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Original Research Article

Effects of Statins as an Adjunct to Antidepressants on Clinical Outcomes and TyG Index in Depression: A Prospective Observational Study

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Abstract

Introduction: Major depressive disorder (MDD) represents a significant global health concern, characterized by a pervasive low mood, loss of interest or pleasure and a range of cognitive and somatic symptoms. Statins biological effects have spurred interest in the potential utility of statins in various conditions beyond cardiovascular disease, including neurological and psychiatric disorders. Given their established safety profile and the growing understanding of their pleiotropic actions, statins represent a promising class of medications for potential repurposing as adjunctive therapies in the management of depression.

Methods: This study employed a prospective observational design to evaluate the effects of adjunctive statin therapy on clinical outcomes and the TyG index in individuals with depression over a 12-month period. The study included two groups of participants: the Adjunctive Statin Group with Antidepressant and the Antidepressant-Only Group. The Adjunctive Statin Group consist of patients with a diagnosis of MDD who were receiving a stable dose of antidepressant medication and whose treating physician had initiated statin therapy as part of their clinical management within one month prior to or at the time of study enrollment. The Antidepressant-Only Group served as the control group and comprised patients with MDD who were also receiving a stable dose of antidepressant medication but will was not prescribed a statin during the study period.

Results: The mean age was similar between groups (45.2 vs. 44.6 years, p=0.74), with a comparable proportion of females (53.3% vs. 56.7%, p=0.71). Both groups were having overweight with BMI values (27.1 vs. 26.8 kg/m², p=0.66) and a comparable mean duration of depression (~6.5–6.8 years, p=0.72). Baseline HAM-D, MADRS, and PHQ-9 scores did not differ significantly (all p>0.7), confirming that the groups started with similar severity of depressive symptoms. Medication classes were comparable, with SSRIs being the most commonly prescribed (~55%). As expected, only the adjunctive group received statins (45% atorvastatin, 35% rosuvastatin, 20% simvastatin). Baseline triglycerides, glucose, and TyG index values were nearly identical across groups (p-values 0.74–0.87).

Conclusion: The results have the potential to contribute to our understanding of novel treatment strategies for major depressive disorder, considering the intricate interplay between mental health and metabolic factors. By carefully observing and analyzing the outcomes in a naturalistic clinical setting, this research seeks to inform future clinical practice and guide further investigations into the therapeutic potential of statins in the management of depression.

Keywords: Statins, Antidepressants, TyG Index, Depression.

Introduction

Major depressive disorder (MDD) represents a significant global health concern, characterized by a pervasive low mood, loss of interest or pleasure, and a range of cognitive and somatic symptoms. [1] This debilitating condition affects an estimated 5% of adults worldwide, with a higher prevalence observed in women. [2] In the United States, recent data indicates that nearly three in ten adults have experienced depression at some point in their lives, and approximately 18% are currently affected. [3] The clinical presentation of MDD includes persistent sadness, irritability, feelings of emptiness or hopelessness, diminished interest in previously enjoyed activities, significant changes in appetite and weight, sleep disturbances, fatigue, feelings of worthlessness or excessive guilt, and impaired concentration. [4] These symptoms can profoundly impact an individual's personal, social, and occupational functioning, highlighting the substantial burden of this disorder. [5] Furthermore, depression is associated with increased healthcare utilization and a higher risk of comorbid medical conditions such as cardiovascular disease and diabetes. [6] Given the widespread prevalence and substantial impact of MDD, there remains a critical need for ongoing research to identify and refine effective treatment strategies that extend beyond the current standard of care.

While antidepressant medications and psychotherapy are established first-line treatments for MDD, a considerable proportion of patients fail to achieve full remission or experience an inadequate response. [7] Studies indicate that response rates to initial antidepressant treatment typically range from 50% to 60%, and a substantial number of individuals continue to experience significant symptoms despite multiple treatment attempts. [8] The majority of currently available antidepressants primarily target the monoaminergic neurotransmitter systems, such as serotonin, norepinephrine, and dopamine. [9] Despite their efficacy for many, the limitations of these treatments, including delayed onset of action, potential side effects, and incomplete symptom resolution in a significant subset of patients, underscore the importance of exploring novel or adjunctive therapeutic approaches. [10]

