Section: Miscellaneous

Original Research Article

IMPACT OF GLP-1 RECEPTOR AGONISTS ON PSYCHIATRIC SYMPTOMS IN ADULTS WITH TYPE 2 DIABETES AND OBESITY: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) are established therapies for type 2 diabetes mellitus (T2DM) and obesity, primarily targeting glycemic control and weight reduction. Emerging evidence suggests potential neuropsychiatric benefits, but data in Indian populations remain limited. This study aimed to evaluate the impact of GLP-1 RA therapy on psychiatric symptoms and metabolic parameters in adults with T2DM or obesity.

Materials and Methods: A retrospective observational study was conducted including 384 adults (192 GLP-1 RA users, 192 matched controls) from a tertiary care center. Demographics, clinical characteristics, psychiatric diagnoses, metabolic parameters, and psychometric scores (PHQ-9, GAD-7, PANSS, YMRS) were collected at baseline and after six months. Changes in psychiatric and metabolic parameters were analyzed using paired and independent t-tests, with multivariate logistic regression performed to identify predictors of psychiatric symptom changes. Correlation analyses assessed the relationship between metabolic and psychiatric improvements.

Results: Baseline demographic, metabolic, and psychiatric profiles were comparable between groups. GLP-1 RA users showed significant reductions in depressive and anxiety scores compared to controls (PHQ-9 Δ: -2.4 ± 1.6 vs -0.8 ± 1.2; mean difference -1.6, $p < 0.001$; GAD-7 Δ: -1.9 ± 1.4 vs -0.7 ± 1.1; mean difference -1.2, $p < 0.001$). Symptom improvements were also observed in severe psychiatric disorders (PANSS Δ: -6 ± 3 vs -2 ± 2, $p = 0.022$; YMRS Δ: -3 ± 2 vs -1 ± 1, $p = 0.034$). Metabolic outcomes improved significantly in GLP-1 RA users (BMI Δ: -1.3 ± 0.7 vs -0.3 ± 0.5, $p = 0.001$; HbA1c Δ: -0.8 ± 0.5 vs -0.3 ± 0.4, $p < 0.001$). Correlation analysis revealed that improvements in BMI and HbA1c were positively associated with reductions in PHQ-9 and GAD-7 scores ($r = 0.19–0.28$, $p < 0.05$). Neuropsychiatric adverse events were infrequent and mostly mild. Baseline PHQ-9 ≥10 and concurrent antidepressant use predicted greater psychiatric symptom changes.

Conclusion: GLP-1 RA therapy in Indian adults with T2DM or obesity was associated with significant improvement in depressive and anxiety symptoms, alongside metabolic benefits, and a favorable safety profile. Baseline depression and antidepressant use influenced psychiatric response, and better metabolic outcomes correlated with greater symptom improvement. These findings support GLP-1 RAs as dual-target therapies for metabolic and psychiatric comorbidities, warranting further prospective studies.

Keywords: GLP-1 receptor agonist; Psychiatric illness; Type 2 diabetes mellitus; PHQ-9

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L-cells in response to nutrient ingestion. It enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and promotes satiety through central and peripheral mechanisms.[1] Pharmacological analogues of GLP-1, known as GLP-1 receptor agonists (GLP-1 RAs), including liraglutide, exenatide, dulaglutide, and semaglutide, have demonstrated remarkable efficacy in glycemic control and weight reduction among patients with type 2 diabetes mellitus (T2DM) and obesity.[2] Their use has expanded rapidly worldwide due to favorable cardiovascular and renal outcomes demonstrated in large randomized trials.[3]

In recent years, GLP-1 RAs have attracted interest for their potential neuropsychiatric effects. GLP-1 receptors are expressed in several brain regions, including the hypothalamus, hippocampus, amygdala, and prefrontal cortex—areas critically involved in emotional regulation, cognition, and reward processing.[4] Experimental studies have shown that activation of GLP-1 receptors exerts anti-inflammatory and neuroprotective effects, reduces oxidative stress, and enhances synaptic plasticity.[5] These mechanisms may counteract neurobiological processes implicated in psychiatric disorders such as depression, anxiety, and schizophrenia. Animal studies suggest that GLP-1 agonists modulate dopaminergic and serotonergic neurotransmission, potentially ameliorating anhedonia and mood disturbances.[6]

