Melatonin as an Adjunctive Treatment for Psoriasis: A Pilot Study Evaluating Sleep Quality, Dermatology Life Quality Index, and Disease Severity

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Abstract

Psoriasis is a chronic immune-mediated inflammatory skin disease that frequently co-occurs with sleep disturbance, and this combination can substantially impair patients' quality of life. Beyond its established role in circadian rhythm regulation, melatonin has been shown to exert anti-inflammatory and immunomodulatory effects, raising interest in its use as an adjunctive therapy in psoriasis However, clinical evidence regarding oral melatonin in this context remains scarce. This pilot randomized controlled trial included five patients with moderate -to-severe psoriasis who were treated with methotrexate and received adjunctive oral melatonin (n=2) and placebo (n=3) for 8 weeks Disease severity, sleep quality, dermatology-specific quality of life, and safety were assessed using the Psoriasis Area and Severity Index, Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and Dermatology Life Quality Index. All five patients showed improvement in psoriasis severity over the follow-up period, although the extent of response varied. Between-group differences were more evident for sleep outcomes. By week 8, participants receiving adjunctive melatonin consistently reported good sleep quality, with Pittsburgh Sleep Quality Index (PSQI) scores decreasing from 4 at baseline to 1 in both cases In contrast, sleep outcomes in the methotrexate-alone group were more heterogeneous and less stable, with PSQI scores decreasing from baseline values of 7–9 to 2–6. In the melatonin group, better sleep was associated with gradual and sustained improvements in dermatology-specific quality of life. Oral melatonin was well tolerated, with no emergent safety signals or increase in daytime sleepiness. These findings suggest that adjunctive melatonin may provide additional, patient-relevant benefits in the management of psoriasis and support further evaluation in larger controlled trials.

Keywords: *Psoriasis; Melatonin; Methotrexate; PASI*

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory disorder and remains a therapeutic challenge in clinical dermatology. As described by De Rie et al. (2004), it is characterized by scaly, erythematous plaques that arise from increased keratinocyte proliferation together with overactivation of immune system. Although psoriasis is primarily a skin disease, many patients report substantial impacts on daily functioning, including reduced quality of life and psychological distress. In recent years, sleep disturbance has been recognized as a serious but often under-addressed consequence of psoriasis. Melikoglu (2017) noted that poor sleep is highly prevalent among individuals with psoriasis and is associated with a higher overall disease burden. This growing body of work suggests that sleep problems are not merely secondary complaints but an integral part of the patient experience that warrants attention in routine care and research.

Importantly, the interaction between sleep and psoriasis is bidirectional. On the one hand, sleep deprivation or poor sleep quality contributes to heightened systemic inflammation by stimulating the release of pro-inflammatory cytokines such as TNF-α and IL-6, thereby exacerbating psoriasis symptoms, as described by Halioua et al. (2022). Conversely, psoriasis symptoms, such as pruritus and pain, can disrupt sleep, creating a vicious cycle that worsens both conditions.

Kudrnáčová and Kudrnáč (2023), for instance, reported that sleep problems are strongly associated with lower quality of life, even in patients whose visible skin lesions have clinically improved. This indicates that sleep disturbance is an important and clinically relevant aspect of psoriasis-related morbidity. Several mechanisms have been suggested to explain this link. Hawro et al. (2020) highlighted nocturnal pruritus (nighttime itching) as a key contributor to sleep loss. Other research has emphasized the roles of chronic systemic inflammation and disruptions in circadian rhythms in disturbing normal sleep patterns. In addition,

altered melatonin signaling has been proposed as a contributing factor in psoriasis with co-existing sleep problems, as shown in preclinical work by Zhu et al. (2024).