Statins, primarily known for their efficacy in lowering cholesterol levels, are widely prescribed for the prevention and treatment of cardiovascular diseases. [11] These agents exert their primary effect by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in the cholesterol biosynthesis pathway. [12] Beyond their well-established lipid-lowering properties, statins exhibit a range of pleiotropic effects, including anti-inflammatory, immunomodulatory, antioxidant, and antithrombotic activities. [13] These diverse biological effects have spurred interest in the potential utility of statins in various conditions beyond cardiovascular disease, including neurological and psychiatric disorders. [14] Given their established safety profile and the growing understanding of their pleiotropic actions, statins represent a promising class of medications for potential repurposing as adjunctive therapies in the management of depression. Several preliminary studies and meta-analyses have explored this potential, with some suggesting a modest but significant benefit of adjunctive statin therapy in reducing depressive symptom severity. [15] Furthermore, a large observational study indicated a lower risk of psychiatric hospitalization for depression in patients receiving both an SSRI and a statin compared to those on an SSRI alone. [16] While these findings are encouraging, the evidence remains somewhat inconsistent, necessitating further investigation to clarify the role of statins as an adjunctive treatment for depression in real-world clinical settings.

In addition to exploring the impact of statins on clinical outcomes in depression, this study aims to investigate their effects on metabolic parameters, specifically the triglyceride-glucose (TyG) index. The TyG index, calculated using fasting triglyceride and glucose levels, serves as a reliable and convenient surrogate marker for insulin resistance (IR). [17] Insulin resistance has been increasingly recognized as a potential contributing factor to the development and progression of MDD, with several studies reporting a positive association between higher TyG index values and an increased risk and severity of depression. [18] Moreover, the TyG index has been shown to be associated with increased cardiovascular risk and metabolic disorders, conditions that frequently co-occur with depression. [19]

Objective: To evaluate the effects of adjunctive statin therapy on depressive symptom severity and metabolic outcomes, specifically the triglyceride–glucose (TyG) index, in patients with major depressive disorder receiving standard antidepressant treatment, and to compare these outcomes with those observed in patients receiving antidepressant therapy alone.

Methods

This study employed a prospective observational design to evaluate the effects of adjunctive statin therapy on clinical outcomes and the TyG index in individuals with depression over a 12-month period. The observational nature of the study allows for the examination of treatment decisions

made by the patients' treating physicians in the context of routine clinical care, enhancing the ecological validity and generalizability of the findings.[61] Participants were recruited from outpatient psychiatry department. All participants were provided written informed consent prior to enrollment, and the study protocol were adhered to ethical guidelines for observational research. The study included two groups of participants: the Adjunctive Statin Group and the Antidepressant-Only Group. The Adjunctive Statin Group consist of patients with a diagnosis of MDD who were receiving a stable dose of antidepressant medication and whose treating physician had initiated statin therapy as part of their clinical management within one month prior to or at the time of study enrollment. The Antidepressant-Only Group served as the control group and comprised patients with MDD who were also receiving a stable dose of antidepressant medication but will was not prescribed a statin during the study period.

Eligible Participation, individuals were adults aged 18 years or older with a confirmed diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) or the International Classification of Diseases, 10th Revision (ICD-10) criteria. [2] All participants received a stable dose of at least one antidepressant medication for a minimum of four weeks prior to enrollment to ensure that the effects of the adjunctive statin therapy can be more readily discerned. [20] Individuals in the Adjunctive Statin Group initiated statin therapy, with the type and dosage determined by their treating physician, within the specified timeframe. Exclusion criteria were included a history of known contraindications to statin therapy, a pre-existing diagnosis of a psychotic disorder, unstable medical conditions that could potentially confound the assessment of depressive symptoms or the TyG index, and pregnancy or breastfeeding. [21]

Two parallel groups (adjunctive statin vs antidepressant-only), 1:1 allocation.

Primary endpoint: mean change in HAM-D from baseline to 12 months.

Hypothesis: adjunctive statins produce a greater reduction in HAM-D than antidepressant-only.

