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Steroid Induced Psychosis: Current Understanding and Novel Approaches to Management

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ABSTRACT
Corticosteroids are widely used for their potent anti-inflammatory and immunosuppressive properties, but they can cause significant neuropsychiatric side effects, including steroid-induced psychosis (SIP). SIP manifests as hallucinations, delusions, mood disturbances, or cognitive impairment, with higher risk at doses exceeding 40 mg/day of prednisone. The condition typically appears within days to weeks of corticosteroid initiation but may also arise during dose tapering or cessation. Pathophysiological mechanisms include hypothalamic-pituitary-adrenal (HPA) axis dysregulation, elevated dopamine activity, neurotransmitter imbalances, and genetic vulnerabilities. Diagnosis is clinical, supported by symptom rating scales and causality assessment tools. Management primarily involves dose reduction and, if needed, antipsychotics. Novel interventions such as anti- glucocorticoid agents, mood stabilizers, and neurostimulation are under exploration. Early psychiatric involvement plays a pivotal role in improving outcomes. This review highlights current knowledge and emerging strategies for managing SIP.

KEYWORDS: steroid induced psychosis, corticosteroids

I. INTRODUCTION

Corticosteroids are commonly used for their strong anti-inflammatory and immunosuppressive effects in conditions like asthma, autoimmune diseases, and cancer [1]. However, they can also cause a variety of neuropsychiatric side effects, such as anxiety, mood issues, cognitive problems, and psychosis [2,3]. One serious but often overlooked complication is steroid-induced psychosis (SIP), which can show up as hallucinations, delusions, agitation, or confusion [4].

The occurrence of SIP ranges from 5% to 18%, with a higher risk for doses over 40 mg/day of prednisone or its equivalent [5,6]. Some symptoms may improve when the steroid dose is reduced, while others might need immediate psychiatric care [7]. Possible reasons for SIP include problems with the HPA axis, increased dopamine activity, and imbalances in serotonin and glutamate [8,9]. Genetic factors and a person's mental health history can also play a role in how susceptible someone is [10].

Traditionally, treatment has involved lowering the dose and using antipsychotic or mood-stabilizing medications [11]. However, growing awareness of SIP and its different symptoms has sparked interest in new treatment approaches. These include early psychiatric involvement, individualized medication plans, and the addition of non-drug methods like psychoeducation and therapy [12,13].

EPIDEMIOLOGY

Steroid-induced psychosis (SIP) is a well-recognized yet inconsistently reported adverse effect of corticosteroid therapy. The prevalence of psychiatric complications among corticosteroid users varies significantly, with estimates ranging from 2% to 60%, depending on factors such as corticosteroid dosage, treatment duration, and the criteria used to define psychiatric symptoms. Among these, severe psychiatric events, especially psychosis are reported in approximately 5–6% of patients receiving corticosteroids [16]. In a meta-analysis of over 2,500 patients, around 6% experienced severe psychiatric manifestations, while nearly 28% developed milder mood or cognitive disturbances [3]. A more recent pooled review estimated the prevalence of corticosteroid-induced psychiatric symptoms at 5.7%, many of which initially present subtly and may progress if unrecognized or untreated [17]. There is a strong dose-response relationship between corticosteroid administration and psychiatric adverse effects. Individuals receiving prednisone at doses of ≤40 mg/day had a 1.3% risk of psychiatric symptoms, whereas this risk increased to 4.6% for doses

