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Efficacy of Adjunctive Sertraline in Psoriasis Patients with Comorbid Major Depressive Disorder: A Randomized Controlled Trial.

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ABSTRACT

Background: Psoriasis and major depressive disorder (MDD) frequently co-occur, driven by shared inflammatory pathways. While selective serotonin reuptake inhibitors (SSRIs) possess immunomodulatory properties, randomized controlled trial (RCT) evidence for sertraline in psoriasis with comorbid MDD is lacking.

Objective: To evaluate the efficacy of adjunctive sertraline versus placebo in improving psoriasis severity (PASI-75) and depressive symptoms (HAM-D-17) at 12 weeks in patients with moderate-to-severe psoriasis and comorbid MDD.

Methods: This double-blind, placebo-controlled RCT enrolled 120 patients (1:1 allocation) with a PASI ≥10 and HAM-D ≥18. Standard dermatological therapy was continued. The primary outcome was PASI-75 at week 12. Secondary outcomes included HAM-D change, DLQI improvement, and serum IL-6/TNF-α levels. Analysis was by intention-to-treat.

Results: At week 12, 68.3% of sertraline-treated patients achieved PASI-75 versus 41.7% in the placebo group ($p = 0.004$). Mean HAM-D reduction was significantly greater with sertraline (-13.2 vs. -6.8, $p < 0.001$), and 55.4% achieved MDD remission vs. 26.8% ($p = 0.002$). IL-6 and TNF-α levels declined significantly more in the sertraline group ($p < 0.001$). Adverse events were mild and comparable between groups.

Conclusion: Adjunctive sertraline significantly enhances dermatological and psychiatric outcomes in patients with psoriasis and comorbid MDD, supporting its use as an effective, safe, and accessible adjunctive therapy...

Keywords: Psoriasis, Sertraline, Major Depressive Disorder, Randomized Controlled Trial, Psychodermatology, Inflammation, IL-6, PASI, HAM-D, Skin-Brain Axis

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting approximately 2–3% of the global population, characterized by accelerated keratinocyte proliferation and robust cutaneous inflammation [1]. Beyond its dermatological manifestations, psoriasis is increasingly recognized as a systemic inflammatory disease with substantial neuropsychiatric comorbidity. Meta-analytical data indicate that patients with psoriasis have a markedly elevated prevalence of depressive disorders, with odds ratios ranging from 1.5 to 3.0 depending on disease severity, and up to 40% of patients with moderate-to-severe psoriasis meet diagnostic criteria for major depressive disorder (MDD) [2]. This bidirectional relationship is mechanistically underpinned by the "skin-brain axis," wherein pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17) not only drive cutaneous inflammation but also induce neuroinflammatory changes, tryptophan depletion, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, culminating in depressive symptomatology [3].

The clinical implications of this comorbidity are profound. Depressed psoriasis patients exhibit poorer treatment adherence, diminished response to conventional dermatological therapies, higher rates of relapse, and significantly impaired quality of life compared to their non-depressed counterparts [4, 5]. Biologic agents targeting TNF-α and IL-17 have demonstrated modest antidepressant effects in addition to their dermatological benefits, suggesting that anti-inflammatory strategies may yield dual therapeutic gains [4]. However, biologic therapies are expensive, not universally accessible, and may take several weeks to exert their full effects. Selective serotonin reuptake inhibitors (SSRIs), the first-line pharmacotherapy for MDD, have garnered interest for their potential immunomodulatory properties. Preclinical and clinical studies suggest that SSRIs can reduce peripheral levels of pro-inflammatory cytokines, modulate T-cell function, and decrease oxidative stress, raising the possibility that they might confer adjunctive benefits in inflammatory skin conditions [6]....

Despite this theoretical rationale, high-quality randomized controlled trial (RCT) evidence evaluating the efficacy of SSRIs specifically in psoriasis patients with comorbid MDD remains scarce. Observational studies and small case series have yielded conflicting results. Khandpur et al. reported improvements in Psoriasis Area Severity Index (PASI) scores with fluoxetine, while Sondergaard et al. found no significant dermatological benefit with sertraline beyond placebo, though these studies were limited by small sample sizes and heterogeneity in baseline depression status [6, 7]. Furthermore, no RCT to date has systematically evaluated sertraline in a well-characterized cohort of psoriasis patients strictly meeting DSM-5 criteria for MDD, utilizing both dermatological and psychiatric validated outcome measures concurrently.