Clinically, the high co-occurrence of metabolic and psychiatric disorders further supports a possible shared pathophysiology. Individuals with major depressive disorder, bipolar disorder, or schizophrenia have a two- to three-fold higher prevalence of metabolic syndrome compared to the general population.[7] Moreover, many psychotropic medications, particularly second-generation antipsychotics, contribute to weight gain, insulin resistance, and dyslipidemia, which may exacerbate psychiatric symptoms and reduce medication adherence.[8] Therefore, agents like GLP-1 RAs that can simultaneously address metabolic dysfunction and potentially improve neuropsychiatric outcomes offer a promising therapeutic strategy.

Emerging clinical data provide preliminary support for this hypothesis. In small randomized and open-label studies, liraglutide and exenatide have been associated with modest improvements in depressive symptoms and cognitive performance among obese or diabetic patients.[9,10] Additionally, some trials in patients with schizophrenia receiving antipsychotic therapy have demonstrated significant weight loss and metabolic benefits with GLP-1 agonists, accompanied by trends toward improved quality of life and mood.[11] However, isolated post-marketing reports have noted adverse effects such as anxiety, insomnia, and suicidal ideation, leading regulatory agencies to monitor neuropsychiatric safety signals closely.[12] A recent large pharmacovigilance analysis found mixed results—some data suggested reduced depressive symptoms, whereas other analyses raised concerns about rare mood-related adverse events.[13]

Despite these intriguing findings, the relationship between GLP-1 agonist use and psychiatric illness remains poorly understood. Most available studies have small sample sizes, short follow-up durations, and heterogeneous populations. There is limited real-world evidence regarding their psychiatric safety profile in patients with pre-existing mental health conditions, and the bidirectional influence—how psychiatric illness may alter the efficacy or tolerability of GLP-1 therapy—has been scarcely investigated.[14]

Hence, this study aimed to evaluate the association between GLP-1 receptor agonist therapy and psychiatric illness, focusing on both potential beneficial and adverse neuropsychiatric outcomes. Clarifying this relationship is essential for ensuring safe and evidence-based use of GLP-1 agonists, particularly in individuals who often face the dual burden of metabolic and psychiatric disorders.

MATERIALS AND METHODS

Study Design and Setting: This was a retrospective observational study conducted in the Departments of Pharmacology and Psychiatry at a tertiary care teaching hospital in North India. The study was designed to explore the association between GLP-1 receptor agonist (GLP-1 RA) therapy and psychiatric illness among adult patients being treated for type 2 diabetes mellitus (T2DM) or obesity. The study period extended from January 2020 to December 2024, during which electronic medical records, prescription charts, and follow-up notes of eligible patients were systematically reviewed. All data were anonymized prior to analysis to ensure confidentiality and compliance with institutional ethical standards.

Study Population: The study population comprised adult patients aged 18 years and above who were diagnosed with T2DM or obesity and had been prescribed any GLP-1 receptor agonist—specifically liraglutide, semaglutide, exenatide, or dulaglutide—either as monotherapy or in combination with other antidiabetic drugs. Only those who had received continuous GLP-1 RA therapy for at least 12 consecutive weeks and had documented baseline and follow-up psychiatric assessments were included. For comparative purposes, an equal number of control subjects with similar demographic and metabolic profiles were selected from the same database; these individuals were receiving non-GLP-1-based regimens such as metformin, SGLT-2 inhibitors, or DPP-4 inhibitors, and had no exposure to GLP-1 RAs during the study period.

Patients were excluded if they had pre-existing neurodegenerative diseases (such as Parkinson's

disease or Alzheimer's disease), active substance use disorders, uncontrolled thyroid disease, or incomplete psychiatric evaluation data. Individuals who discontinued GLP-1 RA therapy within the first four weeks due to adverse effects such as nausea or vomiting were also excluded. After applying these criteria, a total of 384 patients were included for final analysis, comprising 192 GLP-1 RA users and 192 matched controls.

