A Review on Psychiatric Symptoms in Neuropsychiatric Systemic Lupus Erythematosus

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Abstract

Aim: This paper aims to synthesize current evidence on the epidemiology, pathophysiology, and clinical manifestations of selected psychiatric syndromes in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), including acute confusional state, mood disorders, and psychosis.

Material and methods: A PubMed search was conducted in August 2025, limited to English-language publications from 1st January 2001 to 15th August 2025. Search terms included “systemic lupus erythematosus”, “neuropsychiatric systemic lupus erythematosus”, “mood disorders”, “anxiety disorder”, “psychosis” and “acute confusional state.” Meta-analyses, clinical trials, cohort studies and review articles were screened and analyzed. In total, 60 articles met inclusion criteria.

Results: NPSLE affects 20-97% of patients. Mood disorders (11.5-37.4%) and anxiety (19.2-32.9%) are most common, associated with higher disease activity, disability, and reduced quality of life. Psychosis is less frequent (1.0-4.3%) but represents one of the most severe syndromes, linked to younger age at diagnosis, higher disease activity, and autoantibody positivity. Acute confusional state (ACS) is rare (0.0-3.3%) yet often associated with poor outcomes and elevated intrathecal cytokine levels. Pathogenesis across syndromes is multifactorial, involving autoantibodies, cytokine-driven neuroinflammation, and blood–brain barrier dysfunction.

Conclusions: Psychiatric manifestations in NPSLE range from common mood disorders to rare but severe conditions such as ACS and lupus psychosis, significantly worsening prognosis. Current diagnostic approaches remain limited by symptom overlap with primary psychiatric conditions and treatment-related effects. Improved epidemiological surveillance, biomarker validation, and interdisciplinary management strategies are critical to advancing diagnostic accuracy.

Keywords: SLE, NPSLE; mood disorders; psychosis; acute confusional state

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystem involvement. Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses central and peripheral nervous system involvement, including psychiatric syndromes. These manifestations arise from inflammatory and ischemic mechanisms and are associated with substantial morbidity and mortality. They may reflect primary SLE activity or be secondary to treatment effects and disease-related complications. NPSLE remains a diagnostic and therapeutic challenge, often requiring multidisciplinary management.

This review summarizes the current state of knowledge on selected psychiatric manifestations such as acute confusional state, mood disorders and psychosis, which contribute substantially to morbidity and diagnostic complexity.

Material and methods

An electronic search on the PubMed database was conducted in August 2025. The search results were limited to publications from 1st January 2001 to 15th August 2025 published in English. The following key words were used: “systemic lupus erythematosus”, “neuropsychiatric systemic lupus erythematosus”, “mood disorders”, “anxiety disorder”, “psychosis” and “acute confusional state”. Meta-analyses, clinical trials, cohort studies and review articles were included and analyzed. Case reports and articles published before 2001 were excluded. An exception was made for 1 classification document from 1999. Data were synthesized with a focus on epidemiology, clinical features, and pathophysiological mechanisms.

Two independent reviewers screened titles and abstracts; disagreements were resolved by consensus. In total, 60 articles met inclusion criteria.

In preparing this work, ChatGPT was used for the purpose of translation and editing only. Afterwards, the manuscript was reviewed and edited for its intellectual content and academic rigour.

Results

Diagnostic challenges

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes damage to many tissues and organs. Diagnosing SLE is challenging due to the wide variety of clinical manifestations. SLE can appear in a variety of ways, from skin and joint symptoms to renal involvement, as well as neurological or psychiatric symptoms. Moreover, approximately 70% of patients follow a relapsing-remitting course [1]. This heterogeneity leads to a diffuse clinical picture that can mimic other autoimmune, infectious, or psychiatric diseases. Based on the binomial coefficient, according to criteria from 1982, 330 combinations of symptoms could have been used to determine

