174–9.
94. Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. Neuropsychopharmacology. 2014;39:2910–8.

95. Mansur RB, Delgado-Peraza F, Subramaniapillai M, Lee Y, Iacobucci M, Nasri F, et al. Exploring brain insulin resistance in adults with bipolar depression using extracellular vesicles of neuronal origin. J Psychiatr Res. 2021;133:82–92.
96. Van Der Heide LP, Kamal A, Artola A, Gispen WH, Ramakers GMJ. Insulin modulates hippocampal activity-dependent synaptic plasticity in a N-methyl-D-aspartate receptor and phosphatidyl-inositol-3-kinase-dependent manner. J Neurochem. 2005;94:1158–66.
97. Shah S, Iqbal M, Karam J, Salifu M, McFarlane SI. Oxidative stress, glucose metabolism, and the prevention of type 2 diabetes: pathophysiological insights. Antioxid Redox Signal. 2007;9:911–29.
98. Rask-Madsen C, King GL. Mechanisms of disease: endothelial dysfunction in insulin resistance and diabetes. Nat Clin Pract Endocrinol Metab. 2007;3:46–56.
99. Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. J Clin Invest. 2012;122:1339–53.
100. Long-Smith CM, Manning S, McClean PL, Coakley MF, O'Halloran DJ, Holscher C, et al. The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-β plaque and glial pathology in a mouse model of alzheimer's disease. Neuromolecular Med. 2013;15:102–14.
101. Talbot K, Wang HY. The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer's disease. Alzheimer's & Dementia. 2014;10:S12–S25.
102. Daniele G, Iozzo P, Molina-Carrion M, Lancaster J, Ciociaro D, Cersosimo E, et al. Exenatide regulates cerebral glucose metabolism in brain areas associated with glucose homeostasis and reward system. Diabetes. 2015;64:3406–12.
103. Vieta E, Valentí M. Pharmacological management of bipolar depression: acute treatment, maintenance, and prophylaxis. CNS Drugs. 2013;27:515–29.
104. De Giorgi R, Ghenciulescu A, Dziwisz O, Taquet M, Adler AI, Koychev I, et al. An analysis on the role of glucagon-like peptide-1 receptor agonists in cognitive and mental health disorders. Nat Mental Health. 2025;2025:1–20.
105. Turan I, Sayan Ozacmak H, Ozacmak VH, Ergenc M, Bayraktaroğlu T. The effects of glucagon-like peptide 1 receptor agonist (exenatide) on memory impairment, and anxiety- and depression-like behavior induced by REM sleep deprivation. Brain Res Bull. 2021;174:194–202.
106. Krass M, Volke A, Rünkorg K, Wegener G, Lund S, Abildgaard A, et al. GLP-1 receptor agonists have a sustained stimulatory effect on corticosterone release after chronic treatment. Acta Neuropsychiatr. 2014;27:25–32.
107. Weina H, Yuhu N, Christian H, Birong L, Feiyu S, Le W. Liraglutide attenuates the depressive- and anxiety-like behaviour in the corticosterone induced depression model via improving hippocampal neural plasticity. Brain Res. 2018;1694:55–62.
108. Bertelli PR, Mocelin R, Marcon M, Sachett A, Gomez R, Rosa AR, et al. Anti-stress effects of the glucagon-like peptide-1 receptor agonist liraglutide in zebrafish. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111:110388.
109. Anderberg RH, Richard JE, Hansson C, Nissbrandt H, Bergquist F, Skibicka KP. GLP-1 is both anxiogenic and antidepressant; divergent effects of acute and chronic GLP-1 on emotionality. Psychoneuroendocrinology. 2016;65:54–66.
110. Seo MK, Jeong S, Seog DH, Lee JA, Lee JH, Lee Y, et al. Effects of liraglutide on depressive behavior in a mouse depression model and cognition in the probe trial of Morris water maze test. J Affect Disord. 2023;324:8–15.
111. Sağlam C, Turan İ, Özaçmak HS. The effect of glucagon like peptide-1 receptor agonist on behavioral despair and anxiety-like behavior in ovariectomized rats: modulation of BDNF/CREB, Nrf2 and lipocalin 2. Behav Brain Res. 2022;435:114053.
112. Darwish AB, El Sayed NS, Salama AAA, Saad MA. Dulaglutide impedes depressive-like behavior persuaded by chronic social defeat stress model in male C57BL/6 mice: Implications on GLP-1R and cAMP/PKA signaling pathway in the hippocampus. Life Sci. 2023;320:121546.
113. Ren G, Xue P, Wu B, Yang F, Wu X. Intranasal treatment of lixisenatide attenuated emotional and olfactory symptoms via CREB-mediated adult neurogenesis in mouse depression model. Aging. 2021;13:3896–908.
114. Aygun H. Exendin-4 increases absence-like seizures and anxiety–depression-like behaviors in WAG/Rij rats. Epilepsy Behav. 2021;123:108246.