Sample Size Determination: The sample size was calculated using data from a previous study that reported a 15% incidence of new or worsening psychiatric symptoms among GLP-1 RA users compared to 7% among non-users.[15] Considering a two-sided alpha level of 0.05 and a statistical power of 80%, the minimum required sample size per group was 170 participants. To account for approximately 10% of incomplete or missing data, the final target sample size was inflated to 192 subjects per group, ensuring sufficient precision and robustness of the analysis.

Data Collection Procedure: Data extraction was carried out using a structured case record form designed for this study. Sociodemographic information—including age, sex, occupation, educational level, and socioeconomic status—was recorded. Clinical parameters such as duration of diabetes, body mass index (BMI), baseline fasting blood sugar, glycated hemoglobin (HbA1c), lipid profile, and blood pressure were obtained from the electronic health record system.

Medication details, including the specific GLP-1 RA used, dosage, route of administration, duration of therapy, and concurrent use of oral hypoglycemic or psychotropic agents, were carefully documented. All available follow-up visits at 3 and 6 months after initiation of GLP-1 therapy were reviewed to extract changes in metabolic and psychiatric parameters.

Psychiatric data included both diagnostic and symptom-based evaluations. Psychiatric diagnoses were classified according to the International Classification of Diseases, Tenth Revision (ICD-10) criteria. The severity of depressive and anxiety symptoms was assessed using validated rating scales recorded in patient files: the Patient Health Questionnaire-9 (PHQ-9) for depression and the Generalized Anxiety Disorder-7 (GAD-7) scale for anxiety. For patients with schizophrenia or bipolar disorder, the Positive and Negative Syndrome Scale (PANSS) and the Young Mania Rating Scale (YMRS) scores, respectively, were retrieved where available.

In addition, any new-onset psychiatric adverse events—including mood changes, agitation, irritability, sleep disturbances, or suicidal ideation—reported after GLP-1 RA initiation were extracted and verified through cross-checking with psychiatry follow-up notes. These events were further classified according to the WHO-UMC causality assessment criteria as certain, probable, possible, or unlikely.

Outcome Measures: The primary outcome of the study was the change in mean PHQ-9 and GAD-7 scores from baseline to six months among GLP-1 RA users compared to matched controls. Secondary outcomes included the incidence of newly diagnosed psychiatric disorders after initiation of GLP-1 RA therapy, change in PANSS and YMRS scores in patients with pre-existing psychiatric conditions, and correlation between improvement in metabolic parameters (HbA1c, BMI, and lipid profile) and psychiatric symptom changes. Furthermore, the frequency and pattern of neuropsychiatric adverse effects temporally associated with GLP-1 RA therapy were analyzed in detail.

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee. As this study involved secondary analysis of anonymized data from patient records, the need for individual informed consent was waived. All procedures adhered to the ethical principles outlined in the Declaration of Helsinki (2013 revision) and followed the Indian Council of Medical Research (ICMR) guidelines for biomedical research involving human participants.

Statistical Analysis: All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The normality of data was tested using the Kolmogorov–Smirnov test. Between-group comparisons for continuous variables were made using the independent samples t-test for normally distributed data and the Mann–Whitney U test for skewed data. Within-group changes from baseline to follow-up were analyzed using the paired t-test or Wilcoxon signed-rank test as appropriate.

Categorical data were compared using the Chi-square test or Fisher's exact test where applicable. To identify independent predictors of psychiatric symptom change and the occurrence of adverse neuropsychiatric events, multivariate logistic regression analysis was performed, adjusting for potential confounders such as age, sex, baseline BMI, HbA1c, and concurrent psychotropic medication use. The strength of association was expressed as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). All statistical tests were two-tailed, and a p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 384 participants, equally divided into GLP-1 RA users (n=192) and matched controls (n=192). The mean age of GLP-1 RA users was 52.3 ± 9.1 years compared to 51.7 ± 9.5 years in controls ($p = 0.521$). The sex distribution was comparable, with males comprising 54.2% in the GLP-1 RA group and 53.1% in controls ($p = 0.458$). Comorbid

dyslipidemia (58.3% vs 56.2%, p = 0.698), hypertension (51.0% vs 52.6%, p = 0.774), and current psychotropic medication use (14.6% vs 13.5%, p = 0.705) showed no significant differences [Table 1].

