

Effects of Glucocorticoids on Mood, Memory, and the Hippocampus

Treatment and Preventive Therapy

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Corticosteroids, such as prednisone and dexamethasone, are commonly prescribed medications that suppress the immune system and decrease inflammation. Common side effects of long-term treatment with corticosteroids include weight gain, osteoporosis, and diabetes mellitus. This paper reviews the literature on psychiatric and cognitive changes during corticosteroid therapy and potential treatment options. Hypomania and mania are the most common mood changes during acute corticosteroid therapy, although depression has also been reported. However, depression is reported to be more common than mania during long-term treatment with corticosteroids. A decline in declarative and working memory is also reported during corticosteroid therapy. Corticosteroids are associated with changes in the temporal lobe, detected by structural, functional, and spectroscopic imaging. The mood and cognitive symptoms are dose dependent and frequently occur during the first few weeks of therapy. Other risk factors are not well characterized. Controlled trials suggest that lithium and phenytoin can prevent mood symptoms associated with corticosteroids. Lamotrigine and memantine also have been shown to reverse, at least partially, the declarative memory effects of corticosteroids. Uncontrolled trials suggest that antipsychotics, anti-seizure medications, and perhaps some antidepressants can also be useful for normalizing mood changes associated with corticosteroids. Thus, both the symptoms and treatment response are similar to those of bipolar disorder. Moreover, corticosteroid-induced mood and cognitive alterations have been shown to be reversible with dose reduction or discontinuation of treatment.

Key words: corticosteroid; depression; psychosis; mania; memory; glutamate

Introduction

For the past 60 years, prescription corticosteroids have been used in the treatment of medical conditions, such as asthma, allergies, arthritis, and dermatological diseases, and to prevent transplant rejection. These medications' systemic side effects, such as diabetes, osteoporosis, infection, glaucoma, and cataracts,

are well documented.¹ However, the effects of these medications on the brain have not been extensively described.

Beginning shortly after their first use in the late 1940s, case reports of severe mood disturbances, psychosis, and even suicide associated with the use of corticosteroids began to appear in the literature.²⁻⁴ The current review will focus primarily on prospective or controlled studies. The interested reader is referred to several reviews of corticosteroid-induced psychiatric symptoms that provide a more detailed discussion of this older literature.⁵⁻⁸ Psychiatric disorders with prescription corticosteroids are classified as substance-induced mood disorders,

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psychotic disorders, or dementia or delirium in the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).⁹ This diagnostic category includes other prescription medications (e.g., interferon) as well as illicit drugs (e.g., cocaine) and require evidence by history, physical examination, or laboratory findings that the symptoms are etiologically related to the substance.

The study of the central nervous system (CNS) effects of corticosteroids is important for two reasons. First, these are very commonly prescribed medications. In the United Kingdom, 0.9% of adults in the General Practice Research Database are currently receiving corticosteroids.¹⁰ Similarly, data from a large health maintenance organization in the United States found that 1.0% of adult men and 1.2% of adult women receive at least 2000 mg of prednisone equivalents in a 12-month period.¹¹ Thus, millions of people are potentially at risk for developing psychiatric symptoms or cognitive disturbances from corticosteroids. Second, these medications provide a model system by which to explore the effects of stress and cortisol on the human brain. An extensive literature in animal models suggests that stress or corticosteroid administration is associated with changes in the hippocampus and other brain regions.^{12,13} However, research on the effects of prolonged stress or corticosteroid administration on the human brain is limited.

This review examines mood symptoms, psychosis, and cognitive changes, as well as neuroimaging and histological findings, in people treated with corticosteroids. Potential interventions that might prevent or reverse the effects of corticosteroids on the brain are also discussed.

Psychiatric Symptoms during Acute, High-Dose Corticosteroid Exposure

As discussed above, the early literature on psychiatric symptoms with corticosteroids consisted primarily of case reports. Lewis and Smith reviewed 79 of these case reports and

added 14 new case reports to the literature.¹⁴ These were primarily, but not exclusively, reports of symptoms during acute corticosteroid therapy (mean duration approximately 11 days). They reported that 40.5% of literature cases were primarily depressive in nature, 27.8% primarily manic, 7.6% mixed, 13.9% psychosis, and 10.1% delirium. However, in the 14 cases collected by the authors, 50% had manic symptoms and only 7% depression. A concern with case reports is publication bias in which the most severe symptoms, such as suicidal ideation and psychosis, are more likely to be reported than euphoria or hypomania.