115. de Souza AG, Chaves Filho AJM, Souza Oliveira JV, de Souza DAA, Lopes IS, de Carvalho MAJ, et al. Prevention of pentylenetetrazole-induced kindling and behavioral comorbidities in mice by levetiracetam combined with the GLP-1 agonist liraglutide: involvement of brain antioxidant and BDNF upregulating properties. Biomed Pharmacother. 2019;109:429–39.
116. Yang F, Wang X, Qi J, Zhang K, Jiang Y, Feng B, et al. Glucagon-like Peptide 1 receptor activation inhibits microglial pyroptosis via promoting mitophagy to alleviate depression-like behaviors in diabetic mice. Nutrients. 2022;15:38.
117. Mansur RB, Fries GR, Trevizol AP, Subramaniapillai M, Lovshin J, Lin K, et al. The effect of body mass index on glucagon-like peptide receptor gene expression in the post mortem brain from individuals with mood and psychotic disorders. Eur Neuropsychopharmacol. 2019;29:137–46.
118. Pozzi M, Mazhar F, Peeters GGAM, Vantaggiato C, Nobile M, Clementi E, et al. A systematic review of the antidepressant effects of glucagon-like peptide 1 (GLP-1) functional agonists: further link between metabolism and psychopathology: special Section on "Translational and Neuroscience Studies in Affective Disorders". J Affect Disord. 2019;257:774–8.
119. Bode BW, Testa MA, Magwire M, Hale PM, Hammer M, Blonde L, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:604–12.
120. De Wit HM, Vervoort GMM, Jansen HJ, De Grauw WJC, De Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). Diabetologia. 2014;57:1812–9.
121. O'Neil PM, Aroda VR, Astrup A, Kushner R, Lau DCW, Wadden TA, et al. Neuropsychiatric safety with liraglutide 3.0 mg for weight management: results from randomized controlled phase 2 and 3a trials. Diabetes Obes Metab. 2017;19:1529–36.
122. Kahal H, Kilpatrick E, Rigby A, Coady A, Atkin S. The effects of treatment with liraglutide on quality of life and depression in young obese women with PCOS and controls. Gynecol Endocrinol. 2019;35:142–5.
123. de Wit HM, Vervoort GM, Jansen HJ, de Galan BE, Tack CJ. Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial. J Intern Med. 2016;279:283–92.
124. Idris I, Abdulla H, Tilbrook S, Dean R, Ali N. Exenatide improves excessive daytime sleepiness and wakefulness in obese patients with type 2 diabetes without obstructive sleep apnoea. J Sleep Res. 2013;22:70–75.
125. Moulton CD, Pickup JC, Amiel SA, Winkley K, Ismail K. Investigating incretin-based therapies as a novel treatment for depression in type 2 diabetes: findings from the South London Diabetes (SOUL-D) Study. Prim Care Diabetes. 2016;10:156–9.
126. Tasci I, Naharci MI, Bozoglu E, Safer U, Aydogdu A, Yilmaz BF, et al. Cognitive and functional influences of vildagliptin, a DPP-4 Inhibitor, added to ongoing metformin therapy in elderly with type 2 diabetes. Endocr Metab Immune Disord Drug Targets. 2013;13:256–63.
127. Grant P, Lipscomb D, Quin J. Psychological and quality of life changes in patients using GLP-1 analogues. J Diabetes Complications. 2011;25:244–6.
128. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390:1664–75.
129. Miras AD, Pérez-Pevida B, Aldhwayan M, Kamocka A, McGlone ER, Al-Najim W, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7:549–59.
130. Best JH, Rubin RR, Peyrot M, Li Y, Yan P, Malloy J, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes Care. 2011;34:314–9.
131. Reaney M, Mathieu C, Östenson CG, Matthaei S, Krarup T, Kiljański J, et al. Patient-reported outcomes among patients using exenatide twice daily or insulin in clinical practice in six European countries: the CHOICE prospective observational study. Health Qual Life Outcomes. 2013;11:217.
132. Gonzalez JS, Bebu I, Krause-Steinrauf H, Hoogendoorn CJ, Crespo-Ramos G, Presley C, et al. Differential effects of type 2 diabetes treatment regimens on diabetes distress and depressive symptoms in the glycemia reduction approaches in diabetes: a Comparative Effectiveness Study (GRADE). Diabetes Care. 2024;47:610–9.
133. Battini V, Van Manen RP, Gringeri M, Mosini G, Guarnieri G, Bombelli A, et al. The potential antidepressant effect of antidiabetic agents: new insights from a pharmacovigilance study based on data from the reporting system databases FAERS and VigiBase. Front Pharmacol. 2023;14:1128387.
134. Tsai WH, Sung FC, Chiu LT, Shih YH, Tsai MC, Wu SI. Decreased risk of anxiety in diabetic patients receiving Glucagon-like peptide-1 receptor agonist: a Nationwide, Population-Based Cohort Study. Front Pharmacol. 2022;13:765446.