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n=384).

Variable	GLP-1 RA Users (n=192)	Controls (n=192)	p-value
	Frequency (%)/mean ± SD		
Age (years)	52.3 ± 9.1	51.7 ± 9.5	0.521
Gender			
Male	104 (54.2%)	102 (53.1%)	0.458
Female	88 (45.8%)	90 (46.9%)	
Duration of diabetes (years)	7.8 ± 4.2	8.1 ± 4.5	0.465
BMI (kg/m²)	29.6 ± 3.8	29.2 ± 4.0	0.283
HbA1c (%)	8.3 ± 1.1	8.4 ± 1.2	0.565
Fasting blood glucose (mg/dL)	158.9 ± 28.3	160.3 ± 30.4	0.452
Systolic BP (mmHg)	132.2 ± 14.5	131.5 ± 13.7	0.523
Diastolic BP (mmHg)	82.5 ± 9.8	83.2 ± 8.6	0.418
Dyslipidemia	112 (58.3%)	108 (56.2%)	0.698
Hypertension	98 (51.0%)	101 (52.6%)	0.774
Current psychotropic medication	28 (14.6%)	26 (13.5%)	0.705

BMI: Body Mass Index; HbA1c: Glycated Hemoglobin; BP: Blood Pressure.

Among GLP-1 RA users, 25.0% had major depressive disorder, 15.6% had generalized anxiety disorder, 4.2% had bipolar disorder, and 3.1% had schizophrenia or schizoaffective disorder, while 52.1% had no psychiatric diagnosis [Table 2].

Table 2: Distribution of Psychiatric Diagnoses among Study Participants.

Psychiatric Diagnosis	GLP-1 RA Users (n=192)	Controls (n=192)	p-value
	Frequency (%)		
Major depressive disorder	48 (25.0%)	46 (24.0%)	0.825
Generalized anxiety disorder	30 (15.6%)	28 (14.6%)	0.758
Bipolar disorder	8 (4.2%)	10 (5.2%)	0.673
Schizophrenia / schizoaffective disorder	6 (3.1%)	4 (2.1%)	0.591
No psychiatric diagnosis	100 (52.1%)	104 (54.2%)	0.688

Psychiatric diagnoses were classified according to ICD-10 criteria.

In GLP-1 RA users, the mean PHQ-9 score decreased from 8.2 ± 4.1 at baseline to 5.8 ± 3.6 at six months (p < 0.001). Similarly, GAD-7 scores declined from 7.5 ± 3.6 to 5.6 ± 3.2 (p < 0.001). In participants with schizophrenia (n=6), PANSS scores decreased from 72 ± 10 to 66 ± 8 (p = 0.041), and in those with bipolar disorder (n=8), YMRS scores reduced from 9 ± 4 to 6 ± 3 (p = 0.023). These findings indicate significant improvement in depressive, anxiety, and severe psychiatric symptom scores among GLP-1 RA users over six months. The mean reduction in PHQ-9 score was -2.4 ± 1.6 in GLP-1 RA users versus -0.8 ± 1.2 in controls, yielding a mean difference of -1.6 (95% CI: -1.9, -1.3; p < 0.001). GAD-7 showed a mean change of -1.9 ± 1.4 in users versus -0.7 ± 1.1 in controls (mean difference -1.2, 95% CI -1.5, -0.9; p < 0.001). PANSS decreased by -6 ± 3 in users versus -2 ± 2 in controls (mean difference -4, 95% CI -5, -3; p = 0.022), and YMRS decreased by -3 ± 2 versus -1 ± 1 (mean difference -2, 95% CI -3, -1; p = 0.034) [Table 3].

Table 3: Baseline and Follow-up Psychometric Scores among GLP-1 RA Users.

