

**Psychiatric Adverse Drug Reactions:  
Steroid Psychosis**

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Each year there are 1 1/2 million hospitalizations caused by adverse drug reaction in the United States. As many as 5% of all hospital admissions are directly or indirectly caused by these problems which are responsible for almost 15% of all hospital days. Thirty percent of patients admitted for an adverse drug reaction experience a second such reaction while hospitalized. Adverse drug reactions are often misdiagnosed early in their course. It is estimated that three billion dollars a year are spent treating adverse drug reactions and that between 18 and 30% of patients who are hospitalized for other reasons will experience a significant adverse drug reaction during their hospital stay. If a patient does experience an adverse drug reaction, it is likely that his hospital days will be doubled. Adverse drug reactions have been implicated in up to 5% of hospital deaths.

The purpose of this paper is to review the adverse psychiatric effects produced by corticosteroids; to define their incidence and symptom presentation and to make recommendations for their management. The early literature concerning the mental changes produced by corticosteroids was confused and at times quite contradictory. Much of this was no doubt related to the fact that the early preparations were not well standardized, that these medications were often initially prescribed for the most severely ill patients and that they were generally prescribed concurrently with several other medications. All these factors, we have subsequently learned, greatly effect both the incidence and presentation of steroid induced mental changes, the specific nature of which remained uncertain for many years. Various authors reported euphoria and depression to be the major presentations of steroid psychosis while others reported mania, paranoid reactions, schizophrenia and various toxic syndromes.

A study undertaken by my colleagues and I reported in 1979 defined the symptoms of steroid psychosis in 14 patients who had no central nervous system lesions. This study suggested that patients receiving daily doses of greater than 40mg of Prednisone or its equivalent were at greatest risk for developing a steroid psychosis. These reactions were twice as likely to occur during the first five days of treatment as subsequently. Premorbid personality, a history of previous psychiatric disorder or a history of a previous steroid psychosis did not clearly increase the patient's risk of developing a psychotic reaction during any given course of subsequent therapy. The steroid psychoses we saw presented as a spectrum psychosis with symptoms ranging from affective through schizophreniform to those of organic brain syndrome. No characteristic stable presentation was observed in these 14 patients, but the most prominent symptom constellation to appear during the course of the illness consisted of emotional lability, anxiety, distractibility, pressured speech, sensory flooding, insomnia, depression, perplexity, agitation, auditory and visual hallucinations, intermittent memory impairment, mutism, disturbances of body image, delusions, apathy and hypomania. We found that phenothiazines administered in low to moderate doses, (50-200mg CPZ or equivalent daily) produced an excellent response in all the patients studied. We cautioned against the use of tricyclic antidepressants while patients remained on steroids as in all situations where this regimen was tried, the patient's clinical condition worsened.

Since our study, several other critical reviews of the literature and new studies have become available. This newer literature provides longitudinal insight into the nature of

steroid induced mental change. The incidence of steroid psychosis varies widely in the literature ranging from 13 to 62%, with a weighted average of 27.6% for some steroid induced mental change, the vast majority of which are mild to moderate and do not herald the development of a full-blown psychosis or affective syndrome. The incidence of a severe psychiatric syndrome in the more than 2,500 patients reported in the literature ranges from 1.6 to 50% with a weighted average of 5.7%. The incidence of steroid psychoses in patients with lymphoma, multiple sclerosis, severe intractable asthma, ulcerative colitis, regional enteritis, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and severe poison ivy or oak is estimated at between 3 and 6%. The patients most at risk for developing steroid psychosis are those with systemic lupus erythematosus (39%) and pemphigus (21%).

Steroid psychoses are twice as likely to occur in females as in males, but if one corrects for the higher incidence in females of the disorders for which steroids are typically used, particularly systemic lupus erythematosus with a nine to one female incidence and rheumatoid arthritis with a three to one female incidence, then the total incidence of steroid induced psychosis in men and women is roughly equal with a slight female predominance.

The type of psychiatric disturbance seen is in fact, difficult to classify as patient's symptoms tend to change radically during the course of the illness. Overall, approximately 40% of patients present predominantly with a depressive disorder, 25% with mania, 5% with a bipolar disorder-cyclical form; 15% with an agitated schizophreniform or paranoid psychosis and 10% as an acute progressive delirium. Three-quarters of all patients with steroid psychosis evidence affective symptoms some time during the course of their illness. A frank psychotic state without mood disturbance occurs in 10 to 15% of patients while some psychotic features, (i.e., a marked impairment of reality testing) associated with affective symptoms occurs in 70% of patients.

The dose of the steroid administered has a clear relationship to the likelihood of the patient developing a subsequent steroid psychosis. There is a statistically significant increase in the incidence of psychiatric disturbances with increasing daily doses of steroid. Patients treated with a mean daily dose of Prednisone below 40mg/day in The Boston Collaborative Drug Surveillance Study, had an incidence of psychotic symptoms of 1.3% while patients treated with doses between 41 and 80mg/day had an incidence of 4.6%. Patients receiving more than 80mg/day of Prednisone or its equivalent had an incidence of steroid psychosis of 18.4%. The average daily dose of steroids for patients who developed psychosis was 59.5mg/day of Prednisone or equivalent as compared with 31.1mg/day for patients who did not develop adverse psychiatric effects.

Several studies have shown that no relationship exists between the response to the first course of steroid treatment and response to a second course of drug, that is, the presence or absence of a psychiatric disturbance during the initial course of steroid treatment, does not predict response to a subsequent course of treatment.

