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Full Length Article

Don't forget me in amidst of COVID-19 pandemic: A case series and review of literature on steroid associated psychiatric manifestations

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ABSTRACT

There is a sudden upsurge in the use of steroids due to the ongoing COVID-19 pandemic, especially in patients with severe or critical COVID-19 infection. There are reports of excessive use of steroids, both in terms of use in patients who do not require the same and use in doses higher than the recommended. There are reports of the emergence of different adverse outcomes of excessive steroid use in the form of diabetes mellitus and a higher incidence of mucormycosis. However, little attention has been paid to the mental health impact of the use of steroids. This review attempts to evaluate the existing data in terms of incidence of psychiatric side effects of steroids, and the risk factors for steroid associated psychiatric manifestations. Additionally, an attempt is made to discuss the pathogenesis of steroid-associated psychiatric side effects and why it is likely that the incidence of psychiatric side effects may be more in patients with COVID-19 infection. There is a need to improve the awareness about the psychiatric side effects of steroids, both among the physicians and mental health professionals, as in any patient presenting with new-onset psychiatric symptoms while having COVID-19 infection or during the post-COVID-19 infection phase, a possibility of steroid associated side effect needs to be considered.

1. Introduction

COVID-19 virus is a contagious infection which spreads by close contact and it has been detected in various body fluids including saliva (Warsi et al., 2021). World Health Organization (WHO) has categorized the severity of COVID-19 infection as non-serious, serious, and critical in the context of the use of steroids. The WHO defines severe COVID-19 infection as oxygen saturation <90% on room air, respiratory rate >30 breaths per minute in adults and children >5 years old; ≥ 60 in children less than two months; ≥ 50 in children 2–11 months; and ≥40 in children 1–5 years old; along with signs of severe respiratory distress (i.e., accessory muscle use, inability to complete entire sentences; and in children, very intense chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs). Critical COVID-19 is defined as the presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy (World Health Organization, 2020). According to WHO, systemic corticosteroids should be used to treat patients with severe and critical COVID-19. On the other hand, the WHO recommends not to use steroids in patients with non-serious COVID-19 infection (WHO, 2020). In terms of the type of steroids, use of dexamethasone or other agents such as hydrocortisone or prednisone has been recommended. In terms of the doses, a dose of 6 mg/day for dexamethasone, or hydrocortisone 160 mg/day, or prednisone 40 mg/day, or methylprednisolone 32 mg/day for 7–10 days are recommended (WHO, 2020). However, some researchers have also evaluated the role of budesonide inhalers in the dose of 800 μg per actuation twice daily to reduce the likelihood of a need for urgent medical care and time to recovery (Ramakrishnan et al., 2021).

However, there are reports of indiscriminate use of steroids in patients with COVID-19, with some of the patients self-medicating themselves on being tested positive for the COVID-19 infection. Additionally, some of the clinicians prescribing steroids, even in patients who are not very ill and in whom steroids are not recommended. Further, in patients with severe COVID-19 infection, the steroids are being used in doses more than recommended. The excessive use of steroids has been linked to the unmasking of diabetes mellitus, poor control of diabetes mellitus in patients already diagnosed with diabetes mellitus, and the development of mucormycosis.

Based on the available data on patients with COVID-19 infection, the WHO estimated that the use of corticosteroids might not increase the risk

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of neuropsychiatric effects (WHO, 2020). However, it is crucial to understand that indiscriminate use of steroids is associated with physical complications and can lead to psychiatric manifestation.

It is also well known that patients with COVID-19 infection have a higher rate of neuropsychiatric manifestations during the acute phase of COVID-19 infection and the post-COVID phase (Taquet et al., 2021; Varatharaj et al., 2020). Multiple pathogenesis mechanisms have been suggested for the development of neuropsychiatric manifestations in patients with COVID-19, which include the neurotropic effect of the COVID-19 virus, increase in blood-brain permeability, neuroinflammation, dysregulated immune-modulation, stress response, and hypoxic injury (Jansen et al., 2021; Banerjee and Viswanath, 2020). However, steroids in patients with COVID-19 infection influence the incidence of psychiatric manifestations during the acute phase, but the influence of steroids on the manifestations of post-COVID-19 stage has not been discussed much. In this report, we present 2 cases that developed steroid-induced psychiatric manifestations and discuss the psychiatric issues that may be seen in patients with COVID-19 and during the post-COVID phase due to steroids, based on the available literature on steroid associated psychiatric manifestations. We also try to formulate an assessment plan to understand the role of steroids in psychiatric manifestations in patients with COVID-19 infection.

2. Case-1

Mr. A, a 25-year-old male, presented with a history of being diagnosed with COVID-19 infection two weeks back. He was hospitalized for the COVID-19 illness and required non-ventilatory oxygen support. During the hospital stay, he also received nebulization with budesonide (twice daily), Inj piperacillin 4.5 gm thrice daily, Inj dexamethasone 6 mg IV OD and Inj low molecular heparin 6 ml subcutaneously twice daily. He was also detected to have high blood sugar for the first time during the admission and was started on Inj Insulin 20 U SC BD and Insulin 15U subcutaneously twice daily. Within 2–3 days of admission and the start of the medications, the patient started having sleep disturbances, would talk irrelevantly, expressed grandiose delusions, and had euphoric to irritable mood. He would try to remove his oxygen mask, not lie down still, and come out of bedtime and again, due to which he had to be physically restrained. He would become angry about being restrained and try to break the restraints. Because of the same, he was started on Tab risperidone, but he did not show much improvement, and resultantly he was referred to our center after two weeks of being tested positive. Throughout this period, there was no history of disorientation or other cognitive deficits. There was no history of mental illness in the patient, and there was a family history of mental illness in his younger brother in the form of depression. On mental state examination, at the time of presentation to our center, the patient was euphoric, with occasional irritability, and had grandiose delusions of ability and association. He was distractible, able to recognize his relatives, and was well oriented to place. He would not sit still and would become abusive when attempts were made to de-escalate. However, there was no history suggestive of akathisia or any history of neurological deficit; neither the examination was suggestive of the same. His routine investigations in the form of a haemogram, renal function test, liver function test, serum electrolytes, and computerized tomography of the brain did not show any abnormality.

Given the temporal correlation of onset of the psychiatric manifestations with steroids, a diagnosis of steroid-induced mania was considered. His COVID reverse transcriptase-polymerase chain reaction (RTPCR) test was repeated, which came out to be positive. During the hospital stay, he had worsening of the COVID-19 symptoms and again required non-ventilatory oxygen support. Because of the symptoms of COVID-19, dexamethasone 6 mg per day was continued. He was initially started on Tab olanzapine 10 mg/day and clonazepam 4 mg daily as he was unmanageable. However, because of severe agitation, olanzapine was increased up to 20 mg/day, and clonazepam was increased to 12 mg/day. His respiratory status was closely monitored, and over the next 3–4 days, he improved, and oxygen support was removed. However, his dexamethasone was continued. Although his agitation came down with psychotropics, he continued to voice grandiose ideas, and resultantly inpatient psychiatry care was planned.

3. Case-2

B, a 31-year-old male, presented with aggressive behavior to the emergency. Exploration of the history revealed that the patient was maintaining well a week before the presentation. To start with, he developed fever and shortness of breath. He was evaluated by a physician, investigated, and found to have a COVID-19 infection. He was started on dexamethasone 6 mg/day. Within one day of beginning steroids, his physical condition began to worsen. His family was informed about his deteriorating health, and on listening to the news that his physical health condition is not good, the patient became very much distressed. While being shifted to our hospital, on the way while they had stopped briefly, he jumped into a nearby river and had to be rescued, resuscitated, and brought to our center. On assessment at our center, initially, he was drowsy. His routine investigations did not reveal any abnormality. He was managed symptomatically with dexamethasone 6 mg/day, Inj low molecular heparin 6 ml subcutaneously twice daily, injection piperacillin 4.5 mg IV thrice daily, inj pantoprazole 40 mg once daily, Inj metronidazole 400 mg IV thrice daily. He also required non-invasive oxygen support. During the hospital stay, initially, he had sleep disturbance, became irritable with the family members, and heard that he would die. His physical health condition improved in 6 days, and he was sent for home isolation. However, by the seventh day, he started to remain fearful, the voice that people are trying to harm him, speak irrelevantly, and often voice about the difficulty in breathing. The emergence of these symptoms led to bringing him back to the hospital. On examination, he was found to have a delusion of persecution and was agitated. There was no disturbance in the level of consciousness and content of consciousness. There was no past or family history of mental disorders. A diagnosis of steroid-associated psychosis was considered, and he was managed with Inj lorazepam 4 mg/day and olanzapine 10 mg/day. As his physical health condition had improved, the steroid was gradually tapered off. With this, his condition improved. A further plan is to taper off the psychotropics over the next 3–4 weeks.

4. Discussion

The COVID-19 pandemic is becoming a nightmare for everyone, including mental health professionals. Available evidence suggests that patients with COVID-19 infection have a high prevalence of neuropsychiatric manifestations during the acute and post-COVID phases (Taquet et al., 2021; Varatharaj et al., 2020). The medications used to manage COVID-19 infection that can lead to the development of psychiatric manifestations, include hydroxychloroquine, steroids, azithromycin, etc. (Garcia et al., 2020). On the other hand, Tocilizumab can improve depression, fatigue, and pain (Garcia et al., 2020; Biggioggero et al., 2018). Among all these medications, steroids have been most commonly related to the development of psychiatric manifestations.

In terms of the mechanism of steroid-induced psychiatric manifestations, various authors have proposed different mechanisms. It is suggested that hypothalamic–pituitary–adrenal axis activation by stress or chronic exposure to a high level of corticosteroids sets in multiple pathways, which include down-regulation of glucocorticoid receptors and alteration in the levels of various neurotransmitters (e.g., decreased serotonin and increased dopamine activity in certain brain regions). This alteration in the neurotransmitters contributes to depressive or psychotic symptoms (Bhangle et al., 2013). It is also suggested that exposure to higher corticosteroid levels leads to the underproduction of other steroidal hormones such as dehydroepiandrosterone (DHEA), DHEA sulfate, and allopregnanolone to loss of neuronal reparative processes, anxiety,

and depression (Bhangle et al., 2013). Additionally, high corticosteroid levels have a toxic impact on the hippocampus and brain areas, contributing to psychiatric manifestations (Bhangle et al., 2013; Wolkowitz et al., 2009). If one tries to understand the pathogenesis of psychiatric manifestations in the context of COVID-19, it can be said that patients with COVID-19 are vulnerable to develop psychiatric manifestations due to the neurotrophic effect of the virus, hypoxic injury, ongoing medications, or complications arising due to the COVID-19 infection (Conde et al., 2020; Garcia et al., 2020). These vulnerable factors can possibly act as fertile soil for clinical manifestation of steroid-associated psychiatric manifestations in patients with COVID-19 infection. Hence, a high degree of sensitivity is required to understand the contribution of steroids to psychiatric manifestations.

The psychiatric manifestation with the use of steroids has been described since the 1950s. Rome et al. (1952) classified the psychiatric manifestations of steroids in 4 different grades of severity (grade 1: mild euphoria, lessened fatigue; grade-2: heightened euphoria, appearing hypomanic; grade-3: various responses including anxiety, phobia, obsession, or depression; and grade-4: grossly psychotic). Glaser (1953), in the subsequent year, simplified the steroid-associated psychiatric manifestations into two major categories, i.e., primarily affective disorder of elation or depression and second category as a complex with organic components and toxic psychosis. However, over the years, it has become more evident that steroids are associated with a wide range of psychiatric manifestations (Table 1).

The incidence rate of psychiatric manifestations with the use of the steroid has varied widely. The clinic-based small sample size studies have reported an incidence rate of 2–62%, with a weighted incidence rate of 6% (Warrington and Bostwick, 2006). Studies that have evaluated the incidence of steroid-associated psychiatric side effects in consultation-liaison psychiatry practice have reported that about 1.25% of referrals are for steroid-related psychiatry manifestations (Cottencin et al., 2010). A large population-based study that used the administrative and pharmacy claims data (n = 2025) of adults receiving glucocorticoids for >60 days, based on self-reported adverse events by the participants, reported that sleep disturbances and mood symptoms were widespread among those receiving corticosteroids (Curtis et al., 2006). A study from the United Kingdom, which was based on 'The Health Improvement Network (THIN)' database of anonymized electronic medical records from general practices across the country, assessed the incidence of neuropsychiatric manifestations based on the data of 786,868 courses of oral glucocorticoids, prescribed to 372,696 patients. This study showed that highest adjusted hazard ratio, compared to those not exposed to oral glucocorticoids, after controlling for age, gender, practitioner, and the underlying medical condition were for suicide and suicide attempt (adjusted HR: 6.89), followed by delirium, confusion or disorientation (adjusted HR: 5.14), mania (adjusted HR: 4.35), depression without psychotic symptoms (adjusted HR: 1.83), and panic disorder (adjusted HR: 1.45) (Fardet et al., 2012).

Table 1
Steroid associated psychiatric manifestations (Kenna et al., 2011; Bhangle et al., 2013).

- Psychosis
- Mood disorders (hypomania, mania, mixed states, depression)
- Anxiety and panic disorder
- Delirium
- Suicidal thinking and behavior in the context of affective syndromes
- Aggressive behavior (including attempted murder)
- Catatonia
- Insomnia
- Agitation with clear consciousness
- Depersonalization
- Isolated cognitive impairments (impaired attention, concentration, memory, and word-finding difficulties)
- Reversible dementia
- Drug dependency
- Drug withdrawal

These high rates of psychiatric manifestations with steroids suggest that these should be used judiciously in patients with COVID-19 infection. Whenever possible, these should be used only within the limits of the recommended doses. Further, understanding this risk of psychiatric manifestations in the context of COVID-19 infection during the acute phase of the illness is crucial. Hence, whenever patients with these psychiatric manifestations are referred to a psychiatrist, they should closely evaluate the association of psychiatric manifestations with the use of steroids. It is quite possible that in the background of COVID-19 infection, it may not be possible to pinpoint a single etiology for the psychiatric manifestations, but the contribution of steroids to the psychiatric manifestations must be considered, and if these are not required, these should be tapered off.

Further, it is also essential to note that steroid withdrawal can also lead to psychiatric manifestations, such as fatigue, anorexia, discouragement, and depression. Later studies have reported other psychiatric symptoms, too, during the glucocorticoid discontinuation phase in the form of irritability, labile affect, apathy, multiple somatic complaints (e.g., pseudo-rheumatism; facial paresthesias/cranial dysesthesias; faintness), depersonalization, cognitive symptoms in the form of impairment in concentration and memory, difficulty maintaining sequential thought, psychotic symptoms and suicidal behavior (Wolkowitz et al, 1990, 1997; Dixon and Christy, 1980). Older studies have reported an incidence of psychiatric manifestations in 21% of patients while the steroids are being tapered, and these subside after 2–8 weeks of discontinuation (Freyberg et al., 1951). A study based on the THIN database, which evaluated the data of 21,995 adult patients, who had received oral steroids for the long-term, reported the risk of depression (incidence rate ratios: 1.13; 95% CI, 1.00–1.28; P = .04) and delirium/confusion (incidence rate ratios: 2.67; 95% CI: 1.96–3.63; P < .001) to be significantly higher during the discontinuation period when compared to 3–5 month period before the stoppage of steroids (Fardet et al., 2013). The issue of symptoms related to steroid withdrawal in the context of COVID-19 is crucial, as there can be a significant impact of these symptoms with the symptoms of post-COVID syndrome or long COVID. Although many hypotheses have been proposed for post-COVID or long COVID symptoms (Jansen et al., 2021; Banerjee and Viswanath, 2020), the contribution of continued use of steroid or withdrawal of steroid has not received much attention.

In terms of risk factors for developing psychiatric side effects, data from clinic-based studies suggest that the psychiatric manifestations are usually seen during the early part of the therapy and are related to the dose of glucocorticoids. In general, most of the psychiatric side effects are seen during the first two weeks of treatment; however, a wide range of onset of neuropsychiatric manifestations include one day to as late as two months (Kenna et al., 2011). Regarding the dose of steroids, available data clearly shows that the incidence of psychiatry manifestations with steroids increases with higher doses; however, no association is noted between the amount of steroids and the severity of psychiatric manifestations. In one of the earliest Boston collaborative drug surveillance program, it was noted that the incidence of psychiatric manifestations was 1.3% with prednisone dose of less than 40 mg/day, which increased to 4.6% with an increase in the daily dose of prednisone to 41–80 mg/day, and further rose to 18.4% with the increase in the dose of prednisone to more than 80 mg/day (Boston Collaborative Drug Surveillance Program, 1972). Some of the clinic-based data suggest the risk of depression increases with longer duration of steroid use, and the dose associated with the development of delirium is higher than that for hypomania/mania (Warrington and Bostwick, 2006; Cottencin et al., 2010; Kenna et al., 2011; Bhangle et al., 2013). Other risk factors for the psychiatric manifestations has been listed In Table 2.

In the context of COVID-19, the dose of 6 mg/day of dexamethasone can be considered equivalent to 40 mg/day of prednisolone. In this contest, it can be said the incidence of psychiatric manifestations is expected to be low. However, if the steroids are used in doses more than

Table 2
Risk factors associated with development of steroid associated manifestations.

Clinic Based studies
• Early part of the therapy: during the initial 2 weeks, with a range of one day to as late as two months
• Higher dose of glucocorticoids
• Higher serum levels of glucocorticoids
• Longer duration of steroid use
• Use of oral steroids (compared to inhaled steroids)
• Higher cerebral spinal fluid/serum albumin ratio (a marker of blood–brain barrier damage)
• Hypoalbuminemia
• Female gender (lack of consensus)
• Past psychiatric history (lack of consensus)
• SLE (limited evidence)
General population-based data (THIN Database)
• Female gender (depression, panic disorder and Suicidal Behavior)
• Male gender (mania and delirium/confusion/disorientation)
• Increasing age: depression, mania, delirium/confusion/disorientation
• Lower age: suicidal behavior & panic disorder
• Higher doses: Depression, Delirium, Mania, Panic Disorder
• Past history of a glucocorticoid-induced neuropsychiatric disorder
• Past history of mental disorder

this recommended dose, it is essential to remember that patients with COVID-19 will have a higher incidence of psychiatric adverse effects. In both our cases, the patients developed psychiatric manifestations while receiving steroids in the recommended doses. The unmasking of psychiatric manifestations in such a scenario may be attributed to other associated factors such as hypoxia.

Other risk factors for steroid-associated psychiatric manifestations found in clinic-based studies include higher serum levels of corticosteroids, higher cerebral spinal fluid/serum albumin ratio (a marker of blood-brain barrier damage), and hypoalbuminemia (Kenna et al., 2011; Drozdowicz and Bostwick, 2014). It is important to note that the inhibitor of the Cytochrome P450 enzyme (CYP) 3A4 that metabolizes prednisone's biologically active metabolite can increase the risk of steroid-induced psychosis. This would be an essential consideration while using steroids and medications like fluvoxamine, which is an inhibitor of this enzyme and has been proposed to be beneficial in the management of COVID-19 infection (Lenze et al., 2020). This should also be kept in mind while using steroids in patients with known psychiatric illness and receiving fluvoxamine or fluoxetine, both of which are considered to be moderate inhibitors of CYP3A4.

There is a lack of consensus for the female gender, presence of past psychiatric history, and systemic lupus erythematosus being risk factors for the development of steroid-associated psychiatric manifestations (Kenna et al., 2011; Drozdowicz and Bostwick, 2014). The THIN database suggests that women are at higher risk of depression and lower risk of mania and delirium/confusion/disorientation (Farlet et al., 2012). It was also seen that the risk of depression, mania, and delirium/confusion/disorientation increases with age, whereas the risk for suicidal behavior and panic disorder increases with decreasing age (Farlet et al., 2012). The THIN database also confirms the association of psychiatric manifestations with higher doses of glucocorticoids. Additionally, THIN database reports the association of past psychiatric history with the development of all kinds of steroid-associated psychiatric side effects (Fardet et al., 2012). The data from the THIN database also suggests that a history of a glucocorticoid-induced psychiatric disorder is associated with a higher risk of having a recurrence of the same condition after a subsequent course (hazard ratio = 1.32, 95% CI = 1.00–1.74) (Farlet et al., 2012). However, a history of steroid use was associated with a lower risk of psychiatric manifestations (Farlet et al., 2012). In terms of underlying physical illnesses, except for delirium, a specific medical condition is not a risk factor (Farlet et al., 2012). All these associations in the context of COVID-19 again emphasize a need to improve the clinicians' awareness about these risk factors so that the clinicians keep these facts while considering the prescription of steroids and while considering the possible etiological cause for psychiatric manifestations in patients with COVID-19.

In terms of the type of steroids, it is crucial to understand that risk of psychiatric side effects is higher with oral steroids when compared to the inhaled steroids (Warrington and Bostwick, 2006; Cottencin et al., 2010; Kenna et al., 2011; Bhangle et al., 2013). The majority of the data on the association of corticosteroids and psychiatric manifestations is for prednisone. However, it is suggested that this could be because prednisone is the most commonly used corticosteroid in clinical practice.

In terms of psychiatric manifestations during the withdrawal period, the THIN database suggests that the risk of both depression and delirium/confusion during the withdrawal period increases with the use of long-acting glucocorticoids (Farlet et al., 2013). This could again have important implications while attempts are being made to understand long-COVID or post-COVID symptoms.

Usually, reduction in the dose of steroids is recommended, when patient presents with psychiatric manifestations (Kenna et al., 2011). However, if the patients do not respond to reduction in the doses, stopping of steroids, or starting of psychotropics have to be considered, depending on the severity of the psychiatric manifestations (Parasherand Bez, 2020). In our first case, in view of the respiratory status, dexamethasone was continued, and psychotropics were added. In the second case, in view of the marked agitation and florid psychopathology, psychotropics had to be used, in addition to stoppage of steroids.

While choosing psychotropics the issue of drug interactions between the psychotropics and medications used for management of COVID-19 infection should be kept in mind. While choosing antidepressants, the issue of common electrolyte abnormalities in patients with COVID-19 must be kept in mind (Lippi et al., 2020). Similarly, the issue of QTc prolongation with use of antipsychotics along with medications used for management of COVID-19 must be kept in mind (Plasencia-Garcia et al., 2021).

Keeping these facts in mind in the context of an ongoing pandemic, psychiatrists, when called to evaluate the patients with the acute phase of COVID-19 infection or during the post-COVID-19 phase, or when they evaluate presenting with new-onset psychiatric manifestations, should focus on taking a history for COVID-19 infection, especially the severity of the COVID-19 infection, also should carefully evaluate the history of ongoing steroids or recent stoppage of steroids. These can help in understanding the possible cause of psychiatric manifestations and deciding about the course of the treatment. Further, for patients who are on steroids and require the use of antidepressants, the clinicians should be careful before prescribing fluvoxamine or fluoxetine.

Further, if the mental health professionals are involved in screening all patients with COVID-19 for mental health issues at the time of admission to the COVID-19 wards or ICUs, or are involved in monitoring of patients with COVID-19 at home, they should carefully document the mental status prior to starting of corticosteroids. This can help in establishing the association of psychiatric manifestations with the exposure to corticosteroids. Additionally, patients who are at risk for development of corticosteroids associated psychiatric manifestations, should be closely be monitored and the dose of steroids should be carefully determined, by balancing the severity of physical illness(es) and the risk for development of psychiatric manifestations.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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