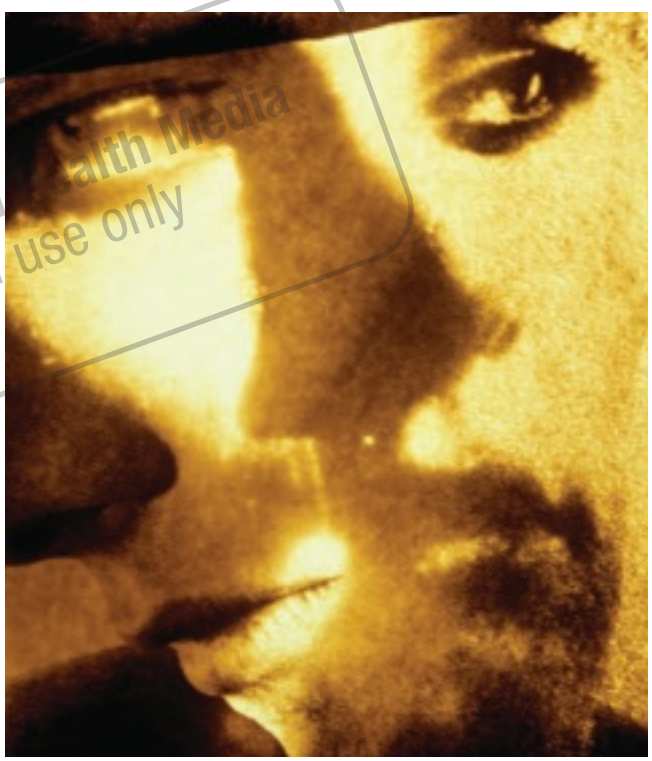
Current PSYCHIATRY

Corticosteroid psychosis: Stop therapy or add psychotropics?

Off-label antipsychotics, mood stabilizers, and anticonvulsants could help



© 2010 BRANDTNER & STAEDELI / GETTY

Mrs. E, age 31, develops rapid, pressured speech and insomnia for 4 consecutive nights, but reports a normal energy level after receiving high-dose methylprednisolone for an acute flare of systemic lupus erythematosus (SLE).

Her medical history indicates an overlap syndrome between SLE and systemic sclerosis for the last 5 years, migraine headaches, and 4 spontaneous miscarriages, but she has no psychiatric history. Her family history is negative for psychiatric illness and positive for diabetes mellitus, hypertension, and coronary artery disease.

Mrs. E lives with her husband and 10-year-old son. She admits to multiple stressors, including her health problems and financial difficulties, which recently led to the family's decision to move to her mother-in-law's house. Mrs. E denies using illicit drugs, cigarettes, or alcohol.

Mrs. E is admitted to the hospital, and her corticosteroid dosage is reduced with a switch to prednisone, 60 mg/d. She is started on risperidone, 1 mg at bedtime, which is titrated without adverse effect. Her psychotic symptoms improve over 4 days, and she is discharged on prednisone, 60 mg/d, and risperidone, 0.5 mg in the morning and 2 mg at night.

After completing her corticosteroid course, Mrs. E experiences complete resolution of psychiatric symptoms and is tapered off risperidone after 6 months.

Corticosteroid use can cause a variety of psychiatric syndromes, including mania, psychosis, depression, and delirium. A meta-analysis reports severe psychotic reactions in 5.7% of patients taking corticosteroids and mild-to-moderate reactions in 28% of patients.[1] Hypo-

Andrew J. Muzyk, PharmD
Clinical pharmacist

Shannon Holt, PharmD
Clinical pharmacist

Jane P. Gagliardi, MD
Assistant professor of psychiatry and behavioral sciences
Assistant professor of medicine

. . . .

Duke University School of Medicine
Durham, NC

Corticosteroid psychosis

Clinical Point

High corticosteroid dose is the primary risk factor for psychosis but does not predict onset, severity, type of reaction, or duration

ONLINE ONLY

Discuss this article at http://CurrentPsychiatry.blogspot.com

Table 1

Grading scale for corticosteroid-induced psychiatric symptoms

Grade	Symptoms
Grade 1	Mild, nonpathologic, and subclinical euphoria
Grade 2	Reversible acute or subacute mania and/or depression
Grade 3	Bipolar disorder with relapses possible without steroids

Source: Reference 4

mania, mania, and psychosis are the most common psychiatric reactions to acute corticosteroid therapy.[2] This article reviews case reports and open-label trials of antipsychotics, mood stabilizers, and anticonvulsants to treat corticosteroid-induced mania and psychosis and outlines treatment options.