the diagnosis of SLE [2]. The newest criteria developed by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) from 2019 [3] allow 911 possible combinations of symptoms, as shown in Figure 1. The entry criterion is defined as the presence of antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or equivalent, confirmed at least once. Diagnosis is precluded in the absence of ANA. If present, subsequent criteria are to be assessed. A criterion is excluded if a more plausible alternative explanation is identified. Additional criteria are categorized into clinical and immunological domains. The clinical domains are defined to include constitutional manifestations (fever), hematologic abnormalities, neuropsychiatric involvement, mucocutaneous lesions, serosal disease, musculoskeletal manifestations (joint involvement), and renal pathology, each characterized by specific descriptors. Immunological domains include antiphospholipid antibodies (Abs), complement abnormalities, and SLE-specific Ab. Each manifestation is assigned an appropriate weighted score. Recognition of a criterion on a single occasion is considered sufficient. Simultaneous occurrence of criteria is not required. Within each domain, only the highest weighted item is counted toward the cumulative score. Classification is established when at least one clinical criterion is present and the total score reaches ≥10 points [3].

Figure 1. Derivation of the total number of possible symptom combinations meeting the 2019 EULAR/ACR classification criteria for SLE. Calculations performed in Python. Author's own work. The total number of valid combinations equals 911.

Let $G_1 = \{G_1^{(1)}, G_1^{(2)}, \ldots, G_1^{(n_1)}\}$ and $G_2 = \{G_2^{(1)}, G_2^{(2)}, \ldots, G_2^{(n_2)}\}$, where $G_i^{(j)}$ denotes the j-th group from the i-th list.

For each group, we define the options:

$$O_i^{(j)} = \{0, \max(G_i^{(j)})\} \qquad \forall i \in \{1,2\}, \forall j$$

The set of all possible combinations:

$$C = O_1^{(1)} \times O_1^{(2)} \times \cdots \times O_1^{(n_1)} \times O_2^{(1)} \times O_2^{(2)} \times \cdots \times O_2^{(n_2)}$$

Filtering condition:

$$\mathcal{V} = \left\{(c_1, c_2) \in C \ : \ \Phi(c_1, c_2) = 1\right\}$$

$$\text{where } \Phi(c_1, c_2) = \begin{cases} 1 & \text{if } \sum_{i=1}^{n_1} c_1^{(i)} + \sum_{j=1}^{n_2} c_2^{(j)} \geq S_{\min} \text{ and } \exists\, k: \ c_1^{(k)} > 0 \\ 0 & \text{otherwise} \end{cases}$$

The total number of valid combinations:

$$|\mathcal{V}| = \sum_{c_1 \in \prod_{i=1}^{n_1} O_1^{(i)}} \ \sum_{c_2 \in \prod_{j=1}^{n_2} O_2^{(j)}} \Phi(c_1, c_2)$$

Epidemiology

Epidemiological data on SLE are lacking for 79.8% of countries worldwide [4]. Incidence and prevalence vary markedly by sex, age, and geography, and are generally higher in high-income countries [4]. Females are affected far more often than males, with an estimated female-to-male ratio of approximately 6–10:1 [5-8]. Globally, the incidence is estimated at 5.14 (1.40-15.13) per 100,000 person-years, corresponding to roughly 0.40 million new diagnoses annually [4]. Rates also differ by ethnicity: individuals of Black ethnicity have a higher incidence and prevalence than those of White ethnicity [5,9]. Males tend to develop SLE at a later age compared to females [5,10]. The retrospective cohort study performed by Rees et al, 2014 [5] revealed the peak age of incidence for women (40-49 years) was earlier than that for men (60-69 years). The incidence was greater in females compared with males for all ages [5]. Meta-analysis by Lee et al (2024) underscored a significant 2.87-fold elevation in the standardized mortality ratio (SMR) among patients with SLE compared to the general population. SMR was also higher for SLE females (SMR: 3.261, $p < .001$) than for SLE males (SMR: 2.747, $p < .001$) [11].

