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

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

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

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), currently used for metabolic conditions, have demonstrated potential antidepressant effects via neuromodulatory pathways. This systematic review aims to provide evidence on the antidepressant effects of GLP-1 RAs and elucidate their underlying mechanism of action.

Methods: We examined studies that investigated the effect of GLP-1 RAs on depressive symptoms. A comprehensive search was performed, and articles were retrieved from MEDLINE, PubMed, and PsychINFO. Both animal and human studies were included.

Results: 18 preclinical studies, 5 observational studies, and 3 clinical studies were included in our systematic review. Among the preclinical studies, 15 out of 18 (83 %) reported significant antidepressant-like effects, associated with enhanced neuroplasticity, reduced neuroinflammation, and neurotransmitter alterations. Observational studies indicated mixed results, with 4 out of 5 studies reporting reductions in depressive symptoms. However, only 1 of the 3 clinical trials showed statistically significant antidepressant effects.

Discussion: GLP-1 RAs show promise as treatment for depression through multiple neuromodulatory mechanisms. While there is strong preclinical evidence, observational results are mixed, and clinical findings are still preliminary. There is a need for short and long-term studies to establish whether GLP-1 RAs are capable of treating and/or preventing depressive symptoms and episodes in adults with major depressive disorder (MDD).

1. Introduction

Mood disorders are significant public health concerns, with Major Depressive Disorder (MDD) ranking 13th in disability-adjusted life years (DALYs) globally. (Maj et al., 2020; Santomauro et al., 2021). Current first-line treatments consist of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and psychotherapy (McIntyre et al., 2023). However, many individuals are unable to achieve adequate symptom relief with these interventions (McIntyre et al., 2023). A significant proportion (30%) of patients continue to experience ongoing persistent depressive symptoms despite multiple first-line treatment attempts, a condition known as treatment-resistant depression (TRD) (McIntyre et al., 2023). Taken together, the aforementioned findings indicate that there is a need for new treatments and preventative strategies for depression.

Emerging evidence demonstrates a connection between psychiatric and metabolic disorders; namely, that there exists a link between depression and diabetes (Fanelli et al., 2025). These two conditions often co-occur and share overlapping risk factors such as genetics, psychosocial history, and lifestyle (Fanelli et al., 2025). Many studies have also reported a bidirectional relationship between depression and diabetes (Zheng et al., 2024). Individuals with diabetes have a 2–3 times increased risk of being diagnosed with depression compared to the general population, while individuals with depression have a 60% increased risk of developing type 2 diabetes mellitus (T2DM) (Bădescu et al., 2016; Zheng et al., 2024). Thus, given this bidirectional

* Corresponding author.
E-mail addresses: angela.kwan@alumni.utoronto.ca (A.T.H. Kwan), roger.mcintyre@bcdf.org (R.S. McIntyre).
[1] Both authors contributed equally to this work

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association, new therapeutic treatments capable of targeting both conditions could hold substantial therapeutic promise.

GLP-1RAs, initially developed for the treatment of T2DM and obesity, have since demonstrated effects beyond glycemic control, including actions in central nervous system (CNS) regions relevant to depression (e.g., hippocampus, amygdala, and prefrontal cortex). In these brain regions, GLP-1 RAs modulate neuroinflammation, neuroplasticity, and neurotransmitter signaling that is often disrupted in MDD (Athauda and Foltynie, 2016; Au et al., 2025; Fu et al., 2020; McIntyre et al., 2025b; West et al., 2025). In animal models, GLP-1 RAs reduce microglial activation and central proinflammatory cytokines, which mitigates neuroinflammation associated with depressive behavior (Yang et al., 2022). Liraglutide and exenatide have also been shown to increase hippocampal neurogenesis and synaptic plasticity while upregulating BDNF expression (Salcedo et al., 2012; Vieta and Oliva, 2025). Additionally, GLP-1 RA signaling has been found to influence key neurotransmitters such as serotonin and dopamine in brain regions relating to emotion and motivation, thus contributing to antidepressant-like behavioral effects (Anderberg et al., 2016a).

Emerging data report modest but significant reductions in depressive symptoms with GLP-1 RA treatment, particularly in patients with T2DM or obesity (Chen et al., 2024; Pozzi et al., 2019). Together, these findings suggest that GLP-1 RAs may share overlapping mechanisms with conventional antidepressants and offer therapeutic benefits by directly targeting neurobiological dysfunction in MDD. Additionally, alterations in gut microbiota have been shown to influence an antidepressant response through inflammatory and metabolic pathways, which highlights the relevance of gut-brain axis mechanisms in mood regulation. Given their action in the gastrointestinal tract, GLP-1 RAs may engage similar pathways to exert potential antidepressant effects (Borgiani et al., 2025). These findings indicate that GLP-1 receptors have the potential for neuromodulation through several mechanisms.

Several recent reviews have addressed the potential psychiatric applications of GLP-1 RAs. For example, De Giorgi et al. (2025) and Detka et al. (2021) discussed the potential antidepressant effects of GLP-1 RAs, with an emphasis on their mechanism of action, including neuroprotection, inflammation, and gut-brain crosstalk (De Giorgi et al., 2025; Detka and Głombik, 2021). A meta-analysis by Chen et al. (2024), which included participants from five randomized controlled trials and one cohort study, found a small but statistically significant reduction in depression scores in GLP-1 RA treated patients compared to controls (Chen et al., 2024). Similarly, Pozzi et al. (2019), in a meta-analysis of eight studies, reported significant reductions in depression rating scores with GLP-1 RAs, with strong effects observed in diabetic populations that did not exclude depressed patients (Pozzi et al., 2019). However, neither meta-analysis integrated mechanistic or preclinical evidence, which are valuable in elucidating GLP-1 RAs anti-depressant effects through modulations in neuroinflammation, metabolism, and central nervous system pathways. Currently, much of the evidence supporting GLP-1 RAs comes from preclinical research or studies involving populations with metabolic disorders. These findings may help inform future clinical trials, but more research is needed before a consensus can be made about the role of GLP-1 RAs in psychiatry (Vieta and Oliva, 2025).

Our review aims to clarify the role of GLP-1 RAs in psychiatry by synthesizing preclinical, observational, and clinical data with an explicit focus on depressive symptomatology and potential antidepressant mechanisms. This integrative approach allows us to identify what is already known, highlight gaps in the literature, and provide guidance for future studies aimed at demonstrating the therapeutic potential of GLP-1 RAs in depression. To our knowledge, this is the first review that synthesizes preclinical, observational, and clinical data regarding the anti-depressant potential of GLP-1RAs.

2. Methods

2.1. Data sources and searches

In accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines ("PRISMA 2020 checklist," n.d.), a systematic search was conducted on Medline, Pubmed and PsychINFO from database inception to March 12, 2025. A comprehensive search strategy was implemented using terms related to GLP-1 RAs and depressive disorders. The full search string is available in *Supplementary Note 1*. An additional search was completed for clinical trials in progress with GLP-1 and depression. No language or publication date restrictions were imposed. This review was not prospectively registered on PROSPERO or any other public registry. The study was initiated as an exploratory systematic review and evolved in scope during the review process. We acknowledge the lack of preregistration as a methodological limitation.

