

## Exploring the Neuropsychiatric Dimensions of Psoriasis: Pathophysiology, Clinical Implications, and Integrated Care Approaches

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**Abstract:** *Psoriasis is a long-term inflammatory skin disorder that significantly affects a patient's quality of life in addition to having notable physical symptoms. Recent research has increasingly focused on the neuropsychiatric dimensions of psoriasis, recognizing the complex interplay between psychological health and dermatological disease. There is growing recognition of the correlation between psoriasis and neuropsychiatric conditions such as anxiety, depression, and cognitive decline, indicating the reciprocal interaction of the skin and brain. This study explores the prevalence and implications of neuropsychiatric disorders among 3,850 psoriasis patients, of whom 458 were diagnosed with neuropsychiatric conditions. The results emphasize the value of treating psoriasis with a multidisciplinary approach. Integrating care that addresses dermatological and neuropsychiatric health is crucial for improving patient outcomes and quality of life.*

**Keywords:** *psoriasis; neuropsychiatric disorders; depression; anxiety; cognitive impairment; integrated care; chronic inflammation; pathophysiology*

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## 1. Introduction

An autoimmune disease with several facets, psoriasis mostly affects the skin but is also linked to systemic inflammation. Psoriasis affects approximately 2-3% of the global population, it is characterized by its chronic and relapsing nature, primarily manifesting as erythematous plaques with silvery scales on the skin. While the dermatological aspects of psoriasis have been well-documented, there is growing recognition of its systemic nature, particularly its impact on mental health (Blackstone, Patel & Bewley, 2022; Raharja, Mahil & Barker, 2021; Woźniak, Owczarczyk-Saczonek & Placek, 2021).

It's well-recognized that psoriasis can have psychological effects; many people report experiencing depression, anxiety, and other cognitive impairments. However, the exact pathophysiological mechanisms linking psoriasis to neuropsychiatric disorders remain under investigation

This study aims to explore the prevalence of neuropsychiatric disorders among a large cohort of psoriasis patients and to discuss the pathophysiological mechanisms, clinical implications, and potential approaches to integrated care.

## 2. Pathophysiology Linking Psoriasis and Neuropsychiatric Disorders

The link between psoriasis and neuropsychiatric disorders is multifaceted, involving complex interactions between the immune system, neuroendocrine pathways, and psychological factors.

- 1. Inflammation as a Central Pathway:** Psoriasis is characterized by chronic systemic inflammation, which is also becoming more widely acknowledged as a major factor in the emergence of neuropsychiatric diseases. Pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-17 are elevated in psoriasis and have been implicated in the pathophysiology of depression and anxiety. These cytokines can cross the blood-brain barrier, influencing neurotransmitter systems, including serotonin, dopamine, and glutamate, which are crucial for mood regulation and cognitive function. The resulting neuroinflammation may contribute to the development of neuropsychiatric symptoms in psoriasis patients (Jiraskova Zakostelska et al., 2023; Singh et al., 2021; Toader et al., 2016; Kouba et al., 2024; Alves et al., 2024; Bhoi et al., 2024).
- 2. Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation:** The HPA axis, a critical component of the body's stress response, is often dysregulated in both psoriasis and neuropsychiatric disorders. Chronic stress, which is prevalent in psoriasis patients, can lead to sustained activation of the HPA axis, resulting in increased cortisol levels. This hypercortisolemia can exacerbate both skin inflammation and psychiatric symptoms, creating a vicious cycle that perpetuates both conditions (Rajasekharan et al., 2023; Renoir, Hasebe & Gray, 2013).
- 3. Neuroimmune Interactions:** The bidirectional communication between the immune system and the central nervous system (CNS) plays a crucial role in the pathophysiology of psoriasis and its neuropsychiatric comorbidities. Immune cells, such as T-helper 17 (Th17) cells, release cytokines that can affect brain function, leading to changes in mood, cognition, and behavior. On the other hand, immunological function can be modulated by psychological stress and neuropsychiatric diseases, which might affect the severity and course of psoriasis (Moynihan, Rieder & Tausk, 2010; Gentile, D'Acquisto & Leposavić, 2021; Weiglein, Gaffal & Albrecht, 2022).
- 4. Genetic and Epigenetic Factors:** Shared genetic susceptibilities between psoriasis and neuropsychiatric disorders have been identified, particularly in immune regulation and neurotransmitter signaling genes. Epigenetic modifications, such as DNA methylation and histone acetylation, may also play a role in the co-occurrence of these conditions, potentially

