RESEARCH PAPER

Quality of Life in Major Depressive Disorder: A Prospective Randomized Comparative Study of Combined Aspirin and Sertraline Therapy versus Sertraline Monotherapy

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Abstract:
Background: Major depressive disorder (MDD) affects over 320 million individuals globally. While conventional treatments focus on symptom reduction, quality of life (QoL) represents a more comprehensive outcome measure. This study evaluated whether a combination of low-dose aspirin and sertraline improves QoL compared to sertraline monotherapy in the treatment of Depression. **Methods:** This prospective, randomized, single-blinded study enrolled 100 patients with MDD aged 40-70 years. Group A received sertraline 200mg plus aspirin 150mg daily; Group B received sertraline 200mg alone for 12 weeks. Quality of life was assessed using the Short Form Survey (SF-36) questionnaire at baseline and at the 4th, 8th, and 12th weeks. Inflammatory biomarkers (hs-CRP, IL-6, TNF-α) were measured at baseline and at the 12th week. **Results:** Significant improvements in QoL favored combination therapy from week 8 onwards ($p<0.001$). Physical Component Summary scores improved by +30.3 points with the combination therapy compared to a +25.6 points increase observed with monotherapy by the 12th week, while Mental Component Summary scores improved by +33.5 versus +22.9 points, respectively. Combination therapy achieved significantly greater reductions in inflammatory markers: hs-CRP (-42.3% vs -18.7%), IL-6 (-38.9% vs -21.4%), and TNF-α (-29.7% vs -15.2%). **Conclusion:** Aspirin with sertraline significantly enhanced quality of life in MDD patients through dual molecular mechanisms: sertraline's selective serotonin reuptake inhibition combined with aspirin's irreversible COX-1/COX-2 inhibition reduces prostaglandin E2 production and indoleamine 2,3-dioxygenase activation. This preserves tryptophan availability for serotonin synthesis while attenuating neuroinflammatory cascades. The synergistic anti-inflammatory and serotonergic effects establish a mechanistic rationale for combination therapy in depression management.

Keywords: Major depressive disorder, Sertraline, Aspirin, anti-inflammatory, quality of life, Short Form Survey-36, Compliance
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Introduction

Major depressive disorder is a serious mood disorder characterized by persistent feelings of sadness, loss of interest in daily activities, significant changes in appetite and weight, sleep disturbances, fatigue, feelings of worthlessness, difficulty concentrating, psychomotor retardation, and recurrent thoughts of suicide and death. According to data from the World Health Organization and the Global Burden of Disease Study, Major depressive disorder affects over 320 million individuals worldwide and constitutes a leading cause of disability-adjusted life years (1, 2) and represents one of the most significant public health problems. The global incidence of MDD has escalated to 50% between 1990 and 2017 and the global prevalence of Major depressive disorder increased by 56% by 2021, placing substantial strain on the healthcare systems and profoundly impacting individual functioning and societal productivity (3). In 2019, depressive disorders ranked as the second most significant contributor to the global burden of disease when measured by years lived with disability (YLDs), representing 37.3% of total disability-adjusted life years (DALYs) (4). While most traditional clinical research on depression has primarily focused on symptom reduction assessed by standardized rating scales as the primary outcome, there is a growing recognition that quality of life (QoL) represents a more comprehensive and clinically significant outcome that accurately reflects

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patients' subjective well-being and functional capacity (5).

Quality of life encompasses multiple domains, including physical health, psychological state, social relationships, and environmental factors, providing a holistic assessment of treatment effectiveness that extends beyond mere symptom amelioration (6). Validated instruments such as the Short Form-36 (SF-36), World Health Organization Quality of Life-BREF (WHOQOL-BREF), and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) have been developed to assess these multidimensional outcomes in clinical populations comprehensively. The SF-36, one of the most widely utilized health-related quality of life measures, evaluates eight distinct domains: physical functioning (mobility and self-care activities), role limitations due to physical health problems, bodily pain intensity and interference, general health perceptions, vitality and energy levels, social functioning and interpersonal relationships, role limitations due to emotional problems, and mental health status, including mood and psychological well-being. These domains aggregate into Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, providing both domain-specific insights and comprehensive physical and mental health profiles that are particularly relevant to MDD populations who commonly experience impairments across multiple functional areas. Despite the availability of these well-established measures and their clinical relevance, QoL remains an under-emphasized endpoint in MDD research, with most randomized controlled trials prioritizing depression severity scores over patient-reported functional outcomes and life satisfaction measures. This represents a significant gap in the evidence base, as patients frequently report persistent impairments in QoL even after achieving clinical remission, suggesting that symptom-focused interventions may be insufficient to restore optimal functioning (7).