Symptoms

Corticosteroid-induced psychosis represents a spectrum of psychological changes that can occur at any time during treatment. Mild-to-moderate symptoms include agitation, anxiety, insomnia, irritability, and restlessness, whereas severe symptoms include mania, depression, and psychosis.[3] Case reports reveal:

- mania and hypomania in 35% of patients with corticosteroid-induced psychosis
- acute psychotic disorder in 24% of patients, with hallucinations reported in one-half of these cases
- depression, which is more common with chronic corticosteroid therapy, in 28% of patients.[4]

Delirium and cognitive deficits also have been reported, although these symptoms generally subside with corticosteroid reduction or withdrawal.[4,5]

Psychiatric symptoms often develop after 4 days of corticosteroid therapy, although they can occur late in therapy or after treatment ends.[6] Delirium often resolves within a few days, psychosis within 7 days, and mania within 2 to 3 weeks, whereas depression can last for more than 3 weeks.[4] A 3-level grading system can gauge severity of corticosteroid-induced psychosis; grade 2 or 3 warrants treatment (***Table 1***).[4]

Risk factors

High corticosteroid dose is the primary risk factor for psychosis. The Boston Collaborative Drug Surveillance Program reported that among individuals taking prednisone, psychiatric disturbances are seen in:

- 1.3% of patients taking <40 mg/d
- 4.6% of patients taking 40 to 80 mg/d
- 18.4% of patients taking >80 mg/d.[7]

However, the corticosteroid dosage does not predict onset, severity, type of reaction, or duration.[3,7] Female patients are at higher risk of corticosteroid-induced psychosis, even after one controls for medical conditions diagnosed more often in women, such as SLE and rheumatoid arthritis.[3] Previous episodes of corticosteroid-induced psychosis, history of psychiatric illness, and age are not associated with corticosteroid-induced psychosis.[3]

Treatment

Management includes tapering corticosteroids, with or without adding medications to treat the acute state. Decreasing corticosteroids to the lowest dose possible—<40 mg/d—or gradually discontinuing therapy to prevent triggering adrenal insufficiency may improve psychotic symptoms and avoids the risk of adverse effects from adjunctive medications.

Psychopharmacologic treatment may be necessary, depending on the severity of psychosis or the underlying disease, particularly if corticosteroids cannot be tapered or discontinued. Evidence from open-label trials (***Table 2***)[8-12] and case reports indicates that psychotic symptoms could be prevented and treated with off-label antipsychotics, mood stabilizers, and anticonvulsants.

Consider your patient's underlying medical condition when selecting psychotropics. For example, try to avoid prescribing:

- antipsychotics to patients with cardiac conduction abnormalities

Table 2

Corticosteroid-induced psychosis: Adjunctive treatment studies

Medication and source	Patient population	Results
Olanzapine (Brown et al, 2005[8])	12 outpatients experiencing manic or mixed symptoms received olanzapine, mean 8.5 mg/d	Reductions on YMRS, HRSD, and BPRS with no change in extrapyramidal symptom side-effect scales, weight, or glucose measurements
Lithium (Falk et al, 1979[9])	27 patients diagnosed with multiple sclerosis or retrobulbar neuritis treated with corticotropin received lithium	38% of lithium patients developed psychiatric symptoms compared with 62% of controls
Phenytoin (Brown et al, 2005[10])	39 patients received phenytoin, 300 mg/d, or placebo at prednisone therapy initiation	Patients receiving phenytoin reported a smaller increase in ACT score compared with controls
Levetiracetam (Brown et al, 2007[11])	30 outpatients receiving corticosteroids randomized to levetiracetam, 1500 mg/d, or placebo	No significant change in HRSD, YMRS, or ACT scores
Lamotrigine (Brown et al, 2003[12])	5 patients on chronic corticosteroid treatment received open-label lamotrigine, mean dose 340 mg/d	No significant difference in HRSD, YMRS, or the depression subscale of the Internal State Scale

ACT: Internal State Scale Activation subscale; BPRS: Brief Psychiatric Rating Scale; HRSD: Hamilton Rating Scale for Depression; YMRS: Young Mania Rating Scale

• lithium to patients who need diuretic or angiotensin-converting enzyme inhibitor therapy or those with underlying renal insufficiency.