2.2. Study selection

Title and abstracts were independently screened by two authors (S.G.S and S.L) with conflicts resolved through discussion using the Covidence reference software. ("Covidence systematic review software.," n.d.) The following inclusion and exclusion criteria were applied to title and abstract screening, as presented in Table 1. One inclusion criterion was "participants with a formal diagnosis of depression at baseline," defined according to DSM/ICD criteria or self-report as specified in the original studies. Studies assessing depressive symptoms as either a primary or secondary outcome were eligible for inclusion. Our search strategy was designed to be intentionally broad to capture both preclinical and clinical studies across a range of populations and methodologies. We excluded studies using GLP-1 receptor antagonists because the aim of the review was to examine the therapeutic potential of GLP-1 RAs in depression. While antagonist studies may offer mechanistic insights, their inclusion would extend beyond the scope of evaluating clinically relevant interventions. To avoid duplicate findings, review articles and meta-analyses were excluded. A list of full-text excluded studies along with specific reasons for exclusion is provided in Supplementary Table 1.

2.3. Data extraction

Data extraction was performed by both S.G.S and S.L. Any conflicts were resolved through discussion. The studies were categorized as preclinical, observational, and clinical. Data extraction categories for

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Studies investigating the use of pharmacologically administered GLP-1 receptor agonists as the primary intervention (e.g., liraglutide, exenatide, semaglutide)	• Case reports, reviews or non-peer reviewed studies
• Human trials, animal models, or cell-based studies	• Studies investigating endogenous GLP-1, GLP-2, or GLP-1 antagonists
• Participants with depression at baseline (with or without healthy controls) according to the DSM/ICD criteria or self-report.	• Participants with comorbid psychiatric disorders (e.g., schizophrenia, bipolar disorder) or neurological conditions (e.g., epilepsy, Parkinson's disease, dementia)
• Depression outcomes measured	• Focused solely on endogenously produced GLP-1.
• Experimental animal models should include a model of depression or a model of diabetes with depression outcome measured.	

preclinical, observational or clinical models included key design features, treatment parameters, behavioural outcomes, and mechanistic findings. Full lists of extracted variables are presented in *Supplementary Note 2*. Risk of bias was assessed using standardized tools appropriate for each study type: the SYRCLE RoB tool for preclinical studies, the Newcastle-Ottawa Scale for observational studies, and the Cochrane RoB 2.0 tool for clinical trials (Hooijmans et al., 2014; Ottawa Hospital Research Institute, n.d.; RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias, n.d.). Each domain was independently evaluated, and studies were categorized as low, unclear, or high risk of bias based on predefined criteria.

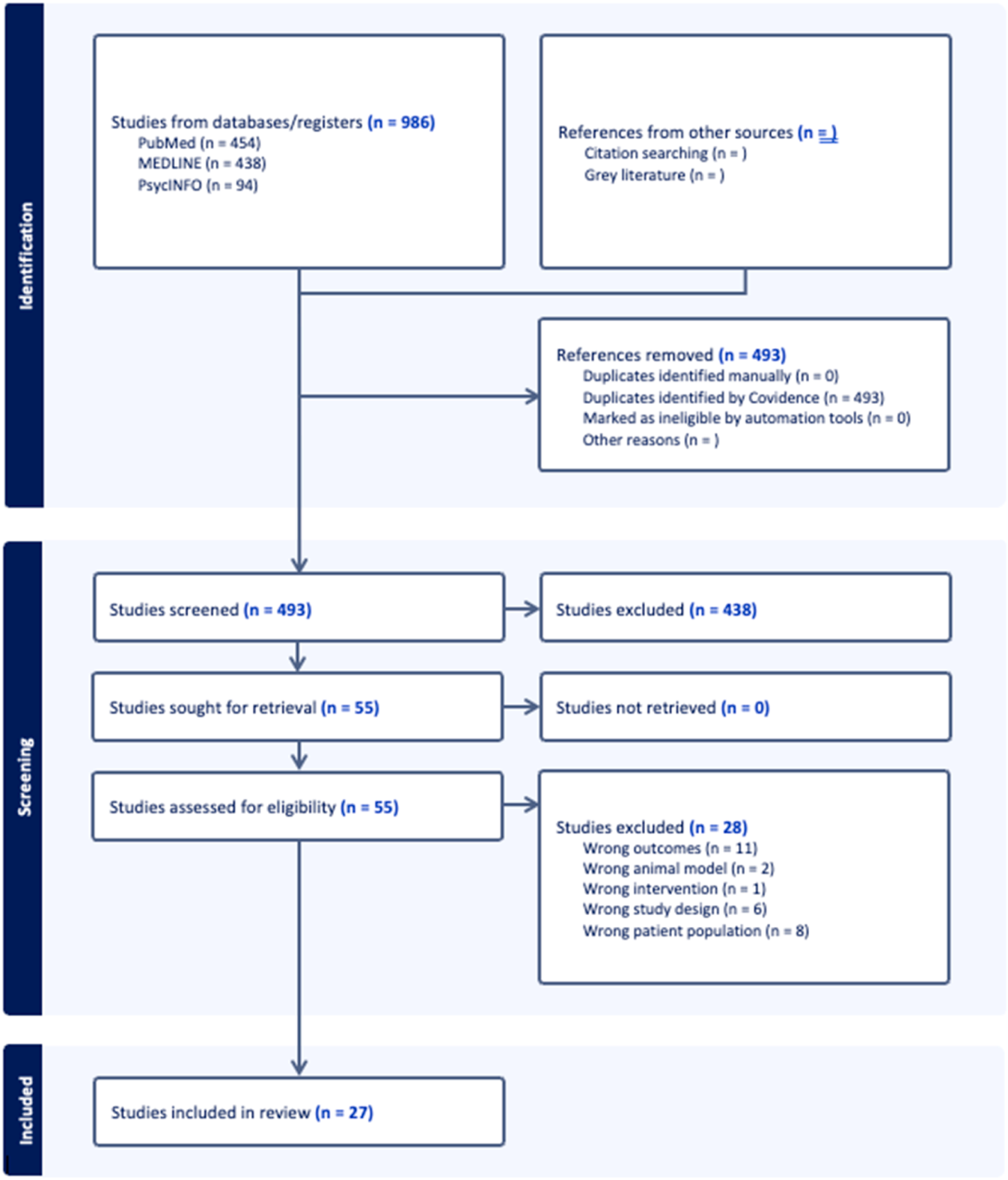

Fig. 1. Included, screening, identification.

2.4. Data synthesis

Given the high degree of heterogeneity across included studies, in terms of study design, intervention types, outcome measures, and populations, we did not perform a meta-analysis and findings were synthesized narratively instead.

3. Results

A total of 493 studies were reviewed for title and abstract screening, 55 studies were further examined in full text review alongside our inclusion/exclusion criteria. 28 papers were excluded, 11 due to wrong outcomes, 8 for wrong patient population, 6 for wrong study design, 2 for wrong animal model, and 1 for wrong intervention Fig. 1. Detailed information on each excluded study and reason for exclusion is provided in Supplementary Table 1. A total of 27 studies were included for inclusion in the systematic review. We reviewed 3 human clinical trials, 5 human observational, and 19 preclinical studies that examine the impact of GLP-1 RAs on depressive symptoms. The clinical and preclinical studies examined biological mechanisms, whereas the observational studies described efficacy data on the effect of GLP-1 RAs on depressive symptomatology. The population in clinical and observational studies include patients with either major depressive disorder (MDD) or metabolic conditions with self-reported depressive symptoms. There were no patients included with bipolar depression.

