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## Psychiatric Disturbance of Corticosteroid Therapy: It's The Time to Overcome

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### ABSTRACT

Corticosteroids are the drugs used for multifarious diseases because of their widespread action. It is suggested that these drug use should not be ceased rapidly, rather than it should be finished gently. Due to their diversity of actions and uses, more no of interactions with the drugs and diseases were recorded. It is well known that there is a strong relationship between corticosteroid use and psychiatric effects. Both the steroid induced psychiatric symptoms and diagnosis are uncertain. Hence Pharmacists are the best person to mould a suitable drug therapy and a management regimen for corticosteroids induced adverse events in patients. They can also play an important role in educating the patients about corticosteroids and their psychic disturbances. Since physicians do not take any interest in to alert the patients about the usage, interactions and highly severe psychiatric problems of steroids, the need of pharmacists becomes very important.

**Keywords:** Steroids, Psychiatric effects, Adverse Drug Reactions

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## INTRODUCTION

Corticosteroids are the widely used drug for multifarious diseases. Cortisone was first legally introduced in July 1950<sup>1</sup> and the reports about psychiatric adverse effects also came out in the same year<sup>2</sup>. Corticosteroids are the compounds having the sterols nucleus with the side chain at Carbon-17 varies and are produced in the adrenal gland from cholesterol. These are two types Glucocorticoids e.g. Beclomethasone, budesonide, hydrocortisone etc. & Mineralocorticoids, e.g. Aldosterone<sup>3</sup>. The important physiological functions of steroid hormones are stress management, immune response, regulation of behaviour & inflammation, blood electrolyte levels, carbohydrate metabolism and protein catabolism. Glucocorticoids like cortisol affect metabolism of carbohydrate, fat and protein, and have vasoconstrictive, immunosuppressive, anti-inflammatory and anti-proliferative actions. Mineralocorticoids like aldosterone are mainly involved in the water and electrolyte balance by regulating ion transport in the epithelial cells of the renal tubules of the kidney<sup>4</sup>. It is suggested that these drug use should not be ceased rapidly, rather than it should be finished gently. Due to their diversity of actions more number of interactions are reported with the drugs and diseases.<sup>3, 5</sup>. And also corticosteroids are associated with a number of serious adverse effects, both physiologic and psychiatric<sup>6</sup>. It is already established that the long term and high doses of corticosteroid use produce several side effects. The systemic side-effects are very much important that include mainly diabetic mellitus, infection, hypertension, osteoporosis, peptic ulcer, weight gain, Cushingoid features and the psychiatric problems<sup>7</sup>. Mental changes in patients are not uncommon after corticosteroid use. Steroid psychosis-related symptoms include depression, mania, psychosis, and delirium<sup>8</sup>. The relationship between corticosteroids and psychiatric adverse effects has been known for several decades<sup>9</sup>. The syndromes are known to be as “steroid psychosis,” which is considered as representative exogenous psychiatric disorder. However, steroid psychosis is not a clearly defined clinical entity but consists of heterogeneous syndromes with obviously different pathophysiological mechanisms<sup>10</sup>. But the exact underlying mechanism of steroid-induced psychiatric problems, diagnosis and their treatment options have been labelled. Both the symptoms and the diagnosis of steroid psychosis are unclear. When corticosteroid induced psychosis emerge, physicians had to face a difficulty in treating the underlying medical diseases. Thus, clinical studies including corticosteroid induced psychiatric disturbances are challenging and they can provide some treatment options and can shed some light on the pathomechanisms of endogenous psychiatric disorders<sup>11</sup>. Also there is an urgent need for clinical research and it should focus on the longitudinal course and therapeutic response of these cases.

Pharmacists can play a vital role in patient's education about corticosteroids. Even though, pharmacists' knowledge about corticosteroid-induced psychiatric problems may be limited, and they can effectively coordinate a multidisciplinary team to provide a suitable drug therapy for the patients. A studious attention is needed by pharmacists in counselling and educating patients and their caregivers to facilitate their knowledge about these potentially serious health problems. Since physicians do not take any interest in to alert the patients about the usage, interactions and highly severe psychiatric problems of steroids, the need of pharmacists becomes very important<sup>12, 13</sup>.