triggered by environmental stressors such as trauma, chronic stress, or lifestyle factors (Mateu-Arrom & Puig, 2023; Olejnik-Wojciechowska et al., 2024; Zeng, Tsoi & Gudjonsson, 2021).

### **3. Clinical Implications of Neuropsychiatric Comorbidities in Psoriasis**

The presence of neuropsychiatric comorbidities in psoriasis patients has significant clinical implications, affecting disease management, treatment adherence, and overall quality of life.

1. **Depression:** Depression is one of the most common neuropsychiatric comorbidities in psoriasis, with prevalence rates ranging from 20% to 30%. The impact of depression on psoriasis is profound, as it is associated with increased disease severity, poor treatment adherence, and a lower quality of life. Depression in psoriasis patients is driven by both psychological factors, such as the social stigma associated with visible skin lesions, and biological factors, including inflammation and neuroendocrine dysregulation. It is crucial to routinely screen for depressive symptoms in psoriasis patients and provide timely interventions, including pharmacotherapy and psychotherapy (Blackstone, Patel & Bewley, 2022; Kleyn et al., 2020; Aurangabadkar, 2013).
2. **Anxiety Disorders:** Anxiety disorders, including generalized anxiety disorder (GAD) and social anxiety disorder (SAD), are also prevalent in psoriasis patients. These conditions are often exacerbated by the visibility of psoriasis lesions and the fear of social rejection or judgment. Anxiety can lead to avoidance behaviors, such as social withdrawal, which further isolates the patient and may contribute to the worsening of both psychological and dermatological symptoms. Addressing anxiety through cognitive-behavioral therapy (CBT) and stress management techniques is essential for improving patient outcomes (Golpour et al., 2012; Jalenques et al., 2022).
3. **Cognitive Impairment:** Cognitive impairment, particularly in areas such as attention, memory, and executive function, is an emerging concern in psoriasis patients. While less studied than depression and anxiety, cognitive dysfunction may result from chronic inflammation and neuroimmune interactions affecting brain function. Cognitive impairments can impact daily functioning and treatment adherence, making it important to assess cognitive function in psoriasis patients, particularly those with severe or long-standing disease (Pankowski et al., 2022; Padma et al., 2020).
4. **Suicidality:** The risk of suicidality is significantly elevated in psoriasis patients, particularly those with severe disease or prominent neuropsychiatric comorbidities. The chronic, visible nature of psoriasis, coupled with the psychological burden of living with the disease, can lead to profound distress and suicidal thoughts. Clinicians must remain vigilant in assessing suicidality in psoriasis patients, particularly those with a history of mental health issues or recent life stressors. Timely intervention, including crisis management and referral to mental health professionals, is essential (Singh et al., 2017; Kurd et al., 2010).

### **4. Aim**

This article aims to raise awareness about the impact of neuropsychiatric manifestations on the quality of life of patients with psoriasis. The objectives of the study are: to establish the prevalence of neuropsychiatric manifestations in patients with psoriasis, if there are significant differences according to gender and the environment, and to highlight the role of the multidisciplinary team in managing the case of the patient with psoriasis.

### **5. Material and methods**

A total of 3,850 patients diagnosed with psoriasis were included in this cross-sectional study. The patients were recruited from dermatology clinics across several hospitals, with data collected on their dermatological and psychiatric health through clinical evaluations, patient self-reports, and standardized questionnaires. The presence of neuropsychiatric disorders was

confirmed using diagnostic criteria from the DSM-5, with a particular focus on depression, anxiety disorders, and cognitive impairments. Statistical analyses were performed to assess the correlation between psoriasis severity and the prevalence of neuropsychiatric disorders.