3.1. Clinical trials (Table 9)

A multicenter, unmasked randomized clinical trial in the USA (Gonzalez JS et al., 2024) investigated the effects of metformin (Glucophage) monotherapy versus other treatments (insulin glargine U-100, sulfonylurea glimepiride, liraglutide, or sitagliptin) on diabetes distress (measured with the 17-item Diabetes Distress Scale) and depressive symptoms (measured with eight-item Patient Health Questionnaire) in 5047 participants aged 21–88. Among the treatment group, 450 participants were assigned to liraglutide treatment. The mean age was 58.0 years, with a demographic of 68 % male and 32 % female and ethnic demographics of 56 % Non-Hispanic White, 18 % Non-Hispanic Black, and 17 % Hispanic.

There were no significant differences in depressive symptoms between liraglutide and other treatment groups, though diabetes distress was significantly lower in the liraglutide group compared to the glimepiride and sitagliptin groups at 1 year ($p = 0.008$). Across treatment groups, there were no significant differences in depressive symptoms, though a secondary outcome of interpersonal distress remained lower in the liraglutide group over 3 years vs. glimepiride and sitagliptin ($p = 0.003$). Regarding liraglutide's impact on diabetes distress, this was not mediated by HbA1c, BMI, or other metabolic factors, suggesting a non-metabolic mechanism. Although there was a possible link between liraglutide treatment and interpersonal distress reduction, there was no further investigation into the mechanism behind this.

Other clinical trials include Kahal et al. (2019), an interventional case control study enrolling 36 women with polycystic ovary syndrome (PCOS) and without PCOS treated with liraglutide. Results reported non-significant changes in depressive scores ($p = 0.42$) suggesting that the antidepressant effects of GLP-1 RAs are dependent on the population, emphasizing the importance of diverse populations. (Rizza et al., 2021), a single arm open interventional study, investigated the combination of insulin with liraglutide for the purpose of deprescribing. Although this study does not investigate any mechanisms relating to the medication itself, it does indicate that the route of administration may confer its own benefits in alleviating depressive symptoms. This is an important consideration for the design of clinical studies where route or administration can influence outcomes.

3.2. Observational studies (Table 8)

Five observational studies were included, with various designs such as cross-sectional (Eren-Yazicioglu et al., 2021), nested case/non-case (Battini V et al., 2023), and prospective observational (Moulton et al., 2016). Participants range between 18–74 in age, with the mean age ranging from 53.33 (Tsai WH et al., 2022) to 55.2 years (Moulton et al., 2016). Sex is mixed in all studies with male participants ranging from 34 % (Eren-Yazicioglu et al., 2021) to 56.8 % (Moulton et al., 2016). Conditions among research study participants included T2DM, elevated BMI, and general antidepressant users (Battini V et al., 2023; Eren-Yazicioglu et al., 2021; Moulton et al., 2016). The type of GLP-1 RAs used include liraglutide, exenatide, semaglutide, lixisenatide, and dulaglutide, which were predominately administered subcutaneously with varied dosing. Some studies show large decreases in depression scores, for example Grant 2011 (Grant P et al., 2011), while others showed worsening outcomes, particularly an increase in depression in the short term (Eren-Yazicioglu et al., 2021).

Battini et al. (2023) employed a nested case/non-case design using FAERS and VigiBase pharmacovigilance data. They reported lower reporting odds ratios (RORs) for depression-related treatment failure in individuals using antidepressants alongside GLP-1 RAs (Battini V et al., 2023). As these findings are derived from spontaneous adverse event reporting systems, they should be interpreted as signal detection rather than direct risk estimation. However, this data suggests that GLP-1 RAs may offer protective benefits against depression. (Grant et al., 2011), a prospective observational study showed that the HADS score dropped from 22 to 12 in the exenatide group, which was statistically significant ($p = 0.041$). In contrast, a cross-sectional observational study by Eren-Yazicioglu et al. demonstrated higher PHQ-9 scores in the short term for patients on exenatide (Eren-Yazicioglu et al., 2021). However, without baseline depression measures, this observed effect may reflect pre-existing group differences rather than a true drug effect. Therefore, the main findings from the observational studies report that the impact of GLP-1 RAs on depressive symptoms is variable but may be linked to fewer antidepressants therapy failures. However, such associations are tempered by influences of population selection (e.g., cohorts with diabetes or elevated BMI).

Tsai et al. (2022) studied exenatide alongside liraglutide and dulaglutide and found that only dulaglutide was associated with a reduction in depression and anxiety scores, suggesting that outcomes may vary by medication type (Tsai WH et al., 2022). In a prospective analysis from the UK (Moulton et al., 2016), Moulton et al. evaluated the effect of incretin-based therapies [GLP1 RAs and dipeptidyl peptidase-IV (DPP-IV)] inhibitors on depression in patients with T2DM. There was an improvement in depressive symptoms independent of glycemic control and BMI. This correlation of improvement in depression scores with changes in high-sensitivity C-reactive protein (hs-CRP) suggests a possible inflammatory mechanism behind the etiology of depression in T2DM (Moulton et al., 2016). Overall, observational data suggest a positive trend in mood improvement measured through self-report scales in GLP-1 RA users, but findings are heterogeneous and often limited by lack of rigorous statistical controls, small sample sizes, or variability in administered intervention.

3.3. Preclinical evidence (Tables 2–7)

There are 19 preclinical studies investigated in this paper ranging from 2015 to 2024. There are 18 animal models and 1 cell model. The cell-based study was excluded from further analysis due to its methodological heterogeneity and lack of an in-vivo animal component (Ma Q et al., 2023). To ensure consistency in mechanistic and behavioural outcome comparisons, we limited our analysis to preclinical studies using animal models only. The animals used include genetically modified mice (C57bl/6 J, C57bl/6 N, BALB/cByJ and ICR) and wistar-albino rats. Various models of depression were applied including medication

induced (dexamethasone, ouabain, corticosterone, lipopolysaccharide), behaviourally induced (forced swim test, chronic unpredictable stress, REM sleep deprivation), and genetically induced. Other models include diabetic models that induce depressive behaviours (nicotinamide, HFD). Various GLP-1 RAs were used including Liraglutide, Exenatide/Exendin-4, Dulaglutide, Semaglutide, Geniposide, and Lixisenatide. The cell-based study used a native GLP-1 (Ma Q et al., 2023).

The preclinical studies used various animal model tests to measure depression. Descriptions of these tests are highlighted in the *Supplementary Note #3.*

3.4. Results by GLP-1 RA

Liraglutide was the most administered treatment among the studies, with seven of the nineteen studies utilizing liraglutide (Abdelkawy YS et al., 2024; Cicekli et al., 2022; Kamble M et al., 2016; Krass et al., 2015; Seo et al., 2023; Sharma AN et al., 2015; Weina et al., 2018). Although Krass et al. investigated both liraglutide and exenatide, we focused on liraglutide-related outcomes to maintain categorizational clarity. Various depression models were used including dexamethasone induced, ouabain induced, behavioural induced [force swim test (FST), tail suspension test (TST)], chronic unpredictable stress, genetic model, and chronic corticosterone administration. The dosing of liraglutide in these studies ranged from 50 μg/kg to 1200 μg/kg. Only five out of the seven studies show an improvement in depression. The behavioural outcomes demonstrated decreased immobility in a FST in five of the seven studies (Abdelkawy YS et al., 2024; Cicekli et al., 2022; Seo et al., 2023; Sharma AN et al., 2015; Weina et al., 2018) while the other two studies yielded statistically insignificant findings in the FST (Kamble M et al., 2016; Krass et al., 2015). Two among three studies (Abdelkawy YS et al., 2024; Weina et al., 2018) also demonstrated decreased immobility in the TST, with the other (Kamble M et al., 2016) showing a non-significant difference in the TST results. The sucrose preference test (SPT), which measures anhedonia and is commonly used as an indicator of depressive-like behaviour, showed that liraglutide improved sucrose preference in both the studies that employed it, suggesting reduced depressive-like behaviour (Abdelkawy YS et al., 2024; Cicekli et al., 2022).