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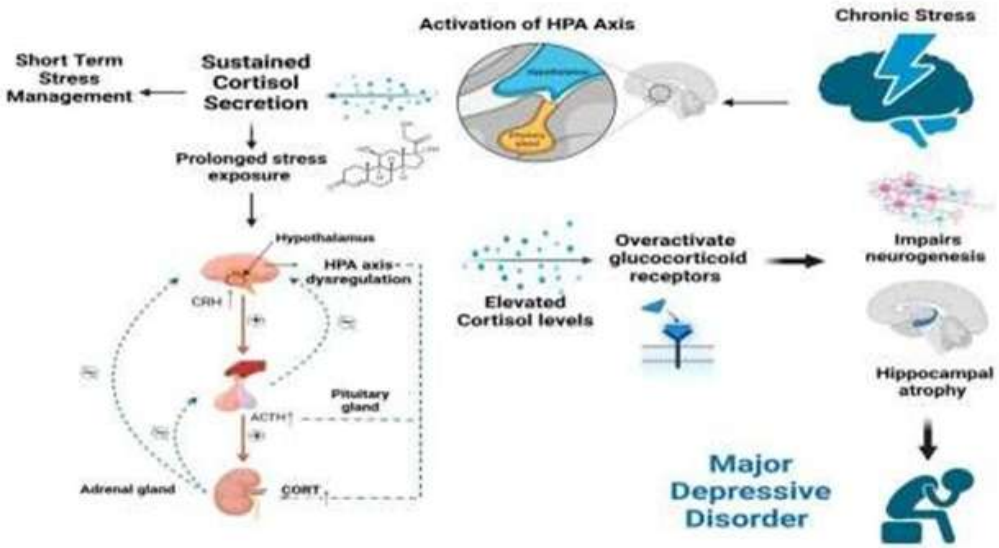
between 41 and 79 mg/day, and dramatically to 18.4% for those on 80 mg/day or higher. Psychotic symptoms constitute about 10–15% of the severe psychiatric reactions reported, though mood disturbances such as mania or depression are more frequently observed .Typically, psychiatric symptoms emerge early in the course of corticosteroid therapy—often within the first 11–12 days—though onset can vary from the first day to up to 60 days. Importantly, symptoms can also develop during dose reduction or after cessation of therapy [18]. Gender-based variability has also been observed, with some evidence suggesting a higher prevalence of steroid-induced psychiatric disorders among women, potentially due to their higher rates of corticosteroid-treated illnesses rather than an intrinsic susceptibility [5].

PATHOPHYSIOLOGY

The causes of steroid-induced psychosis (SIP) are complex. They include changes in hormones, brain chemistry, and brain structure. External corticosteroids disrupt the hypothalamic-pituitary-adrenal (HPA) axis. This disruption impairs negative feedback and creates a condition similar to Cushing's syndrome, which can cause psychiatric symptoms like mood swings and psychosis [8]. Higher levels of glucocorticoids increase dopamine activity in the mesolimbic system. This pathway is linked to hallucinations and delusions [12]. Additionally, corticosteroids affect the serotonin and glutamate systems, which may lead to increased glutamate-related toxicity and impact mood and perception regulation [14]. Long-term steroid use has also been linked to hippocampal shrinkage and decreased brain cell growth, leading to cognitive problems and impulsiveness. In addition, changes in brain inflammation, such as altered cytokine levels and activated microglia, may worsen chemical imbalances and trigger psychosis in vulnerable people. Genetic variations, particularly those related to FKBP5 and the sensitivity of glucocorticoid receptors, may further increase the risk of SIP, especially in individuals with a past psychiatric condition or during periods of acute stress.[15]



CLINICAL MANIFESTATIONS:

The clinical presentation is highly variable and can resemble primary psychiatric disorders, making early identification essential.

ONSET:

- SIP typically begins **within a few days to 2 weeks** of corticosteroid initiation, though it may also occur during dose escalation or withdrawal.
- Symptoms can be **transient or prolonged**, and they often **resolve with dose reduction or cessation** of corticosteroids.

MOOD SMPTOMS:

Euphoria or hypomania is commonly observed early in the course. Irritability, agitation,

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emotional lability, and depression are also frequent. In some cases, mixed affective states with both manic and depressive features can occur.

PSYCHOTIC SYMPTOMS:

Hallucinations (most commonly auditory, but also visual or tactile) and delusions (often paranoid or bizarre) are characteristic. Thought disorganization, pressured speech, or flight of ideas may resemble manic psychosis or schizophrenia-like presentation.

COGNITIVE IMPAIRMENT

Confusion, disorientation, poor concentration, and memory deficits are common. In severe cases, SIP may present with delirium, particularly in elderly or medically ill patients.

BEHAVIORAL CHANGES

Hyperactivity, impulsivity, insomnia, hypersexuality, and aggression can occur, particularly during manic or psychotic phases. Social withdrawal, poor self-care, and catatonic symptoms have been reported in chronic or severe cases.

DIAGNOSIS:

COMPREHENSIVE HISTORY AND TIMING OF ONSET

The cornerstone of diagnosis is establishing a clear temporal relationship between corticosteroid exposure and the onset of psychiatric symptoms. This requires precise documentation of the type of corticosteroid, dose (prednisone-equivalent), route of administration, duration of therapy, and any recent changes in regimen. SIP most often develops within the first few days to weeks after initiating high-dose therapy, although onset during tapering or even after cessation has been reported [5,6]. A symptom timeline aids in differentiating SIP from primary psychiatric disorders and other medication- induced psychoses.