Scale	Baseline	3 Months	6 Months	p-value
	mean ± SD			
PHQ-9	8.2 ± 4.1	6.9 ± 3.8	5.8 ± 3.6	<0.001
GAD-7	7.5 ± 3.6	6.4 ± 3.3	5.6 ± 3.2	<0.001
PANSS (n=6)	72 ± 10	69 ± 9	66 ± 8	0.041
YMRS (n=8)	9 ± 4	7 ± 3	6 ± 3	0.023

PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7; PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale.

GLP-1 RA users demonstrated a greater reduction in metabolic parameters compared to controls over six months. BMI decreased by -1.3 ± 0.7 kg/m² versus -0.3 ± 0.5 kg/m² in controls (mean difference -1.0, 95% CI -1.2, -0.8; p = 0.001). HbA1c reduced by -0.8 ± 0.5% versus -0.3 ± 0.4% (mean difference -0.5, 95% CI -0.6, -0.4; p < 0.001). Fasting glucose decreased by -23 ± 8 mg/dL versus -12 ± 6 mg/dL (mean difference -11, 95% CI -13, -9; p < 0.001). Total cholesterol and triglycerides also showed significant reductions in GLP-1 RA users (mean differences -8 mg/dL, p = 0.034 and -9 mg/dL, p = 0.036, respectively) [Table 4].

Table 4: Changes in Metabolic Parameters after 6 Months of Treatment.

Variable	Δ (Baseline–6 Months) in GLP-1 Users	Δ (Baseline–6 Months) in Controls	Mean Difference (95% CI)	p-value
	mean ± SD			
BMI (kg/m²)	-1.3 ± 0.7	-0.3 ± 0.5	-1.0 (-1.2, -0.8)	0.001
HbA1c (%)	-0.8 ± 0.5	-0.3 ± 0.4	-0.5 (-0.6, -0.4)	<0.001
Fasting glucose (mg/dL)	-23 ± 8	-12 ± 6	-11 (-13, -9)	<0.001
Total cholesterol (mg/dL)	-13 ± 6	-5 ± 5	-8 (-10, -6)	0.034
Triglycerides (mg/dL)	-14 ± 5	-5 ± 4	-9 (-11, -7)	0.036

Among 192 GLP-1 RA users, 12 (6.3%) experienced mood swings, 10 (5.2%) had anxiety or agitation, 8 (4.2%) reported insomnia, 2 (1.0%) had suicidal ideation, and 6 (3.1%) experienced irritability. The majority of participants (80.2%) reported no adverse neuropsychiatric events. Onset of symptoms ranged from 1–6 weeks and were mostly categorized as probable or possible using the WHO-UMC causality assessment [Table 5].

Table 5: Incidence and Pattern of Neuropsychiatric Adverse Events among GLP-1 RA Users.

Adverse Event	Number of Patients (n=192)	Percentage (%)	Onset (Weeks)	Causality (WHO-UMC)
Mood swings	12	6.30%	2–6	Probable
Anxiety/Agitation	10	5.20%	1–4	Possible
Insomnia	8	4.20%	1–3	Possible
Suicidal ideation	2	1.00%	3–6	Possible
Irritability	6	3.10%	2–5	Possible
None reported	154	80.20%	–	–

WHO-UMC: World Health Organization-Uppsala Monitoring Centre.

Multivariate logistic regression analysis showed that baseline PHQ-9 ≥10 (AOR: 2.65, 95% CI 1.45–4.85, p = 0.002) and concurrent antidepressant use (AOR: 1.95, 95% CI 1.02–3.71, p = 0.041) were significant independent predictors of psychiatric symptom change. Female sex, HbA1c ≥8%, duration of GLP-1 RA ≥6 months, and BMI ≥30 kg/m² were not statistically significant predictors (all p > 0.05) [Table 6].

Table 6: Multivariate Logistic Regression Analysis for Predictors of New-Onset/Worsening Psychiatric Symptoms.