Melatonin is best known for regulating the circadian rhythm and the sleep–wake cycle, but growing evidence shows that its actions are far broader. Its relevance to skin health was first emphasized by Fischer et al. (1999), and later, described by Karaaslan and Suzen (2015), who reported notable antioxidant and immune-modulating effects. Mechanistically, melatonin can modulate key immune pathways involved in psoriasis by downregulating Th1 and Th17 responses, leading to reduced production of pro-inflammatory cytokines such as IL-17, IL-23, and IFN-γ, while simultaneously enhancing regulatory T-cell (Treg) activity to restore immune balance (Zhang and Yao, 2023). In addition to its immunomodulatory role, melatonin possesses potent antioxidant properties that may help mitigate oxidative stress and protect against drug-induced organ toxicity, including methotrexate-related hepatotoxicity, as suggested by experimental and clinical studies (Jahovic et al., 2003; Abdallah et al., 2024). To date, most clinical investigations have examined melatonin in topical form. A recent randomized clinical trial, for example, reported that a melatonin-containing topical preparation improved clinical outcomes in patients with plaque psoriasis (Mohammadi et al., 2024). However, evidence for oral melatonin as an adjunct systemic therapy in psoriasis remains limited. From a safety perspective, melatonin is generally considered safe and well-tolerated, most reported adverse events mild and transient, such as daytime sleepiness, headache, dizziness, and minor sleep-related disturbances, and rarely require treatment discontinuation. No serious or life-threatening adverse effects have been consistently reported, although long-term safety data remain limited (Besag et al., 2019). At the same time, much of the existing literature continues to focus on clinician-rated measures of skin severity, whereas sleep quality and other patient-reported outcomes have received comparatively little attention. Given the bidirectional relationship between sleep disturbance and psoriasis activity, approaches that directly target sleep-related symptoms may help improve outcomes that are especially meaningful to patients.

In this context, the present study set out to provide a preliminary assessment of adjunctive oral melatonin in individuals with moderate to severe plaque psoriasis treated with methotrexate. The objectives were to examine changes in psoriasis severity, sleep quality, and health-related quality of life, as well as to monitor the safety and tolerability of this combined therapeutic strategy in a real-world clinical setting.

2. Objectives

1). To preliminarily assess clinical outcomes in disease severity, between combination therapy with melatonin and methotrexate and methotrexate monotherapy in patients with psoriasis.

2). To preliminarily assess melatonin in sleep quality improvement in psoriasis patients.

3). To assess the safety of combination therapy with melatonin and methotrexate in patients with psoriasis

3. Materials and Methods

3.1 Study Design and Population

This study was conducted as a prospective, evaluator-blinded controlled trial. Adult patients with moderate- to- severe plaque psoriasis were consecutively enrolled during routine clinical practice.

The inclusion criteria were as follows:

(1) age ≥18 years; and

(2) a confirmed diagnosis of plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score ≥10.

The exclusion criteria included:

(1) guttate, erythrodermic, or pustular psoriasis;

(2) use of topical therapy within 2 weeks prior to enrollment;

(3) phototherapy or systemic therapy within 4 weeks prior to enrollment;

(4) biologic therapy within 6 months prior to enrollment;

(5) significant renal or hepatic impairment;

(6) acute or chronic infection;
(7) psychiatric disorders, insomnia, or other conditions that could interfere with clinical evaluation;
(8) pregnancy or breastfeeding;
(9) plans for conception during the study period or within three months after study completion;
(10) known allergy to melatonin;
(11) known allergy to methotrexate; and
(12) inability to attend scheduled follow-up visits

3.2 Allocation and Blinding

Eligible patients were consecutively enrolled and randomly allocated using a computer-generated sequence. Clinical outcome assessments, including PASI evaluation, were performed by dermatologists who were blinded to treatment allocation to minimize assessment bias. To maintain participant blinding, oral melatonin (Circadin™ 2 mg) and matching placebo tablets were identical in appearance, packaging, and administration schedule, and were administered 2 hours before bedtime in both groups. Participants were not informed of their group assignment throughout the study period.

3.3 Study Intervention and Follow-up

All consecutive patients meeting the eligibility criteria were invited to participate. Participants were allocated into two treatment groups. One group received methotrexate 15 mg once weekly in combination with folic acid 5 mg daily and a matching oral placebo tablet administered 2 hours before bedtime. The second group received methotrexate 15 mg once weekly with folic acid 5 mg daily and oral melatonin (Circadin™) 2 mg administered 2 hours before bedtime.

