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Corticosteroid-induced mania: Prepare for the unpredictable

Head off this common psychiatric side effect

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Can corticosteroids "unlock" hidden potential for mania, or are steroid-induced mood symptoms a temporary reaction? And when these mood symptoms occur, what is the best way to treat them?

Psychiatric symptoms develop in 5% to 18% of patients treated with corticosteroids. These effects—most often mania or depression—emerge within days to weeks of starting steroids. To help you head off manic and mixed mood symptoms, this paper examines how to:

- treat steroid-induced mania or mixed bipolar symptoms
- reduce the risk of a mood episode in patients who require sustained corticosteroid therapy.

'STEROID PSYCHOSIS'

Jane Pauley, NBC's *Today Show* broadcaster, described in her autobiography how hypomania developed within weeks after she started cortico-

steroids for idiopathic urticaria edema: "I was so energized that I didn't just walk down the hall, I felt like I was motoring down the hall. I was suddenly the equal of my high-energy friends who move fast and talk fast and loud. I told everyone that I could understand why men felt like they could run the world, because I felt like that. This was a new me, and I liked her!"[1]

Pauley's hypomania led to a manic episode and eventually to depression. She was started on antidepressants, which triggered another manic episode. Pauley—who had no history of bipolar disorder—spent 3 weeks in a New York psychiatric hospital.[1]

Diagnostic symptoms. Corticosteroids' psychiatric effects—cognitive, mood, anxiety, and psychotic symptoms—were first described as "steroid psychosis." Psychosis can occur, but mood symptoms are more common:

- Among 122 patients, 40% experienced depression, followed by mania (28%), psychosis (14%), delirium (10%), and mixed mood episodes (8%).[2]
- Among 130 patients, mania was most prevalent (35%), followed by depression (28%), mixed mood episodes (12%), delirium (13%), and psychosis (11%).[3]
- Corticosteroids caused 54% of organic mania cases on a hospital psychiatric consult service.[4]
- In a prospective study of 50 patients treated with corticosteroids, 13 developed hypomania and 5 developed depression.[5]

Steroid-induced symptoms emerge from 3 to 4 days to a median of 11 days after a patient starts corticosteroid therapy. After steroids are discontinued, depressive symptoms persist approximately 4 weeks, mania 3 weeks, and delirium a few days. Approximately one-half of patients with steroid psychosis improve in 4 days and one-half within 2 weeks.[2,6]

Risk of psychiatric symptoms was 1.3% with dosages <40 mg and 18.4% with dosages >80 mg

WHO IS AT RISK?

Corticosteroids include the steroids produced in the adrenal gland (such as corticosterone) and their synthetic—and often more potent—analogues (such as prednisone).[7] Because of their glucocorticoid, immunosuppressant, mineralocorticoid, and anti-inflammatory properties, steroids are used as replacement therapy and to treat a wide variety of illnesses (*Table 1*).

Age and gender. Patient age appears unrelated to development of psychiatric symptoms after corticosteroid use.[2] One study suggested women are twice as likely as men to develop psychiatric symptoms (77 versus 38 cases in 115 patients),[3] but many illnesses that require corticosteroid treatment occur more frequently in women. Other researchers found a slight female predominance (58% versus 42% of cases) when they excluded patients with systemic lupus erythematosus and rheumatoid arthritis, which are more common in women than in men.[2]

Dosage. Higher corticosteroid dosages increase the risk of psychiatric symptoms. In patients taking prednisone, the Boston Collaborative Drug Surveillance Project[8] found the incidence of psychiatric side effects to be:

- 1.3% in patients taking <40 mg
- 4.6% in those taking 41 to 80 mg
- 18.4% in those taking >80 mg.