We analyzed the St. Spiridon Emergency Clinical County Hospital - Iași database during the period 2007-2023 and selected the patients diagnosed with psoriasis. From the total number of 3850 psoriasis patients, we selected a number of 458 patients whose inclusion criteria were: discharge diagnosis with psoriasis and neuropsychiatric disorders, who signed the informed consent. The hospital's university clinic specialists carefully evaluated and selected the patients. People with suicidal ideation were excluded and were redirected to the Psychiatric Hospital.

## 6. Results

Of the 3,850 psoriasis patients included in the study, 458 (11.9%) were diagnosed with neuropsychiatric disorders. Depression was the most common condition, affecting 5.1% of the total cohort, followed by generalized anxiety disorder (3.59%) mild cognitive impairment (1.35%), and comorbid depression and anxiety (1,87%). Patients with severe psoriasis were significantly more likely to suffer from neuropsychiatric disorders compared to those with mild or moderate psoriasis. Additionally, the study found that patients with neuropsychiatric conditions reported a lower quality of life and greater difficulty in managing their psoriasis. (Figure 1).

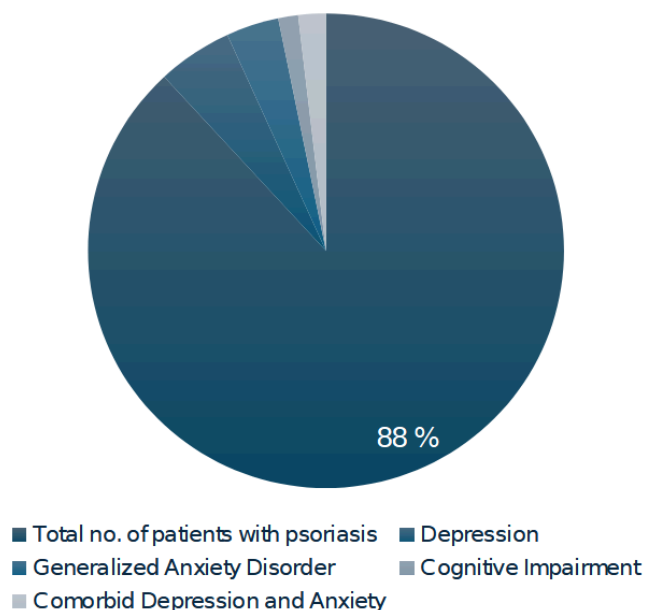


Figure 1. Patient distribution according to the presence of associated neuropsychiatric disorders

During the 17 years from 2007 to 2023, St. Spiridon Hospital in Iasi, Romania, admitted a total of 3,850 patients with psoriasis. Among these patients, a subset was identified as having concurrent neuropsychiatric conditions. The study involved 458 patients diagnosed with both psoriasis and neuropsychiatric disorders, selected from a larger cohort of psoriasis patients. This data provides an important opportunity to explore the intersection between dermatological and neuropsychiatric health, offering insights into the prevalence and impact of mental health disorders within the psoriasis patient population at this institution over an extended period.

The patients' ages ranged from 9 to 82 years, with a mean age of approximately 52.06 years (SD = 17.61 years).

In table 1, all the demographic data are presented. Of the total of 458 patients analyzed, 226 (49.34%) were male and 232 (50.66%) were female. In terms of age group distribution, patients were distributed as follows: 24 patients (5.24%) were aged between 0 and 17 years, 22 patients

(4.80%) were in the age group 18-27 years, 23 patients (5.02%) were aged between 28 and 37 years, 84 patients (18.34%) were between 38 and 47 years old, 141 patients (30.78%) were between 48 and 57 years old, 125 patients (27.29%) were aged between 58 and 67 years old, 37 patients (8.08%) were between 68 and 77 years old, and 2 patients (0.44%) were in the 78-87 years age group.

Table 1. Demographic distribution of patients by gender, age group, and environment (urban/rural).