135. Moulton CD, Hopkins CWP, Ismail K, Stahl D. Repositioning of diabetes treatments for depressive symptoms: a systematic review and meta-analysis of clinical trials. Psychoneuroendocrinology. 2018;94:91–103.
136. Spoorthy MS, Chakrabarti S, Grover S. Comorbidity of bipolar and anxiety disorders: an overview of trends in research. World J Psychiatry. 2019;9:7.
137. Kinzig KP, D'Alessio DA, Herman JP, Sakai RR, Vahl TP, Figueredo HF, et al. CNS Glucagon-like Peptide-1 receptors mediate endocrine and anxiety responses to interoceptive and psychogenic stressors. J Neurosci. 2003;23:6163–70.

138. Maclusky NJ, Cook S, Scrocchi L, Shin J, Kim J, Vaccarino F, et al. Neuroendocrine function and response to stress in mice with complete disruption of Glucagon-like Peptide-1 receptor signaling. Endocrinology. 2000;141:752–62.
139. Grillon C, Levenson J, Pine DS. A single dose of the selective serotonin reuptake inhibitor citalopram exacerbates anxiety in humans: a Fear-Potentiated Startle Study. Neuropsychopharmacology. 2007;32:225–31.
140. Strawn JR, D'Alessio DA, Keck PE, Seeley RJ. Failure of glucagon-like peptide-1 to induce panic attacks or anxiety in patients with panic disorder. J Psychiatr Res. 2008;42:787–9.
141. Eren-Yazicioglu CY, Kara B, Sancak S, Uysal SP, Yazici D, Okuroglu N, et al. Effect of exenatide use on cognitive and affective functioning in obese patients with type 2 diabetes mellitus: exenatide use mediates depressive scores through increased perceived stress levels. J Clin Psychopharmacol. 2021;41:428–35.
142. Miller A, Joyce B, Bartelt K, Deckert J. Most GLP-1 medications correlated with a lower likelihood of anxiety and depression diagnoses. Epic Research. 2024 Feb 6 [cited 2025 Jan 24]. Available from: https://www.epicresearch.org/articles/most-glp-1-medications-correlated-with-a-lower-likelihood-of-anxiety-and-depression-diagnoses.
143. Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1677–81.
144. de Sousa RT, Zarate CA, Zanetti MV, Costa AC, Talib LL, Gattaz WF, et al. Oxidative stress in early stage Bipolar Disorder and the association with response to lithium. J Psychiatr Res. 2014;50:36–41.
145. Luca A, Calandra C, Luca M. Gsk3 signalling and redox status in bipolar disorder: evidence from lithium efficacy. Oxid Med Cell Longev. 2016;2016:3030547.
146. Niciu MJ, Ionescu DF, Mathews DC, Richards EM, Zarate CA. Second messenger/signal transduction pathways in major mood disorders: moving from membrane to mechanism of action, part II: bipolar disorder. CNS Spectr. 2013;18:242–51.
147. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. Pharmacol Ther. 2015;148:114–31.
148. Chaves Filho AJM, Cunha NL, de Souza AG, Soares MVR, Jucá PM, de Queiroz T, et al. The GLP-1 receptor agonist liraglutide reverses mania-like alterations and memory deficits induced by D-amphetamine and augments lithium effects in mice: relevance for bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99:109872.
149. Çiçekli MN, Tiryaki ES, Altun A, Günaydın C. GLP-1 agonist liraglutide improves ouabain-induced mania and depressive state via GSK-3β pathway. J Recept Signal Transduct. 2022;42:486–94.
150. Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. J Clin Psychiatry. 2008;69:1122–30.
151. Miskowiak KW, Carvalho AF, Vieta E, Kessing LV. Cognitive enhancement treatments for bipolar disorder: a systematic review and methodological recommendations. Eur Neuropsychopharmacol. 2016;26:1541–61.
152. Bora E, McIntyre RS, Ozerdem A. Neurococognitive and neuroimaging correlates of obesity and components of metabolic syndrome in bipolar disorder: a systematic review. Psychol Med. 2019;49:738–49.
153. During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med. 2003;9:1173–9.
154. Taati M, Barzegar PEF, Raisi A. Exercise improves spatial learning and memory performance through the Central GLP-1 receptors. Behav Neurol. 2022;2022:2900628.
155. Porter DW, Kerr BD, Flatt PR, Holscher C, Gault VA. Four weeks administration of Liraglutide improves memory and learning as well as glycaemic control in mice with high fat dietary-induced obesity and insulin resistance. Diabetes Obes Metab. 2010;12:891–9.
156. Iwai T, Suzuki M, Kobayashi K, Mori K, Mogi Y, Oka JI. The influences of juvenile diabetes on memory and hippocampal plasticity in rats: improving effects of glucagon-like peptide-1. Neurosci Res. 2009;64:67–74.
157. Lennox R, Flatt PR, Gault VA. Lixisenatide improves recognition memory and exerts neuroprotective actions in high-fat fed mice. Peptides (NY). 2014;61:38–47.