When appropriate, collaborate with the provider who prescribed the corticosteroids because tapering or discontinuation might not be possible.

Antipsychotics

Open-label trial. Olanzapine reduced psychiatric symptoms in a 5-week, open-label trial of 12 outpatients experiencing manic or mixed symptoms secondary to corticosteroids.[8] At baseline, patients had a mean score of 15.25 on the Young Mania Rating Scale (YMRS) on a mean prednisone dose of 14.4 mg/d. After receiving olanzapine, 2.5 mg/d titrated to a maximum 20 mg/d (mean 8.5 mg/d), subjects demonstrated a significant decrease on the YMRS (P = .002), Hamilton Rating Scale for Depression (HRSD) (P = .005), and Brief Psychiatric Rating Scale (BPRS) (P = .006) with no change in extrapyramidal side-effect scales, weight, or glucose measurements.

Case reports. Among antipsychotics, olanzapine has the greatest number of case reports for treating corticosteroid-induced psychosis, mainly for mania.[13-15] Benefit with olanzapine was demonstrated at dosages from 2.5 to 15 mg/d and improvement occurred within days to weeks. Several patients remained symptom-free with olanzapine and continued corticosteroid therapy.

Other reports describe benefit with risperidone for a variety of psychiatric symptoms—including hypomania, hallucinations, and delusions—associated with corticosteroid therapy.[16-19] Risperidone dosing ranged from 1 to 4 mg/d, and symptoms improved within days to weeks.

One case report describes quetiapine for the treatment of corticosteroid-induced mania.[20] The patient's symptoms improved within 10 hours of initiating quetiapine, 25 mg/d, and YMRS score decreased from 31 before therapy to 5 at discharge. No case reports exist for ziprasidone or aripiprazole.

Mood stabilizers

Cohort study. One study suggests that lithium may be effective for preventing

continued on page 67

Clinical Point

Benefit with olanzapine was seen at dosages from 2.5 to 15 mg/d, and improvement occurred within days to weeks

continued from page 63

and treating corticosteroid-induced psychosis. A retrospective cohort study examined records of patients diagnosed with multiple sclerosis or retrobulbar neuritis who were treated with corticotropin.[9] Corticotropin has been reported to cause psychotic reactions in up to 11% of patients through a mechanism thought to mirror corticosteroid-induced psychosis (***Box, page 68***).[21-23] Psychiatric symptoms developed in 38% of patients treated with lithium compared with 62% of controls. No patients pretreated with lithium maintained at 0.8 to 1.2 mEq/L reported mood disturbances or psychotic reactions.

Case reports. Among mood stabilizers, lithium has the greatest number of case reports on its use for prevention and treatment of corticosteroid-induced psychosis. In these reports, patients pretreated with lithium did not experience a relapse of psychosis related to chronic corticosteroid therapy.[24-27] Case reports also describe benefit with valproic acid and carbamazepine.[28-30]

Anticonvulsants

Trials. In a 1-week trial, 39 patients without previous psychiatric diagnosis or psychotropic use were randomly assigned to phenytoin, 300 mg/d, or placebo as prednisone therapy was initiated.[10] Compared with placebo, the phenytoin group reported a smaller increase on the Internal State Scale Activation subscale (ACT), a self-report measure of mania symptom severity. No significant differences were found on the YMRS or HRSD scales. Based on the ACT scale finding, the authors concluded that phenytoin attenuated manic or hypomanic effects of prednisone.

A study of levetiracetam, 1500 mg/d, showed no significant change in HRSD, YMRS, or ACT scores from baseline to end point for either levetiracetam or placebo.[11]

A 12-week, open-label trial of lamotrigine in 5 patients receiving corticosteroids continuously for 6 months showed no significant difference in mood changes as measured by the HRSD, YMRS, or the depression subscale of the Internal State Scale.[12]

Case reports show that lamotrigine and gabapentin have been used effectively to prevent manic symptoms in patients receiving corticosteroid therapy.[31,32]

Treatment recommendations

Establishing a treatment algorithm for corticosteroid-induced psychosis is hampered by the lack of prospective placebo-controlled trials. However, most case

Corticosteroid psychosis

Clinical Point

Consider adding a low-dose atypical antipsychotic to corticosteroid therapy; lithium may be second-line with precautions

reports describe benefit from administrating atypical antipsychotics and lithium.