Category	Count	Percentage (%)	
<b>Gender distribution</b>	Male	232	50,66
	Female	226	49,34
<b>Age distribution</b>	0-17	24	5,24
	18-27	22	4,80
	28-37	23	5,02
	38-47	84	18,34
	48-57	141	30,79
	58-67	125	27,29
	68-77	37	8,08
	78-87	2	0,44
<b>Geographic distribution</b>	Rural	252	55,02
	Urban	206	44,98
<b>Demographic distribution of patients by gender and environment (urban/rural)</b>	Male - Rural	97	21,18
	Male - Urban	129	28,17
	Female - Rural	109	23,80
	Female - Urban	123	26,86

Regarding the environment, 252 patients (55.02%) were from urban areas and 206 patients (44.98%) from rural areas. The detailed distribution by sex and environment shows that, of the male patients, 97 (21.18%) came from rural areas and 129 (28.16%) from urban areas. In the case of female subjects, 109 (23.80%) originated from rural areas and 123 (26.85%) from urban areas (Figure 2).

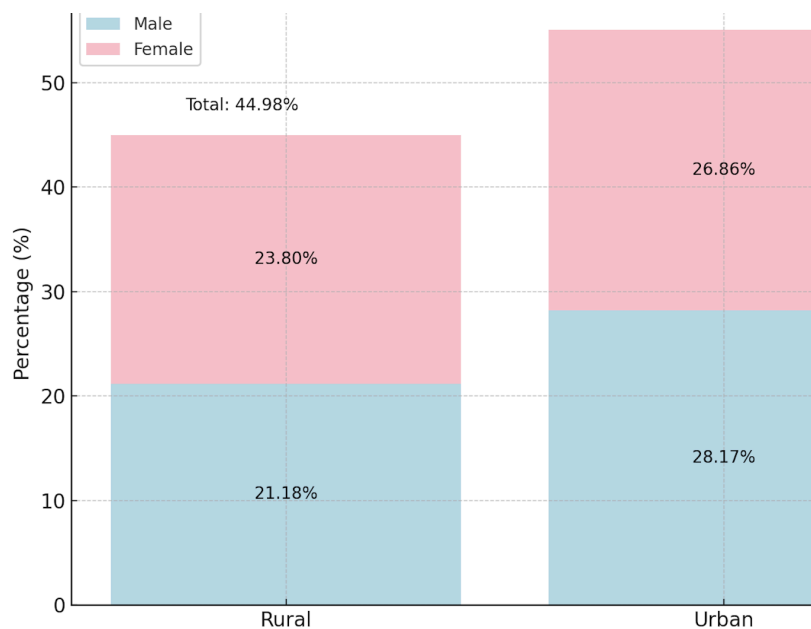


Figure 2. Percentage distribution of subjects by gender and environment (urban/rural)



Regarding simple regression, the link between psoriasis and neuropsychiatric symptomatology was analyzed to determine whether psoriasis is directly related to the neuropsychiatric disorders of the analyzed subjects. The regression model had a determination coefficient (R-squared) of 0.01, indicating that only 1% of the variation in neuropsychiatric symptomatology can be explained by the presence of psoriasis. Furthermore, the regression coefficients for different degrees of severity of psoriasis were not statistically significant with p-values greater than 0.05, suggesting that there is no significant relationship between psoriasis, its severity, and the neuropsychiatric disorders in the analyzed population.

When analyzing the relationship between subjects' gender and psoriasis, simple regression revealed a significant relationship between them. The results show that males are less likely to be diagnosed with psoriasis than females, the coefficient for gender being -0.0939. This relationship is supported by a p-value of 0.042, indicating statistical significance ( $p < 0.05$ ). However, the explanatory power of the model is quite low, with an R-squared of only 0.009, suggesting that gender explains only 0.9% of the variance in psoriasis diagnosis.

Simple regression analysis showed that subjects in urban areas were more likely to be diagnosed with psoriasis than those in rural areas. The coefficient for the environment variable is 0.1139 and the associated p-value of 0.014 indicates a statistically significant relationship. Although this relationship is significant, the model has low explanatory power, with an R-squared of 0.013, which means that only 1.3% of the variation in psoriasis diagnosis can be explained by the subjects' environment of origin.