NPSLE refers to NP manifestations attributable to SLE. Studies published since 2001 report a prevalence of NPSLE varying from 20 to 97% [12,13,14]. The American College of Rheumatology (ACR) defined 19 neuropsychiatric syndromes seen in NPSLE (Table 1) [15]. These symptoms are mainly a consequence of the inflammatory process and ischemic mechanisms, and are associated with higher morbidity and mortality [12,16]. They may be primarily related to SLE or secondary to treatment and complications of the disease. Moreover, the pathogenesis of NPSLE is multifactorial, ranging from genetic predisposition, vasculopathy, neuroendocrine-immune imbalance, neuronal dysfunction/ damage mediated by Abs and inflammatory mediators, blood-brain barrier dysfunction to direct neuronal death [17]. Patients with NPSLE exhibit increased disease activity reflected by SLE disease activity index - 2000 (SLEDAI-2K) score [17,18,19,20,21]. Neuropsychiatric events are associated with reduced quality of life and increased organ damage [22]. Onset of NPSLE may occur at any point during the SLE disease course, even before the beginning of systemic manifestations [23]. In approximately half of patients, neuropsychiatric symptoms appear together with the first symptoms of lupus or within the first year of diagnosis [24]. Furthermore, meta-analysis by Liu et al (2024) showed that patients with pre-existing mental disorders were more susceptible to developing SLE [25]. The meta-analysis by Pamuk et al (2024) revealed that the frequencies of overall NPSLE, seizures, and psychosis were less common in late-onset (≥50-year-old) SLE patients than in early-onset (<50-year-old). In contrast, peripheral neuropathy was more common in the late-onset SLE group [26]. The prevalence of the analyzed psychiatric disorders in NPSLE patients is presented in Table 2. NPSLE is a challenge for the rheumatologist, both at a diagnostic and therapeutic level [2,12,13].

Table 1. Neuropsychiatric syndromes seen in NPSLE distinguished by The American College of Rheumatology [15].

Central nervous system	Peripheral nervous system
1. Aseptic meningitis 2. Cerebrovascular disease 3. Demyelinating syndrome 4. Headache 5. Movement disorder 6. Myelopathy 7. Seizure disorder 8. Acute confusional state 9. Anxiety disorder 10. Cognitive dysfunction 11. Mood disorder 12. Psychosis	1. Acute Inflammatory Demyelinating Polyradiculoneuropathy 2. Autonomic disease 3. Mononeuropathy (single/ multiplex) 4. Myasthenia gravis 5. Neuropathy, cranial 6. Plexopathy 7. Polyneuropathy

Table 2. The prevalence of analyzed psychiatric disorders in NPSLE patients [25,27,30].

Psychiatric sign	Prevalence [%]
Mood disorder	**11.5 - 37.4 [27]**
Anxiety disorder	**19.2 - 32.9 [30]**
Psychosis	**1.0 - 4.3 [25]**
Acute confusional state	**0.0 - 3.3 [25]**

Mood disorder and anxiety

Mood disorders are among the most common psychiatric manifestations, affecting between 11.5%-37.4% [27] of patients depending on study design and population [25,27,28]. Distinguishing SLE-related mood disorders from primary psychiatric diseases is difficult because symptoms often mimic or overlap. Depression and bipolar disorder occur at higher rates in patients with SLE than in the general population [28,29]. Meta-analyses by Zhang et al (2017) revealed the prevalence of major depression among SLE patients to be 24% according to the DSM and/or ICD diagnostic criteria, while prevalence estimates of depression were 30% for the Hospital Anxiety and Depression Scale (HADS) and 38% for the Center for Epidemiologic Studies Depression Scale (CES-D), respectively. The corresponding pooled prevalence of anxiety was 40%, as assessed by the HADS using a cutoff score of ≥8 [31]. Reported prevalence rates of dysthymic disorder in NPSLE showed considerable variability across studies. Notably, studies with lower methodological quality tended to yield higher prevalence estimates when DSM and/or ICD diagnostic criteria were applied (18% vs 3%) [31]. The analysis by Huang et al (2014) based on data of 1609 SLE patients from the Hopkins Lupus Cohort revealed the following risk factors for depression: recent SLE diagnosis, disability, cutaneous activity, longitudinal myelitis, and current prednisone use of 20 mg/day or higher [32]. A cross-sectional study by Liao et al (2022) showed that family income, manifestations in musculoskeletal and neuropsychiatric systems, and disease activity in SLE are positively correlated with