### **Incidence**

It is very important to think carefully about the baseline prevalence of psychiatric illness. According to a report from the National Institute of Mental Health (2011), except the developmental and substance use disorders the prevalence of serious mental illness was found out 4% in adults<sup>14</sup>. A meta-analysis conducted by, Lewis and Smith involving 11 uncontrolled studies by 935 adult patients, found the incidences of 13% to 62% psychiatric reactions and stated an average incidence of 27.6%. The severity of psychiatric reactions was found out by 3 point scale scored according to mild, moderate, severe the reaction and found out that most of the reactions were considered as mild or moderate. The authors from the same article also showed a best assessment of severe corticosteroid-introduced psychiatric disturbances. They specified in their meta-analysis study of 2555 patients from 13 uncontrolled studies, the occurrence of 5.7% average psychiatric incidence contributed by corticosteroids<sup>8</sup>. Naber et al stated in his study containing 50 ophthalmologic patients without any psychiatric symptoms, received a high-dose methylprednisolone or fluocortolone for 8 days. In which within 3 days of therapy 26% developed mania, and 10% developed depression<sup>15</sup>. Also in a double-blind crossover prospective study of Wolkowitz et al found that eight subjects developed symptoms of mild hypomania and 1 of depression from 12 healthy volunteers who were received 80 mg of prednisone or placebo for 5 days<sup>16</sup>. Likewise Bolanos et al observed in his case-control study of 20 patients who were under the long-term low-dose corticosteroid therapy and 14 volunteers with similar illnesses who were not receiving corticosteroid therapy a 60% lifetime risk of corticosteroid-induced mood or anxiety disorder. Here the dose of corticosteroid (prednisolone) was 7.5mg/day and time period for the therapy was more than 6 months. In this study 20 patients compared with the 14 volunteers and discovered that patient presented more commonly with depression than with mania<sup>12</sup>. When go through the children response, Mitchell et al observed 1500 children during Acute Lymphoblastic Leukaemia (ALL) therapy, found an incidence of 6% behavioural adverse effect due to Dexamethasone. The behavioural adverse effects include both the externalising and internalising

behaviour abnormalities. Also he provided a good estimate on developing depression for girls and aggressive domain for boys<sup>17</sup>.

### **Risk Factors**

By assessing the literatures there is a few threads to identify individuals at risk for steroid psychosis. The risk factors for corticosteroids are mainly the dose, gender and the concurrent diseases. Gender considered as one of the risk factor to develop steroid psychosis. Females have statistically significant, increased risk for psychiatric disturbances than males<sup>18, 19, 20</sup>. Dosage was also shows a direct relation with the occurrence of adverse effects. A high dose seems to be a primary risk factor for psychosis. The Boston Collaborative Drug Surveillance Program reported that among patients taking prednisone, psychiatric disturbances are seen in 1.3% of patients taking <40 mg/day, 4.6% of patients taking 40-80 mg/day and 18.4% of patients taking >80 mg/day<sup>21</sup>. Hence, it is well contributed that high steroid dose is a reason for the precipitation of psychotic symptoms in these patients<sup>22</sup>. Rosenberg et al reported an incidence of developing mental disturbances in 33% of patients suffering from pemphigus who were under corticosteroid treatment<sup>23</sup>. So other concurrent diseases are associated with the development of mental disturbances, e.g. rheumatoid arthritis, psoriasis<sup>1</sup>, ulcerative colitis<sup>24</sup>, and asthma<sup>25</sup>. A history of previous psychiatric problems or a steroid psychosis can increase a patient's risk for developing psychotic reaction. Other risk factors include hypoalbuminuria and use of drugs which can increase circulating levels of corticosteroid like cytochrome P450 enzyme inhibitor<sup>18, 20</sup>.

### **Psychiatric Adverse Events**

Approximately 60% reports are came out about the psychiatric adverse events due to the regular intake of corticosteroid for their drug therapy of various deseases<sup>9, 12</sup>. Mania is related with usage of high-dose steroids and occur much earlier in the course of treatment, whereas Depression developed with long-term corticosteroid use<sup>12, 15, and 26</sup>. According to the evidence based studies, it was shown that patients experienced 26% mania and 10% depression during the therapy of Prednisolone 80mg/day dose for five days<sup>15</sup>. Psychiatric adverse effects can also occur in patients receiving lower doses of corticosteroids for variable duration<sup>27, 28</sup>. Cognitive impairment and psychosis, presenting with confusion, hallucinations and delusions, have also been reported<sup>29, 30</sup>. The most commonly reported corticosteroid-induced psychiatric disturbances are affective, including mania, depression, or mixed states<sup>12</sup>.