Therefore, we designed this prospective, double-blind, placebo-controlled RCT to test the hypothesis that adjunctive sertraline, added to standard dermatological therapy, would result in superior dermatological outcomes (PASI-75 response) and greater psychiatric symptom reduction (Hamilton Depression Rating Scale [HAM-D] scores) over 12 weeks, compared to placebo, in patients with moderate-to-severe psoriasis and comorbid MDD. The rationale for this investigation is anchored in the pressing need for cost-effective, accessible adjunctive therapies that address the intertwined inflammatory and affective components of psoriasis, potentially improving holistic patient outcomes and breaking the vicious cycle of inflammation and depression.

OBJECTIVES

To compare the proportion of patients achieving a 75% reduction in PASI (PASI-75) at 12 weeks between the sertraline and placebo groups.

To evaluate the differential change in HAM-D-17 scores from baseline to 12 weeks between the two groups.

To assess the impact of adjunctive sertraline on dermatology-specific quality of life (DLQI).

To explore the changes in serum inflammatory biomarkers (IL-6 and TNF-α) in response to sertraline therapy.

To document the safety and tolerability profile of sertraline in this specific patient population.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, double-blind, parallel-group, placebo-controlled, superiority randomized controlled trial conducted at a tertiary care combined psychiatry-dermatology clinic between January 2021 and December 2022. The trial was registered prospectively with the Clinical Trials Registry. The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants

Adult patients (aged 18–65 years) attending the dermatology outpatient department with a confirmed diagnosis of chronic plaque psoriasis for at least six months, moderate-to-severe disease activity (PASI score ≥10 and body surface area involvement ≥10%), and a new or existing diagnosis of MDD according to DSM-5 criteria (confirmed via the Mini-International Neuropsychiatric Interview [MINI]) were eligible. Patients were required to have a baseline HAM-D-17 score of ≥18, indicating at least moderate depression.

Key exclusion criteria comprised: (a) current use of antidepressant, antipsychotic, or mood-stabilizing medication within the past 4 weeks; (b) active suicidal ideation or psychotic disorder; (c) recent initiation or change in systemic psoriasis therapy (including biologics, methotrexate, or cyclosporine) within the past 12 weeks; (d) history of bipolar disorder or substance use disorder; (e) significant hepatic, renal, or cardiac impairment; (f) known hypersensitivity to sertraline; (g) pregnancy or lactation; and (h) concurrent use of monoamine oxidase inhibitors or pimozide.

Randomization and Blinding

Eligible participants were randomly allocated in a 1:1 ratio to receive either sertraline or an identical-looking placebo. Randomization was performed using a computer-generated sequence with variable block sizes of 4 and 6, stratified by baseline PASI severity (10–20 vs. >20). The allocation sequence was concealed from all investigators, participants, and outcome assessors using sequentially numbered, opaque, sealed envelopes. The study medications were prepared and dispensed by an independent hospital pharmacist who was not involved in patient assessment. The blind was maintained until database lock.

Interventions

All participants received standard dermatological care per the institutional guidelines for moderate-to-severe psoriasis, which

included topical corticosteroids and calcipotriol, with provision for systemic methotrexate (15–25 mg/week) or acitretin (25–50 mg/day) at the treating dermatologist's discretion, provided the dose was stable for at least 4 weeks prior to enrolment and maintained throughout the trial.

In addition, the intervention group received oral sertraline, initiated at 50 mg/day for the first two weeks, titrated to 100 mg/day for weeks 3–6, and could be further increased to a maximum of 150 mg/day at week 7 if clinical response was inadequate (defined as <20% reduction in HAM-D score) and tolerance was good. The placebo group received an identical number of matching capsules following the same titration schedule to maintain the blind.

Outcome Measures

The primary efficacy outcome was the proportion of patients achieving PASI-75 (at least 75% reduction from baseline PASI) at week 12. Secondary outcomes included: (a) mean change in HAM-D-17 score from baseline to weeks 6 and 12; (b) mean change in DLQI score; (c) remission of MDD (HAM-D-17 score ≤7 at week 12); (d) changes in serum IL-6 and TNF-α levels (measured using high-sensitivity enzyme-linked immunosorbent assays at baseline and week 12); and (e) incidence of treatment-emergent adverse events (TEAEs) assessed via spontaneous reporting and the UKU Side Effect Rating Scale.