Five studies examined Exendin or its synthetic analogue Exenatide with depression-induced models, including the forced swim test (FST), T2DM-induced depression, and REM sleep deprivation. Four of the five studies indicated improvements in depressive symptoms (Anderberg

Table 2
Liraglutide in preclinical models.

Citation	Species & Strain / Dose	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
Abdelkawy 2024	Swiss albino mice, Male / Liraglutide 0.2 mg/kg, i.p., daily for 28 days	Dexamethasone induced	Y	FST: Liraglutide decreased immobility by >75 % ($p < 0.0001$). TST: Decreased immobility by >78 % ($p < 0.0001$). SPT: Increased preference by 72 % ($p < 0.0001$). OFT: Increased activity by 77 % ($p = 0.0067$)	Neurotransmitters: Increase: dopamine ($p = 0.001$), serotonin ($p = 0.0001$) norepinephrine ($p = 0.001$). Inflammatory markers: Decrease IL-1β by >35 % ($p < 0.0001$). Neuroplasticity: Increase BDNF 70 % ($p < 0.0001$). Increase CREB by four-fold ($p < 0.0001$)
Çiçekli 2022	Wistar Albino rats, male / Liraglutide 0.1, 0.2, or 0.4 mg/kg, s.c., for 10 days	Ouabain-induced bipolar disorder model (mania and depressive state)	Y	FST: Liraglutide (200 & 400 μg/kg) significantly reduced immobility time $p < 0.001$). Liraglutide 100 μg/kg showed no significant effect ($p > 0.05$). SPT: Liraglutide 200 & 400 μg/kg restored sucrose preference ($p < 0.001$ and $p = 0.002$, respectively). OFT: Liraglutide (200 & 400 μg/kg) reduced hyperlocomotion ($p < 0.001$)	Inflammatory markers: Liraglutide at the doses of 200 ($p < 0.005$) and 400 μg/kg ($p < 0.018$) prevented ouabain-induced decreased serum total anti-oxidant (TAS) level.. Liraglutide at the doses of 200 ($p = 0.001$) and 400 μg/kg ($p < 0.001$) prevented ouabain-induced total oxidative stress level changes. Liraglutide at the doses of 200 and 400 μg/kg inhibited ouabain-induced lipid peroxidation ($p = 0.005$ and $p = 0.018$, respectively). Liraglutide significantly prevented GSK-3β dephosphorylation at all doses (100, 200, 400μg/kg) ($p < 0.001$)
Kamble 2016	Wistar rats and swiss albino, Male / Liraglutide 0.1 or 0.2 mg/kg, i.p., for 7 days	Forced Swim Test (FST) and Tail Suspension Test (TST)	N	FST: p = NS. TST: p = NS at 100 and 200 μg/kg. OFT: Reduced peripheral square crossings ($p < 0.05$ at 100 and 200 μg/kg). EPM: Decrease closed arms count $p < 0.05$ for 200 μg/kg. Open arms p = NS	Mechanism not specified
Seo 2023	C57BL/6 J mice, male / Liraglutide 0.3 mg/kg, s.c., once daily for 3 weeks	Chronic Unpredictable Stress (CUS)	Y	FST: Reduced immobility time ($p < 0.01$)	Mechanism not specified
Krass 2015	C57BL/6 J, Male; Rat (Flinders Sensitive Line - FSL) / Liraglutide 1.2 mg/kg s.c. once daily for 14 days	Genetic model of depression in FSL rats	N	Mice: FST p = NS. Light-Dark Box p = NS. OFT p = NS. Rats: FST p = NS. OFT p = NS.	Inflammatory Markers: Sustained increase in corticosterone after chronic liraglutide treatment ($P < 0.0001$) under both basal and stress conditions in the mouse model.
Sharma 2015	Wistar albino rat, Female / Liraglutide 0.05 mg/kg, i.p., daily for 3 weeks	Forced Swim Test (FST), olanzapine (Zyprexa)-induced metabolic dysfunction	Y	FST: Decreased immobility time ($p < 0.05$).	Mechanism not specified
Weina 2018	C57BL/6 N Mice, Male / Liraglutide 5 or 20 nmol/kg, i.p., for 15 days	Chronic corticosterone (CORT) administration	Y	FST: Decreased immobility time ($p < 0.01$) for 20 nmol/kg. TST: Decreased immobility time ($p < 0.001$) for 20 nmol/kg. OFT: Increased time in the centre for 5 nmol/kg ($p < 0.05$) and 20 nmol/kg ($p < 0.01$). EPM: p = NS	Neuroplasticity: Increased doublecortin (DCX) expression in the hippocampus ($p = 0.149$) at 20 nmol/kg. Increased density of DCX+ immature neurons in the dentate gyrus ($p < 0.05$) at 20 nmol/kg. Inflammatory Markers: Reduced ACTH levels ($p < 0.0001$) at 5 and 20 nmol/kg.

Table 3
Exenatide in preclinical models.

Citation	Species & Strain	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
Anderberg 2016	Sprague-Dawley Rats, Male / Exendin (0.2 μg) once a day, intra-LV, for 9 days	Forced Swim Test (FST)	Y	Acute administration (1 injection): FST: p = NS. OFT: Decreased activity ($p < 0.05$). EPM: p = NS Chronic administration (all injections): FST: Decreased immobility by ($p < 0.005$). EPM: Decreased time in open arms (p < 0.05)	Acute administration: Neurotransmitters. Increased serotonin turnover in the amygdala (5-HIAA/5-HT ratio) ($p < 0.05$). Chronic administration: Neurotransmitters. Modulated serotonin receptor expression in the amygdala (5-HT2A, 5-HT2C, $p < 0.05$).
Komsuoglu Celikyurt 2014	BALB/cByJ mice, male / Exenatide 0.1 μg/kg, s.c., twice daily for 2 weeks	Streptozotocin + Nicotinamide induced T2DM	Y	FST: Reduced immobility ($p < 0.05$). EPM: Increased time spent in open arms ($p < 0.05$). Increased number of entries to open arms ($p < 0.001$)	Mechanism not specified
Turan 2021	Wistar-albino rats, Male / Exenatide 0.5 μg/kg, subcutaneously) daily for 9 days	REM sleep deprivation (SD) for 72 h using the multiple platform method.	N	FST: p = NS. OFT: Decrease in number of crossing squares and rearing activity ($p < 0.05$). EPM: p = NS	Neuroplasticity: Increase in hippocampal CaMKII ($p < 0.05$)
Ventorp 2017	Wistar rats, male / 0.5μg/mL/kg exendin-4 once daily for 5 days	Lipopolysaccharide (LPS)-induced depressive-like behavior.	Y	FST: Decreased immobility time ($p < 0.05$)	Neurotransmitters: Increased striatal dopamine ($p = 0.059$)
Yang 2022	Male db/db (BKS.Cg-Dock7m +/+ Leprdb/JNju) mice / EX-4 (5 μg/kg) injected intraperitoneally (i.p.) once daily for four days	db/db diabetic mice model	Y	FST: Decreased immobility time ($p < 0.001$). TST: Decreased immobility time ($p < 0.001$). OFT: Increased total distance in OFT ($p < 0.05$)	Neuroinflammation:reduced IL-1β levels ($P < 0.001$). -reduced caspase-1 ($p < 0.05$). GSDMD ($p < 0.05$). Decreased intracellular ROS fluorescence ($p < 0.01$)

Table 4
Dulaglutide in preclinical models.

