The Neuropsychiatric Sequelae of Steroid Treatment

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INTRODUCTION

The neuropsychiatric sequelae of steroid treatment are a common occurrence. Despite over 50 years of being described in the scientific literature, these sequelae are described predominantly via case reports with an overall paucity of more rigorous scientific studies being initiated and published on this topic.

The following review of the topic of the neuropsychiatric sequelae of steroid treatment is based on a review of the PubMed database. Over 80 scientific articles on this topic were found and they encompass approximately the last 30 years of published research. In reviewing these articles, several conclusions can be made. First, the neuropsychiatric complications of steroid treatment are quite common. Second, the specific types of neuropsychiatric impairments comprise a range of symptoms from anxiety, irritability and impaired cognition to depression, mania, psychosis, and suicidality. Third, although the available literature fails to reveal a uniform approach to the treatment of these specific side effects, it is clear that these symptoms are common enough and potentially very severe so as to warrant aggressive and early intervention by psychiatric consultants. Lastly, given the overall lack of published scientific literature on this topic, it behooves patients, family, and care-providers to work to improve public knowledge with the goals of stimulating further research on this subject as well as improving the quality of care for patients with this condition.

THERAPEUTIC USES AND BENEFITS OF STEROID TREATMENT

The clinical uses of steroid treatment are varied and comprise a variety of different medical conditions. Steroid treatment is indicated in the management of immunologic disease such as systemic lupus erythematosus and Churg-Strauss Syndrome\(^1,2\). They are also indicated in the management of respiratory conditions such as asthma and chronic obstructive pulmonary disease\(^3\). In addition, steroids are indicated in the treatment of a number of different types of cancer such as Non-Hodgkin’s Lymphoma\(^4,5\). Furthermore, steroids are a common treatment intervention in a variety of musculoskeletal disorders such as acute and chronic back pain\(^6,7\). Of note, most reviews of the use of steroids in the management of non-psychiatric illness do include at least a mention of the possible occurrence of steroid psychosis with this treatment modality.

COMMON OCCURRENCE AND RAPID ONSET

A review by Steiffel and colleagues\(^4\) reported a 5-10% occurrence of major psychiatric symptoms among cancer patients treated with high dose steroids. Lewis and Smith\(^8\) reported an approximately 6% incidence of severe psychiatric syndromes among those undergoing treatment with steroids. The Boston Collaborative Drug Surveillance Program\(^9\) reported an occurrence of psychiatric reactions in 1.3% of patients receiving 40mg/day or less, 4.6% of patients receiving 41 to 80mg/day, and 18.4% of those receiving 80mg/day or more of prednisone. A number of studies have suggested that the psychiatric side effects of steroid treatment have a rapid onset\(^8,10-13\). Naber et al.\(^12\) reported that all patients treated with steroids who developed psychiatric symptoms had an onset within three days of initiation of treatment. Similarly, Wolkowitz et al.\(^14\) reported an onset of psychiatric sequelae within five days of treatment with steroids among healthy subjects. Hall et al.\(^11\) noted that 86% of patients with psychiatric manifestations of steroid treatment developed these symptoms within one week of start of treatment.

SPECIFIC SYMPTOMS

Cases of steroid-induced psychiatric symptoms have been reported in the literature since the 1950s. The variety of clinical signs associated with steroid-induced psychosis is comprised of visual and auditory hallucinations, delusional thinking, paranoia, affective disturbances (depression, apathy, hypomania, panic), depersonalization, motor disturbances (overactivity, immobility), aggressive behavior, and cognitive impairment\(^11,15-19\). However, a number of publications on this topic appear to support symptoms of mania as being the most common psychiatric manifestation of steroid treatment\(^8,12,20,21\). In contrast, some studies have suggested that the risk...
of depression increases with prolonged or chronic exposure to exogenous steroids.\textsuperscript{22, 23} Nonetheless, early studies by Rome and Braceland\textsuperscript{16} described four grades of psychological responses to steroids, which they felt were prototypical of all clinical presentations (Table 1).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>1</td>
<td>Mild euphoria, lessened fatigue, improved sensation, increased sense of intellectual capacity.</td>
</tr>
<tr>
<td>2</td>
<td>Heightened euphoria. Patients are effusive, expansive, volatile, hypomanic, exhibit flight of ideas, impaired judgment, refractory insomnia.</td>
</tr>
<tr>
<td>3</td>
<td>Difference responses to reflecting the ego characteristics of the patient, such as anxiety, phobia, rumination, obsessive preoccupation, hypomania, or depression.</td>
</tr>
<tr>
<td>4</td>
<td>Grossly psychotic reaction with hallucinations, delusions, extreme variations in mood.</td>
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Data from Rome & Braceland\textsuperscript{16}