EXCLUSION OF MEDICAL AND PSYCHIATRIC MIMICS

A broad range of conditions can mimic or exacerbate SIP, including delirium, metabolic encephalopathies, primary psychotic disorders, mood disorders with psychotic features, central nervous system (CNS) infections, endocrine abnormalities (e.g., thyroid dysfunction, Cushing's syndrome, hypercalcemia), autoimmune encephalitis, and substance-related psychosis [17]. A targeted workup should include complete blood count, serum electrolytes, renal and hepatic function tests, fasting glucose, calcium, and thyroid profile. Urine toxicology is valuable for excluding coexisting substance use. Neuroimaging (CT or MRI) is indicated for atypical presentations or focal neurological signs, while electroencephalography (EEG) can detect seizure activity or diffuse encephalopathy. Infection screening and autoimmune panels should be performed if clinically warranted.

SYMPTOM QUANTIFICATION AND MONITORING

Objective assessment tools enhance diagnostic precision and facilitate longitudinal monitoring. The Brief Psychiatric Rating Scale (BPRS) quantifies psychotic symptoms, while the Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) evaluate mood-related features. The Confusion Assessment Method (CAM) is useful for identifying coexistent delirium, and the Clinical Global Impression–Severity (CGI-S) scale offers an overall measure of illness severity. Routine use of these scales promotes standardized assessment across multidisciplinary teams and research settings [2].

CAUSALITY ASSESSMENT

Determining whether corticosteroids are the direct cause of psychosis from structured causality assessment tools. The Naranjo Adverse Drug Reaction Probability Scale and the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) system classify the likelihood of a causal relationship as certain, probable, possible, or unlikely. While these methods cannot replace clinical judgment, they provide a reproducible framework for assigning causality in both clinical and research contexts [22].

RISK FACTOR EVALUATION

A final diagnostic consideration is the identification of patient-specific risk factors that may predispose to SIP. Established risk determinants include higher corticosteroid doses (particularly ≥40 mg/day of prednisone equivalent), rapid dose escalation, female sex, advanced age, a personal or family history of psychiatric illness, and coexisting systemic diseases such as systemic lupus erythematosus, asthma, or chronic obstructive pulmonary disease. Recognizing these variables allows for proactive measures, such as

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gradual dose titration, early psychiatric monitoring, and patient education on potential warning signs.

MANAGEMENT:

CONVENTIONAL TREATMENT:

STEROID DOSE REDUCTION

Tapering or discontinuation of the offending corticosteroid is widely recognized as the primary approach in the management of steroid-induced psychosis. When possible, the steroid dose should be reduced to 40 mg or less of prednisone equivalent per day. Studies have shown that around 75–90% of psychiatric symptoms improve significantly with dose reduction alone. Alternate-day dosing or switching to less penetrant corticosteroids like Alternate-day dosing or switching to less penetrant corticosteroids like budesonide may be helpful in certain cases.

ANTIPSYCHOTIC AGENTS

If discontinuing steroids is not an option due to the patient's underlying condition, or if the psychiatric manifestations are particularly severe, additional pharmacological treatment becomes necessary. In such instances, initiating low-dose atypical antipsychotics such as risperidone, olanzapine, or quetiapine is recommended. These agents are typically started at minimal effective doses and gradually tapered once the patient's symptoms stabilize. In acute agitation, haloperidol may be employed.
Risperidone (1–2 mg/day) is most frequently reported in case series.[4]

NOVEL APPROACHES:

ANTIGLUCOCORTICOID AGENTS

Anti-glucocorticoid agents such as **mifepristone**, **metyrapone**, and **ketoconazole** have shown potential in counteracting the effects of excess corticosteroids by either blocking glucocorticoid receptors or reducing cortisol synthesis. These mechanisms may help mitigate the neuropsychiatric manifestations associated with steroid-induced psychosis.