Citation	Species & Strain	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
Darwish 2023	C57BL/6 J, Male / Dulaglutide 0.6 mg/kg i.p., once per week for 4 weeks	Chronic Social Defeat Stress (CSDS)	Y	SPT: Increased ($P < 0.0001$). EPM: Increase time in open arms ($P < 0.0001$)	Neuroplasticity: Increased BDNF in hippocampus ($P < 0.0001$). Inflammatory markers: Decrease in NLRP3 inflammasome, IL-1β, IL-18, IL-6, and TNF-α by 59 % ($P < 0.0001$), 67 % ($P < 0.0001$), 58 % ($P < 0.0001$), 75 % ($P < 0.0001$), and 69 % ($P < 0.0001$) respectively
Jin 2024	Mouse ICR, Male / Dulaglutide 0.3 or 0.6 mg/kg i.p., 2x/week for 3 weeks	Chronic Mild Stress (CMS)	Y	FST: Decrease in floating time ($p < 0.01$) at both doses. TST: Decrease in immobility time for 0.3 mg/kg ($p < 0.01$) and 0.6 mg/kg (p < 0.05). OFT: Increase time spent in centre ($p < 0.05$) at both doses.	Normalization of stress-induced upregulation of amino acid levels. Decrease in L-Tyrosine ($p < 0.01$), L-Phenylalanine ($p < 0.01$), L-Arginine ($p < 0.01$).

Table 5
Semaglutide in preclinical models.

Citation	Species & Strain	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
dePaiva 2024	C57BL/6 Mouse / Semaglutide 0.05 mg/kg i.p. weekly for 18 weeks	High fat diet (HFD) induced T2DM	Y	FST: decreased immobility time (p < 0.0001). TST: Decreased immobility time ($p < 0.05$). EPM: significant reduced time in the closed arm (p < 0.01). significantly increased time in the open arm (p < 0.0001)	Neurotransmitters: Increase in 5-HT (p < 0.05). Inflammatory markers: Decrease in TLR4 ($p < 0.001$), MyD88 ($p < 0.05$), NFkB ($p < 0.01$), TNF-a ($p < 0.01$), IL-1β ($p < 0.05$), IL-6 ($p < 0.05$), Nitrotyrosin ($p < 0.001$), Neuroplasticity. increased pCREB ($p < 0.0001$)

et al., 2016b; Komsuoglu Celikyurt I et al., 2014; Ventorp F et al., 2017; Yang et al., 2022). In experiments conducted by Anderberg et al. (2016a), the acute intervention did not produce measurable changes in forced swim test outcomes. However, animals displayed reduced willingness to enter the open arms of the elevated plus maze and showed lower locomotor activity within the central portion of the open field arena. Both findings are typically interpreted as increased anxiety-like behaviour. By contrast, chronic administration resulted in a significant decrease in immobility in the FST (suggesting an antidepressant effect) and showed no significant changes in anxiety-related behaviour in the EPM. Komsuoglu Celikyurt et al. (2014) similarly reported reduced immobility in the FST after exenatide treatment, along with increased time spent in the open arms of the EPM, suggesting reduced anxiety-like behaviour (Komsuoglu Celikyurt I et al., 2014). Ventorp et al. (2017) and Yang et al. (2022) also demonstrated reduced immobility in the FST, indicating an antidepressant-like effect (Ventorp F et al., 2017; Yang et al., 2022). However, Turan et al. (2021) found no significant changes in the FST, indicating no significant changes in depressive behaviour

Table 6
Geniposide in preclinical models.

Citation	Species & Strain	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
Sun 2021	C57BL/6 J mouse, male / 20 mg/kg or 100 mg/kg Geniposide by i.p. injection	High fat diet (HFD) + corticosterone	Y	FST: Decreased immobility time. Low dose: ($p < 0.01$). High dose: $p < 0.001$). OFT: Increased time in central region. Low dose: p = NS. High dose: ($p < 0.001$)	Neuroplasticity/neurogenesis: Increased CREB phosphorylation with geniposide. Low dose: ($p < 0.05$). High dose: ($p < 0.01$)
Zhao 2018	ICR mice, Male / Geniposide 50 mg/kg or100 mg/kg once daily for 15 days	Repeated Restraint Stress (RRS)	Y	FST: Decreased immobility time ($p < 0.05$). TST: Decreased immobility time ($p < 0.05$) at both doses. SPT: Increased ($p < 0.05$) at 100 mg/kg. OFT: Increased crossings ($p < 0.05$) at 100 mg/kg.	Normalization of stress-induced upregulation of inflammatory markers. Decrease in IL-1β ($p < 0.05$) for 50 mg/kg and ($p < 0.01$) for 100 mg/kg and TNF-α ($p < 0.05$) for 50 mg/kg and ($p < 0.01$) for 100 mg/kg in the hippocampus

Table 7
Lixisenatide in preclinical models.

Citation	Species & Strain	Model	Improved Depression (Y/N)	Behavioural outcomes	Mechanisms
Ren 2021	C57BL/6 N Mice, Male / Lixisenatide with two dosages (10 nmol/kg/d and 50 nmol/kg/d) administrated by intranasal treatment from day-15 to day-40	Chronic Unpredictable Mild Stress (CUMS)	Y	FST: Decreased immobility ($p < 0.01$) at 50 nmol/kg. TST: Decrease immobility ($p < 0.01$) at 50 nmol/kg. OFT: Increased centre time ($p = 0.001$) at 50 nmol/kg. EPM: Increased open arm time ($p < 0.001$) at 50 nmol/kg.	Neuroplasticity: Increase in: Olfactory bulb DCX/BrdU+ cells ($p < 0.001$) at 50 nmol/kg. Hippocampal DCX/BrdU+ cells ($p < 0.05$) at 50 nmol/kg. CREB phosphorylation ($p < 0.05$) at 50 nmol/kg.

Table 8
Observational models.

Citation	Study Design	Sample Size & Age	Interventions	Improved Depression (Y/N)
Moulton 2016	Prospective analysis of a subset from an observational primary care cohort study (SOUL-D)	$N = 1444$. Age mean = 55.2 ± 10.5	Exenatide among other incretin-based therapies.	(Y) Incretin-based therapies are associated with improved depressive symptoms independent of glycemic control and BMI ($p = 0.006$), possibly through anti-inflammatory pathways.
Battini 2023	Nested case/non-case study using pharmacovigilance databases (FAERS and VigiBase)	FAERS: 121,368 depressed patients experiencing therapy failure, 423,943 as non-cases. VigiBase: 85,267 depressed patients experiencing therapy failure, 562,041 as non-cases. Age range = 18–74 y	Semaglutide, Dulaglutide, Exenatide, Lixisenatideand Liraglutide among other anti-diabetic agents.	(Y) Patients taking GLP-1 RAs had lower depression-related adverse events and therapy failure. Estimated reduction in depression therapy failure ranged from reporting odds ratio (ROR) of 0.546 (FAERS) to 0.717 (VigiBase).
Grant 2011	Prospective, observational study (non-randomized)	$N = 138$ (71 in the Exenatide group, 67 in the Insulin group). Age mean = 57.81 years (Exenatide group), 59.12 years (Insulin group)	Exenatide and Insulin	(Y) Exenatide treatment resulted in a significant improvement in the hospital anxiety and depression scale (HADS) ($p = 0.041$). The observed changes were independent of BMI and HbA1c reductions, suggesting a direct effect on mood regulation.
Eren-Yazicioglu 2021	Cross-sectional study	$N = 43$ (23 on exenatide, 20 without exenatide). Age mean = 53.47 ± 8.74	Exenatide	(N) Exenatide use leads to higher depressive scores in the short term ($P = 0.048$), likely through increased perceived stress levels.
Tsai 2022	Population-based cohort study using National Health Insurance Research Database (NHIRD) of Taiwan.	GLP-1 Agonist Users: 10,690. Non-users: 42,766 (Propensity Score Matched). Age mean = 53.33 years ± 13.04	Liraglutide, Dulaglutide, Exenatide	(Y) Dulaglutide subgroup: Significant reduction in depression and anxiety ($p < 0.001$). (N) Across all treatments ($p > 0.05$).

despite changes in neuroplasticity reported (Turan et al., 2021).