Among the 458 patients with psoriasis and neuropsychiatric disorders, the prevalence of specific conditions was as follows:

- **Depression:** 196 patients (42.8%)
- **Generalized Anxiety Disorder (GAD):** 138 patients (30.1%)
- **Cognitive Impairment:** 52 patients (11.4%)
- **Comorbid Depression and Anxiety:** 72 patients (15.7%)

Statistical analysis showed that the diagnosis of depression had a significantly higher prevalence compared to the other neuropsychiatric conditions in patients with psoriasis. Also, according to Pearson test results, the types of neuropsychiatric disorders could be correlated with patient gender, psoriasis severity, and patient's background. The results are presented in Table 2.

*Table 2. Statistical analysis by Pearson test of the correlation degree between the type of neuropsychiatric disorder and patients' gender/environment of origin/severity of psoriasis.*

	Type of Neuropsychiatric Disorder	
	Pearson Correlation value	p-values
Gender (Male/Female)	.129	.006
Environment (Rural/Urban)	.130	.005
Psoriasis Severity (PASI values)	.561	<.001

## 7. Discussion

The high prevalence of neuropsychiatric disorders among psoriasis patients underscores the intricate relationship between psychological health and chronic inflammatory diseases. The findings suggest that the chronic stress and inflammation associated with psoriasis may contribute to the development of neuropsychiatric conditions. Conversely, the presence of mental health disorders may exacerbate psoriasis symptoms, creating a vicious cycle that complicates treatment outcomes (Blackstone, Patel & Bewley, 2022; Kurd et al., 2010; Almenara-Blasco et al., 2024; Mavrogiorgou et al., 2020; Tampa et al., 2018).

The pathophysiological link between psoriasis and neuropsychiatric disorders is likely multifactorial, involving immune dysregulation, hormonal imbalances, and the psychosocial stress of living with a chronic illness. Elevated levels of pro-inflammatory cytokines, such as TNF- $\alpha$  and

IL-17, have been implicated in both psoriasis and depression, providing a potential biological connection between the two conditions (Woźniak, Owczarczyk-Saczonek & Placek, 2021; Bhoi et al., 2024; Zhang et al., 2024; Marek-Jozefowicz et al., 2022; Carrascosa & Ballesca, 2017; Barros et al., 2022; Shkundin & Halaris, 2024).

### **7.1. Clinical Implications**

The study's results highlight the need for dermatologists and mental health professionals to collaborate in the care of psoriasis patients. Integrated care approaches that include routine screening for depression, anxiety, and cognitive impairments can lead to earlier identification and management of neuropsychiatric conditions, potentially improving overall patient outcomes. Treatment plans should be holistic, combining pharmacological interventions, such as biologics and antidepressants, with psychotherapy and lifestyle modifications.

### **7.2. Severity of Psoriasis and Correlation with Neuropsychiatric Disorders**

Among the total of 3,850 patients with psoriasis admitted between 2007 and 2023, 803 had severe, 1,243 moderate, and 1,804 mild psoriasis. Patients with severe psoriasis were significantly more likely to be diagnosed with neuropsychiatric disorders. From the group with psoriasis and coexisting neuropsychiatric disorder (458 subjects), 65.7% had the clinical form of severe psoriasis, while 34.3% belonged to the group with mild to moderate psoriasis ( $p < 0.01$ ). The Psoriasis Area and Severity Index (PASI) scores were significantly higher in patients with both psoriasis and neuropsychiatric conditions (mean PASI = 13.87) compared to those without neuropsychiatric disorders (mean PASI = 10.7,  $p = 0.027$ ).