All participants were instructed to apply topical olive oil throughout the 8-week treatment period. Safety monitoring included complete blood count and liver function tests performed at baseline and week 2. Disease severity was assessed using the Psoriasis Area and Severity Index (PASI), and treatment-related adverse effects associated with methotrexate and melatonin were evaluated at each study visit (weeks 0, 4, and 8). Sleep quality, daytime sleepiness, and dermatology-related quality of life were assessed using the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Dermatology Life Quality Index at baseline and week 8. The PSQI score ranges from 0 to 21, with higher scores indicating poorer sleep quality A global score >5 considered indicative of clinically significant sleep disturbance. The ESS score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness Scores ≥10 are considered indicative of excessive daytime sleepiness. The total duration of treatment and follow-up was 8 weeks.

4. Results and Discussion

4.1 Results

Five patients with moderate to severe plaque psoriasis were included in this randomized controlled trial. Baseline patient characteristics were summarized in Table 1. Patients ranged in age from 23 to 61 years, and included four men and one woman. Body mass index ranged from 20.6 to 28.3 kg/m². None of the patients had significant underlying medical conditions, and the duration of psoriasis ranged from 2 to 30 years. None of the patients had a history of smoking or alcohol consumption.

All patients had received prior psoriasis treatment, most commonly topical corticosteroids. Three patients had a history of methotrexate use, and one patient had previously undergone narrowband ultraviolet B (NB-UVB) phototherapy.

Table 1 Baseline patients characteristics

Patient	Age (yr)	Sex	BMI (kg/m^2)	Previous medical illness	Duration of disease (yr)	Previous treatment	PASI	DLQI	PSQI	ESS
1	47	Male	21.9	None	3	Topical steroid	16.1	22	7	1
2	23	Male	22.14	None	2	Topical steroid	14.2	25	4	2
3	36	Female	28.3	None	13	Methotrexate, Topical steroid	18.9	22	9	1
4	59	Male	20.6	None	30	Methotrexate, Topical steroid	27.5	15	4	1
5	61	Male	27.3	None	20	Methotrexate, Topical steroid, NB-UVB	29.4	22	8	3

Abbreviations: PASI, Psoriasis Area and Severity Index; BMI, body mass index; DLQI, Dermatology Life Quality Index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

Table 2 Treatment outcomes

Patient	Treatment	PASI				DLQI		PSQI		ESS	
		Baseline	wk 4	wk 8	PASI 75	Baseline	wk 8	Baseline	wk 8	Baseline	wk 8
1	MTX + placebo	16.1	3.9	1.2	Yes	22	1	7	2	1	0
2	MTX + Melatonin	14.2	9.9	3.1	Yes	25	2	4	1	2	2
3	MTX + placebo	18.9	13.9	9.1	No	22	1	9	4	1	0
4	MTX + Melatonin	27.5	24.2	17.5	No	15	6	4	1	1	0
5	MTX + placebo	29.4	20.7	16.6	No	22	15	8	6	3	0

Abbreviations**:** PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

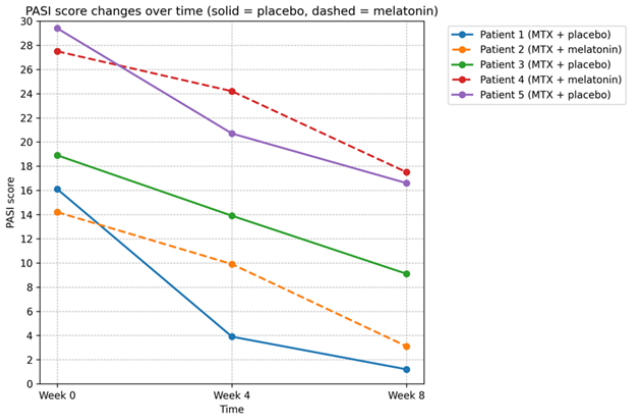

Figure 1 Changes in PASI scores from baseline to week 4 and 8 in individual patients treated with methotrexate 15 mg/week plus placebo or oral melatonin 2 mg.