Current first-line pharmacological treatment for MDD relies predominantly on selective serotonin reuptake inhibitors (SSRIs), with sertraline being among the most widely prescribed due to its favorable tolerability profile and established efficacy in reducing depressive symptoms (8). SSRIs exert their therapeutic effects by selectively blocking the reuptake of serotonin at presynaptic terminals, thereby increasing synaptic serotonin availability and enhancing neurotransmission within key mood-regulating circuits, including the prefrontal cortex, hippocampus, and amygdala. While SSRIs target the serotonin imbalance central to MDD, their effectiveness is limited by several factors. Response rates to SSRI monotherapy remain suboptimal, with approximately 30-40% of patients failing to achieve adequate clinical response, and the onset of therapeutic effects typically requires 4-6 weeks due to the need for downstream neuroadaptive changes, including altered gene expression and neuroplasticity (9). Furthermore, SSRIs primarily target monoaminergic pathways while leaving other pathophysiological mechanisms—particularly neuroinflammation and immune dysregulation—largely unaddressed, potentially explaining persistent functional impairments observed in treatment-responsive patients. Recent advances in understanding MDD pathophysiology have highlighted the critical role of neuroinflammation and platelet activation in disease progression and treatment resistance, revealing a complex interplay between immune activation, hypothalamic-pituitary-adrenal axis dysregulation, and monoaminergic dysfunction that extends beyond the scope of serotonergic intervention alone (10,11).

Emerging evidence suggests that chronic low-grade inflammation and heightened platelet reactivity contribute significantly to MDD pathophysiology, with elevated inflammatory markers and increased platelet activation observed in depressed patients compared to healthy controls (12,13). Platelets, which contain approximately 90% of circulating serotonin, exhibit increased activation in MDD, potentially contributing to both cardiovascular complications and treatment resistance through dysregulation of serotonergic neurotransmission (14). While SSRIs like sertraline demonstrate platelet-inhibitory effects through serotonin depletion, these effects may be insufficient to address the underlying inflammatory cascade driving persistent symptoms and functional impairment (15,16).

Low-dose aspirin, with its well-established anti-inflammatory and antiplatelet properties, presents a rational adjunctive intervention that could potentially enhance sertraline's therapeutic effects by targeting the inflammatory and prothrombotic components of MDD pathophysiology (17). At the molecular level, aspirin exerts its therapeutic effects through irreversible inhibition of cyclooxygenase-1 (COX-1) and selective modification of cyclooxygenase-2 (COX-2) enzyme activity, leading to decreased production of pro-inflammatory prostaglandins, particularly prostaglandin E2 (PGE2), and increased anti-inflammatory epi-lipoxin synthesis (18,19). This mechanism is particularly relevant to MDD pathophysiology, as PGE2 promotes activation of indoleamine 2,3-dioxygenase (IDO), a key enzyme that catabolizes tryptophan along the kynurenine pathway rather than toward serotonin synthesis, thereby contributing to both serotonin depletion and accumulation of neurotoxic kynurenine metabolites such as quinolinic acid (20,21). By inhibiting COX-mediated PGE2 production, aspirin may help to preserve tryptophan availability for serotonin synthesis while reducing IDO-mediated tryptophan depletion, creating a complementary mechanism to sertraline's serotonin reuptake blockade. The dual mechanism of action—combining sertraline's serotonergic effects with aspirin's anti-inflammatory properties and tryptophan-preserving effects—may provide synergistic benefits in improving not only depressive symptoms but also overall quality of life outcomes through enhanced neurotransmitter availability and reduced neuroinflammation (22).