the severity of depression and anxiety; patients with SLEDAI scores above 8.5 are significantly more likely to experience mental disorders, underscoring the need for routine depression and anxiety screening as well as appropriate treatment interventions [33]. The high burden of mood disorders in SLE has been associated with increased disability and reduced health-related quality of life (HRQoL). Meta-analysis by Zhao et al (2023) showed that depression was associated with increased body pain, functional disability, higher disease activity, and decline in HRQoL in patients with SLE. It also may lead to impaired occupational functioning [34]. Major depressive disorder was the most frequently reported coexisting psychiatric condition associated with suicidal behavior in SLE patients [35]. A population-based cohort study of predominantly African American individuals with SLE, carried out by Heiman et al (2018), revealed that depression was a strong correlate of low medication adherence. As depressive symptoms worsened, the risk of non-adherence to treatment increased [36]. Accurate diagnosis of non-adherence is crucial and helps prevent misinterpreting disease manifestations as treatment failure, thereby avoiding unnecessary or potentially harmful escalation of therapy [37]. Greater perceived control and confidence in care are associated with lower depressive and anxiety symptoms. [32,38].

Pathophysiology of mood disorder in SLE is complex [39], reflecting the interplay of immune-mediated processes, vascular injury, neuroendocrine dysregulation, and steroid-related effects [40]. They are associated with antiphospholipid Abs [39,41,42,43], anti-P [42,44], anti-N-methyl-D-aspartate (NMDA) Abs [42,44], and anti-GAPDH Abs [42,44]. For example, anti-NMDA Abs present in cerebrospinal fluid (CSF) bind to NR2A/B subunits, inducing apoptotic neuronal death [39].

Psychosis

Psychosis was defined by the 2019 EULAR/ACR criteria as *(1) delusions and/or hallucinations without insight and (2) absence of delirium* [3]. Hallucinations are usually auditory and visual [40]. It may occur either in the context of active systemic disease or as an isolated neuropsychiatric manifestation. Psychosis may be present at the onset of SLE [33]. Due to its potential to mimic primary psychiatric disorders, proper identification is crucial. Psychosis may, in some cases, coexist with confusion, memory deficits, or mood disturbances, obscuring the distinction from acute confusional state or mood disorder with psychotic features. Lupus psychosis is relatively uncommon, with a reported prevalence ranging from 1.0 - 4.3 [25]. It is more frequently observed in younger patients. Meta-analysis by Pamuk et al [26] revealed that psychosis was more common in patients diagnosed with SLE before the age of 50. Psychosis, although relatively rare, is one of the most severe neuropsychiatric syndromes associated with NPSLE. It appears to be associated with higher disease activity scores at onset [45]. In a cohort of 537 SLE patients, psychosis was associated with positive

antiphospholipid Abs and occurred more frequently with renal and cutaneous involvement [45]. The prognosis is generally favorable with prompt immunosuppressive therapy [46,47]. Lupus psychosis has been associated with younger age at SLE diagnosis, male sex, African ancestry, and prior neuropsychiatric events [47].

The pathophysiology of psychosis in NPSLE is multifactorial and incompletely understood. Presumably, it results from interacting immunological, vascular, and neurochemical mechanisms. Cytokines and immune complexes increase BBB permeability, allowing Abs to access CNS tissue. For example, cytokine-induced neuroinflammation, caused by elevated levels of substances such as IL-6 or TNF-α, can lead to damage of the blood-brain barrier and neuronal toxicity. Elevated intrathecal levels of IL-6 have been observed in patients with psychosis and acute confusional state [48]. Furthermore, specific Ab, such as those targeting the NMDA receptor or ribosomal protein P, can cause Ab-induced neuronal damage [48]. Anti-ribosomal P Abs (anti-P) are linked with SLE psychosis [42,48,49]. However, their clinical significance remains controversial. Meta-analysis by Karassa et al (2006) revealed that anti-P testing has limited clinical value for NPSLE [50].

Steroid psychosis might be a confounding factor in setting the proper diagnosis and treatment. Glucocorticoids (GC), frequently used in SLE management, may cause psychotic episodes at any point during therapy. The administered dose is the most significant risk factor for the development of neuropsychiatric symptoms, and dosage reduction typically results in clinical recovery [45,51]. Low serum levels of albumin were a predictive factor of steroid psychosis [52]. In patients with hypoalbuminaemia, deficiency of circulating GC-binding protein facilitates access of unbound and free GC to the central nervous system, leading to psychiatric symptoms [53].