Assumptions (a priori)

- Type I error (α, two-sided): 0.05 → Zα/2=1.96Z_{α/2}=1.96Zα/2=1.96
- Power (1−β): 85% → Zβ=1.036Z_{β}=1.036Zβ=1.036
- Clinically important mean difference in HAM-D change (Δ): 3.5 points
- SD of the change score (σ): 6.0 points (conservative, based on typical variability in MDD trials)
- Allocation ratio: 1:1

$$n\_\text{per group} = \frac{2\,(Z\_\alpha/2 + Z\_\beta)^2\,\sigma^2}{\Delta^2}$$

Calculation

$$(Z\_\alpha/2 + Z\_\beta)^2 = (1.96 + 1.036)^2 = (2.996)^2 = 8.976$$

$$n = \frac{2 \times 8.976 \times 6^2}{3.5^2} = \frac{2 \times 8.976 \times 36}{12.25} = \frac{646.272}{12.25} = 52.8 \approx 53 \text{ per group}$$

Allowance for loss to follow-up / non-adherence

Assume **12% attrition**:

$$n\_\text{adjusted} = \frac{53}{0.88} = 60.2 \Rightarrow \mathbf{60 \text{ per group}}$$

Final sample size

$\mathbf{N = 120}$ participants (60 adjunctive-statin, 60 antidepressant-only).

Data on the specific antidepressant medication(s) used, including the type, dosage, and duration of treatment, were collected for each participant at baseline and throughout the study period. Similarly, for participants in the Adjunctive Statin Group, detailed information regarding the type of statin prescribed (e.g., Atorvastatin, Simvastatin, Rosuvastatin), the dosage, and the clinical indication for statin initiation (e.g., hyperlipidemia, cardiovascular risk prevention) were recorded.

The primary clinical outcome of interest changed in the severity of depressive symptoms, which were assessed at baseline and at 3, 6, and 12-month follow-up visits using standardized and validated depression rating scales. These included the Hamilton Depression Rating Scale (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Patient Health Questionnaire-9 (PHQ-9).[22] Response to treatment was defined as a ≥50% reduction from baseline in the total score on the chosen depression scale, while remission was defined as achieving a score below a pre-specified threshold on the same scale (e.g., HAM-D < 7, MADRS < 10, PHQ-9 < 5).[23]

The secondary outcome of interest was changed in the triglyceride-glucose (TyG) index. Fasting blood samples were collected from all participants at baseline and at the 3, 6, and 12-month follow-up visits after an overnight fast of at least 8 hours. Plasma triglyceride and fasting glucose levels were measured using standard laboratory assays at a central, certified laboratory. The TyG index was calculated for each participant at each time point using the established formula: ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].[24]

Data collection was scheduled in-person visits conducted at baseline and the designated follow-up intervals. At each visit, comprehensive information was gathered, including demographic characteristics, detailed medical history, relevant lifestyle factors such as diet, exercise habits, smoking status, and alcohol consumption, as well as a complete list of all concomitant medications. Adherence to both the prescribed antidepressant

and statin medications was assessed through patient self-report, and where feasible, through the review of pharmacy records.

Statistical Analysis: Statistical analyses were performed using appropriate software. Descriptive statistics was used to characterize the baseline demographic and clinical features of the participants in both study groups. Comparisons of continuous variables between the groups at baseline was performed using independent samples t-tests or non-parametric alternatives such as the Mann-Whitney U test, as appropriate. Categorical variables were compared using chi-square tests or Fisher's exact tests.

Longitudinal changes in depressive symptom scores and the TyG index within each group over the 12-month study period was analyzed using paired t-tests or Wilcoxon signed-rank tests. To assess the effect of adjunctive statin therapy on the changes in these outcomes over time, mixed-effects models or repeated measures analysis of variance (ANOVA) were employed. These analyses were control for baseline values of the outcome variables and other potential confounding factors, such as age, sex, baseline depression severity, the specific type and dosage of antidepressant and statin medications, and the presence of relevant comorbidities.

Results

Table 1: Baseline Characteristics of Study Participants

Characteristic	Adjunctive Statin Group (N=60)	Antidepressant-Only Group (N=60)	p-value
Age (years), mean ± SD	45.2 ± 10.8	44.6 ± 11.2	0.74
Sex (female, %)	32 (53.3%)	34 (56.7%)	0.71
BMI (kg/m²), mean ± SD	27.1 ± 3.6	26.8 ± 3.5	0.66
Duration of Depression (years)	6.8 ± 3.9	6.5 ± 4.1	0.72
Baseline HAM-D Score, mean ± SD	22.4 ± 4.8	22.1 ± 4.7	0.81
Baseline MADRS Score, mean ± SD	30.6 ± 6.5	30.2 ± 6.2	0.76
Baseline PHQ-9 Score, mean ± SD	16.7 ± 3.9	16.5 ± 4.0	0.83
Antidepressant Medication(s) (%)	SSRI 55%, SNRI 25%, TCA 10%, Others 10%	SSRI 53%, SNRI 27%, TCA 12%, Others 8%	0.92
Comorbidities (%)	Hypertension 28%, Diabetes 22%, Hyperlipidemia 30%	Hypertension 27%, Diabetes 20%, Hyperlipidemia 28%	0.88
Statin Medication (type, %)	Atorvastatin 45%, Rosuvastatin 35%, Simvastatin 20%	N/A	–
Baseline Triglycerides (mg/dL)	172.4 ± 38.6	169.8 ± 40.2	0.74
Baseline Glucose (mg/dL)	102.5 ± 12.7	101.8 ± 13.2	0.81
Baseline TyG Index, mean ± SD	8.77 ± 0.46	8.75 ± 0.48	0.87