Among these agents, **mifepristone**, a glucocorticoid receptor antagonist, has demonstrated benefits in clinical trials for **psychotic depression**, improving symptoms by modulating HPA axis activity. **Metyrapone** and **ketoconazole**, which inhibit cortisol biosynthesis, have also been used successfully in treating psychiatric symptoms associated with hypercortisolemia, particularly in conditions like Cushing's syndrome. Although the direct evidence for these agents in **steroid-induced psychosis** remains limited, isolated case reports and pilot studies suggest they may serve as promising adjuncts in **resistant or recurrent cases** where conventional treatments are insufficient [19]

MOOD STABILIZERS AND ADJUNCTIVE THERAPIES

Lithium has been used prophylactically in patients with a history of steroid-induced psychiatric symptoms who require further corticosteroid treatment. Other agents such as **valproic acid**, **carbamazepine**, **lamotrigine**, and **SSRIs** (particularly in cases with depressive features) have also been trialed, especially in prolonged or mixed mood- psychotic presentations.[20]

NEUROSTIMULATION OR BRAIN MODULATION:

Experimental techniques like **rTMS** and **tDCS** show potential in altering abnormal brain activity associated with psychosis. While data specific to **steroid-induced psychosis** is limited, emerging theories suggest that **closed-loop neurostimulation** targeting disrupted **gamma and alpha rhythms** may offer future therapeutic benefits.[21]

ELECTROCONVULSIVE THERAPY:

For **refractory cases** or when rapid symptom resolution is needed, **ECT** has been employed successfully, particularly for severe depression or psychosis not responding to medications

EARLY PSYCHIATRIC INVOLVEMENT:

Early psychiatric involvement is crucial in steroid-induced psychosis (SIP) when symptoms such as hallucinations, delusions, or severe mood changes arise. Timely evaluation aids in accurate diagnosis, ruling out primary psychotic conditions, and starting appropriate treatment promptly, leading to shorter symptom duration and better clinical outcomes.

CASE STUDIES:

Case 1: Augmentation with Valproate and Risperidone in SLE

A 46-year-old woman with systemic lupus erythematous developed acute psychosis while on low-dose prednisolone. She was treated with **valproic acid** and **risperidone**, leading to rapid symptom resolution.[23]

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Case 2: Olanzapine with Steroid Taper in High-Dose SLE-Related SIP

A patient on high-dose prednisolone (55 mg/day) developed psychotic symptoms. **Olanzapine** was initiated along with gradual steroid taper, resulting in remission within one week [24].

Case 3: Olanzapine Monotherapy in Adolescent SLE-Related Psychosis

A 14-year-old girl with SLE developed severe psychosis after chronic steroid therapy. Haloperidol caused extrapyramidal symptoms; switching to **olanzapine 7.5 mg/day** led to complete remission in 15 days, maintained during follow-up [24]

Case 4: Risperidone Used in Adolescent with Nephrotic Syndrome (2006)

A 12-year-old patient developed steroid-induced psychosis while continuing corticosteroids for nephrotic syndrome. The psychosis was successfully managed with risperidone, which was maintained as long as steroid therapy continued [25].

Case 5: Pediatric Asthmatic Child – Self-Resolving Psychosis with Steroid Cessation

An 8-year-old girl receiving nasal corticosteroid spray and oral prednisone developed acute psychotic symptoms. These resolved spontaneously within 48 h of stopping steroids, without antipsychotic use [26].

Case 6: Pediatric Acute Lymphoblastic Leukemia – Risperidone Rescue

A 14-year-old girl treated with high-dose dexamethasone for leukemia developed psychosis. Symptoms did not improve after steroid cessation alone, but risperidone 1 mg nightly led to resolution within three days and full recovery by three weeks [27].

II. CONCLUSION:

Steroid-induced psychosis (SIP) is a significant but often underrecognized neuropsychiatric complication of corticosteroid therapy. While its prevalence varies depending on dose, duration, and patient susceptibility, the risk increases markedly with high-dose regimens, particularly above 40 mg/day prednisone equivalent. The pathophysiology is multifactorial, involving HPA axis disruption, neurotransmitter dysregulation, structural brain changes, and possible genetic predispositions. Clinically, SIP can mimic primary psychiatric disorders, underscoring the need for careful history- taking, exclusion of mimics, and standardized symptom monitoring. Management hinges on timely recognition, steroid dose reduction where feasible, and adjunctive pharmacologic strategies most often atypical antipsychotics. In selected cases, mood stabilizers, anti- glucocorticoid agents, or neurostimulation techniques may be beneficial, particularly in refractory or recurrent presentations. Early psychiatric involvement and individualized treatment planning improve prognosis, while case studies highlight the potential for full recovery when interventions are initiated promptly. Ultimately, increased clinical vigilance, patient education, and proactive risk mitigation remain central to preventing severe outcomes and ensuring optimal quality of life in patients requiring corticosteroid therapy.

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