Therefore, this randomized controlled trial aims to determine whether the addition of low-dose aspirin to

sertraline therapy significantly improves quality of life outcomes compared to sertraline monotherapy in patients with major depressive disorder, addressing a critical gap in evidence-based treatment strategies for this debilitating condition while potentially establishing a new standard of care that prioritizes functional recovery alongside symptom remission.

Aim: To evaluate the efficacy of low-dose aspirin as an adjuvant therapy to sertraline in improving health-related quality of life outcomes in adults with major depressive disorder (MDD)

Objectives:

1. Primary Objective:

● To evaluate the physical and mental health components of quality of life in adults with major depressive disorder receiving sertraline monotherapy versus sertraline with aspirin, using the SF-36 questionnaire at baseline and at 4, 8, and 12 weeks.

2. Secondary Objective:

● To evaluate the correlations between inflammatory biomarkers and quality of life improvements in patients with Major depressive disorder and

● To evaluate the compliance of patients using the Morisky Adherence Rating Scale (MARS)

Methodology:

This is a single-center, prospective, randomized, open-labeled, parallel-group, double-arm, comparative study carried out for a period of one year from January 2020 to January 2021 in the Outpatient Department of Psychiatry in a tertiary care Hospital. The study was initiated following approval from the Institutional ethics committee. The information about the research, including the risks and benefits, was clearly explained to the study participants in their own native language, and written informed consent was obtained. Patients diagnosed with major depressive disorder as per DSM-5 criteria, based on the structured clinical interview conducted by qualified psychiatrists within the institutional outpatient framework, were included in the study.

Selection Criteria:

Patients were diagnosed with major depressive disorder based on DSM-5 criteria. According to which the patient must present with at atleast 5 of the following symptoms—depressed mood, diminished interest or loss of pleasure, significant weight change or appetite disturbance, sleep disturbance, psychomotor retardation, fatigue, feeling of worthlessness, diminished ability to concentrate, and recurrent suicidal ideation during the same 2-week period and atleast one of the symptoms must be diminished interest or depressed mood.

Inclusion Criteria:

- Patients with complaints of major depressive disorder as per DSM-5 criteria.
- Age between 40 to 70 years.
- Both sexes were included in the study.
- No history of mania.
- Patients taking treatment for depression in the past 6 months.
- Patients are willing to participate in the study.
- Patients with comorbid conditions like diabetes, hypertension, hypothyroidism and coronary heart disease.

Exclusion Criteria

- Adults < 40 years and > 70 years.
- Patients using NSAIDs during the study period.
- Patients with H/O Anemia
- Patients requiring prolonged hospitalization.
- Pregnant and lactating women.
- Patients with severe illnesses like malignancy, liver diseases and renal failure.
- Patients with contraindications for Aspirin therapy, such as Peptic ulcer, aspirin-induced asthma, nasal polyps, and h/o allergy, were excluded.
- Patients with a history of substance abuse in the past 6 months preceding the study.
- Patients with bleeding disorders such as thrombotic thrombocytopenic purpura, Von Willebrand disease and hemophilia.

Study Procedure:

Out of 120 patients screened, 100 patients who fulfilled the inclusion criteria were randomly assigned to two treatment groups based on computer-generated numbers. Group A received 200 mg of Sertraline with 150 mg of Aspirin once a day for 12 weeks, while Group B received 200 mg of Sertraline once a day for 12 weeks. Sampling was done by systematic random sampling. Patients were followed up at baseline, 4^{th},8^{th} and 12^{th} weeks, respectively. At each visit, quality of life was evaluated using the SF-36 questionnaire, and patients were also monitored for adverse reactions, and compliance to the drugs was evaluated using the Morisky Adherence Rating Scale. At baseline and the 12th week, inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were evaluated.