In table 1, The mean age was similar between groups (45.2 vs. 44.6 years, p=0.74), with a comparable proportion of females (53.3% vs. 56.7%, p=0.71).

Both groups had overweight BMI values (27.1 vs. 26.8 kg/m², p=0.66) and a comparable mean duration of depression (~6.5–6.8 years, p=0.72). Baseline HAM-D, MADRS, and PHQ-9 scores did not differ significantly (all p>0.7), confirming that the groups started with similar severity of depressive symptoms. Medication classes were comparable, with SSRIs being the most commonly prescribed (~55%).

As expected, only the adjunctive group received statins (45% atorvastatin, 35% rosuvastatin, 20% simvastatin). Baseline triglycerides, glucose, and TyG index values were nearly identical across groups (p-values 0.74–0.87).

Table 2: Changes in Depressive Symptoms and TyG Index over Time

Outcome Measure	Group	Baseline, Mean ± SD	3 Months	6 Months	12 Months	p-value (within group)	p-value (between groups)
HAM-D Score	**Adjunctive Statin Group**	**22.4 ± 4.8**	**16.8 ± 4.2**	**13.2 ± 3.8**	**10.4 ± 3.2**	**<0.001**	**0.02**
	Antidepressant-Only Group	22.1 ± 4.7	18.2 ± 4.5	15.7 ± 4.0	13.8 ± 3.6	<0.001	
MADRS Score	**Adjunctive Statin Group**	**30.6 ± 6.5**	**23.4 ± 6.1**	**19.2 ± 5.4**	**15.6 ± 4.9**	**<0.001**	**0.03**
	Antidepressan	30.2 ± 6.2	25.2 ± 6.0	21.8 ± 5.6	18.9 ± 5.2	<0.001	

	t-Only Group						
PHQ-9 Score	**Adjunctive Statin Group**	**16.7 ± 3.9**	**12.2 ± 3.4**	**9.4 ± 2.9**	**7.3 ± 2.5**	**<0.001**	**0.01**
	Antidepressant-Only Group	16.5 ± 4.0	13.5 ± 3.7	11.4 ± 3.2	9.8 ± 2.8	<0.001	
TyG Index	**Adjunctive Statin Group**	**8.77 ± 0.46**	**8.45 ± 0.42**	**8.28 ± 0.40**	**8.12 ± 0.38**	**<0.001**	**0.04**
	Antidepressant-Only Group	8.75 ± 0.48	8.68 ± 0.45	8.61 ± 0.44	8.57 ± 0.43	0.08	

In table 2, HAM-D (Hamilton Depression Rating Scale): Both groups improved significantly over time ($p<0.001$ within groups). By 12 months, the adjunctive statin group had a lower mean HAM-D score (10.4 vs. 13.8). The between-group difference was statistically significant ($p=0.02$), favoring statin use.

MADRS (Montgomery–Åsberg Depression Rating Scale): Both groups showed significant improvement ($p<0.001$). The statin group improved more rapidly and maintained lower scores at 12 months (15.6 vs. 18.9, $p=0.03$ between groups).

PHQ-9 (Patient Health Questionnaire-9): Both groups improved steadily ($p<0.001$). The statin group showed greater symptom reduction (7.3 vs. 9.8 at 12 months, $p=0.01$). This highlights a stronger effect of adjunctive therapy on patient-reported depressive symptoms.

TyG Index (Metabolic Marker): The statin group exhibited a progressive and significant reduction (8.77 → 8.12, $p<0.001$). The antidepressant-only group had minimal non-significant change (8.75 → 8.57, $p=0.08$). Between-group comparison confirmed a significant difference ($p=0.04$), indicating that adjunctive statins improved metabolic profile alongside mood.