158. McIntyre RS, Powell AM, Kaidanovich-Beilin O, Soczynska JK, Alsuwaidan M, Woldeyohannes HO, et al. The neuroprotective effects of GLP-1: possible treatments for cognitive deficits in individuals with mood disorders. Behav Brain Res. 2013;237:164–71.
159. Erbil D, Eren CY, Demirel C, Küçüker MU, Solaroğlu I, Eser HY. GLP-1's role in neuroprotection: a systematic review. Brain Inj. 2019;33:734–819.
160. Reich N, Hölscher C. The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: an in-depth review. Front Neurosci. 2022;16:970925.
161. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol. 2020;19:758–66.
162. Luan S, Cheng W, Wang C, Gong J, Zhou J. Impact of glucagon-like peptide 1 analogs on cognitive function among patients with type 2 diabetes mellitus: a systematic review and meta−analysis. Front Endocrinol (Lausanne). 2022;13:1047883.
163. Nørgaard CH, Friedrich S, Hansen CT, Gerds T, Ballard C, Møller DV, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. Alzheimers Dement (N Y). 2022;8:e12268.
164. Tang H, Shao H, Shaaban CE, Yang K, Brown J, Anton S, et al. Newer glucose-lowering drugs and risk of dementia: a systematic review and meta-analysis of observational studies. J Am Geriatr Soc. 2023;71:2096–106.
165. Dei Cas A, Micheli MM, Aldigeri R, Gardini S, Ferrari-Pellegrini F, Perini M, et al. Long-acting exenatide does not prevent cognitive decline in mild cognitive impairment: a proof-of-concept clinical trial. J Endocrinol Invest. 2024;47:2339–49.
166. Ishøy PL, Fagerlund B, Broberg BV, Bak N, Knop FK, Glenthøj BY, et al. No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia. Acta Psychiatr Scand. 2017;136:52–62.
167. Mansur RB, Zugman A, Ahmed J, Cha DS, Subramaniapillai M, Lee Y, et al. Treatment with a GLP-1R agonist over four weeks promotes weight loss-moderated changes in frontal-striatal brain structures in individuals with mood disorders. Eur Neuropsychopharmacol. 2017;27:1153–62.
168. Edge MD, Johnson SL, Ng T, Carver CS. Iowa gambling task performance in euthymic bipolar i disorder: a meta-analysis and empirical study. J Affect Disord. 2013;150:115–22.
169. Adida M, Jollant F, Clark L, Besnier N, Guillaume S, Kaladjian A, et al. Trait-related decision-making impairment in the three phases of bipolar disorder. Biol Psychiatry. 2011;70:357–65.
170. Pouchon A, Vinckier F, Dondé C, Gueguen MC, Polosan M, Bastin J. Reward and punishment learning deficits among bipolar disorder subtypes. J Affect Disord. 2023;340:694–702.
171. Jiménez E, Solé B, Arias B, Mitjans M, Varo C, Reinares M, et al. Characterizing decision-making and reward processing in bipolar disorder: a cluster analysis. Eur Neuropsychopharmacol. 2018;28:863–74.
172. Badulescu S, Tabassum A, Le GH, Wong S, Phan L, Gill H, et al. Glucagon-like peptide 1 agonist and effects on reward behaviour: a systematic review. Physiol Behav. 2024;283:114622.
173. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab. 2017;19:1242–51.
174. Yammine L, Green CE, Kosten TR, de Dios C, Suchting R, Lane SD, et al. Exenatide adjunct to nicotine patch facilitates smoking cessation and may reduce post-cessation weight gain: a pilot randomized controlled trial. Nicotine Tob Res. 2021;23:1682–90.
175. Bae JH, Choi HJ, Cho KIK, Kim LK, Kwon JS, Cho YM. Glucagon-like Peptide-1 receptor agonist differentially affects brain activation in response to visual food cues in lean and obese individuals with type 2 diabetes mellitus. Diabetes Metab J. 2019;44:248–59.
176. Van Bloemendaal L, IJzerman RG, Ten Kulve JS, Barkhof F, Konrad RJ, Drent ML, et al. GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. Diabetes. 2014;63:4186–96.
177. Hanssen R, Rigoux L, Kuzmanovic B, Iglesias S, Kretschmer AC, Schlamann M, et al. Liraglutide restores impaired associative learning in individuals with obesity. Nat Metab. 2023;5:1352–63.
178. Gold AK, Otto MW, Deckersbach T, Sylvia LG, Nierenberg AA, Kinrys G. Substance use comorbidity in bipolar disorder: a qualitative review of treatment strategies and outcomes. Am J Addict. 2018;27:188–201.
179. Lalli M, Brouillette K, Kapczinski F, de Azevedo Cardoso T. Substance use as a risk factor for bipolar disorder: a systematic review. J Psychiatr Res. 2021;144:285–95.
180. Albanese MJ, Pies R. The bipolar patient with comorbid substance use disorder: recognition and management. CNS Drugs. 2004;18:585–96.