Psychiatric history. Past psychiatric illness does not seem to be a risk factor for psychiatric side effects of corticosteroids,[9] although patients with a history of posttraumatic stress disorder are more likely to suffer depression while taking corticosteroids.[10]

Corticosteroid exposure. Patients who did not experience psychiatric side effects with corticosteroids in the past appear not to be protected if corticosteroids are used again. One report examined 17 cases of steroid-induced psychiatric illness in

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patients with previous exposure to corticosteroid therapy. Six patients had previous psychiatric side effects while taking corticosteroids, and 11 did not.[2]

BIPOLAR TRIGGER?

Do corticosteroids' acute psychiatric side effects have long-term sequelae? Longitudinal evidence is scarce, but a few reports suggest corticosteroids could play a role in the onset of primary bipolar I disorder:

- A 28-year-old woman with no known mood symptoms before a short course of prednisone experienced six episodes of mania and depression when not taking corticosteroids during the subsequent 18 months.[11]
- Among 16 patients with first-onset mood symptoms after corticosteroid use, a retrospective chart review found 7 had recurrent manic and depressive symptoms unrelated to additional corticosteroid use.[12]

Although intriguing, these case reports are inconclusive. Because bipolar type I incidence in the general population is 1.5%,[13] many persons with bipolar disorder undergo corticosteroid treatment. Nevertheless, these results—especially from the retrospective review[12]—suggest that corticosteroid use may contribute to the onset of bipolar I illness.

SYMPTOMATIC TREATMENT

Corticosteroid-induced side effects are usually managed by tapering off the steroids and treating the psychiatric symptoms.[2,3] Simply tapering off the steroids—without additional treatments—led to recovery in 33 of 36 patients.[2] Stopping corticosteroids is not always possible or desirable, however, especially in many medically complicated cases seen by psychiatric consult services.

In a recent case, I was asked to see a man, age 69, on the oncology service who was receiving corticosteroids every 2 weeks as part of his chemotherapy. The patient was admitted to the hospital for acute mental status changes 2 days after his last corticosteroid dose. He had pressured speech, grandiosity, and had not slept in 2 days. We started risperidone, 1 mg bid, and most of his manic symptoms resolved within 2 days. His chemotherapy was continued without corticosteroids. If this had not been not possible, I would have recommended continuing risperidone prophylactically.

Table 1

Medical conditions for which corticosteroids are commonly used

Disorder	Indications for corticosteroids
Acute adrenal insufficiency	Acute; replacement therapy
Addison's disease	Chronic; replacement therapy
Asthma	Acute and chronic; anti-inflammatory
Inflammatory bowel disease	Acute; anti-inflammatory
Multiple sclerosis	Acute; exacerbations, immunosuppressant
Organ transplant	Chronic; immunosuppressant
Rheumatoid arthritis	Chronic; anti-inflammatory
Systemic lupus erythematosus	Acute; severe exacerbation, immunosuppressant (high doses are used)

continued

Table 2

Mood stabilizers with evidence of benefit in treating corticosteroid-induced mania

Indication	Medication	Dosage/blood level	Evidence
Preventing psychiatric effects in patients requiring long-term corticosteroids	Lithium	0.8 to 1.2 mEq/L	Prospective trial (27 with multiple sclerosis)[24]
Preventing recurrence of manic symptoms in patients requiring additional steroid pulses	Carbamazepine	600 mg qd (to therapeutic range of 8 to 12 µg/mL)*	Case report[16]
	Gabapentin	300 mg tid	Case report[26]
Treating steroid-induced manic symptoms	Olanzapine	Initially 2.5 mg/d, titrated to 20 mg/d	Open-label trial (12 patients)[14]
	Lithium	0.7 mEq/L	Case report[15]
	Quetiapine	25 mg qhs and 12.5 mg bid prn	Case report[17]
	Carbamazepine	600 mg qd (to therapeutic range of 8 to 12 µg/mL)*	Case reports[12,16]
	Haloperidol	2 to 20 mg/d*	Case reports[12,16]
Treating steroid-induced depressive symptoms	Fluoxetine	20 mg/d	Case report[18]
	Amitriptyline	30 mg/d (usual effective range is 50 to 300 mg/d)*	Case report[12]
	Lamotrigine	Up to 400 mg/d	Case report[19]
	Lithium	0.1 to 0.8 mEq/L	Case reports[20, 21]
Treating steroid-induced psychotic symptoms	Haloperidol	5 mg IV on day 1, then 2 mg po bid	Case report[22]
	Risperidone	1.5 mg/d	Case report[23]