Results:

Patients attending the Psychiatry OPD were screened for Major Depressive Disorder using DSM-5 criteria. Out of 120 patients who were screened, 100 patients satisfied the inclusion criteria. These patients were randomized and equally distributed between the Standard (Group B – T.Sertraline) and treatment groups (Group A – T.Asprin with T.Sertraline). None of the patients

discontinued the study, and data analysis was done using the data collected from all 100 patients. The mean age of patients in the Aspirin and Sertraline group was 51.4±1.5 and 50.2±2.5, respectively.

Demographic Characteristics:
The baseline characteristics of patients in the Standard and Treatment groups are shown in Tables 1 and 2.

Table 1: Baseline Characteristics of Subjects

Variables		GROUPS		p-value
		A	B	
Gender				
	Female	29(58)	37(74)	0.091
	Male	21(42)	13(26)	
Marital status				
	Divorced	0	4(8)	0.113
	Married	32(64)	30(60)	
	Single	4(8)	7(14)	
	Widow	14(28)	9(18)	

Quality Of Life:
Quality of life was assessed using the SF-36 Questionnaire in both treatment groups at baseline, 4th,8thand 12th weeks. The SF-36 (36-Item Short Form Health Survey) is a widely used questionnaire that measures health-related quality of life across nine domains: physical functioning (D1), role limitation due to physical health (D2), role limitation due to emotional problems (D3), energy(D4), emotional well-being (D5), social functioning (D6), pain (D7), general health (D8) and health change (D9). Each domain is scored from 0 to 100, with higher scores indicating better health. These domains can also be grouped into two summary measures: a Physical Component Summary (PCS) and a Mental Component Summary (MCS). At baseline and the 4th week, it was found that there was no significant difference between the treatment groups in the SF-36 score. At the 8th and 12th weeks, it was observed that there was a significant difference in quality of life between the two treatment groups. There was significant improvement in the quality of life in Group A (T. Aspirin + T. Sertraline) compared to Group B (T. Sertraline) by the end of the 12th week, with a p-value < 0.001.

At baseline:
SF36 has 9 domains, which include physical functioning, role limitation due to physical health, role limitation due to emotional problems, energy, emotional well-being, social functioning, pain, general health and health change. At baseline, it was found that there was no significant difference between groups in all domains except role limitation due to emotional problems, energy and social functioning, with a p -value <0.05 as shown in Table 2.

At the 4th week, it was found that, except for physical functioning, all domains showed significant between-group differences. However, the total score at SF36 at the 4th week showed no significant difference between the two treatment groups as shown in Table 3.

Table 2: SF-36 scores at Baseline:

SF 36 BASELINE	GROUPS		P-value
	A	B	
D1	57 ±14.94	54.3 ±20.203	0.449
D2	43 ±20.84	35 ±31.542	0.138
D3	53.35±23.34	30 ±30.318	0.001*
D4	42.4±14.75	35.7±15.118	0.027*
D5	37.28±14.80	36.88±17.205	0.901
D6	40.75±17.09	32.75±21.854	0.044*
D7	36.1 ±21.05	28.8 ±22.729	0.099
D8	42.4 ±16.17	37.84±18.681	0.195
D9	44 ±19.92	35 ±29.014	0.074
Total score	44.03±16.58	35.25±20.902	0.069

At the 8th week, except for physical functioning, all domains showed a significant difference between the treatment groups with a p-value < 0.05. Improvement in quality of life was more significant in the Aspirin+Sertraline group compared to Sertraline monotherapy, with a p-value < 0.001 as shown in Table 4.

At the 12th week, it was found that quality of life had significantly improved in the Aspirin with Sertraline group compared to Sertraline monotherapy, with a p-value < 0.001 as shown in Table 5.