Consider adding a low-dose atypical antipsychotic with which case studies report quick symptom resolution and patients tolerating these agents. Monitor carefully for metabolic changes, a risk associated with antipsychotics and corticosteroids. Lithium would be a good second-line therapy because of its demonstrated benefit for both prophylaxis and treatment of psychiatric disturbances.

Lithium use can be complicated and dangerous in patients who have underlying diseases associated with renal dysfunction, however—such as nephrotic syndromes and SLE—leading some authors to suggest valproic acid or carbamazepine instead.[33] In addition, corticosteroid-induced changes in sodium balance could increase the risk of lithium toxicity.[34]

When patients cannot tolerate atypical antipsychotics or lithium, case reports support the use of valproic acid, carbamazepine, lamotrigine, or gabapentin to treat symptoms of corticosteroid-induced psychosis.

Box

Pathophysiology of corticosteroid-induced psychosis

How corticosteroids cause psychosis is not well understood. One theory suggests that corticosteroids act at steroid-specific receptors and suppress filtering by the hippocampus of irrelevant stimuli.[21]

Supporting this theory of hippocampal change, a study of 17 patients receiving corticosteroid therapy for >6 months found decreased hippocampal volume compared with a control group.[22] Other possible causes include suppressed hypothalamus-pituitary axis and enhanced dopamine neurotransmission.[23]

Related Resources

- Cerullo MA. Expect psychiatric side effects from corticosteroid use in the elderly. Geriatrics. 2008;63(1):15-18.
- Sirois F. Steroid psychosis: a review. Gen Hosp Psychiatry. 2003;25:27-33.
- Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis, and management. Drug Safety. 2000;22(2):111-122.
- Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006;81(10):1361-1367.

Drug Brand Names

Aripiprazole • Abilify
Carbamazepine • Tegretol
Corticotropin • Acthar
Gabapentin • Neurontin
Lamotrigine • Lamictal
Levetiracetam • Keppra
Lithium • Lithobid, Eskalith, others
Methylprednisolone • Medrol
Olanzapine • Zyprexa
Phenytoin • Dilantin
Prednisone • Deltasone
Quetiapine • Seroquel
Risperidone • Risperdal
Valproic acid • Depakene
Ziprasidone • Geodon

Disclosure

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

References

1. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes: a report of 14 cases and a review of the literature. J Affect Disord. 1983;5:319-332.
2. Bolanos SH, Khan DA, Hanczyc M, et al. Assessment of mood states in patients receiving long-term corticosteroid therapy and in controls with patient-rated and clinician-rated scales. Ann Allergy Asthma Immunol. 2004;92:500-505.
3. Warrington TP, Bostwick JM. Psychiatric adverse effect of corticosteroids. Mayo Clin Proc. 2006;81(10):1361-1367.
4. Sirois F. Steroid psychosis: a review. Gen Hosp Psychiatry. 2003;25:27-33.
5. Newcomer JW, Craft S, Hershey T, et al. Glucocorticoid-induced impairments in declarative memory performance in adult humans. J Neurosci. 1991;14:2047-2053.
6. Hall RC, Popkin MK, Stickney SK, et al. Presentation of the steroid induced psychosis. J Nerv Ment Dis. 1979;167:229-236.
7. The Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol Ther. 1972;13:694-698.
8. Brown ES, Chamberlain W, Dhanani N, et al. An open-label trial of olanzapine for corticosteroid-induced mood symptoms. J Affect Disord. 2004;83:277-281.

Bottom Line

First-line treatment for corticosteroid-induced psychosis is to taper or discontinue corticosteroid therapy. If this is not possible because of comorbid disease or severe psychosis, consider adding low-dose atypical antipsychotics in patients with manic or hypomanic symptoms. Consider mood stabilizers such as lithium or valproic acid as second-line treatment in patients with normal renal function.