Changes in psoriasis severity over the 8-week treatment period were summarized in Table 2 and Figure 1. All patients showed a reduction in Psoriasis Area and Severity Index (PASI) scores from baseline to week 8. In the methotrexate plus placebo group, the percentage improvement in PASI at week 8 ranged from 43.5% to 92.5%. One of the three patients in this group achieved a PASI 75 response The degree of clinical improvement varied considerably between individuals. In the methotrexate plus melatonin group, both patients demonstrated a reduction in PASI scores at week 8, with percentage improvements of 78.2% and 36.3%, respectively. One patient in this group achieved a PASI 75 response.

Improvements in dermatology-specific quality of life, assessed using the Dermatology Life Quality Index (DLQI), were observed in all patients during the study period (Table 2). Patients receiving adjunctive melatonin showed marked and relatively consistent improvement in DLQI scores, which decreased from 25 to 2 in one patient and from 15 to 6 in one patient by week 8. In contrast, DLQI outcomes in the methotrexate plus placebo group were more variable. Two patients demonstrated substantial improvement, with DLQI scores reduced to 1. In contrast, one patient continued to report impaired quality of life at week 8, with a DLQI score of 15 despite improvement in PASI.

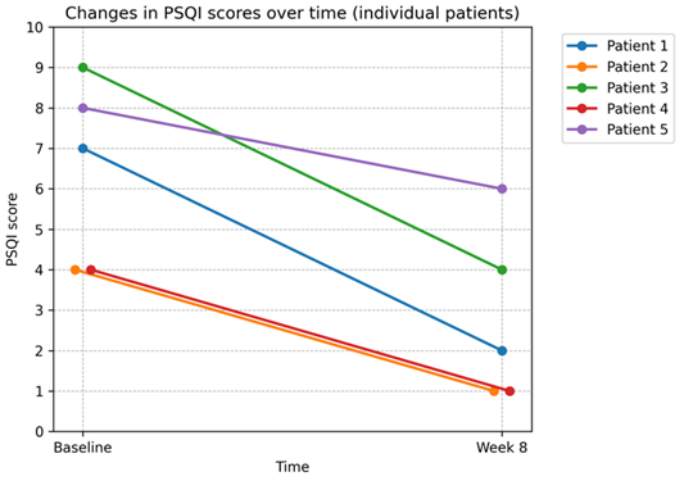

Figure 2 Changes in Pittsburgh Sleep Quality Index (PSQI) scores from baseline to week 8 in individual patients treated with methotrexate plus placebo or melatonin.

Sleep quality outcomes, assessed using the Pittsburgh Sleep Quality Index (PSQI), were also summarized in Table 2 and Figure 2. PSQI scores improved in all patients over the course of the study. Both patients in the methotrexate plus melatonin group achieved PSQI scores of 1 at week 8, indicating a shift from impaired to good sleep quality (PSQI $\leq$ 5). In the methotrexate plus placebo group, improvement in PSQI scores were generally less than 70%. At week 8, PSQI scores ranged from 2 to 6, and one patient continued to report poor sleep quality. Daytime sleepiness, measured using the Epworth Sleepiness Scale (ESS), was low at baseline and remained minimal throughout the study in both treatment groups. No increase in daytime sleepiness was observed in patients receiving adjunctive melatonin.

No serious adverse events were reported during the 8-week treatment period. Laboratory monitoring, including complete blood count and liver function tests, showed no clinically significant abnormalities. Oral melatonin at a dose of 2 mg nightly was well tolerated, and no patients discontinued treatment due to adverse effects.

4.2 Discussion

This pilot randomized controlled trial assessed clinical, sleep-related, and quality-of-life outcomes in patients with moderate to severe plaque psoriasis treated with methotrexate, with or without adjunctive oral melatonin, over an 8-week period.

All patients showed improvement in psoriasis severity, as reflected by reductions in Psoriasis Area and Severity Index (PASI) scores, consistent with the established efficacy of methotrexate. The extent of PASI improvement, however, varied among individuals in both treatment arms. Among those receiving melatonin, responses ranged from moderate to marked improvement. A similarly broad range of skin responses was observed in patients treated with methotrexate plus placebo.