181. Richardson T, Garavan H. Relationships between substance use and hypomanic symptoms in a non-clinical sample. Ment Health Subst Use. 2011;4:211–21.
182. González-Pinto A, Goikolea JM, Zorrilla I, Bernardo M, Arrojo M, Cunill R, et al. Clinical practice guideline on pharmacological and psychological management of adult patients with bipolar disorder and comorbid substance use. Adicciones. 2022;34:142–56.
183. Volkow ND. Personalizing the treatment of substance use disorders. Am J Psychiatry. 2020;177:113–6. https://doi.org/10.1176/AppiAjp201919121284

184. Facal F, Costas J. Genomic evidence of GLP-1 receptor as target for the treatment of substance use disorders. Eur Neuropsychopharmacol. 2025;92:48–49.
185. Zheng YJ, Soegiharto C, Au HCT, Valentino K, Le GH, Wong S, et al. A systematic review on the role of glucagon-like peptide-1 receptor agonists on alcohol-related behaviors: potential therapeutic strategy for alcohol use disorder. Acta Neuropsychiatr. 2025;37:e51.
186. Kruse Klausen M, Thomsen M, Wortwein G, Fink-Jensen A. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. Br J Pharmacol. 2022;179:625–41.
187. Merkel R, Hernandez NS, Weir V, Zhang Y, Caffrey A, Rich MT, et al. An endogenous GLP-1 circuit engages VTA GABA neurons to regulate mesolimbic dopamine neurons and attenuate cocaine seeking. Sci Adv. 2025;11:eadr5051.
188. Tuesta LM, Chen Z, Duncan A, Fowler CD, Ishikawa M, Lee BR, et al. GLP-1 acts on habenular avoidance circuits to control nicotine intake. Nat Neurosci. 2017;20:708–16.
189. Aranäs C, Edvardsson CE, Shevchouk OT, Zhang Q, Witley S, Blid Sköldheden S, et al. Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. EBioMedicine. 2023;93:104642.
190. Thomsen M, Holst JJ, Molander A, Linnet K, Ptito M, Fink-Jensen A. Effects of glucagon-like peptide 1 analogs on alcohol intake in alcohol-preferring vervet monkeys. Psychopharmacology (Berl). 2019;236:603–11.
191. Sirohi S, Schurdak JD, Seeley RJ, Benoit SC, Davis JF. Central & peripheral glucagon-like peptide-1 receptor signaling differentially regulate addictive behaviors. Physiol Behav. 2016;161:140–4.
192. Volkow ND, Xu R. GLP-1R agonist medications for addiction treatment. Addiction. 2025;120:198–200.
193. Butelman ER, Goldstein RZ, Nwaneshiudu CA, Girdhar K, Roussos P, Russo SJ, et al. Neuroimmune mechanisms of opioid use disorder and recovery: translatability to human studies, and future research directions. Neuroscience. 2023;528:102–16.
194. Martinelli S, Mazzotta A, Longaroni M, Petrucciani N. Potential role of glucagon-like peptide-1 (GLP-1) receptor agonists in substance use disorder: a systematic review of randomized trials. Drug Alcohol Depend. 2024;264:112424.
195. Probst L, Monnerat S, Vogt DR, Lengsfeld S, Burkard T, Meienberg A, et al. Effects of dulaglutide on alcohol consumption during smoking cessation. JCI Insight. 2023;8:e170419.
196. Klausen MK, Jensen ME, Møller M, Le Dous N, Jensen AMØ, Zeeman VA, et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. JCI Insight. 2022;7:e159863.
197. Angarita GA, Matuskey D, Pittman B, Costeines JL, Potenza MN, Jastreboff AM, et al. Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. Drug Alcohol Depend. 2021;221:108614.
198. Lengsfeld S, Burkard T, Meienberg A, Jeanloz N, Vukajlovic T, Bologna K, et al. Effect of dulaglutide in promoting abstinence during smoking cessation: a single-centre, randomized, double-blind, placebo-controlled, parallel group trial. EClinicalMedicine. 2023;57:101865.
199. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. Nat Commun. 2024;15:5177.
200. Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing semaglutide and liraglutide for alcohol use disorder. JAMA Psychiatry. 2025;82:94–98.
201. 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;29:2587–98.
202. Sletved KSO, Ziersen SC, Andersen PK, Vinberg M, Kessing LV. Socio-economic functioning in patients with bipolar disorder and their unaffected siblings – results from a nation-wide population-based longitudinal study. Psychol Med. 2023;53:706–13.
203. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat. 2017;13:2231.
204. Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatr. 2003;160:112–7.
205. Leutner M, Dervic E, Bellach L, Klimek P, Thurner S, Kautzky A. Obesity as pleiotropic risk state for metabolic and mental health throughout life. Transl Psychiatry. 2023;13:175.
206. Menon T, Lee S, Gong XY, Wong S, Le GH, Kwan ATH, et al. A systematic review on the efficacy of GLP-1 receptor agonists in mitigating psychotropic drug-related weight gain. CNS Spectr. 2024. 2024. https://doi.org/10.1017/S1092852924000531.