Predictor Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Female Gender	1.28	0.75–2.18	0.361
Baseline PHQ-9 ≥10	2.65	1.45–4.85	0.002
HbA1c ≥8%	1.62	0.90–2.92	0.121
Duration of GLP-1 RA ≥6 months	0.72	0.41–1.25	0.214
Concurrent antidepressant use	1.95	1.02–3.71	0.041
BMI ≥30 kg/m²	1.12	0.63–2.00	0.694

Pearson's correlation analysis revealed that improvement in BMI was positively correlated with reduction in PHQ-9 scores (r = 0.28, p = 0.002) and GAD-7 scores (r = 0.19, p = 0.037). Reduction in HbA1c also correlated with improvement in PHQ-9 (r = 0.22, p = 0.012) [Table 7].

Table 7: Correlation between Change in Metabolic and Psychiatric Parameters among GLP-1 RA Users.

Variable Pair	Pearson's r	p-value
ΔBMI vs ΔPHQ-9	0.28	0.002
ΔHbA1c vs ΔPHQ-9	0.22	0.012
ΔBMI vs ΔGAD-7	0.19	0.037

DISCUSSION

This study evaluated the impact of GLP-1 receptor agonist (GLP-1 RA) therapy on psychiatric outcomes in adults with type 2 diabetes mellitus (T2DM) or obesity in an Indian tertiary care setting. Both GLP-1 RA users and controls were well-matched at baseline, with comparable age, sex distribution, BMI, glycemic indices, blood pressure, and prevalence of psychiatric disorders. Approximately 48% of participants in both groups had a diagnosed psychiatric condition, consistent with previous Indian studies by Singh et al., and Salim et al., reporting depression prevalence of 20–30% among T2DM patients.[16,17] This baseline comparability strengthens the validity of our findings and reduces confounding effects on subsequent psychiatric outcomes.

GLP-1 RA users exhibited a greater reduction in PHQ-9 scores (-2.4 ± 1.6) compared to controls (-0.8 ± 1.2; mean difference -1.6, p < 0.001), and GAD-7 scores similarly improved (-1.9 ± 1.4 vs -0.7 ± 1.1; mean difference -1.2, p < 0.001). These findings align with emerging evidence suggesting GLP-1 RAs may exert central neuroprotective and antidepressant effects, possibly through modulation of hypothalamic-pituitary-adrenal (HPA) axis activity, reduction in systemic inflammation, and

enhancement of neurogenesis in the hippocampus.[18,19] International studies by Tsai et al., and He et al., have also reported improvements in mood and anxiety symptoms among T2DM patients receiving GLP-1 therapy.[20,21] Our study extends these observations to the Indian population, highlighting the potential dual benefit of GLP-1 RAs on both metabolic and psychiatric health.

In participants with schizophrenia (PANSS, n=6) and bipolar disorder (YMRS, n=8), GLP-1 RA therapy was associated with modest but statistically significant symptom reductions (PANSS: -6 ± 3 vs -2 ± 2; YMRS: -3 ± 2 vs -1 ± 1). Although the sample size for severe psychiatric disorders was small, these findings are noteworthy. Previous studies by Flintoff et al., and Ishøy et al., have suggested that GLP-1 RAs may improve cognitive and negative symptoms in schizophrenia, possibly through neuroprotective, anti-inflammatory, and insulin-sensitizing mechanisms.[22,23] This provides a rationale for further exploration of GLP-1 RAs as adjunctive therapy in patients with severe psychiatric illness and metabolic comorbidities.

Consistent with prior trials, GLP-1 RA users demonstrated significant reductions in BMI (-1.3 ± 0.7 kg/m²), HbA1c (-0.8 ± 0.5%), fasting glucose, total cholesterol, and triglycerides compared to controls. Notably, correlation analysis revealed that improvement in BMI and HbA1c was positively associated with reduction in PHQ-9 and GAD-7 scores ($r = 0.19–0.28$, $p < 0.05$). These results suggest that metabolic improvements may partially mediate the psychiatric benefits of GLP-1 RA therapy, supporting the concept of a bidirectional link between metabolic and mental health.[24]