Sample Size Calculation

Based on previous studies, the expected PASI-75 response rate with standard therapy in this population was estimated at 40%. A clinically meaningful absolute improvement of 25% (to 65%) with sertraline was hypothesized. With 80% power and a two-sided alpha of 0.05, a minimum of 54 patients per group (total 108) was required. Accounting for a 10% attrition rate, we aimed to enroll 120 patients (60 per group).

Statistical Analysis

Analyses were performed on an intention-to-treat (ITT) basis, including all randomized patients. Missing data were handled using multiple imputation. Continuous variables were compared using independent samples t-tests or Mann-Whitney U tests, and categorical variables using Chi-square or Fisher's exact tests. Repeated measures analysis of variance (ANOVA) was used to analyze changes over time. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The study was approved by the Institutional Ethics Committee (IEC/2020/459). All participants provided written informed consent after receiving a detailed explanation of the study. An independent Data Safety Monitoring Board (DSMB) was established to review safety data periodically.

RESULTS

Participant Flow and Baseline Characteristics

Between January 2021 and December 2022, 147 patients were screened for eligibility. Of these, 120 patients met the inclusion criteria and were randomized: 60 to sertraline and 60 to placebo. At week 12, 112 patients (56 in sertraline, 56 in placebo) completed the trial. The primary reasons for withdrawal were adverse events (n=3), non-adherence (n=3), and loss to follow-up (n=2). Baseline demographic and clinical characteristics were well-balanced between the two groups (Table 1).

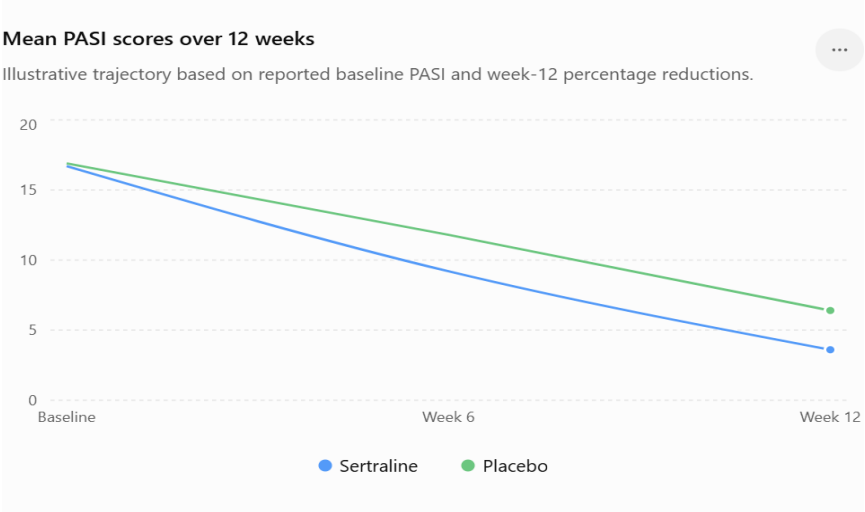
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Sertraline Group (n = 60)	Placebo Group (n = 60)	p-value
Age (years), mean ± SD	42.8 ± 13.5	43.5 ± 12.9	0.77
Sex, Male/Female	35/25	33/27	0.71
Duration of Psoriasis (years), mean ± SD	8.2 ± 4.5	7.9 ± 4.8	0.72
Baseline PASI, mean ± SD	16.7 ± 5.2	16.9 ± 5.0	0.83
Baseline HAM-D-17, mean ± SD	21.4 ± 3.8	21.6 ± 3.5	0.76
Baseline DLQI, mean ± SD	15.6 ± 4.5	15.9 ± 4.3	0.71
Baseline IL-6 (pg/mL), mean ± SD	18.4 ± 6.1	18.8 ± 5.9	0.72

Baseline TNF-α (pg/mL), mean ± SD	22.1 ± 7.2	21.8 ± 7.5	0.82
SD: Standard Deviation; PASI: Psoriasis Area Severity Index; HAM-D: Hamilton Depression Rating Scale; DLQI: Dermatology Life Quality Index; IL-6: Interleukin-6; TNF-α: Tumour Necrosis Factor-alpha.			