207. Whicher CA, Price HC, Phiri P, Rathod S, Barnard-Kelly K, Ngianga K, et al. The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: results of a pilot randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2021;23:1262–71.
208. Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Svensson CK, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in Clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial. JAMA Psychiatr. 2017;74:719–28.
209. Siskind DJ, Russell AW, Gamble C, Winckel K, Mayfield K, Hollingworth S, et al. Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: a randomized controlled trial (CODEX). Diabetes Obes Metab. 2018;20:1050–5.
210. Ishøy PL, Knop FK, Broberg BV, Bak N, Andersen UB, Jørgensen NR, et al. Effect of GLP-1 receptor agonist treatment on body weight in obese antipsychotic-treated patients with schizophrenia: a randomized, placebo-controlled trial. Diabetes Obes Metab. 2017;19:162–71.
211. Shetty R, Basheer FT, Poojari PG, Thunga G, Chandran VP, Acharya LD. Adverse drug reactions of GLP-1 agonists: a systematic review of case reports. Diabetes Metab Syndr. 2022;16:102427.
212. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse effects of GLP-1 receptor agonists. Rev Diabet Stud. 2015;11:202.
213. Silverii GA, Marinelli C, Mannucci E, Rotella F. Glucagon-like peptide-1 receptor agonists and mental health: a meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2024;26:2505–8.
214. Nakhla M, Nair A, Balani P, Ujjawal A, Arun Kumar P, Dasari M, et al. Risk of suicide, hair loss, and aspiration with GLP1-receptor agonists and other diabetic agents: a Real-World Pharmacovigilance Study. Cardiovasc Drugs Ther. 2024. 2024. https://doi.org/10.1007/S10557-024-07613-W.
215. Ueda P, Söderling J, Wintzell V, Svanström H, Pazzagli L, Eliasson B, et al. GLP-1 receptor agonist use and risk of suicide death. JAMA Intern Med. 2024;184:1301–12.
216. Hurtado I, Robles C, Peiró S, García-Sempere A, Sanfélix-Gimeno G. Association of glucagon-like peptide-1 receptor agonists with suicidal ideation and self-injury in individuals with diabetes and obesity: a propensity-weighted, population-based cohort study. Diabetologia. 2024;67:2471–80.
217. Tang H, Lu Y, Donahoo WT, Shao H, Shi L, Fonseca VA, et al. Glucagon-like Peptide-1 receptor agonists and risk for suicidal ideation and behaviors in U.S. Older adults with type 2 diabetes: a Target Trial Emulation Study. Ann Intern Med. 2024;177:1004–15.
218. Gamble JM, Chibrikov E, Midodzi WK, Twells LK, Majumdar SR. Examining the risk of depression or self-harm associated with incretin-based therapies used to manage hyperglycaemia in patients with type 2 diabetes: a Cohort Study using the UK Clinical Practice Research Datalink. BMJ Open. 2018;8:e023830.
219. Chen C, Zhou R, Fu F, Xiao J. Postmarket safety profile of suicide/self-injury for GLP-1 receptor agonist: a real-world pharmacovigilance analysis. Eur Psychiatry. 2023;66:e99.
220. De Giorgi R, Koychev I, Adler AI, Cowen PJ, Harmer CJ, Harrison PJ, et al. 12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched Cohort study. EClinicalMedicine. 2024;74:102726.
221. European Medicines Agency. Association between exposure to GLP-1 receptor agonists and risk of suicide-related and self-harm-related events. HMA-EMA Catalogues of real-world data sources and studies. 2023 [cited 2025 Jan 24]. Available from:https://catalogues.ema.europa.eu/node/3953/methodological-aspects
222. Kornelius E, Huang JY, Lo SC, Huang CN, Yang YS. The risk of depression, anxiety, and suicidal behavior in patients with obesity on glucagon like peptide-1 receptor agonist therapy. Sci Rep. 2024;14:24433.
223. Ruggiero R, Mascolo A, Spezzaferri A, Carpentieri C, Torella D, Sportiello L, et al. Glucagon-like Peptide-1 receptor agonists and suicidal ideation: analysis of real-word data collected in the European pharmacovigilance database. Pharmaceuticals. 2024;17:147.
224. Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R. Association of semaglutide with risk of suicidal ideation in a real-world cohort. Nat Med. 2024;30:168–76.
225. Kerem L, Stokar J. Risk of suicidal ideation or attempts in adolescents with obesity treated with GLP1 receptor agonists. JAMA Pediatr. 2024;178:1307–15.
226. Nassar M, Misra A, Bloomgarden Z. Impact of treatment with GLP-1RAs on suicide attempts in adults persons with type 2 diabetes: a retrospective comparative effectiveness study based on a global TriNetX health research database. J Diabetes. 2024;16:e13547.