* Dosage not included in published report; recommendation based on experience or anecdotal information

No double-blind, placebo-controlled studies have examined prevention or treatment of steroid-induced mania or other psychiatric symptoms. Uncontrolled trials and case reports suggest benefit from some symptomatic and preventive treatments (*Table 2*).

Treating manic and mixed mood symptoms. Twelve outpatients with manic or mixed symptoms from corticosteroid use received olanzapine in a 5-week, open-label trial. Flexible dosing started at 2.5 mg/d and was increased as needed (maximum 20 mg/d). One patient dropped out for lack of efficacy. For the others, manic and mixed symptoms improved significantly, as indicated by scores on the Young Mania Rating Scale, Hamilton Rating Scale for Depression, and Brief Psychotic Rating Scale.[14] Patient weight, blood glucose, and involuntary movements did not change significantly.

Evidence from case reports indicates that lithium,[15] carbamazepine,[12,16,] haloperidol,[12,16] or

quetiapine[17] also can successfully treat steroid-induced manic symptoms.

Treating other psychiatric symptoms. Case reports support electroconvulsive therapy,[2,15] fluoxetine,[18] amitriptyline,[12] lamotrigine,[19] or lithium[20,21] for steroid-induced depression, and haloperidol[22] or risperidone[23] for steroid-induced psychosis.

In four cases,[6] tricyclic antidepressants appeared to worsen corticosteroids' psychiatric side effects. These case patients might have had steroid-induced delirium instead of mood disorders or psychosis, however, and the tricyclics' anticholinergic effects could have worsened the delirium.[9]

PREVENTING STEROID-INDUCED SYMPTOMS

Although clear guidelines on when to start preventive treatments do not exist, potential candidates for pretreatment with lithium or other agents include patients who:

- have developed psychiatric symptoms multiple times after repeated corticosteroid use
- are at high risk if psychiatric side effects occur.

Lithium. Prophylactic lithium was given to 27 patients with multiple sclerosis and taking corticosteroids for acute exacerbations. None developed psychiatric symptoms.[24] At the same clinic, 6 of 44 patients with multiple sclerosis or retrobulbar neuritis developed psychiatric side effects after using corticosteroids without lithium.

Be cautious when using prophylactic lithium because some conditions treated with corticosteroids—such as systemic lupus erythematosus—can impair renal function.[20] Corticosteroids also can affect sodium balance and increase the risk of lithium intoxication.[25]

Check renal function before and during lithium titration, and initiate corticosteroid therapy when lithium is at effective blood levels (0.8 to 1.2 mEq/L). Monitor lithium levels and renal function frequently during steroid treatment.

Other mood stabilizers. Two case reports describe patients who repeatedly developed manic symptoms after multiple corticosteroid doses. Carbamazepine, 600 mg qd,[16] and gabapentin, 300 mg tid,[26] prevented manic symptoms after additional corticosteroid pulses.

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Bottom Line

Psychiatric symptoms—especially mania—are a common, unpredictable side effect of corticosteroid use. Taper the corticosteroid, if possible, and add a mood stabilizer or antipsychotic to alleviate symptoms. Consider prophylactic lithium for patients with medical conditions that require frequent or high-dose corticosteroid treatment.

continued

Related resources

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DRUG BRAND NAMES

Amitriptyline • Elavil
Carbamazepine • Tegretol
Fluoxetine • Prozac
Gabapentin • Neurontin
Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Eskalith, others
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal

DISCLOSURES

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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