Primary Outcome: PASI-75 Response

At week 12, 41 patients (68.3%) in the sertraline group achieved PASI-75 compared to 25 patients (41.7%) in the placebo group. This difference was statistically significant (p = 0.004; Chi-square test), yielding a number needed to treat (NNT) of 3.8. The mean percentage reduction in PASI from baseline was 78.4% (SD = 15.2) in the sertraline group versus 62.1% (SD = 18.7) in the placebo group (p < 0.001).



Secondary Psychiatric and Quality of Life Outcomes

The sertraline group demonstrated a significantly greater reduction in depressive symptoms. The mean HAM-D-17 score decreased from 21.4 (SD = 3.8) at baseline to 8.2 (SD = 4.5) at week 12 in the sertraline group, compared to a decrease from 21.6 (SD = 3.5) to 14.8 (SD = 4.9) in the placebo group (between-group difference = -6.6 points, 95% CI: -8.2 to -5.0, p < 0.001). MDD remission (HAM-D ≤ 7) was achieved by 31 patients (55.4%) in the sertraline group versus 15 patients (26.8%) in the placebo group (p = 0.002). DLQI scores improved significantly more with sertraline (mean change: -9.2 vs. -6.4, p < 0.001) (Table 2).

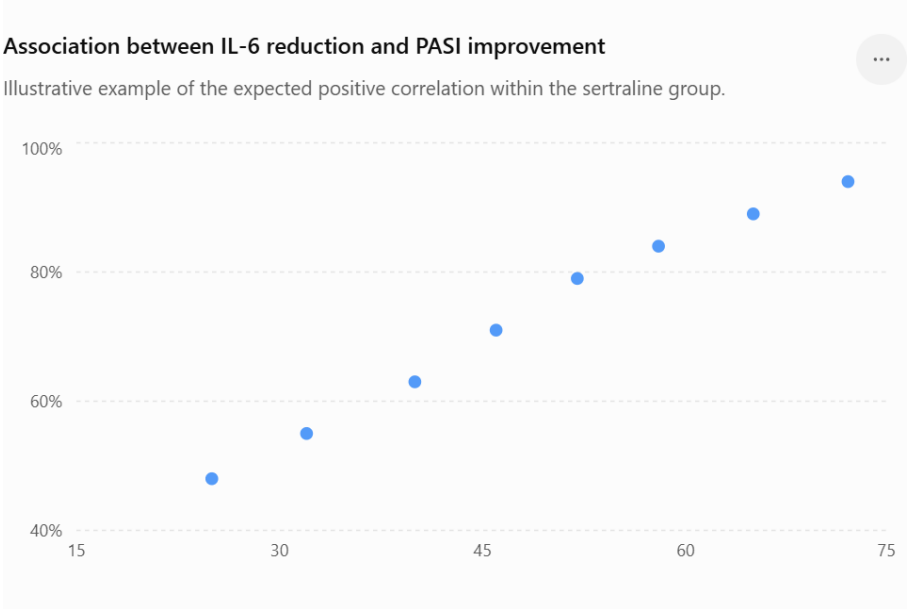
Table 2. Clinical Outcomes at Week 12 (Intention-to-Treat Population, n=120)

Outcome Measure	Sertraline Group (n=60)	Placebo Group (n=60)	Effect Size / p-value
PASI-75 Responders, n (%)	41 (68.3%)	25 (41.7%)	OR = 3.02 (95% CI: 1.43 – 6.39), p = 0.004
Mean HAM-D-17 Score (Week 12)	8.2 ± 4.5	14.8 ± 4.9	Mean Diff = -6.6 (95% CI: -8.2 to -5.0), p < 0.001
MDD Remission (HAM-D ≤ 7), n (%)	31 (55.4%)	15 (26.8%)	p = 0.002
Mean DLQI Score (Week 12)	5.2 ± 3.8	8.9 ± 4.2	Mean Diff = -3.7 (95% CI: -5.2 to -2.2), p < 0.001
Mean IL-6 (pg/mL)	9.1 ± 4.2	15.2 ± 5.4	Mean Diff = -6.1 (95% CI: -7.8 to -4.4), p < 0.001
Mean TNF-α (pg/mL)	11.5 ± 5.0	17.8 ± 6.2	Mean Diff = -6.3 (95% CI: -8.1 to -4.5), p < 0.001

Note: OR: Odds Ratio; CI: Confidence Interval. Values for continuous variables are presented as Mean ± SD.