9. Falk WE, Mahnke MW, Poskanzer DC. Lithium prophylaxis of corticotropin-induced psychosis. JAMA. 1979;241:1011-1012.
10. Brown ES, Stuard G, Liggin JD, et al. Effect of phenytoin on mood and declarative memory during prescription corticosteroid therapy. Bio Psychiatry. 2005;57:543-548.
11. Brown ES, Frol AB, Khan DA, et al. Impact of levetiracetam on mood and cognition during prednisone therapy. Eur Psychiatry. 2007;22:448-452.
12. Brown ES, Frol A, Bobadilla L, et al. Effect of lamotrigine on mood and cognition in patients receiving chronic exogenous corticosteroids. Psychosomatics. 2003;44(3):204-208.
13. Goldman LS, Goveas J. Olanzapine treatment of corticosteroid-induced mood disorders. Psychosomatics. 2002;43(6):495-497.
14. Brown ES, Khan DA, Suppes T. Treatment of corticosteroid-induced mood changes with olanzapine. Am J Psychiatry. 1999;156(6):968.
15. Budur K, Pozuelo L. Olanzapine for corticosteroid-induced mood disorders. Psychosomatics. 2003;44(4):353.
16. Herguner S, Bilge I, Yavuz Yilmaz A, et al. Steroid-induced psychosis in an adolescent: treatment and prophylaxis with risperidone. Turk J Pediatr. 2006;48:244-247.
17. DeSilva CC, Nurse MC, Vokey K. Steroid-induced psychosis treated with risperidone. Can J Psychiatry. 2002;47:388-389.
18. Kato O, Misawa H. Steroid-induced psychosis treated with valproic acid and risperidone in a patient with systemic lupus erythematosus. Prim Care Companion J Clin Psychiatry. 2005;7(6):312.
19. Kramer TM, Cottingham EM. Risperidone in the treatment of steroid-induced psychosis. J Child Adolec Psychopharmacol. 1999;9:315-316.
20. Siddiqui Z, Ramaswamy S, Petty F. Quetiapine therapy for coricosteroid-induced mania. Can J Psychiatry. 2005;50(1):77-78.
21. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;21(1):25-31.
22. Brown ES, Woolston DJ, Frol A, et al. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol Psychiatry. 2004;55:538-545.
23. Schatzberg AF, Rothschild AJ, Langlais PJ, et al. A corticosteroid/dopamine hypothesis for psychotic depression and related states. J Psychiat Res.1985;19(1):57-64.
24. Sabet-Sharghi F, Hutzler JC. Prophylaxis of steroid-induced psychiatric syndromes. Psychosomatics. 1990;31(1):113-114.
25. Siegal FP. Lithium for steroid-induced psychosis. N Engl J Med. 1978;299(3):155-156.
26. Goggans FC, Weisberg LJ, Koran LM. Lithium prophylaxis of prednisone psychosis: a case report. J Clin Psychiatry. 1983;44(3):111-112.
27. Merrill W. Case 35-1998: use of lithium to prevent cortico-steroid-induced mania. N Engl J Med. 1999;340(14):1123.
28. Himelhoch S, Haller E. Extreme mood lability associated with systemic lupus erythematosus and stroke successfully treated with valproic acid. J Clin Psychopharmacol. 1996;16(6):469-470.
29. Kahn D, Stevenson E, Douglas CJ. Effect of sodium valproate in three patients with organic brain syndromes. Am J Psychiatry. 1998;145(8):1010-1011.
30. Abbas A, Styra R. Valproate prophylaxis against steroid induced psychosis. Can J Psychiatry. 1994;39(3):188-189.
31. Preda A, Fazeli A, McKay BG, et al. Lamotrigine as prophylaxis against steroid-induced mania. J Clin Psychiatry. 1999;60(10):708-709.
32. Ginsberg DL, Sussman N. Gabapentin as prophylaxis against corticosteroid-induced mania. Can J Psychiatry. 2001;44:455-456.
33. Wada K, Yamada N, Yamauchi Y, et al. Carbamazepine treatment of corticosteroid-induced mood disorder. J Affect Disord. 2001;65:315-317.
34. Saklad S. Management of corticosteroid-induced psychosis with lithium. Clin Pharm. 1987;6(3):186.