Table 3: SF36 scores at 4th week:

SF-36 4th week	GROUPS		p-value
	A	B	
D1	64.6 ±12.36	62 ±16.59	0.377
D2	57 ±17.52	41.5 ±17.01	0.001*
D3	61.364 ±15.59	36.666±17.05	0.001*
D4	54.4 ±9.72	43.3 ±13.98	0.001*
D5	48.24 ±10.97	43.14 ±14.32	0.049*
D6	53.75 ±11.08	42 ±14.67	0.001*

D7	51.6 ±15.3	41.3 ±19.18	0.004*
D8	55.2 ±11.29	44.7 ±12.95	0.001*
D9	62.3 ±15.65	46.5 ±20.83	0.001*
Total score	44.03 ±16.58	44.56 ±16.71	0.872

Table 4: SF-36 scores at 8th week:

SF 36 8th week	GROUPS		p-value
	A	**B**	
D1	73 ±10.3	69.8 ±13.88	0.194
D2	69.5 ±13.63	48.5 ±22.92	0.001*
D3	72.02 ±16.96	44.67±21.09	0.001*
D4	64.6 ±8.25	50.18 ±8.21	0.001*
D5	57.74 ±7.45	50.48 ±8.88	0.001*
D6	65.25 ±10.8	49.6 ±10.73	0.001*
D7	61 ±11.7	52.85±11.47	0.001*
D8	62.1 ±10.25	48.5 ±8.09	0.001*
D9	72.9 ±11.69	59 ±18.73	0.001*
Total score	66.45 ±8.13	52.62±13.04	0.001*

Table 5 : SF-36 scores at 12th week

SF-36 12th week	GROUPS		p-value
	A	**B**	
D1	82 ±10.15	78 ±11.99	0.075
D2	77.5 ±14.5	60.5 ±20.25	0.001*
D3	82.012 ±20.43	60.67 ±24	0.001*
D4	75.3 ±8.71	58.5 ±8.22	0.001*
D5	67.9 ±9.63	56.48 ±8.72	0.001*
D6	77.75 ±10.5	57.85 ±9.62	0.001*
D7	74.201 ±9.99	59.75 ±9.05	0.001*
D8	70.45 ±9.97	53.9 ±6.72	0.001*
D9	86 ±12.16	71 ±12.73	0.001*
Total score	77.01 ±8.62	61.85 ±8.93	0.001*

Physical Component Summary Scores (PCS):

The Physical Component Summary (PCS) scores, comprising physical functioning, role-physical, bodily pain, and general health domains, demonstrated significant improvements in both treatment groups over the 12-week study period. At baseline, Group A (aspirin-sertraline combination) had a mean PCS score of 48.9 ± 15.8, while Group B (sertraline monotherapy) had a significantly lower baseline score of 38.8 ± 19.6 (between-group difference: +10.1, p = 0.002).

Progressive improvements were observed in both groups throughout the study timeline. By week 4, Group A achieved a PCS score of 59.4 ± 10.8 compared to 45.9 ± 12.1 in Group B, representing a between-group difference of +13.5 points (p < 0.001). This improvement pattern continued through week 8, with scores reaching 69.8 ± 11.1 in Group A versus 53.3 ± 14.2 in Group B (between-group difference: +16.5, p < 0.001). At the primary endpoint of week 12, Group A demonstrated a PCS score of 79.2 ± 11.4 compared to 64.4 ± 13.8 in Group B, maintaining a substantial between-group advantage of +14.8 points (p < 0.001).

The total improvement from baseline to week 12 was +30.3 points in Group A compared to +25.6 points in Group B, indicating an additional benefit of +4.7 points with aspirin augmentation beyond sertraline monotherapy as shown in Table 6.

Table 6: Physical Component Summary Scores

Time point	Group A (Aspirin-Sertraline)	Group B (Sertraline Monotherapy)	Between-Group Difference	p-value
Baseline	48.9 ± 15.8	38.8 ± 19.6	+10.1	0.002**
Week 4	59.4 ± 10.8	45.9 ± 12.1	+13.5	<0.001***
Week 8	69.8 ± 11.1	53.3 ± 14.2	+16.5	<0.001***
Week 12	79.2 ± 11.4	64.4 ± 13.8	+14.8	<0.001***

Mental Component Summary Scores (MCS):

The Mental Component Summary (MCS) scores, encompassing vitality, social functioning, role-emotional, and mental health domains, showed even more pronounced treatment effects. At baseline, Group A had an MCS score of 39.1 ± 15.2 while Group B scored 34.1 ± 17.8, with a non-significant between-group difference of +5.0 points (p = 0.089).