Discussion

The present study demonstrated that adjunctive statin therapy in patients with depression receiving standard antidepressant treatment resulted in superior improvements in depressive symptoms, as measured by HAM-D, MADRS, and PHQ-9 scores, compared to antidepressant therapy alone. In addition, statin use was associated with a significant reduction in TyG index, a metabolic marker of insulin resistance, which suggests that metabolic benefits may underlie part of the observed antidepressant effect.

Comparison with Previous Studies:

Our results are consistent with accumulating evidence that statins may exert psychotropic benefits beyond their lipid-lowering properties. A recent meta-analysis of randomized controlled trials by Köhler et al. (2019) reported that adjunctive statin therapy significantly improved depressive symptoms compared with placebo, especially in patients with comorbid cardiovascular risk factors. Similarly, O'Neil et al. (2018) highlighted the anti-inflammatory and neuroprotective mechanisms of statins, which could explain their role in augmenting antidepressant response. [25] The current findings reinforce these observations, showing a greater reduction in clinician-rated (HAM-D, MADRS) and patient-reported (PHQ-9) depression severity scores in the statin group across 12 months.

Several biological mechanisms have been proposed to explain these effects. Depression is characterized by chronic low-grade inflammation and altered lipid/glucose metabolism. Statins reduce pro-inflammatory cytokines (e.g., IL-6, TNF-α) and enhance endothelial function, both of which may contribute to improved neuroplasticity and mood regulation. Our observation of a significant decline in TyG index in the statin group provides further support for the metabolic–psychiatric link. Prior studies, such as that by Kim et al. (2017), [26] demonstrated that insulin resistance is associated with poor antidepressant response, and improvements in metabolic profile are paralleled by mood stabilization. [27] The adjunctive statin therapy in our study, therefore, appears to act on both metabolic and psychiatric domains.

Clinical Implications

The consistent superiority of statin augmentation across multiple validated depression scales suggests that this approach may provide clinically meaningful benefits for patients with partial or inadequate response to antidepressants. Importantly, SSRIs and SNRIs were the predominant antidepressant classes in both groups, aligning with common clinical practice, yet adjunctive statin use provided added efficacy. Furthermore, the progressive reduction in TyG index underscores that statins may not only improve psychiatric outcomes but also reduce long-term cardiometabolic risks—a crucial consideration given the elevated prevalence of metabolic syndrome in patients with depression. [28]

Correlation with Previous Evidence

Despite these limitations, the findings align with earlier clinical and translational studies. Haghighi et al. (2015) demonstrated that simvastatin added to

fluoxetine significantly reduced depressive symptoms in a randomized trial. [29] More recently, Salagre et al. (2020) suggested that the anti-inflammatory effects of statins may particularly benefit patients with treatment-resistant depression. 30 Our data extend these observations to show that improvements are maintained over one year and are accompanied by favorable changes in metabolic indices. This supports the growing concept of a bidirectional relationship between metabolic dysregulation and depression, where interventions targeting both pathways can yield synergistic benefits.

In summary, our study highlights the potential role of adjunctive statin therapy as a dual-action strategy for managing depression, offering both enhanced antidepressant efficacy and improved metabolic outcomes. These findings support the integration of metabolic considerations into psychiatric treatment plans and underscore the need for larger randomized trials to confirm the efficacy, safety, and optimal statin type/dose in depression management.

Strengths and Limitations

The strengths of this study include a well-matched baseline profile, use of multiple validated depression rating scales, and longitudinal follow-up for 12 months. However, limitations must be acknowledged. First, the study was observational, which precludes definitive conclusions regarding causality. Second, the sample size, while moderate, limits subgroup analyses such as statin type–specific efficacy. Third, potential confounders like diet, physical activity, and adherence to antidepressant or statin therapy were not fully controlled.

Conclusion

This prospective observational study aims to provide real-world evidence regarding the effects of statins as an adjunct to antidepressants on clinical outcomes in depression and the triglyceride-glucose (TyG) index. The results have the potential to contribute to our understanding of novel treatment strategies for major depressive disorder, considering the intricate interplay between mental health and metabolic factors. By carefully observing and analyzing the outcomes in a naturalistic clinical setting, this research seeks to inform future clinical practice and guide further investigations into the therapeutic potential of statins in the management of depression.

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