Within this overall pattern, patients with a longer history of psoriasis appeared to demonstrate less pronounced short-term improvement in PASI scores. In this series, Patient 4, with a 30-year disease duration, and Patient 5, with 20 -years of disease duration, did not achieve PASI 75 during the 8-week period despite continued systemic therapy. Although disease duration alone does not reliably predict therapeutic response, long-standing psoriasis may reflect a more entrenched and biologically complex inflammatory state. Differences in underlying inflammatory pathways and persistent immune activation may further contribute to variability in therapeutic outcomes (Man et al., 2023). These factors may partly account for the more limited PASI improvement observed in patients with a disease duration of more than 10 years in this series. However, given the small sample size and descriptive design, these observations should be interpreted cautiously, and no definitive conclusions can be drawn regarding the effect of either disease duration or adjunctive melatonin on clinical efficacy. Overall, the data do not indicate a consistent additional short-term benefit of melatonin on PASI responses beyond that achieved with methotrexate alone.

By contrast, differences between treatment groups were more apparent in sleep-related and patient-reported outcomes. Patients receiving adjunctive melatonin reported notable improvements in sleep quality, accompanied by consistent and clinically meaningful gains in Dermatology Life Quality Index (DLQI) scores. In the methotrexate plus placebo group, changes in quality of life were more variable, with one patient continuing to report substantial impairment despite objective improvement in skin severity.

The contrast between Patient 4 and Patient 5 may help to illustrates this relationship particularly well. Although Patient 4 did not reach PASI 75, adjunctive melatonin appeared to be associated with marked improvement in sleep and notable improvement in quality of life. In comparison, Patient 5, who did not receive melatonin but achieved a similar degree of PASI improvement, continued to report impaired quality of life. Taken together, these observations suggest that better sleep may be associated with improvements in quality of life, even when skin clearance remains incomplete.

Although mechanistic assessments were not undertaken, the observed pattern of improvement in sleep and quality of life was consistent with known biological actions of melatonin. Experimental and review studies have highlighted its role in circadian rhythm regulation and its anti-inflammatory and immunomodulatory effects, including modulation of nuclear factor-κB signaling and interleukin-17–related pathways that are relevant to psoriasis pathophysiology (Fischer et al., 1999; Karaaslan & Suzen, 2015; Zhang & Yao, 2023). Melatonin has also been reported to exert hepatoprotective effects through antioxidant mechanisms and the reduction of oxidative stress (Jahovic et al., 2003; Abdallah et al., 2024). In the present series, no clinically significant liver enzyme abnormalities were observed in patients receiving adjunctive melatonin. Although the small sample size precludes any conclusions regarding hepatoprotection, this finding is reassuring in the context of the known risk of methotrexate-associated hepatotoxicity. Taken together, melatonin's antioxidant and anti-inflammatory properties may theoretically attenuate methotrexate-induced oxidative and hepatic toxicity, providing a biologically plausible rationale for its use as an adjunct in systemic psoriasis therapy.

Adjunctive oral melatonin at a dose of 2 mg nightly was well tolerated, with no evident safety signals or observed increase in daytime sleepiness. Taken together, these results support the short-term safety and practical feasibility of melatonin as an adjunctive treatment for patients with moderate to severe plaque psoriasis receiving systemic therapy, particularly those with prominent sleep disturbance or impaired quality of life.

However, this study has several limitations, including the small sample size, short follow-up duration, and reliance on subjective sleep assessment tools rather than objective sleep measures. In addition, the study was not designed or powered to detect differences in clinical efficacy. Nevertheless, as a descriptive

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case series, these real-world observations provide preliminary support for further investigation of adjunctive melatonin in psoriasis.

5. Conclusion

In conclusion, adjunctive oral melatonin was well tolerated and was associated with consistent improvements in sleep quality and dermatology-specific quality of life in patients with moderate-to- severe plaque psoriasis receiving methotrexate. Although its effect on short-term skin severity remains uncertain, the observed benefits in patient-reported outcomes support the potential role of melatonin as a complementary adjunct in systemic psoriasis therapy. Clinically, melatonin may be particularly relevant for a subset of psoriasis patients, especially those with comorbid insomnia or disproportionately high DLQI scores despite relatively low or modestly improved PASI, in whom residual sleep disturbance and quality-of-life impairment remain significant unmet needs. Given the small sample size and pilot nature of this study, these findings should be interpreted cautiously, and larger controlled studies are warranted.

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