A previous history of psychological difficulties does not predict the development of steroid psychosis. Litz, in his study at Johns Hopkins, noted that even the most "highly unstable and poorly integrated" patients did not experience any untoward emotional reactions after ACTH or cortisone therapy when compared to their more emotionally stable counterparts. Thus, a patient's past psychiatric history is not a reliable predictor of developing a future steroid psychosis. In a review of the steroid literature approximately 20% of the patients reported to have developed a steroid psychosis had a history of previous psychiatric disorders, 80% did not.

Steroid psychoses tend to be acute in their onset and although mental changes can occur at any time during the course of therapy, most occurred within the first six to 10 hours following the administration of ACTH, or within the first four to six days following the oral administration of corticosteroids. The most frequent initial presentation of an impending steroid psychosis was a state of cerebral hyperexcitability, clearly perceived and reported by the patient. Patients characterize these states as being marked by increased irritability, lability of mood, a profound dysphoria, hyperacusis, and pressured or driven thought processes. These changes often antecede other more serious disturbances of cognition by 72 to 96 hours. Once a steroid psychosis is fully defined it is likely to present as a spectrum psychosis, with the most prominent symptoms consisting of profound distractibility, pressured speech, anxiety, emotional lability, severe insomnia, sensory flooding, depression, perplexity, auditory and visual hallucinations, agitation, intermittent memory impairment, mutism, delusions, disturbances of body image, apathy and hypomania. Prior to the advent of treatment with phenothiazines, it was noted that these conditions spontaneously remitted in from two weeks to seven months after the discontinuation of steroids, with 80% of the cases reported in the literature having remitted untreated by the sixth week. Administration of phenothiazines dramatically reduces this period. The current duration of psychiatric symptoms in patients who develop a steroid psychosis treated with phenothiazines ranges in the literature from one to 150 days with a mean duration until total recovery of 22 days. However, it should be noted that 40% of patients begun on timely treatment with a low to moderate dose of phenothiazines, respond within one week and that 55% of all such patients are fully recovered within two weeks. More than 90% of all patients with steroid psychosis treated with phenothiazines in whom steroids are discontinued will recover within six weeks. Delirium is the presentation with the shortest duration of symptoms. Such cases clear quite rapidly following institution of appropriate treatment and cessation of steroid therapy, usually within six days. Patients who develop a full blown affective syndrome have the longest treated course with an average duration of symptoms of 25 days.

Once a diagnosis is made and treatment instituted, the literature suggests that a complete recovery is likely to occur in 90% of patients. Three percent of patients with steroid psychosis commit suicide. The remaining 5-7% will have an ongoing psychotic or depressive disorder or develop recurrent psychiatric symptoms. Ninety two percent of patients who have steroids tapered fully recover, while 84% of patients who are maintained on steroids but treated with antipsychotic medicines show full recovery of symptoms. ECT, in the 11 cases reported in the literature has been universally effective in reversing the course of steroid psychosis.

Several studies have shown that patients, even those with affective disorder produced by steroids, tend to do poorly when treated concurrently with tricyclic antidepressants and steroids. These patients may also show an exacerbation of symptoms even after the tapering of steroids, when tricyclics are used. For this reason it is recommended that tricyclic and other antidepressant medications be withheld until after the patient's steroid psychosis has been appropriately treated with neuroleptics.

Various treatment approaches are available for steroid psychosis. The most widely used and effective treatment strategy is to discontinue steroids where possible, and to treat the patient with phenothiazines or other antipsychotic medications. The most frequently used drug regimens include Mellaril 50 to 200mg q.d.; Thorazine 50 to 200mg p.o., q.d. or Haloperidol 2 to 10mg p.o., q.d. Our study suggested that Mellaril is probably the agent of choice as it was highly efficacious and was considerably less likely than Haloperidol to produce a dystonia or dyskinesia which would require further drug treatment. Additionally, Falk and colleagues have shown that prophylactic treatment with lithium carbonate may be useful to prevent the development of corticotropin induced psychosis. In their study, 27 patients treated with lithium carbonate, whose blood level was maintained at between 0.8 to 1.2 mEq/l for a 31-day course of ACTH treatment for multiple sclerosis or retrobulbar neuritis, failed to develop any significant mental effects, while an untreated control group of 44 patients had a 14% incidence of steroid induced psychoses. Further studies confirming this finding are needed.

Steroids alter the central nervous system through a variety of mechanisms. It is because of their wide ranging metabolic effects that the presentations and course of the steroid psychoses may change so dramatically. Recent research has shown that corticosteroids alter the sodium potassium pump and ion flux across membranes effecting ATP and norepinephrine metabolism particularly in the reticular activating system. Steroids have a direct effect on major target cells in the hippocampus as well as on limbic neurons, increasing norepinephrine uptake in cells of both the limbic system and cerebral cortex. Glucocorticoids have been shown to potentiate ischemic injury to neurons, an important effect in patients with vasculitis such as those with systemic lupus erythematosus. These findings may explain the high incidence of steroid psychosis in patients with lupus and pemphigus. Corticosteroids also effect carrier proteins, displacing drugs and other toxic substances and decrease central nervous system serotonin levels by shunning tryptophan metabolism from the tryptophan-serotonin pathway to the tryptophan-kynurenine pathway and by altering cyclical AMP, cyclical GAMP, acetylcholine, dopamine and endorphines in the central nervous system.

In conclusion, steroid induced mental changes are common. The overall incidence of steroid psychosis when steroids are used to control systemic medical disorders varies between 3 and 6%. The clinician usually has a window of from 24 to 96 hours to initiate treatment and abort the full-blown picture of steroid psychosis. Early treatment with psychotropic medications and discontinuation of steroids where possible, produces rapid clearing and control of the steroid psychoses.

## **SUGGESTED READING**

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