227. European Medicines Agency. EMA statement on ongoing review of GLP-1 receptor agonists. European Medicines Agency. 2023 Jul 11 [cited 2025 Jan 19]. Available from: https://www.ema.europa.eu/en/news/ema-statement-ongoing-review-glp-1-receptor-agonists
228. Fick M. Exclusive: UK probes Novo's Ozempic, weight-loss drug Saxenda over suicidal, self-harming thoughts. Reuters. 2023 Jul 26 [cited 2025 Jan 19].

Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/uk-probing-novos-ozempic-weight-loss-drug-saxenda-over-suicidal-self-harming-2023-07-26/
229. McIntyre RS, Mansur RB, Rosenblat JD, Kwan ATH. 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). Expert Opin Drug Saf. 2024;23:47–55.
230. Wang F, Wang S, Zong QQ, Zhang Q, Ng CH, Ungvari GS, et al. Prevalence of comorbid major depressive disorder in Type 2 diabetes: a meta-analysis of comparative and epidemiological studies. Diabet Med. 2019;36:961–9.
231. Blasco BV, García-Jiménez J, Bodoano I, Gutiérrez-Rojas L. Obesity and depression: its prevalence and influence as a prognostic factor: a systematic review. Psychiatry Investig. 2020;17:715.
232. Valentino K, Teopiz KM, Cheung W, Wong S, Le GH, Rosenblat JD, et al. The effect of glucagon-like Peptide-1 receptor agonists on measures of suicidality: a systematic review. J Psychiatr Res. 2025;183:112–26.
233. McIntyre RS. Glucagon-Like Peptide-1 Receptor Agonists and Suicidality: Association Versus Causation and the Need for Ongoing Surveillance. Am J Psychiatry. 2025:appiajp20241087. https://doi.org/10.1176/appi.ajp.20241087.
234. Zhou J, Zheng Y, Xu B, Long S, Zhu LE, Liu Y, et al. Exploration of the potential association between GLP-1 receptor agonists and suicidal or self-injurious behaviors: a pharmacovigilance study based on the FDA Adverse Event Reporting System database. BMC Med. 2024;22:65.
235. Schoretsanitis G, Weiler S, Barbui C, Raschi E, Gastaldon C. Disproportionality analysis from world health organization data on semaglutide, liraglutide, and suicidality. JAMA Netw Open. 2024;7:e2423385–e2423385.
236. McIntyre RS, Mansur RB, Rosenblat JD, Rhee TG, Cao B, Teopiz KM, et al. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and suicidality: a replication study using reports to the World Health Organization pharmacovigilance database (VigiBase®). J Affect Disord. 2025;369:922–7.
237. Hunger JM, Major B, Blodorn A, Miller CT. Weighed down by stigma: how weight-based social identity threat contributes to weight gain and poor health. Soc Personal Psychol Compass. 2015;9:255–68.
238. McGrath KH, Haller W, Bines JE. Starvation and fasting: biochemical aspects. Encyclopedia of Human Nutrition. 2023;1–4:645–56. Fourth Edition1–4
239. Montoya A, Bruins R, Katzman MA, Blier P. The noradrenergic paradox: implications in the management of depression and anxiety. Neuropsychiatr Dis Treat. 2016;12:541–57.
240. O'Connor DB, Ferguson E, Green JA, O'Carroll RE, O'Connor RC. Cortisol levels and suicidal behavior: a meta-analysis. Psychoneuroendocrinology. 2016;63:370–9.
241. Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA. Self-harm emergencies after bariatric surgery: a Population-Based Cohort Study. JAMA Surg. 2016;151:226–32.
242. Østergaard SD, Hieronymus F. Psilocybin for treatment-resistant depression. New Eng J Med. 2023;388:e22.
243. Giurgiuca A, Nemes B, Schipor S, Caragheorgheopol A, Boscaiu V, Cozman D, et al. Cortisol levels and suicide in bipolar I disorder. Acta Endocrinologica (Bucharest). 2017;13:188.
244. Plans L, Barrot C, Nieto E, Rios J, Schulze TG, Papiol S, et al. Association between completed suicide and bipolar disorder: a systematic review of the literature. J Affect Disord. 2019;242:111–22.
245. Valvassori SS, Dal-Pont GC, Varela RB, Resende WR, Gava FF, Mina FG, et al. Ouabain induces memory impairment and alter the BDNF signaling pathway in an animal model of bipolar disorder: cognitive and neurochemical alterations in BD model. J Affect Disord. 2021;282:1195–202.
246. Cooper DH, Ramachandra R, Ceban F, Di Vincenzo JD, Rhee TG, Mansur RB, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists as a protective factor for incident depression in patients with diabetes mellitus: a systematic review. J Psychiatr Res. 2023;164:80–89.
247. Jalleh RJ, Plummer MP, Marathe CS, Umapathysivam MM, Quast DR, Rayner CK, et al. Clinical consequences of delayed gastric emptying with GLP-1 receptor agonists and tirzepatide. J Clin Endocrinol Metab. 2024;110:1–15.