Regarding dulaglutide, only two studies (Darwish AB et al., 2023; Jin et al., 2024) have investigated its effects on depression at a dose of 0.3 or 0.6 mg/kg/day intraperitoneal, using the chronic social defeat stress (CSDS) model and the chronic mild stress (CMS) model. Both studies reported improvements in depressive-like behaviours. In the Darwish et al. (2023) study, dulaglutide administration led to increased sucrose preference and a significant increase in time spent in the open arms of the EPM, suggesting reduced anhedonia and anxiety, respectively (Darwish AB et al., 2023). Jin et al. (2024) reported that dulaglutide decreased immobility time in both the FST and TST, as well as increased time spent in the center of the open field test (OFT), indicating reduced depressive and anxiety-like behaviors (Jin et al., 2024). The proposed mechanisms include enhanced neuroplasticity (e.g., increased BDNF expression) and reduced inflammation (e.g., decreased levels of inflammasome components such as NLRP3, IL-1β, IL-18, IL-6, and TNF-α) (Darwish AB et al., 2023; Jin et al., 2024). Jin (2024) also noted normalization of stress-induced upregulation of amino acids, including L-tyrosine, L-phenylalanine, and L-arginine (Jin et al., 2024).

There is less available information on other GLP-1 RAs, such as semaglutide, geniposide and lixisenatide. These agents have only been evaluated in one or two preclinical studies each but have consistently demonstrated antidepressant effects across various models, including T2DM-induced depression (de Paiva IHR et al., 2024), corticosterone-induced stress (Sun et al., 2021), chronic unpredictable mild stress (Ren et al., 2021), or genetic models. The underlying

Table 9
Clinical trials.

Citation	Study Design	Sample Size & Age	Interventions	Improved Depression (Y/N)
Gonzalez 2024	Multicentre, unmasked randomized clinical trial	$N = 1739$: Age mean = 58.0 ± 10.2	Liraglutide and Basal insulin (glargine)	(N) No significant differences were observed in depressive symptoms between treatment groups ($p = 0.135$).
Kahal 2019	Interventional case-control study	$N = 36$ women (19 with PCOS, 17 controls). Age mean = 33.9 ± 6.7 for PCOS, 33.5 ± 7.1 for controls	Liraglutide	(N) Depression scores did not significantly change ($p = 0.42$), suggesting liraglutide did not have an anti-depressant effect in this population.
Rizza 2021	Single-arm, open interventional study	$N = 35$. Age mean = 81.4 years	iDegLira (combination of insulin degludec and liraglutide).	(Y) Deprescribing multiple diabetes medications and switching to iDegLira led to improved health outcomes and quality of life. Depression symptoms, as measured by the Geriatric Depression Scale (GDS), significantly decreased ($p = 0.02$).

mechanisms vary but include increased serotonin levels with semaglutide (de Paiva IHR et al., 2024), or enhanced neuroplasticity, such as upregulation of CREB phosphorylation and increased BrdU+ cells, in the hippocampus and olfactory bulb with lixisenatide (Ren G et al., 2021). Additionally, geniposide show anti-inflammatory effects, such as decreased IL-1β and TNF-α levels, as well as increased dopamine activity (Zhao et al., 2018).

A summary of the antidepressant outcomes for each GLP-1 RA across preclinical, observational, and clinical studies is presented in Table 10. Taken together, these results suggest that antidepressant effects of GLP-1RAs are more likely to emerge in chronic treatment regimens and may vary according to the animal model (e.g., depression-induced vs. diabetes-induced), drug intervention, and dosing strategy.

3.5. Results by mechanistic frameworks

Three mechanistic frameworks behind the action of GLP-1 on depression were including, namely, neuroplasticity, decreased neuroinflammation, and increased neurotransmitter expression. These mechanisms have been primary studied in animal models that have induced depression through the methods outlined in Section 3.4.

Firstly, in animal models that identify changes in neuroplasticity as a mechanism of improved depressive outcomes, the following markers were identified: increased BDNF (Abdelkawy YS et al., 2024; Darwish AB et al., 2023), CREB (Abdelkawy YS et al., 2024; de Paiva IHR et al., 2024; Sun B et al., 2021), and DCX expression (Weina et al., 2018) in the dentate gyrus. Secondly, animal models that discuss neuroinflammation as a mechanism of improved depressive outcomes demonstrate decreased neuroinflammation through decreased IL-1β (Abdelkawy YS et al., 2024; Darwish AB et al., 2023; de Paiva IHR et al., 2024; Yang et al., 2022; Zhao Y et al., 2018), decreased oxidative stress (Cicekli et al., 2022), and reduced ACTH levels (Weina et al., 2018). However, there are animal models that do not show improvement in depression (Kamble M et al., 2016; Krass et al., 2015; Turan et al., 2021). While this may reflect normal variation in the effects of GLP-1 RAs on depression, it should also be considered in the context of differing model types. Notably, Krass et al. (2015) is the only study to use a genetically modified mouse model, which may contribute to the observed null effects of GLP-1 RAs (sustained increases in corticosterone level after chronic liraglutide treatment). Thirdly, neurotransmitter levels are also discussed in relation to improved depressive outcomes, with mentions of increasing levels of dopamine (Abdelkawy YS et al., 2024; Ventorp F et al., 2017), serotonin (Abdelkawy YS et al., 2024; Anderberg et al., 2016b; de Paiva IHR et al., 2024) and norepinephrine (Abdelkawy YS et al., 2024).

The previously discussed results are based on depression-induced models; however, several studies have also examined depressive outcomes in diabetes-induced models. With diabetes-induced models (de Paiva IHR et al., 2024; Komsuoglu Celikyurt I et al., 2014; Sharma AN et al., 2015; Sun B et al., 2021; Yang et al., 2022) the anti-depressant mechanisms of GLP-1 RAs are largely similar to depression-induced models, such as neuroplasticity, neuroinflammation and neurotransmitter changes.

Studies using exendin/exenatide in both preclinical and observational settings showing time-dependent effects. Acute administration of exendin was associated with increased anxiety and worsened depressive behaviors, whereas chronic administration was linked to improvements in depressive outcomes (Anderberg et al., 2016b). The mechanisms underlying these differences appear to involve shifts in neurotransmitter regulation and neuroplasticity. Anderberg et al. (2016a) suggested that acute administration increases serotonin turnover in the amygdala, a pattern often associated with heightened anxiety, whereas chronic administration does not alter serotonin turnover but instead induces changes in serotonin receptor expression that confers an anti-depressant effect (Anderberg et al., 2016b).

These mechanistic observations help contextualize the variability in behavioral outcomes. Null findings were more common in studies using short-term dosing, which may not allow sufficient time for neuroplastic adaptations. In contrast, chronic stress or diabetes-induced depression

Table 10
Summary of Antidepressant Effects by GLP-1 RA Type and Study Model.