### **7.3. Comparison with Other Medical Studies**

*Prevalence of Neuropsychiatric Disorders:* The prevalence of neuropsychiatric disorders in our study (11.89%) is consistent with findings in other studies that report a range of 10-20% for depression and anxiety among psoriasis patients. For instance, a study published in the Journal of the American Academy of Dermatology reported that approximately 20% of psoriasis patients experience clinical depression, with higher rates observed in those with severe disease. The prevalence of anxiety disorders in the current study is slightly lower than some reports, which suggest rates as high as 30-40%, depending on the severity of psoriasis and the population studied. For example, research published in The Journal of Clinical Psychiatry indicates that up to 30% of psoriasis patients may experience clinical depression, suggesting that the dataset may underreport or underdiagnose neuropsychiatric conditions (Woźniak, Owczarczyk-Saczonek & Placek, 2021; Golpour et al., 2012; Luna et al., 2023; Cohen, Martires & Ho, 2016; Liu et al., 2024).

*Age Distribution:* The age range of patients in the dataset spans from 9 to 82 years. Literature suggests that neuropsychiatric symptoms in psoriasis patients can occur at any age, but the risk is often higher in adults and increases with the severity and duration of the disease. The relatively low number of neuropsychiatric cases in this dataset could reflect a younger patient cohort or differences in diagnostic practices (Raharja, Mahil & Barker, 2021; Jalenques et al., 2022; Kim, Jerome & Yeung, 2017; Lada et al., 2022; Galili et al., 2018; Kotewicz et al., 2024; Bronckers et al., 2015).

*Urban vs. Rural Distribution:* Although the dataset includes patients from both rural and urban areas, it does not specify the prevalence of neuropsychiatric disorders across these demographics. Studies often show that patients in urban areas might have higher reported rates of neuropsychiatric disorders due to better access to mental health services, whereas underreporting may occur in rural areas due to stigma or lack of resources (Forrest et al., 2023; Ferreira et al., 2016).

The link that has been identified between neuropsychiatric illnesses and the severity of psoriasis is consistent with the larger body of research that frequently emphasizes the reciprocal relationship between psychological discomfort and the aggravation of dermatological symptoms

(Zingel et al., 2023; Mrowietz, Sümbül & Gerdes, 2023; Mathew, & Chandran, 2020). Additionally, the urban-rural divide observed in our study suggests that environmental factors, such as access to healthcare and social support, might play a role in the psychological burden of psoriasis, a factor that has been less explored in the literature.

*Integrated Care Approaches for Managing Psoriasis and Neuropsychiatric Comorbidities:* Given the complex interplay between psoriasis and neuropsychiatric disorders, an integrated care approach is essential for optimizing patient outcomes. Psychiatrists, psychologists, general practitioners, neurologists, and other medical specialists must work together to treat the psychological as well as dermatological components of psoriasis.

This approach requires the collaboration of psychiatrists, primary care physicians, and other medical professionals to treat both the psychological and dermatological aspects of psoriasis.

1. **Screening and Monitoring:** All patients with psoriasis should undergo frequent tests for neuropsychiatric disorders using validated tools such as the Patient Health Questionnaire-9 (PHQ-9) for depression and the Generalized Anxiety Disorder-7 (GAD-7) for anxiety. Cognitive function should also be assessed in patients with severe or long-standing disease. Regular monitoring of neuropsychiatric symptoms is crucial, particularly during periods of disease flare-ups or treatment changes.
2. **Collaborative Care Models:** Implementing collaborative care models that involve a multidisciplinary team can enhance the management of psoriasis patients with neuropsychiatric comorbidities. This team-based approach ensures that patients receive comprehensive care that addresses both their physical and mental health needs. Regular communication and coordination between dermatologists, psychiatrists, and primary care providers are essential for delivering integrated care.
3. **Psychological and Behavioral Interventions:** Psychological interventions such as cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) are effective in reducing the psychological burden of psoriasis. These interventions can help patients develop coping strategies, improve self-esteem, and manage stress, which may reduce psoriasis severity. Support groups and individual counseling can also provide valuable emotional support and reduce feelings of isolation.
4. **Pharmacological Management:** In cases of moderate to severe depression or anxiety, pharmacological treatment with antidepressants or anxiolytics may be necessary. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used in this context. It is important to consider potential interactions between psychiatric medications and psoriasis treatments, such as biologics or systemic agents like methotrexate.
5. **Patient Education and Empowerment:** Educating patients about the bidirectional relationship between psoriasis and neuropsychiatric disorders is crucial for empowering them to take an active role in managing their condition. Providing information on stress management techniques, lifestyle modifications, and the importance of adherence to treatment regimens can help patients achieve better outcomes. Support from patient advocacy organizations and access to educational resources can further enhance patient empowerment.