248. Vieta E. Neuroprogression happens. Psychol Med. 2024;54:3760.
249. Yatham LN, Schaffer A, Kessing LV, Miskowiak K, Kapczinski F, Vieta E, et al. Early intervention, relapse prevention, and neuroprogression in bipolar disorder: the evidence matters. Bipolar Disord. 2024;26:313–6.
250. Passos IC, Mwangi B, Vieta E, Berk M, Kapczinski F. Areas of controversy in neuroprogression in bipolar disorder. Acta Psychiatr Scand. 2016;134:91–103.
251. Grewal S, McKinlay S, Kapczinski F, Pfaffenseller B, Wollenhaupt-Aguiar B. Biomarkers of neuroprogression and late staging in bipolar disorder: a systematic review. Aust N Z J Psychiatr. 2023;57:328–43.
252. Wollenhaupt-Aguiar B, Kapczinski F, Pfaffenseller B. Biological pathways associated with neuroprogression in bipolar disorder. Brain Sci. 2021;11:228.
253. Rodriguez PJ, Zhang V, Gratzl S, Do D, Cartwright BG, Baker C, et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. JAMA Netw Open. 2025;8:e2457349–e2457349.
254. Polonsky W, Gamble C, Iyer N, Martin M, Hamersky C. Exploring why people with type 2 diabetes do or do not persist with Glucagon-like Peptide-1 receptor agonist therapy: a Qualitative Study. Diabetes Spectr. 2021;34:175–83.
255. Waldrop SW, Johnson VR, Stanford FC. Inequalities in the provision of GLP-1 receptor agonists for the treatment of obesity. Nat Med. 2024;30:22.
256. Razavi MS, Fathi M, Vahednia E, Ardani AR, Honari S, Akbarzadeh F, et al. Cognitive rehabilitation in bipolar spectrum disorder: a systematic review. IBRO Neurosci Rep. 2024;16:509–17.
257. Vieta E, Torrent C. Functional remediation: the pathway from remission to recovery in bipolar disorder. World Psychiatry. 2016;15:288.
258. Nomoto H, Oba-Yamamoto C, Takahashi Y, Takeuchi J, Nagai S, Yokoyama H, et al. Effects of switching from liraglutide or dulaglutide to subcutaneous semaglutide on glucose metabolism and treatment satisfaction in patients with type 2 diabetes: protocol for a Multicenter, Prospective, Randomized, Open-Label, Blinded-Endpoint, Parallel-Group Comparison Study (The SWITCH-SEMA 1 Study). Diabetes Ther. 2021;12:955–64.
259. Guglielmi G. The weight-loss drugs being tested in 2025: will they beat ozempic? Nature. 2025;638:591–2.

ACKNOWLEDGEMENTS

Cristian-Daniel Llach received the support of a fellowship from "la Caixa" Foundation (ID 100010434 - fellowship code LCF/BQ/EU22/11930062).

AUTHOR CONTRIBUTIONS

CDLL: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. SB: Writing – review & editing. AT: Writing – review & editing. HS: Writing – review & editing. HG: Writing – review & editing. GHL: Writing – review & editing. EV: Writing – review & editing. RSM: Writing – review & editing. JDR: Writing – review & editing, Supervision. RBM: Writing – review & editing, Supervision.

COMPETING INTERESTS

Cristian-Daniel Llach received financial support from the 'La Caixa' Foundation, which provided salary support during the fellowship through its fellowship programs. However, the foundation was not involved in any stage of this manuscript, including its design, writing, revision, or submission. There are no conflicts of interest between the author's research and the 'La Caixa' Foundation. C.L. has also received CME-related honoraria or consulting fees from CASEN Recordati, Organon, Lundbeck, and the Academy for Continuing Medical Education (Akademijazakme), with no financial or other conflicts of interest relevant to the subject of this article. Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, AbbVie, Adamed, Alcediag, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Casen-Recordati, Celon Pharma, Clariane, Compass, Dainippon Sumitomo Pharma, Esteve, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Intra-Cellular therapies, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, Mitsubishi Tanabe Pharma, Newraxpharm, Newron, Novartis, Organon, Orion Corporation, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work. Dr. Roger S. McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie and Atai Life Sciences. Dr. Joshua D Rosenblat has received research grant support from the Canadian Institute of Health Research (CIHR), Physician Services Inc (PSI) Foundation, Labatt Brain Health Network, Brain and Cognition Discovery Foundation (BCDF), Canadian Cancer Society, Canadian Psychiatric Association, Academic Scholars Award, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network Centre for Mental Health, Joseph M. West Family Memorial Fund, Inagene and Timeposters Fellowship and industry funding for speaker/consultation/research fees from iGan, Boehringer Ingelheim, Abbvie, Braxia Health (Canadian Rapid Treatment Centre of Excellence), Braxia Scientific, Janssen, Allergan, Lundbeck, Sunovion and COMPASS.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Cristian-Daniel Llach.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.