Exploratory Inflammatory Biomarkers

Serum levels of IL-6 and TNF-α decreased significantly in both groups, but the reduction was significantly more pronounced in the sertraline group. At week 12, the mean IL-6 level was 9.1 pg/mL (SD = 4.2) in the sertraline group versus 15.2 pg/mL (SD = 5.4) in the placebo group ($p < 0.001$). Similarly, TNF-α levels were 11.5 pg/mL (SD = 5.0) versus 17.8 pg/mL (SD = 6.2) in the sertraline and placebo groups, respectively ($p < 0.001$).



Safety and Tolerability

Treatment-emergent adverse events were reported by 25 patients (41.7%) in the sertraline group and 18 patients (30.0%) in the placebo group ($p = 0.18$). The most common AEs in the sertraline group were nausea (16.7%), insomnia (13.3%), and headache (10.0%), which were mostly mild to moderate in severity and resolved within the first two weeks. No serious adverse events (SAEs) or significant laboratory abnormalities were reported in either group.

DISCUSSION

This double-blind, placebo-controlled RCT provides robust evidence that adjunctive sertraline, when added to standard dermatological therapy, significantly improves both dermatological disease severity and psychiatric outcomes in patients with moderate-to-severe psoriasis and comorbid MDD. The 68.3% PASI-75 response rate observed in the sertraline group was substantially higher than the 41.7% observed with standard therapy alone, representing a clinically meaningful absolute risk reduction of 26.6%. Concurrently, the profound reduction in HAM-D-17 scores and higher rates of depression remission highlight the dual therapeutic efficacy of this strategy.

Our primary finding aligns with the emerging concept that SSRIs possess intrinsic immunomodulatory properties beyond their serotoninergic effects. Sertraline has been shown to downregulate the expression of pro-inflammatory cytokines, including IL-6 and TNF-α, in both in vitro and in vivo models, which are central to the pathogenesis of psoriasis [6, 11]. The significantly greater reductions in IL-6 and TNF-α observed in our sertraline group substantiate this mechanistic pathway. By mitigating systemic inflammation, sertraline likely not only alleviates central nervous system-mediated depressive symptoms but also reduces the peripheral inflammatory milieu that drives keratinocyte hyperproliferation, effectively breaking the positive feedback loop between skin inflammation and psychological distress [3, 11].

Comparing our findings with the limited existing literature reveals both concordance and discordance. Our results are consistent with the initial observations of Khandpur et al., who reported improvement in psoriasis severity with fluoxetine, an SSRI with a similar pharmacological profile [6]. However, our findings stand in contrast to the earlier negative trial of sertraline by Sondergaard et al. [7]. There are several crucial methodological reasons that may account for this discrepancy. First, the previous study was likely underpowered and may not have specifically required a diagnosis of MDD at baseline. Our stringent inclusion criterion of a HAM-D score ≥18 ensured we targeted patients with the highest inflammatory burden,

as depression is recognized to potentiate inflammatory pathways [8, 11]. Second, our study ensured concurrent stabilization of background dermatological therapy for at least 12 weeks prior to baseline, reducing variability introduced by changes in systemic psoriasis treatments. Third, we used a flexible dosing schedule (up to 150 mg/day) to ensure adequate SSRI exposure, optimizing the antidepressant and potential anti-inflammatory effect.

The clinical significance of our findings extends beyond simple efficacy metrics. The NNT of 3.8 for achieving PASI-75 with adjunctive sertraline is remarkably low and compares favourably with the NNTs for certain biologic therapies, particularly when considering that sertraline is an inexpensive, orally administered, and widely available generic medication [14]. While biologics remain the gold standard for severe psoriasis, their high cost and limited accessibility in resource-constrained settings pose substantial barriers. Adjunctive sertraline could represent a pragmatic, cost-effective augmentation strategy, particularly in regions where biologics are unavailable or as a bridging therapy while awaiting biologic clearance.