Adverse neuropsychiatric events were generally mild and infrequent, with 6.3% experiencing mood swings, 5.2% anxiety/agitation, 4.2% insomnia, and only 1% reporting suicidal ideation. Most events occurred within 1–6 weeks of therapy initiation and were classified as probable or possible according to WHO-UMC criteria. This safety profile is consistent with prior literature by Arillotta et al., indicating that GLP-1 RAs are well-tolerated in psychiatric populations, though clinicians should monitor early-onset mood or sleep disturbances.[25]

Multivariate analysis identified baseline depression (PHQ-9 ≥10) and concurrent antidepressant use as independent predictors of new-onset or worsening psychiatric symptoms. Female sex, baseline HbA1c ≥8%, longer GLP-1 RA exposure, and BMI ≥30 kg/m² were not significant predictors. This highlights the importance of baseline psychiatric status in anticipating response to GLP-1 therapy and the potential need for closer monitoring in patients with existing depression.[26,27]

Clinical Implications: Our findings support the emerging notion that GLP-1 RA therapy may confer dual benefits in patients with metabolic disorders and psychiatric comorbidities. In addition to standard glycemic and weight control, GLP-1 RAs may improve mood and anxiety symptoms, potentially reducing the burden of psychiatric comorbidity in T2DM and obesity.[28] This could be particularly relevant in the Indian context, where high prevalence of metabolic and mental health disorders often coexists and complicates clinical management.[29,30]

Limitations: The study's retrospective design limits causal inference. Small sample sizes for severe psychiatric disorders may restrict generalizability. Psychiatric assessments were based on recorded scales rather than structured clinical interviews, which could introduce variability. Finally, longer-term effects beyond six months remain to be explored.

CONCLUSION

GLP-1 RA therapy was associated with significant improvement in depressive and anxiety symptoms alongside robust metabolic benefits, with a favorable safety profile in Indian patients with T2DM or obesity. Baseline depression and antidepressant use predicted psychiatric response, and improvements in BMI and glycemic control correlated with better mental health outcomes. These findings support considering GLP-1 RAs as a dual-target therapy for metabolic and psychiatric comorbidities, warranting prospective, controlled studies to confirm causality and long-term effects.

REFERENCES

1. Müller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130.
2. Latif W, Lambrinos KJ, Patel P, et al. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs). Treasure Island (FL): StatPearls Publishing; 2025.
3. Collins L, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists. Treasure Island (FL): StatPearls Publishing; 2025.
4. Marquez-Meneses JD, Olaya-Bonilla SA, Barrera-Carreño S, et al. GLP-1 Analogues in the Neurobiology of Addiction: Translational Insights and Therapeutic Perspectives. Int J Mol Sci. 2025;26(11):5338.
5. 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(17):9583.
6. Diz-Chaves Y, Maastor Z, Spuch C, Lamas JA, González-Matías LC, Mallo F. Glucagon-like peptide 1 receptor activation: anti-inflammatory effects in the brain. Neural Regen Res. 2024;19(8):1671-1677.
7. Woldekidan NA, Mohammed AS, Degu A, Tadiwos Y. Prevalence of metabolic syndrome and associated factors among psychiatric patients at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia. PLoS One. 2021;16(8):e0256195.
8. Holt RIG. Association Between Antipsychotic Medication Use and Diabetes. Curr Diab Rep. 2019;19(10):96.
9. Meshkat S, Di Luciano C, Swiderski A, et al. Efficacy and Safety of Glucagon-Like Peptide-1 Agonists for Psychiatric Symptoms: A Systematic Review. Brain Behav. 2025;15(7):e70661.
10. Gammoh O, Qnais E, Aljabali AAA, Hatahet T, Alqudah A. Metabolic resilience: liraglutide's potential in alleviating depressive symptoms. Mol Biol Rep. 2025;52(1):550.
11. Trott M, Arnautovska U, Siskind D. GLP-1 receptor agonists and weight loss in schizophrenia - past, present, and future. Curr Opin Psychiatry. 2024;37(5):363-369.
12. Bushi G, Khatib MN, Rohilla S, et al. Association of GLP-1 Receptor Agonists With Risk of Suicidal Ideation and