GLP-1RA	# Preclinical Studies	Preclinical Outcome	# Observational Studies	Observational Outcomes	# Clinical Trials	Clinical Trials Outcome
Liraglutide	7	5 positive, 2 no effect	2	1 positive, 1 no effect	3 (mixed)	1 positive, 2 negative
Exenatide/Exendin-4	5	4 positive, 1 negative	5 (mixed)	3 positive, 2 negative	N/A	–
Dulaglutide	2	2 positive	2 (mixed)	2 positive	N/A	–
Semaglutide	1	1 positive	1 (mixed)	1 positive	N/A	–
Geniposide	2	2 positive	N/A	–	N/A	–
Lixisenatide	1	1 positive	1 (mixed)	1 positive	N/A	–

models, where baseline inflammation and neuroplasticity deficits are more pronounced, typically demonstrated greater benefit from GLP-1 RAs. Future studies should systematically examine the interaction between model type, treatment duration, and dose-response relationships to enhance translational relevance.

3.6. Risk of bias (Supplementary Tables 2–4)

The overall risk of bias varied across study types. Among preclinical studies (assessed using the SYRCLE tool), most domains were rated as unclear due to insufficient reporting, particularly regarding allocation concealment, random housing, and blinding of outcome assessors. Several studies were judged to have high risk in domains related to allocation concealment and caregiver blinding (Sun B et al., 2021; Turan et al., 2021; Yang et al., 2022). Observational studies (assessed with the Newcastle-Ottawa Scale) demonstrated generally moderate to high quality, with total scores ranging from 7 to 9 out of 9. However, Battini et al. (2023) showed low quality (score of 4/9) due to gaps in selection and outcome bias. Tsai et al. (2022) and Moulton et al. (2016) achieved full scores, indicating low risk of bias (Moulton et al., 2016; Tsai WH et al., 2022). Clinical studies (assessed with the Cochrane RoB 2.0 tool) displayed mixed findings. Kahal et al. (2019) and Gonzalez et al. (2024) was judged as moderate risk across all domains, while Rizza et al. (2021) had high risk primarily due to issues in randomization, deviations from intended interventions, and outcome measurement (Kahal H et al., 2019; Rizza S et al., 2021). The quality of evidence was limited by high or unclear risk of bias in many preclinical studies, while observational studies were generally robust, and clinical trials ranged from moderate to high risk depending on methodological rigor.

4. Discussion

This systematic review aimed to provide a broad overview of the available literature for GLP-1 RAs on outcomes relating to depression. Studies demonstrated improved outcomes for depression, and mechanisms including neuroplasticity, inflammation, and alterations in neurotransmitter levels were reported. In studies without significant improvements in depression outcomes, some (e.g., Anderberg et al., 2016b) studies reported that acute administration of GLP-1 RAs was associated with increased anxiety-like behaviors. Most studies used depression-induced models, while a subset examined depressive outcomes in diabetes-related models. This is relevant given our previous work on GLP-1 RAs as a protective factor for incidence depression in patients with diabetes (Cooper et al., 2023). This allows for a broad assessment of GLP-1 RAs in different venues considering these agonists are used in both patients with and without diabetes. While preclinical studies demonstrate promising antidepressant-like effects across various models, current clinical evidence remains preliminary, with inconsistent findings and limited sample sizes. As such, any conclusions about the therapeutic utility of GLP-1 RAs in depression should be regarded as hypothesis-generating rather than confirmatory. Further research should be conducted to understand the mechanisms of GLP-1 RAs' effect on human depression to better apply these treatments to a generalized population.

Based on GLP-1 RA type in preclinical studies, the most studied was liraglutide, with five out of seven studies showing antidepressant effects. Studies with exenatide reported mixed results that depended on acute versus chronic use, with strong antidepressant benefit from chronic administration while studies with dulaglutide demonstrated consistent improvement in depressive and anxiety behaviours. There was limited information on other GLP-1 RAs with generally no improvement to modest improvement in depressive behaviours. The improvement in depressive symptoms was assessed using behavioural tests such as the FST, TST, and SPT. These outcomes varied depending on the model-type used (depression induced or diabetes induced), which may explain the range of GLP-1 RAs in different disease states. This is relevant given that while GLP-1 RAs are currently licensed as a medication for T2DM, they may show evidence as a potential antidepressant based on recent literature (De Giorgi et al., 2025).

GLP-1 RAs activate neuroplasticity pathways, notably through CREB, BDNF, and DCX as illustrated in our results (McIntyre et al., 2025b). CREB (cyclic adenosine monophosphate response element binding protein) is a transcription factor implicated in the mode of action of many classes of antidepressant drugs which are shown to upregulate its levels (Blendy, 2006). Furthermore, in animal models, higher levels of CREB are also associated with less depressive behaviour (Blendy, 2006). BDNF (brain-derived neurotrophic factor) operates similarly, being a significant factor in the survival and development of neurons, specifically in Alzheimer's Disease and MDD (Correia et al., 2023). Specifically, decreased levels of BDNF are linked to increased depressive symptoms, neuronal loss, and cortical atrophy (Correia et al., 2023). Furthermore, similarly to CREB, BDNF levels are restored with antidepressant therapy (Correia et al., 2023). Other markers of neuroplasticity, such as doublecortin (DCX), which was increased in our included preclinical study (Weina et al., 2018), were also found to show increased expression in an in-vivo study of patients with depression (Xie et al., 2024). The study collected plasma samples from 40 patients with TRD and 35 matched healthy controls. They indicated that DCX was significantly lower in TRD patients alongside BDNF levels but increased following electroconvulsive therapy (ECT). These findings raise the possibility that GLP-1 RAs may engage in overlapping neuroplastic pathways with ECT, such as modulation of BDNF and DCX expression. However, this mechanistic relationship remains theoretical and requires direct investigation in future studies.

Other theories include the monoamine and neuroinflammation theories of depression. The monoamine theory posits that depression is a result of deficiencies in dopamine, norepinephrine, and serotonin (5-HT). The current first-line treatment for depression is a class of antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs) which have been clinically proven to improve depressive symptoms (Cui et al., 2024). Preclinical results from our study report that increased levels of these neurotransmitters after GLP-1 RA administration.. With respect to inflammatory markers, a study by Milaneschi et al., investigated large scale data for the causality of inflammatory markers with depression (Milaneschi et al., 2021). Inflammation was associated with core depressive symptoms of low mood,anhedonia, fatigue, altered sleep, and appetite changes. This is in agreement with our results indicating that GLP-1 RAs may confer improved depressive outcomes through modulating neuroinflammation.

With respect to the clinical findings, one clinical trial (Gonzalez JS et al., 2024) showed no significant reduction in depressive symptoms, though there was a significant decrease in diabetes distress. Other trials performed by Kahal et al. and Rizza et al. (Kahal H et al., 2019; Rizza S et al., 2021) also did not show significant changes in depressive scores, though Rizza et al. showed that the effect of deprescribing could improve mood outcomes. Therefore, some of the mood improvements seen with GLP-1 receptor agonists may be partially confounded by the simultaneous cessation of other treatments. While these clinical studies target depressive symptoms as a primary outcome, they are often focusing on unrelated or secondary outcomes as a function of GLP-1 RA administration. Rizza et al. (Rizza S et al., 2021) focuses on the intervention of deprescribing several diabetes medications and switching to the sole treatment of iDegLira, rather than the GLP-1 RA treatment itself, which may influence the reported outcomes. These clinical studies also indicate that certain populations may respond differently to GLP-1 RAs. For example, in Kahal et al. (2019), all participants had a diagnosis of PCOS and did not show any significant changes in antidepressant effects (Kahal H et al., 2019). Provided that different populations respond differently to medications, this is an important consideration to allow for diversified participation to better characterize the effects of GLP-1 RAs in the real world (Adan, 2023).