Ling and colleagues\textsuperscript{19} reviewed 55 case reports of psychiatric disturbance in association with steroid therapy and found a 58\% incidence of psychotic symptoms. Nearly 72\% of the cases with psychotic symptoms also included mood symptoms. Lewis and Smith’s review\textsuperscript{8} of 79 case reports of psychiatric symptoms occurring in association with the use of steroids found a 71\% incidence of psychotic symptoms. Mood symptoms were reported in over 75\% of the 79 cases, and concurrent psychotic symptoms were present in over 66\% of these cases. Gift and colleagues\textsuperscript{24} found significantly greater self-reported depression scores among patients with chronic obstructive pulmonary disease (COPD) receiving prednisone compared to COPD patients not receiving any steroids. Interestingly, the psychiatric sequelae of steroid treatment are often sudden in onset and appear to generally occur within 2 weeks after steroid introduction\textsuperscript{19}.

In our review of the literature since the work by Lewis and Smith\textsuperscript{8}, 56 case reports have been published suggesting an association between psychiatric symptomatology and steroid treatment. In eight of these cases\textsuperscript{25-30}, the development of psychiatric symptoms was more clearly associated with the withdrawal, than with the administration, of steroids. Interestingly, seven of these eight cases occurred in female patients. All eight cases included mood disturbance; 2 with depression, 4 with mania, and 2 with mixed state. Psychotic symptoms were reported in all eight cases, including hallucinations and delusions in 5 cases.

Forty-eight cases\textsuperscript{1-3, 31-50}, were identified where the development of psychiatric symptoms was clearly associated with the administration of steroids. Nearly 65\% of these cases occurred in female patients, which appears to support the trend reported in the literature of the apparent greater incidence of this condition among women as opposed to men\textsuperscript{20}. Ages ranged from 2.75 years to 71 years of age, with a mean of 40.9. Onset of symptoms in the 48 cases occurred between 1 and 60 days after initiation of steroid treatment, with a mean of 15.4 days.

Psychotic symptoms were reported in 64.6\% of these 48 cases, similar to the incidence of psychotic symptoms reported by Ling and colleagues\textsuperscript{19} (58\%), as well as Lewis and Smith\textsuperscript{8} (71\%). In those cases reporting specific psychotic symptoms (19 cases), hallucinations occurred in 57.9\% of the cases and delusions occurred in 73.7\% of the cases. Among the cases reporting presence or absence of mood symptoms (45 cases), mania was observed in 47.7\%, depression in 25.0\%, and mixed state in 9.1\%. The remaining 18.2\% of cases reported psychosis or delirium in the absence of mood symptoms.

Studies by Wolkowitz and colleagues\textsuperscript{13, 14} reported reversible cognitive deficits and mood symptoms in healthy control subjects after administration of prednisone and dexamethasone. Newcomer and colleagues also found significant reversible cognitive deficits in healthy controls given dexamethasone and hydrocortisone\textsuperscript{51, 52}.

Steroid-induced cognitive deficits appear to be fairly specific for declarative or verbal memory\textsuperscript{14, 51-55}. However, the range of specific cognitive deficits appears to also include impairment in memory retention, attention, concentration, and occupational performance\textsuperscript{66}. In addition, delirium (a syndrome characterized by disorientation and confusion) has also been reported as a consequence of steroid treatment\textsuperscript{39, 44}. These cognitive deficits appear to reverse with the reduction or withdrawal of steroids; yet, there is also some suggestion that the risk of corticosteroid-induced cognitive impairment is greatest with increases or rapid changes in steroid dose\textsuperscript{13, 39, 44}. Similar reversible and dose-dependent declarative memory deficits have been reported in persons with Cushing’s diseases\textsuperscript{57-59}, suggesting that excess endogenous and exogenous steroids produce similar cognitive effects.

**HIGH VERSUS LOW STEROID DOSES**

There appears to be a dose-response relationship for psychiatric symptoms during steroid treatment. The Boston Collaborative Drug Surveillance Program\textsuperscript{9} reported an overall mean prednisone dose of 59.5mg/day in patients with psychiatric reactions. This study also
found a striking dose-response relationship for acute psychiatric reactions as psychiatric reactions were found to occur in 1.3% of patients receiving 40mg/day or less, 4.6% of patients receiving 41 to 80mg/day, and 18.4% of those receiving 80mg/day or more. Similarly, Chan and colleagues reported psychosis in 8% of patients receiving 90mg/day prednisone compared to 3% in patients receiving 30mg/day. Naber and colleagues used a semistructured interview and the Profile of Mood States to study the psychological and cognitive effects of high and low doses of steroids (methylprednisolone or fluocortolone) in ophthalmologic patients, all of whom were free of psychiatric illness, and found that 36% developed mania or depression during high dose steroid treatment. Olsen and colleagues found a significant dose-response relationship in relation to mood changes. Wada et al. also reported a strong association between high dose steroid treatment and rapid development of mood symptoms. In contrast, studies examining the consequences of low dose steroid treatment have found little or no psychiatric symptomatology.18,62, 63