Acute confusional state

Acute confusional state (ACS), clinically overlapping with delirium, represents one of the rarest yet most severe diffuse manifestations of NPSLE and requires urgent intervention [54]. In the 2019 EULAR/ACR classification criteria delirium is defined as: *(1) a change in consciousness or level of arousal with reduced ability to focus, and (2) symptom development over hours to <2 days, and (3) symptom fluctuation throughout the day, and (4) either (4a) acute/subacute change in cognition (e.g. memory deficit or disorientation), or (4b) change in behavior, mood, or affect (e.g. restlessness, reversal of sleep/wake cycle)* [3]. Reported prevalence ranges from 0.0% to 3.3% among patients with SLE [25]. It is frequently associated with high disease activity, elevated Abs titers and poor outcomes, reflecting its strong link with immune-mediated central nervous system dysfunction [54]. Because its features overlap with delirium of other etiologies, ACS can mimic metabolic encephalopathy, infection-related delirium, or drug-induced neurotoxicity. Exclusion of secondary causes is essential for accurate diagnosis.

The pathogenesis of ACS in SLE is multifactorial. Elevated intrathecal IL-6 levels, presence of anti-GRP78 Abs and anti-N-methyl-D-aspartate (NMDA) receptor

NR2 Abs (anti-NMDAR Abs) have been correlated with ACS in NPSLE, suggesting an inflammatory and antibody- mediated mechanism [54-60]. Anti-GRP78 Abs have been reported to bind brain microvascular endothelial cells and disrupt BBB integrity, thereby increasing vascular permeability and facilitating the extravasation of proteins such as albumin and IgG [60]. This BBB dysfunction may allow uncontrolled entry of circulating immune mediators (e.g., IL- 6, anti-NMDAR Abs) into the CNS, promoting neuroinflammation and neuronal injury. Elevated intrathecal IL- 6 may also reflect increased CNS production- reported as upregulated expression in the hippocampus and cerebral cortex of patients with NPSLE [59,60]- although the precise pathways remain incompletely defined [54, 60]. Anti-NMDAR Abs can bind to neuronal NMDA NR2 receptor subunits, leading to receptor dysregulation and, with sufficient exposure, cause excitotoxic injury [54,57,60]. CSF anti-NMDAR NR2 Abs levels have been associated with NPSLE severity [54].

Discussion

This review highlights the substantial burden and heterogeneity of psychiatric syndromes in NPSLE. Mood and anxiety disorders are the most common, whereas psychosis and acute confusional state, although rare, are often linked to worse outcomes. Reported prevalence varies widely between studies, reflecting differences in methodology, diagnostic definitions, and attribution models. The broad range of NPSLE prevalence (20-97%) underscores the lack of standardized diagnostic approaches and the urgent need for harmonized criteria. Furthermore, comprehensive epidemiological data on SLE are lacking for 79.8% of countries, emphasizing the necessity of standardized epidemiological studies to obtain accurate global estimates and guide healthcare planning.

A major challenge is the overlap of NPSLE manifestations with primary psychiatric conditions and treatment-related effects. For instance, steroid-induced psychiatric symptoms may mimic lupus psychosis, while depression can result from both disease activity and psychosocial stressors. This diagnostic ambiguity highlights the necessity of multidisciplinary evaluation and careful attribution.

Although several Abs (e.g., anti-ribosomal P, anti-NMDAR) and inflammatory mediators such as IL-6 have been associated with neuropsychiatric symptoms, their utility as biomarkers remains limited due to inconsistent findings. Advances in fluid biomarkers are promising but require large-scale validation. Overall, psychiatric manifestations in NPSLE remain underrecognized. Future research should prioritize the development of standardized definitions, biomarker validation, and improved attribution models to enhance diagnostic accuracy.

Conclusions

Psychiatric syndromes in NPSLE are common, clinically consequential, and diagnostically challenging. Routine screening for depression and anxiety, careful differentiation from medication effects (particularly glucocorticoids), and early multidisciplinary management are warranted. Standardized definitions, validated biomarkers, and prospective studies are needed to refine diagnosis.

Disclosure

All authors have reviewed and agreed with the final version of the manuscript.
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