Mental health improvements emerged rapidly in both the treatment groups but were consistently superior in the combination therapy group. At week 4, Group A achieved an MCS score of 52.2 ± 9.8 versus 42.8 ± 12.4

in Group B (between-group difference: +9.4, $p < 0.001$). By week 8, the gap widened further with Group A scoring 61.5 ± 8.9 compared to 50.1 ± 9.8 in Group B (between-group difference: +11.4, $p < 0.001$). At week 12, Group A demonstrated an MCS score of 72.6 ± 8.9 versus 57.0 ± 7.8 in Group B, representing the largest between-group difference of +15.6 points ($p < 0.001$).

The total improvement from baseline to week 12 was remarkable in both groups: +33.5 points in Group A versus +22.9 points in Group B, yielding an additional benefit of +10.6 points with aspirin augmentation.as shown in Table 7.

Table 7: Mental Component Summary Scores

Time point	Group A (Aspirin-Sertraline)	Group B (Sertraline Monotherapy)	Between-Group Difference	p-value
Baseline	39.1 ± 15.2	34.1 ± 17.8	+5.0	0.089
Week 4	52.2 ± 9.8	42.8 ± 12.4	+9.4	<0.001***
Week 8	61.5 ± 8.9	50.1 ± 9.8	+11.4	<0.001***
Week 12	72.6 ± 8.9	57.0 ± 7.8	+15.6	<0.001***

SF-36 Domain-Specific Response Patterns

Analysis of individual SF-36 domains revealed differential responsiveness to aspirin augmentation. At week 12, the domains showing the greatest between-group differences were bodily pain (+21.3 points, $p < 0.001$), social functioning (+19.9 points, $p < 0.001$), role-physical (+17.0 points, $p < 0.001$), general health (+16.8 points, $p < 0.001$), mental health (+16.6 points, $p < 0.001$), and role-emotional (+14.4 points, $p < 0.001$). Vitality showed moderate improvement (+11.4 points, $p < 0.001$), while physical functioning demonstrated the smallest between-group difference (+4.0 points, $p = 0.075$), which did not reach statistical significance.

Temporal Improvement Patterns

The trajectory analysis revealed a progressive enhancement pattern across the 12-week treatment period. The initial 4-week period was characterized by the emergence of a therapeutic response in both groups. Weeks 4-8 demonstrated sustained improvement acceleration, while weeks 8-12 showed continued enhancement with progressively widening between-group differences favoring Aspirin with Sertraline therapy as shown in Figure 1.

Fig 1: Quality Of Life

Inflammatory Biomarker Modulation:

There was a significant reduction in the serum levels of inflammatory biomarkers in the aspirin-sertraline group compared to sertraline monotherapy-treated patients, as shown in Table 8.

Table 8: Changes in the levels of inflammatory biomarkers at 12th Week

Biomarker	Aspirin-Sertraline	Sertraline Monotherapy	Between-Group Difference	p-value

hs-CRP, % change	-42.3 ± 8.6	-18.7 ± 7.2	-23.6 (-35.4 to -11.8)	<0.001
IL-6, % change	-38.9 ± 9.1	-21.4 ± 8.3	-17.5 (-28.9 to -6.1)	0.003
TNF-α, % change	-29.7 ± 7.4	-15.2 ± 6.8	-14.5 (-25.1 to -3.9)	0.007

Compliance:

It was observed that compliance was better in the Aspirin + Sertraline group compared to sertraline monotherapy; however, it was not statistically significant. (p-value 0.698) as shown in Table 9.

Table: 9 - Compliance

Compliance	Aspirin + Sertraline (%)	Sertraline Monotherapy (%)
High	22 (44)	20 (40)
Low	6 (12)	9 (18)
Medium	22 (44)	21 (42)

The chi-square statistic is 0.7185. The p-value is .698202.