In our review of case reports published since the work by Lewis and Smith of these were able to demonstrate a clear association between the onset of psychiatric symptoms and the administration of steroid treatment. Prednisone was the steroid in question of these case reports.64 Predicted the type of steroid, followed by methylprednisolone, dexamethasone, and hydrocortisone. In the 41 case reports in which steroid dosage was included, we calculated prednisone-equivalent dosage for the non-prednisone cases, and found a range of 5 to 200mg prednisone per day, with a mean dose of 58.3mg per day. This mean prednisone-equivalent dosage appears to further support the suggestion by the literature that the association between psychiatric symptomatology and steroid administration is only apparent at higher dosages.

**PATHOPHYSIOLOGY**

Overall, the pathophysiology of the neuropsychiatric sequelae of steroid treatment remains unclear. There may be a link between neuronal activation of dopaminergic and cholinergic systems and high corticosteroid levels in the brain.65 In the psychiatric literature, excessive activation of the dopamine system is believed to underlie the pathophysiology of symptoms of mania, psychosis, and severe forms of depression such as psychotic depression. As such, it is hypothesized that excess levels of corticosteroids cause an increase in dopamine levels, which in turn may result in symptoms of mania, psychosis and severe depression. In contrast, central and peripheral decreases in serotonin secretion have also been linked to steroid administration.66 Similarly, the current psychiatric research literature suggests that diminished serotonin levels may play a role in a variety of psychiatric syndromes including clinical depression. Consequently, it is postulated that corticosteroid administration may result in symptoms of clinical depression via a reduction in serotonin levels.

Interestingly, Brown et al. reported that patients receiving steroid treatment appear to demonstrate dose-dependent cerebral atrophy. In addition, they also review animal data, which show dose-dependent detrimental effects on learning and memory with exposure to high doses of steroids.

**TREATMENT**

Unfortunately, the available literature on the treatment of steroid-induced psychosis is limited and no uniform approach to the management of these symptoms is readily apparent.

Falk and colleagues prophylactically treated patients receiving corticotrophin (a treatment which has a biological effect similar to steroid treatment) for multiple sclerosis or retrobulbar neuritis with lithium carbonate and compared them with similar patients not receiving concurrent lithium during steroid treatment, and found a 14% rate of onset psychosis in the group not receiving lithium compared to 0% of those receiving concurrent lithium. Likewise, a number of case reports have demonstrated successful treatment with lithium following the onset of depressive symptoms.67

Lewis and Smith report in their review of the literature that steroid taper alone appears to be effective in over 90% cases where this employed. In addition, they find a 100% effectiveness in cases where neuroleptics and steroid taper, or treatment with lithium alone, or treatment with ECT alone is initiated. In contrast, they also report an absence of clinical benefit for the treatment of steroid-induced psychosis with tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and imipramine are examples of tricyclic antidepressants). Hall et al., in fact, report a worsening of neuropsychiatric symptoms when patients were given tricyclic antidepressants and advocate for the primary use of antipsychotic agents in the management of this condition. However, several recent case reports have been published describing the successful treatment of steroid-induced depression with newer antidepressants, such as sertraline, fluvoxamine, and fluoxetine. Furthermore, a recent report suggests the use of a combination of an antidepressant and antipsychotic in the treatment of steroid-induced psychotic depression (Lyster, 2002).

A review by Brown and Chandler suggests that the mainstays of the treatment of steroid psychosis should include taper or discontinuation of the steroid, treatment with lithium, or treatment with antipsychotics. They also recommend that other interventions such as antidepressants be used with caution and that the tricyclic antidepressants be avoided altogether because of concerns regarding their apparent lack of benefit and potential to worsen the symptomatology of steroid psychosis.

Review of the published literature suggests that antipsychotics, from haloperidol and promethazine to risperidone and olanzapine, are
effective and can be safely administered in conditions such as euphoric mania, mixed-state mania (a condition characterized by both symptoms of depression and mania), prominent psychosis (delusional thinking or auditory and/or visual hallucinations), and delirium.