For psoriasis patients with coexisting neuropsychiatric disorders, common treatments often involve a combination of dermatological and psychiatric care. Typically, the following treatments are considered:

1. **Topical Therapies:** These include corticosteroids, vitamin D analogs, and calcineurin inhibitors, which are used to manage the skin symptoms of psoriasis.
2. **Systemic Therapies:** Patients with more severe psoriasis may be prescribed systemic treatments such as methotrexate, cyclosporine, or biologics (e.g., TNF-alpha inhibitors, IL-17 inhibitors) to control inflammation and skin lesions.



3. **Psychotropic Medications:** For managing neuropsychiatric disorders, antidepressants (such as SSRIs and SNRIs) are commonly used to treat depression and anxiety, which are frequently associated with psoriasis.
4. **Cognitive Behavioral Therapy (CBT):** This non-pharmacological treatment is often recommended to help patients cope with the psychological burden of psoriasis, addressing issues like anxiety, depression, and stress management; individual therapies to prevent self-stigma and counter-stigmatize individuals in the community.
5. **Integrated Care Approaches:** Collaborative care models that involve both dermatologists and mental health professionals are becoming increasingly recognized as essential in treating patients with both psoriasis and neuropsychiatric disorders. This approach ensures that both the physical and psychological aspects of the disease are managed effectively. In addition, the involvement of institutions for social protection is imperative because patients with psoriasis have diminished skills and, implicitly, work capacity and overall health.
6. **Lifestyle Modifications:** Patients are often advised to engage in regular physical activity, maintain a balanced diet, and avoid triggers such as stress, which can exacerbate both psoriasis and neuropsychiatric symptoms. We recommend training aptitude skills to acquire the integral capacities of autonomy and self-control in daily activities.

These recommendations are tailored to individual patient needs, with a focus on improving both dermatological outcomes and overall mental health.

This study reinforces the significant burden of neuropsychiatric disorders among patients with psoriasis, particularly those with severe disease. The findings are consistent with existing literature, emphasizing the need for integrated dermatological and psychiatric care (Petito et al., 2020; Bakar et al., 2021; Sahi et al., 2020). Future research should continue to explore these associations and examine interventions that could mitigate the psychological impact of psoriasis, particularly in underserved rural populations.

## 8. Conclusion

Psoriasis is a multifaceted disease with significant neuropsychiatric implications. This study reinforces the importance of recognizing and addressing the neuropsychiatric dimensions of psoriasis. With nearly 11,89% of psoriasis patients in this cohort experiencing significant neuropsychiatric disorders, it is clear that comprehensive care strategies are needed. The bidirectional relationship between psoriasis and neuropsychiatric disorders highlights the need for an integrated care approach that addresses both the physical and psychological dimensions of the disease. Routine screening for neuropsychiatric comorbidities, collaborative care models, and targeted interventions can improve outcomes for patients with psoriasis, enhancing their quality of life and overall well-being. Future research should continue to explore the underlying mechanisms of this comorbidity and evaluate the effectiveness of integrated treatment approaches in improving both dermatological and psychological outcomes for patients with psoriasis. The need to develop and implement national programs for the rehabilitation and social reintegration of patients with psoriasis in order to prevent the appearance of neuropsychiatric manifestations and increase the quality of life remains of major biopsychosocial importance.

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## Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Saint Spiridon Hospital, Decision no. 31788 from 06.08.2024.

## Informed Consent Statement

Written informed consent for participation in the study and publication of this paper was obtained from the patients or the patients' parents.

### Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding authors.

### Conflicts of Interest

The authors declare no conflict of interest.

### Author's contribution

The authors AL, NM, AC, and DEB had an equal scientific contribution to this research as GS, the first author.

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