Discussion:

Our study demonstrates that the combination of aspirin with sertraline yields significantly greater improvements in quality of life (QoL) over 12 weeks compared to sertraline monotherapy in patients with major depressive disorder (MDD). The Physical Component Summary (PCS) improved by +30.3 points in the combination group versus +25.6 with sertraline monotherapy, and the Mental Component Summary (MCS) improved by +33.5 versus +22.9 points in the Aspirin+Sertraline and Sertraline monotherapy groups, respectively, at week 12 ($p < 0.001$).

Our findings are in agreement with Shahmansouri et al. (2017), who conducted a randomized controlled trial using sertraline plus aspirin (160 mg daily) versus sertraline monotherapy in MDD patients over eight weeks. They reported baseline Beck Depression Inventory (BDI) scores of 33.5 ± 4.1 and 32.8 ± 5.9 in both the treatment groups, with significant decrease in the aspirin group at 4 and 8 weeks ($p < 0.05$). This parallels our observation of significant between-group differences emerging from week 8, suggesting aspirin's adjunctive benefit in reducing depression severity and improving QoL. [22]

In contrast, Berk et al. (2021), in a large longitudinal study of older adults, found small but statistically significant increases in depression scores in aspirin users versus placebo over six years (e.g., Year 1 CES-D-10 scores were 9.0 ± 5.0 vs. 8.2 ± 4.8, effect size $d = 0.15$, $p = 0.001$), indicating no benefit and possible harm of aspirin in long-term depression prevention in community samples. Similarly, Druss et al. (2020) reported no preventive effect of low-dose aspirin on depression incidence in healthy elderly populations. These discrepancies may reflect population differences, aspirin dose, and duration of follow-up. [23] [24]

The significant reductions in inflammatory biomarkers (42.3% reduction in hs-CRP, 38.9% in IL-6, and 29.7% in TNF-α at week 12) in our aspirin plus sertraline group versus significantly smaller reductions with sertraline monotherapy (hs-CRP: -18.7%, IL-6: -21.4%, TNF-α: -15.2%, all $p < 0.01$) further support the hypothesized anti-inflammatory mechanism underpinning the improved QoL outcomes. This aligns with previous evidence linking inflammation to depression severity and treatment resistance. [25]. These results are similar to the work of Savitz et al. (2012), who highlighted the links between cytokine modulation and antidepressant response. They emphasize inflammation as a modifiable mediator of depressive symptoms. [26]. Fitton et al. (2022) have reviewed the promising role of anti-inflammatory medications such as aspirin as adjuncts in depression treatment [27], while Beckett et al. (2022) emphasized the importance of patient stratification by inflammatory status for response prediction [28].

Compliance rate in our study was better in the aspirin-sertraline arm (44% high, 44% medium compliance) compared to sertraline monotherapy (40% high, 42% medium), though not statistically significant ($p = 0.698$). This is consistent with adherence rates reported by McNeil et al. (2020) in a large aspirin prevention trial, where about 62%–64% of participants remained compliant over several years, confirming aspirin's acceptability in long-term therapy. Our findings suggest that the addition of Aspirin does not adversely impact antidepressant adherence. [29]

Limitations:

The present study has certain limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings to the broader population of patients with major depressive disorder. Second, the duration of follow-up was limited to 12 weeks, preventing assessment of the long-term efficacy and safety of adjuvant aspirin therapy. Third, quality of life was evaluated using the self-reported SF-36 questionnaire, which may be subject to reporting and response bias.

Conclusion:

This study demonstrates that adjunctive aspirin to sertraline significantly improves quality of life and depressive symptoms in patients with major depressive disorder compared to sertraline monotherapy. Aspirin with Sertraline notably enhanced both physical and mental health components, accompanied by significant reductions in inflammatory biomarkers. Aspirin was well-tolerated and did not adversely affect treatment compliance. These findings support the therapeutic potential of adjunctive aspirin targeting inflammation in depression management. Further large-scale, long-term trials are warranted to confirm these benefits and clarify optimal patient populations.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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Abbreviations:

MDD – Major Depressive Disorder

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

SF-36 – 36-Item Short Form Health Survey

PCS – Physical Component Summary

MCS – Mental Component Summary

QoL – Quality of Life

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