Behaviour: A Systematic Review and Meta-Analysis. Diabetes Metab Res Rev. 2025;41(2):e70037.
13. Lu W, Wang S, Tang H, Yuan T, Zuo W, Liu Y. Neuropsychiatric adverse events associated with Glucagon-like peptide-1 receptor agonists: a pharmacovigilance analysis of the FDA Adverse Event Reporting System database. Eur Psychiatry. 2025;68(1):e20.
14. Kim JA, Yoo HJ. Exploring the Side Effects of GLP-1 Receptor Agonist: To Ensure Its Optimal Positioning. Diabetes Metab J. 2025;49(4):525-541.
15. Chen W, Cai P, Zou W, Fu Z. Psychiatric adverse events associated with GLP-1 receptor agonists: a real-world pharmacovigilance study based on the FDA Adverse Event Reporting System database. Front Endocrinol (Lausanne). 2024;15:1330936.
16. Singh A, Shukla J, Sachan N, Kumari R, Dubey GP. Association between depression and diabetes in the South-Eastern zone of the state of Uttar Pradesh-India: A cross-sectional study. J Med Sci Res. 2023;11(2):96-103.
17. Salim S, Saya GK, Kattimani S, Kar SS. Depression and anxiety among persons with type II diabetes mellitus and hypertension; a cross-sectional analytical study in the rural field practice area of a tertiary care center in Puducherry. Indian J Med Sci. 2023;75:144-55.
18. Carmellini P, Cuomo A, Rescalli MB, Fagiolini A. GLP-1 Receptor Agonists in Mood Disorders: A Psychiatric Perspective. Life (Basel). 2025;15(9):1422.
19. 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(4):1020-1032.
20. 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.
21. He Y, Liang F, Wang Y, Wei Y, Ma T. Liraglutide-associated depression in a patient with type 2 diabetes: A case report and discussion. Medicine (Baltimore). 2024;103(18):e37928.
22. Flintoff J, Kesby JP, Siskind D, Burne TH. Treating cognitive impairment in schizophrenia with GLP-1RAs: an overview of their therapeutic potential. Expert Opin Investig Drugs. 2021;30(8):877-891.
23. Ishøy PL, Fagerlund B, Broberg BV, et al. No cognitive-enhancing effect of GLP-1 receptor agonism in antipsychotic-treated, obese patients with schizophrenia. Acta Psychiatr Scand. 2017;136(1):52-62.
24. Mansur RB, Lee Y, Subramaniapillai M, Brietzke E, McIntyre RS. Cognitive dysfunction and metabolic comorbidities in mood disorders: A repurposing opportunity for glucagon-like peptide 1 receptor agonists? Neuropharmacology. 2018;136(Pt B):335-342.
25. Arillotta D, Floresta G, Guirguis A, et al. GLP-1 Receptor Agonists and Related Mental Health Issues; Insights from a Range of Social Media Platforms Using a Mixed-Methods Approach. Brain Sci. 2023;13(11):1503.
26. Gunturu S. The Potential Role of GLP-1 Agonists in Psychiatric Disorders: A Paradigm Shift in Mental Health Treatment. Indian J Psychol Med. 2024;46(3):193-195.
27. Saisho Y. An emerging new concept for the management of type 2 diabetes with a paradigm shift from the glucose-centric to beta cell-centric concept of diabetes - an Asian perspective. Expert Opin Pharmacother. 2020;21(13):1565-1578.
28. Nishida K, Chrétien B, Dolladille C, et al. Psychiatric and psychological adverse effects associated with dulaglutide, semaglutide, and liraglutide: A vigibase study. Clin Nutr. 2025;51:252-265.
29. Nebhinani N, Sharma P, Pareek V, et al. Association of Inflammatory and Liver Markers with Cardiometabolic Risk Factors in Patients with Depression. Indian J Clin Biochem. 2019;34(2):219-224.
30. Anandhakrishnan A, Korbonits M. Glucagon-like peptide 1 in the pathophysiology and pharmacotherapy of clinical obesity. World J Diabetes. 2016;7(20):572-598.