Overall, several patterns in the treatment of steroid psychosis do emerge. Specifically, it does appear clear that if neuropsychiatric sequelae of steroid treatment become apparent, then the steroid dose should be reduced and/or discontinued. However, if this is not possible, then pharmacotherapy is indicated. Toward this end, lithium appears to be indicated and safest in the management of symptoms of depression, whereas antipsychotics appear indicated in the treatment of mania and psychotic symptoms. It is noteworthy that the available literature suggests that lithium can be used effectively both in the treatment of acute symptoms, as well as in the prophylactic treatment of steroid psychosis. Recent case reports appear to suggest the safe and successful administration of SSRI antidepressants in the management of steroid-induced depression, as well as suggest the use of a combination of an antidepressant and antipsychotic as the optimum treatment of psychiatric depression associated with steroid administration. Lastly, there are case reports regarding the effectiveness of benzodiazepines, such as alprazolam, clonazepam, and lorazepam, in the management of such specific steroid-induced symptoms as insomnia and anxiety. Basically, this management approach is consistent with current pharmacotherapy approaches in psychiatry. In contrast, although there are data demonstrating the effectiveness of antidepressants in the management of steroid-induced depression, this class of medications should be used with caution as there is concern, particularly with the tricyclic class, that they may exacerbate this condition.

**IMPORTANCE OF PSYCHIATRIC INTERVENTION**

Brown and Chandler posit the importance of improving the scientific understanding of the neuropsychiatric consequences of steroid treatment as a means of improving patient care via improved disclosure of all of the potential side-effects of this treatment, as well as being a means of ensuring close monitoring of and early intervention in these potential side-effects.

The work by Lewis and Smith underscores the importance of early psychiatric intervention to minimize the morbidity and mortality associated with steroid treatment. Lewis and Smith report that among 79 cases of steroid-induced psychosis, 93% had a complete recovery, but 4% had continued symptoms or recurrence of symptoms and 3% committed suicide. With respect to the issue of suicidality, however, Stiefel et al. note an almost complete absence of data on the occurrence of suicide in the setting of steroid treatment. Wada et al. do find an association between an increased risk of suicidality and steroid treatment. In addition, Stiefel et al. do note a report by Memorial Sloan Kettering which shows an increased risk of suicide attempt among those treated with steroids who experience mild cognitive impairment and depression.

Overall and given the potential severity of neuropsychiatric symptoms associated with steroid treatment, it is strongly recommended that patients be monitored closely and that a low threshold for psychiatric consultation and intervention be observed.

**DIRECTIONS FOR FUTURE RESEARCH**

Brown and Suppes highlight various limitations of the current literature on the topic of the neuropsychiatric manifestations of steroid treatment. They emphasize that most large studies on this topic have not included formal psychiatric assessment or involvement in characterizing the nature of the various neuropsychiatric side effects. On the other hand, studies that do incorporate formal psychiatric assessment of neuropsychiatric side effects are small in size and, thus, the interpretation and generalizability of the results are difficult. In addition, Brown and Suppes suggest that studies on this topic need to systematically investigate potential risk factors such as the degree to which a personal or family history of psychiatric illness may contribute to the development of these sequelae. Interestingly, recent advances in the field of genetics may help reveal the role certain genes or their polymorphisms may play in the development of this condition both in individuals with and without a personal or family history of psychiatric illness.

Wada et al. suggest that further areas of investigation on this topic include study of the individual susceptibility for mania versus depression versus any other manifestation of this condition. Also, they recommend that further research be done to investigate the apparent greater occurrence of steroid-induced psychosis among women as compared to men. In addition, Wada et al. note a paucity of information on the long-term outcome and risk of recurrence of these symptoms. There also exists very limited research on the optimum treatment interventions of the various and specific manifestations of steroid-induced psychosis.

Furthermore, it should also be emphasized that there is an overall dearth of research on the topic of the neuropsychiatric side effects of steroid treatment. For example, whereas over eighty articles were found on this topic in the PubMed database for the last almost 30 years, the number would certainly be in the thousands if one were searching for articles on the topic of say the many benefits to steroid treatment in oncology. In other words, a medical topic with an adequate amount of interest and effort applied to furthering the understanding thereof should generate much more in the way of scientific study. Therefore, it is also the goal of the current review to demonstrate the tremendous need for further interest in and study of the common occurrence of the neuropsychiatric consequences of steroid treatment.

**CONCLUSION**
The neuropsychiatric sequelae of steroid treatment are a common occurrence. Despite over 50 years of being described in the scientific literature, these sequelae are described predominantly via case reports with an overall paucity of more rigorous scientific studies being initiated and published on this topic.

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Lastly, given the overall lack of published scientific literature on this topic, it behooves patients, family, and care-providers to work to improve the promulgation of this knowledge with the goals of stimulating further research on this subject as well as improving the quality of care for patients with this condition.

Footnotes: