Four Case Reports of Acute Psychosis Secondary to Low Doses of Prednisone/Prednisolone

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Abstract

Prednisone, the prodrug of prednisolone, has been implicated as the cause of neuropsychiatric symptoms such as depression, mania, agitation, delirium, dementia, psychosis, and many other affective, behavioral, and cognitive changes. Although the literature suggests that patients on 40 mg or more of prednisone a day are at a greater risk for steroid-induced psychosis, patients on <40 mg are still at risk, and therefore, steroid-induced psychosis should not be excluded from the differential. Prednisone is the prodrug of prednisolone, and the two are comparable on a milligram (mg)-to-mg basis. Here are four case studies, three from the literature and one new, that demonstrate acute psychosis secondary to low-dose prednisone/prednisolone use.

Introduction

Since the introduction of corticosteroid use in the 1950s, patients presented with psychiatric side effects regularly [1,2]. The neuropsychiatric effects, often misleadingly termed "steroid psychosis" in the historical literature, can present in any combination of affective, behavioral, or cognitive changes within as soon as three days of starting the steroid treatment [3,4]. The neuropsychiatric effects found related to steroid psychosis include depression (35%), mania (31%), agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium (13%), dementia, and psychosis (14%) [3,5]. These percentages represent the most common presentations of steroid psychosis according to a retrospective study by Lewis and Smith [5].

The Boston Collaborative Drug Surveillance Program specifically monitored 718 patients receiving prednisone for adverse reactions and found a strong dose-response relationship for acute psychiatric reactions [6]. Similarly, Lewis and Smith found that there was an increased incidence of psychiatric reactions to steroid treatment with increasing average daily doses of prednisone [5]. Specifically, it has been found that patients receiving daily doses of 40 mg prednisone are at a greater risk of developing steroid psychosis [4].

Clinically, these findings may have biased physicians to dismiss steroid psychosis as a differential in cases of neuropsychiatric presentation in the presence of low-dose prednisone. However, cases have demonstrated that doses even as low as 2.5 mg of prednisolone daily have consistently been associated with steroid psychosis without any prior history of mental illness. In this study, we discuss three case reports of patients with findings from the literature on low-dose prednisone-induced psychosis as well as a new case presentation.

Case Presentation

Case one

The first case report describes a 77-year-old man with adrenal insufficiency, Hashimoto’s thyroiditis, and no known psychiatric history [7]. The patient presented to the emergency department (ED) with slow response and multiple leg abrasions from a fall. He was discharged with normal consciousness after receiving cortisol 25 mg in the morning, 12.5 mg in the evening, and thyrroxine 50 μg in the morning. Three days later, the patient received a 15-day prescription of prednisolone 10 mg in the morning and 5 mg in the evening. The patient presented to the ED 2.5 months later with hyponatremia (Na = 115 mEq/L), low cortisol, and elevated thyroid-stimulating hormone. He left against medical advice (AMA) after receiving cortisol 50 mg in the morning, cortisone 25 mg, and thyrroxine 100 μg in the evening.

Six days later, the patient presented delirious to the ED with a two-day history of insomnia, bizarre speech, and unusual behavior. An adrenal crisis was suspected, so the patient received 100-mg IV hydrocortisone. His delirium did not clear, so additional cortisone of 50 mg was given in the morning and 25 mg in the evening. The patient did not experience resolution of his symptoms and left AMA. The next day, the patient represented to the ED disoriented and agitated with sexual hallucinations, aggression, and self-harming.
On the morning of day 4, it was noted that the patient's persecutory, jealousy, and bizarre delusions were impairment. Her delusions were maintained, and she was preoccupied with leaving the hospital. Montreal Cognitive Assessment (MOCA) and scored a 16/30 at this time, qualifying for moderate cognitive level of 283 and was given a supplementation of 250 mcg vitamin B12 daily. The patient underwent a with involuntary ordered medication went into effect. On day 3, the patient was found to have a vitamin B12 The patient refused all medications except sulfasalazine until day 4, which was when the probable cause olanzapine 2.5 mg BID was started.

A diagnosis of acute psychosis was made, and she was started on lorazepam 4 mg and haloperidol 5 mg. The patient showed rapid improvement from psychosis and thereafter no longer required antipsychotic treatment. Her mental state remained stable for four days. On the fifth day of hospital readmission, a low dose of daily prednisolone 2.5 mg was re-administered. The patient immediately showed symptoms of agitation, anxiety, and insomnia once again. The low-dose prednisolone was held, and the symptoms disappeared immediately the following day without the use of antipsychotic drugs. Hydrocortisone was administered in this patient as it directly replaces the much-needed missing hormone for Sheehan’s syndrome. Re-administration of prednisolone with the added hydrocortisone showed improvement to her mental state, and a slow titration of prednisolone to 5.0 mg in the morning over six days while tapering off of hydrocortisone occurred. At the conclusion of the case, the patient was on a daily dose of prednisolone 7.5 mg without psychotic symptoms or signs of adrenal insufficiency.

Case three
This case report identified a 21-year-old woman who exhibited symptoms of body, chest, and facial hair [9]. She was diagnosed with hirsutism and had no previous psychiatric history. Her treatment began with low-dose prednisolone 5 mg at night and 2.5 mg in the morning. On day 2, the patient began to display neuropsychiatric symptoms of thought disorder by repeating the phrase “1952.” The patient also reported feeling dazed and increasingly anxious. No pertinent lab results were identified. By day 3, the patient was unable to rest. The patient reported that she could not focus her eyes because her pupils would not constrict and dilate appropriately in the light and dark. The patient also reported clumsiness and misplacing objects. On the fourth day, the patient reported hallucinations and started to again repeat the phrase “1952.” The patient became delusional and reported that she believed someone had hypnotized her. On day 4, the prednisolone was discontinued, and the patient appeared distressed but otherwise free of neuropsychiatric complaints on day 5.

New case presentation
A 65-year-old woman presented to the inpatient psychiatric unit on emergency detention for confusion, disorientation, and bizarre behavior after medical clearance at the ED. The patient’s basic metabolic panel/complete blood count (BM/CBC), urine drug testing (UDS), and urine examination (UA) were all found to be normal, and head CT demonstrated no acute findings. The patient presented with a five-day history of new-onset persecutory, jealousy, and bizarre delusions. During the psychiatric evaluation, the patient voiced distress that she was going to die by a suicide bomber on a plane, and she was adamant that her husband was cheating on her with the female police officer that brought her to the hospital. She was diagnosed with panhypopituitarism secondary to Sheehan’s syndrome and was prescribed prednisolone 10 mg in the morning and 5 mg at night. Following the first dose of prednisolone, the patient became euphoric and experienced insomnia. On day 3, she was anxious and hyperactive. On day 5, the patient experienced agitation, restlessness, and hallucinations. The prednisolone was discontinued on day 7, and she was discharged but was readmitted three days later due to lack of improvement.

On the fourth day, the patient reported hallucinations and started to again repeat the phrase “1952.” The patient also reported feeling dazed and increasingly anxious. No pertinent lab results were identified. By day 3, the patient was unable to rest. The patient reported that she could not focus her eyes because her pupils would not constrict and dilate appropriately in the light and dark. The patient also reported clumsiness and misplacing objects. On the fourth day, the patient reported hallucinations and started to again repeat the phrase “1952.” The patient became delusional and reported that she believed someone had hypnotized her. On day 4, the prednisolone was discontinued, and the patient appeared distressed but otherwise free of neuropsychiatric symptoms on day 5.

The patient refused all medications except sulfasalazine until day 4, which was when the probable cause with involuntary ordered medication went into effect. On day 5, the patient was found to have a vitamin B12 level of 283 and was given a supplementation of 250 mcg vitamin B12 daily. The patient underwent a Montreal Cognitive Assessment (MOCA) and scored a 16/30 at this time, qualifying for moderate cognitive impairment. Her delusions were maintained, and she was preoccupied with leaving the hospital.

On the morning of day 4, it was noted that the patient’s persecutory, jealousy, and bizarre delusions were
beginning to dissolve although the patient had not taken her medication. She no longer believed she would
die by a suicide bomber, and she responded “I don’t know” when asked if her husband was cheating. As this
was the first day of involuntary medication administration, the patient’s olanzapine was modified to 2.5 mg
at night with haloperidol of 2 mg daily IM and benztropine 0.5 mg IM BID as a backup should the patient
refuse.

The patient received her first dose of olanzapine 2.5 mg on the night of day 4. On day 5, benztropine 0.5 mg
nightly was added because of the patient’s concerns of side effects, and a repeat MOCA assessment shows an
improved score of 21/30, reducing the previous qualification to mild cognitive impairment. On day 6,
olanzapine was increased to 5.0 mg. On day 9, the patient denies the content of all the delusions she had on
presentation and expresses an insight into her bizarre behavior being associated with paranoid thoughts.
Without the prednisone, the patient begins to experience swelling and pain in the joints, which were well
managed with ibuprofen 400 mg every eight hours (q8hrs) PRN. On day 11, it was noted that redirectable
residual persecutory delusions were still present when the patient experienced emotional stress. The
patient’s olanzapine was increased to 7.5 mg nightly on day 12 to prevent the oscillating nature of the
patient’s paranoia. On day 15, the patient’s delusions were found to have completely dissolved, and no
residual paranoia was discernible. The patient was discharged home on olanzapine 7.5 mg nightly and
benztropine 0.5 mg nightly.

**Discussion**

Prednisone is a synthetic glucocorticoid, a prodrug to prednisolone, that enters the nucleus of cells and
activates specific nuclear receptors that alters gene expression \[10\]. It decreases inflammation by decreasing
migration of polymorphonuclear leukocytes and reversing capillary permeability and suppresses the
immune response by inhibiting proinflammatory cytokine production. It is well known that adverse effects
are common in patients receiving glucocorticoids in high doses or over a long time period \[10\].

While the patient presented here did have a long-term history of prednisone use, the low dose of 2.5 mg
daily does not match the typical representation of “steroid psychosis” as doses of 40 mg or higher have been
found to pose a much greater risk \[4\]. However, the patient’s delusions and paranoia were clearly dissolving
with no intervention besides discontinuation of her daily 2.5 mg prednisone. After receiving only one dose
of 2.5 mg Zyprexa, the patient also saw a five-point improvement on her MOCA assessment. This
presentation is consistent with the other cases presented here (cases 2 and 3), in which discontinuation of
prednisone/prednisolone saw the resolution of neuropsychiatric symptoms without antipsychotic use.

It is unlikely the patient was experiencing functional psychosis due to the patient’s age and acute onset of
delusions without a past psychiatric history. However, the acute onset of delusions that began to resolve
solely upon discontinuation of her daily prednisone insinuated an organic psychosis due to glucocorticoid
use. While low-dose prednisone is rarely implicated in steroid-induced psychosis, this case series
demonstrates that doses as low as 2.5 mg daily have been implicated in causing acute psychosis.

Limitations to this case review include that prednisone and prednisolone were not considered as separate
pharmacotherapies. This is because prednisone is a prodrug to prednisolone, only requiring metabolism by
the liver to reach glucocorticoid activity, and the two medications are considered comparable on an mg-to-
mg basis. Another limitation is that, per the patient’s MOCA scores, she may have a cognitive impairment
that can be an organic cause of her psychosis. However, the patient’s improvement of symptoms from
steroid discontinuation alone paired with complete resolution of symptoms on discharge makes psychosis
due to cognitive impairment more unlikely.

**Conclusions**

In conclusion, low-dose prednisone and prednisolone can be implicated in acute psychosis. Evidence shows
that discontinuation of low-dose prednisone and prednisolone aided in the cessation of neuropsychiatric
symptoms such as delusions, paranoia, hallucination, agitation, and insomnia as described in the case
reports of these patients. This is relevant as steroid-induced psychosis may be overlooked as a differential if
the dose of prednisone does not match a particular threshold, notably the 40 mg/day standard found by Hall
and his colleagues. Appropriate consideration for steroid-induced psychosis, especially when organic
psychosis is suspected, should not be ruled out solely based on the dose of prednisone or prednisolone. If
steroid-induced psychosis is suspected, discontinuation of the glucocorticoid could be enough to resolve the
symptoms.

**Additional Information**

**Disclosures**

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**References**

1. Rome HP, Braceland FJ: Use of cortisone and ACTH in certain diseases: psychiatric aspects. Proc Staff Meet Mayo Clin. 1950, 25:495-7.
2. Clark LD, Bauer W, Cobb S: Preliminary observations on mental disturbances occurring in patients under therapy with cortisone and ACTH. N Engl J Med. 1952, 246:205-16. 10.1056/NEJM195202072460601
3. Dubovsky AN, Arvika S, Stern TA, Axelrod L: The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. 2012, 53:105-15. 10.1016/j.pyrsym.2011.12.007
4. Hall RC, Popkin MK, Stickney SK, Gardner ER: Presentation of the steroid psychoses. J Nerv Ment Dis. 1979, 167:229-36. 10.1097/00005053-197904000-00006
5. Lewis DA, Smith RE: Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord. 1983, 5:519-32. 10.1016/0165-0327(83)90022-8
6. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther. 1972, 15:694-8. 10.1002/cpt197215part1694
7. Chao SI, Wang TL, Chong CF, Lin JW: Steroid psychosis in an adrenal insufficiency and hypothyroidism patient. J Acute Med. 2012, 2:121-124. 10.1016/j.jaome.2012.09.003
8. Hong SI, Cho DH, Kang HC, Chung DJ, Chung MY: Acute onset of steroid psychosis with very low dose of prednisolone in Sheehan’s syndrome. Endocr J. 2006, 53:255-8. 10.1507/endocrj.53.255
9. Greeves JA: Rapid-onset steroid psychosis with very low dosage of prednisolone. Lancet. 1984, 1:1119-20. 10.1016/s0140-6736(84)92528-5
10. Puckett Y, Gabbar A, Bokhari AA: Prednisone. StatPearls Publishing, Treasure Island (FL); 2021.