Among observational studies, results were mixed on whether GLP-1

RAs showed improved depression symptom severity. Eren-Yazicioglu et al. (Eren-Yazicioglu et al., 2021) showed increased perceived stress and which accords with preclinical models that identify acutely increased anxiety-like behaviours (Anderberg et al., 2016b). This observation may extend into real world data, as evidenced by a large community-based cohort indicating that liraglutide and semaglutide exhibited a 195 % higher risk of major depression, 108 % increase risk for anxiety, and a 106 % elevated risk for suicidal behaviour (Kornelius E et al., 2024). However, some notable remarks from other observational studies includes lower antidepressant treatment failure in GLP-1 RA users (Battini V et al., 2023) and high clinical remission rates with incretin-based therapy (Moulton et al., 2016), potentially linked to inflammatory markers (e.g., hs-CRP). The included clinical and observational studies varied widely in terms of population (e.g. T2DM and obesity), intervention, outcomes (PHQ-9, HADS, GDS) and follow-up. This heterogeneity is a challenge to direct comparisons and may complicate treatment effects due to population-specific responses or differing measurement tool sensitivities. Importantly, no studies focused on bipolar depression. Given that there are treatment differences between unipolar and bipolar depression, this distinction is crucial and should be distinguished in future research should both these disorders be analyzed in tandem.

There have been reports to the European Medicines Agency (EMA) on concerns over the safety of GLP-1 RAs, specifically liraglutide and semaglutide, due to their link with incidents of suicidal ideation and self-harm (EMA statement on ongoing review of GLP-1 receptor agonists | European Medicines Agency (EMA), 2023). In a prior analysis of FDA Adverse Event Reporting System (FAERS) data, we used reporting odds ratios (RORs) to assess suicidality-related events associated with GLP-1 RAs compared to metformin and insulin (McIntyre et al., 2024). While semaglutide and liraglutide showed elevated RORs, no disproportionate reporting was found for other GLP-1 RAs. Most importantly, when evaluated with the Bradford Hill criteria and adjusting for confounding factors, no causal association between GLP-1 RAs and suicidality was found. In a follow-up study, we analyzed suicidality-related reporting odds ratios (RORs) using the WHO VigiBase database (McIntyre et al., 2025a). Similarly, semaglutide, liraglutide, and tirzepatide showed elevated RORs for some suicidality-related outcomes. However, for specific outcomes such as suicide attempts and completed suicides, lower RORs were observed with certain GLP-1 RAs, including semaglutide, dulaglutide, exenatide, and liraglutide. As with FAERS, causal effects could not be established (McIntyre, 2024). A comprehensive review of this literature indicates that although association exists, causality is not yet established. (McIntyre, n.d.; Strumila et al., 2024).

4.1. Clinical trials evidence ongoing

A search of clinicaltrials.gov resulted in three studies investigating GLP-1 RAs for mood disorders. These clinical trials align with the aims of our systematic review and highlight increasing clinical interest in GLP-1 RAs for mood disorders. An ongoing 16-week randomized controlled trial (NCT04466345) is examining the effects of semaglutide in patients with MDD and cognitive dysfunction (University Health Network, Toronto, 2024). A completed study (NCT02423824) similarly evaluated the effects of liraglutide on executive function in individuals with depressive or bipolar disorders who demonstrated below-average cognitive performance (University Health Network, Toronto, 2016). Because the primary and secondary outcomes of the completed study were outside the scope of our inclusion criteria (focused on depressive symptoms), we did not include it in the results section but note it here for completeness. Further, an ongoing trial (NCT06331286) is examining dulaglutide's impact on both mood and cognition in patients with bipolar disorder and obesity, using validated tools such as the 17-item Hamilton Depression Rating Scale (HAM-D17) and the Treatment Emergent Symptom Scale (TESS) (First Affiliated Hospital of Zhejiang University, 2024). Collectively, these investigations reflect growing clinical interest in exploring the therapeutic potential of GLP-1 RAs for mood disorders.

4.2. Methodological limitations

There were several key limitations in the studies investigating GLP-1 RAs for depression affecting their strength and external validity. Specifically for the included observational studies, there was a selection bias as all participants were diagnosed with T2DM or related metabolic syndromes, which is a form of confounding by indication. Furthermore, select studies exclude participants with select mental health diagnoses which influences baseline depression scores (Grant P et al., 2011; Tsai WH et al., 2022). These inconsistencies at baseline can inform changes in outcomes, compounded by the diversity of depression measures. While some studies focus on incidence of depression (Tsai WH et al., 2022). through DSM/ICD diagnostic codes, others use scales for progression, most specifically Patient Health Questionnaire (PHQ-9) (Eren-Yazicioglu et al., 2021; Gonzalez JS et al., 2024; Moulton et al., 2016). Additional scales used include the Hospital Anxiety and Depression Scale (HADS) and Geriatric Depression Scale (GDS) (Grant P et al., 2011; Rizza S et al., 2021). There also exists important heterogeneity in study designs, populations and interventions which limits the ability to draw on overarching conclusions. Many trials were done in the short-term (e.g., 4 weeks) and thus may not provide an accurate estimate of long-term outcomes. The lack of direct comparisons to standard treatment such as antidepressants, in many of these studies, also limits the ability to draw more concrete conclusions about the efficacy of GLP-1 RAs as an intervention for depression.

For the observational findings in particular, several methodological issues warrant caution. Confounding by indication remains a major concern. Patients prescribed GLP-1 RAs in routine care may have unique metabolic or clinical characteristics (e.g., severe obesity or uncontrolled diabetes) that themselves influence depression risk, complicating the attribution of mood changes to the drug. Moreover, most observational studies did not adjust for baseline depression severity or comorbid psychiatric conditions, so apparent changes in depression outcomes could partly reflect these pre-existing differences. Finally, given the inherent limitations of observational designs, these associations cannot establish true causality and should be interpreted as correlational findings susceptible to residual confounding and bias. Furthermore, some studies lack dose-dependent investigations which are key in examining the biological mechanism underlying changes in outcome (e.g. mood, cognition, etc.). As highlighted in the articles, future clinical studies on GLP-1 RAs should aim for longer follow-up periods to measure their long-term effects within psychiatric populations. With respect to bias assessment, preclinical studies had unclear or high risk of bias in key domains, largely due to limited reporting on allocation concealment, randomization, and blinding. While observational studies were generally robust, some lacked detailed confounder control, and clinical trials showed variable methodological rigor. These limitations may reduce confidence in the overall strength of the evidence.

4.3. Future directions and conclusions

Further research should focus on ascertaining the mechanisms wherein GLP-1 RAs affect neural circuits. In addition, the issue of posology is not yet ascertained with respect to optimal dosing for target engagement in brain-based disorders and improvement in psychopathic domains. Although our search strategy was broad and inclusive, we additionally performed a grey literature search and re-examined excluded studies to confirm eligibility decisions. These steps increase our confidence that the included studies provide a comprehensive overview of the available evidence. Taken together, the available evidence suggests that GLP-1 RAs hold promise not only for the treatment but also potentially for the prevention of depressive symptoms, though further investigation is needed.

CRediT authorship contribution statement

Sophie Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Sami George Sabbah:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Angela T.H. Kwan:** Writing – review & editing. **Roger S. McIntyre:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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