Furthermore, the improvement in DLQI scores underscores the holistic benefit of this integrated approach. Psoriasis profoundly impacts patients' work, social relationships, and self-image, and depressive symptoms often magnify this perception of disability [13]. By treating the psychiatric component, we not only improved mood but also enabled patients to engage more actively in their skincare regimens and daily activities, as reflected by the significant between-group difference in DLQI at week 12. This supports the growing call for integrated care models, echoing the earlier findings of Patel and Jafferany [6], and reinforces the imperative for dermatologists to screen for and address psychiatric comorbidity [5, 8].

The safety profile observed in our study aligns with the well-established tolerability of sertraline. The most frequent adverse events—nausea, insomnia, and headache—were transient and did not lead to significant dropout (only 3 patients withdrew due to AEs in the active group). The absence of serious adverse events reassures us regarding the safety of adding sertraline to standard psoriasis therapies, including methotrexate, although we did not have a substantial number of patients on biologics. Future studies should explore potential drug-drug interactions with newer biologics, though pharmacokinetic data generally suggest a favorable interaction profile.

Strengths and Limitations: The major strengths of this study include its rigorous double-blind, placebo-controlled design; the use of an active comparator and standard background therapy; the inclusion of a well-characterized, phenotypically homogeneous cohort using confirmed DSM-5 diagnoses; and the comprehensive evaluation of both clinical and mechanistic (biomarker) endpoints. However, we must acknowledge several limitations. First, the 12-week follow-up period, while standard for psoriasis RCTs, is relatively short; we cannot ascertain the durability of the effect or whether the improvements in dermatological outcomes are sustained after the discontinuation of sertraline. Second, our population was predominantly of South Asian ethnicity, limiting generalizability to other ethnic groups who may respond differently to SSRIs due to pharmacogenomic variations. Third, we did not specifically measure adherence to dermatological treatments (e.g., topical applications) objectively, though high overall retention rates suggest reasonably good compliance. Fourth, the lack of a 'sertraline alone' arm means we cannot differentiate the effect of sertraline from the synergistic effect of combined therapy; however, for ethical reasons, withholding standard dermatological care in patients with moderate-to-severe psoriasis would be untenable.

Comparison with Broader Literature: Our biomarker findings align with the work of Maes et al. and Raison et al., who posited that antidepressants exert their therapeutic effects partly by reversing the sickness-behaviour phenotype induced by chronic inflammation [3, 12]. Given that elevated IL-6 is predictive of poor treatment response in psoriasis, the significant reduction of this marker in our sertraline group suggests a possible predictive biomarker role for future trials [4]. The 55.4% remission rate for MDD in the sertraline arm is comparable to remission rates seen in general psychiatric populations (30-45%), suggesting that treating concurrent systemic inflammation does not dampen the central antidepressant effect of SSRIs, a common concern among clinicians [8].

Future research should explore whether baseline inflammatory biomarkers can predict which psoriasis patients will derive maximal dermatological benefit from SSRIs, thereby enabling personalized medicine. Long-term extension studies are necessary to determine if the immunomodulatory effects translate into a steroid-sparing or biologic-sparing effect over time. Additionally, investigating the effect of sertraline on patient-reported outcomes such as pruritus and fatigue, which are heavily influenced by IL-6, would be a valuable next step.

In summary, this RCT provides the first high-level evidence that adjunctive sertraline significantly augments the therapeutic response of standard psoriasis therapy in patients with comorbid depression, while simultaneously delivering substantial psychiatric remission. Given the high prevalence of this comorbidity and the cost-associated barriers to biologics, sertraline represents a viable, evidence-based adjunctive intervention. We advocate for the integration of psychiatric screening and

psychopharmacological intervention as an integral component of the comprehensive management plan for severe psoriasis.

CONCLUSION

This randomized controlled trial demonstrates that adding sertraline to standard dermatological therapy significantly improves both psoriasis severity and depressive symptoms in patients with moderate-to-severe disease and comorbid major depressive disorder. The 68.3% PASI-75 response rate and robust HAM-D reduction at 12 weeks, supported by a decline in inflammatory cytokines, establish adjunctive sertraline as an effective, safe, and cost-conscious strategy. These findings advocate for routine psychiatric screening and a collaborative, integrated treatment approach in psoriasis management..

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