### **Management Strategies**

The main management strategies of corticosteroids induced psychic disturbances are reduction of the dose, treatment discontinuation or treated with medications normally used in patients with

psychiatric or neurological disorders<sup>31</sup>. In the event that patient suffer corticosteroid induced psychiatric reactions, the use of antipsychotic medications alone or in combination, has proven very helpful. Most of the antipsychotic drugs are emerged to treat the corticosteroid-induced psychiatric adverse effects.eg: risperidone, aripiprazole and lamotrigine<sup>32, 34, 35, 36, 37</sup>. Mood-stabilizing drugs, such as lithium and valproic acid, are able to control the symptoms caused by corticosteroids<sup>38</sup>. A review of literature conducted by Lewis and Smith suggested that usage of single steroid was found to be effective in more than 90% of cases. But there will be a lack of guidelines to treat corticosteroid related psychic problems among the prescribers<sup>8</sup>.

To educate the patients about adverse effects at each patient encounter can enhance early identification for adverse corticosteroid-induced psychiatric reactions. To illustrate this have an example of study conducted by, Reckart and Eisendrath recruited 8 patients with chronic diseases to discuss their experience with corticosteroid adverse effects. Out of 8 patients only one had been interacted by physician about the development of adverse psychiatric disturbance and 5 got psychic problems, but they had not reported about their ADR due to their fear to communicate with physician. The end result of study concluded that an overly stimulating environment exacerbated patient's condition<sup>39</sup>.

In summary, for acute corticosteroid-induced psychiatric disturbances, atypical antipsychotics are generally act as a treatment option to yield the greatest outcome with the lowest adverse effects. Limited data suggest a role for antidepressants in depressed patients who require long-term corticosteroid administration<sup>40</sup>. From a review of the literature, it can be observed that diverse classes of medications have been used to manage a range of psychiatric disturbances that develop in patients taking corticosteroids across the lifespan<sup>41</sup>.

### **Pharmacist Role In Management Of Psychiatric Disturbances**

The role of the pharmacist in the management of psychiatric symptoms has changed over the past several years. They can be actively involved in drug distribution and therapeutic drug monitoring and thus allowing the pharmacist to make pharmacotherapy recommendations and to become involved in designing and monitoring treatment plans. Pharmacists have had a positive impact on the quality of patient care and outcomes in several diseases like asthma, chronic obstructive pulmonary diseases, immunological diseases etc., where the corticosteroids used. Patient can effectively communicate with physicians through pharmacist as they help to improve their approaches to the medications<sup>42, 43</sup>. So it concluded that along with the prescription of specific pharmacological agents, Pharmacists should take a stand and work closely with doctors for identifying and managing psychiatric disturbances.

**Table 1: Drugs used for the treatment of corticosteroid induced psychiatric problems.**

Drugs	Classification	Indication	Adverse event associated with drug use
Aripiprazole	Antipsychotic	Mania	Akathisia, light-headedness.
Chlorpromazine	Antipsychotic	Mania	infertility, sedation, anticholinergic effects, orthostatic hypotension
Haloperidol	Antipsychotic	Psychosis	Extrapyramidal side effects, orthostatic hypotension, neuroleptic malignant syndrome,
Olanzapine	Antipsychotic	Mood changes	weight gain, diabetes, sedation, increased risk of stroke in older dementia patients
Risperidone	Antipsychotic	Psychosis	Akathisia, orthostatic hypotension, increased risk of stroke and mortality in older dementia patients
Sertraline	Antidepressants	Depression and psychosis	agitation, confusion, dizziness, insomnia, hyperthermia, muscle rigidity
Sodium valproate	Mood stabilizers	Mood changes	Ataxia, drowsiness, paraesthesia.
Lithium	Mood stabilizers	Psychosis	Fatigue, nephrotoxicity, skin reactions, polyuria, vertigo, weight gain
Lamotrigine	Mood stabilizers	Cognitive impairment	Double vision, dizziness, loss of coordination, ataxia, skin reaction.

## CONCLUSION

In the current scenario various psychiatric problems such as delirium, depression, mania, psychosis and cognitive/memory impairment occur in a large proportion of patients taking corticosteroids as their regular medications. Even though there are no clinical guidelines on the treatment of psychiatric adverse effects. So the pharmacist should take it as a challenge to overcome this situation by several means of pharmaceutical care. A more proactive approach should be taken whereby unique educational programs are implemented in pharmacy practice to specifically focus on counselling patients and family caregivers in relation to corticosteroid use. Pharmacist should establish relationships with patients to ensure the appropriateness of corticosteroid therapy and patients understanding about the therapy and to monitor the psychic effects of therapy. It can achieve a definite outcome that improve patient's quality of life.

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