Two prospective studies have examined psychiatric symptoms with short-term, high-dose corticosteroid therapy in clinical settings. Naber *et al.* used a semi-structured interview in 50 patients with ophthalmic disorders (i.e., retinitis and uveitis) initially free of psychiatric illness, receiving high dosages of corticosteroids (148 mg/day of prednisone equivalents initially) over an 8-day period.¹⁵ They found that 26% of the patients met diagnostic criteria, except for length of time of symptoms, for mania and 10% for depression during corticosteroid therapy. No psychotic symptoms were observed. In all cases, symptoms began within the first 3 days of therapy and continued throughout the 8 days of treatment.

Brown *et al.* examined a group of 60 asthma patients scheduled to receive prednisone "bursts."¹⁶ Among the 32 patients who returned for assessment, a mean of 4.6 ± 1.4 days after beginning prednisone therapy (mean initial dose 41.9 ± 7.8 mg/day) demonstrated statistically significant increases from base line on the Young Mania Rating Scale (YMRS) and activation subscale of the Internal State Scale (ISS-ACT) (clinician- and patient-rated measures of manic symptoms, respectively). No significant changes were observed on the Hamilton Rating Scale for Depression (HAM-D). Mean scores on assessment measures (with the exception of the HAM-D) showed a significant decrease, returning to baseline values at assessment a mean of

10.8 ± 2.3 days after discontinuing prednisone. Changes in mood did not correlate with changes in asthma symptom severity.

The studies by Naber *et al.*¹⁵ and Brown *et al.*¹⁶ suggest that manic symptoms are the most commonly observed response to acute therapy with relatively high doses of corticosteroids. The symptoms do not appear to be related to changes in symptoms of the medical illness and resolve following corticosteroid discontinuation.

Wolkowitz *et al.* examined the psychiatric side effects in a group of 12 healthy volunteers receiving 80 mg of prednisone daily for 5 days.¹⁷ Most subjects reported some symptoms, including depressed or elevated mood, irritability, lability, insomnia, increased energy, anxiety, or depersonalization, but no group mean changes in psychiatric rating scales could be demonstrated, perhaps due to the heterogeneity of symptoms.

Bender *et al.* found increased symptoms of anxiety and depression in 27 children with severe asthma (ages 8–16 years) given high (mean dose 62 mg/day) versus low doses (mean dose 3 mg/day) of prednisone for less than 14 days.¹⁸ Symptoms of mania were not assessed. These findings suggest that mood symptoms also occur in children receiving corticosteroids. The increase in depression may be in contrast to the manic symptomatology that was reported in adults. However, since only depression and anxiety, not mania, was assessed in these children, it is not possible to determine whether mixed manic and depressive symptoms developed while on high doses of corticosteroids.

Neurocognitive Symptoms and Neuroimaging during Acute, High-Dose Corticosteroid Exposure

The effects of corticosteroids on learning and memory in humans are substantiated by an extensive body of literature on the cognitive effects of corticosteroids in animals (see Lupien and McEwen¹³ for a review). These

data support a dose-dependent effect of corticosteroids on associative learning and spatial working memory, as well as long-term potentiation, indicating an effect of corticosteroids on the cellular processes involved in memory formation.

Human subjects also exhibit changes in cognition during corticosteroid exposure. Occasionally, cognitive impairment, consistent with dementia or delirium, has been reported in patients receiving prescription corticosteroids. Varney *et al.* reported on six adults who developed significant but reversible deficits in cognitive function, including attention, concentration, and verbal memory, while on 20–100 mg/day of prednisone.¹⁹ Wolkowitz *et al.* reported four cases of significant cognitive impairment following several weeks of treatment with high doses of corticosteroids.²⁰

Milder cognitive deficits have also been observed both in clinical samples and in healthy controls given corticosteroids.^{15,17,18,21–24} The most extensively reported cognitive changes involve declarative (verbal) memory assessed using instruments, such as word lists or paragraph recall. Declarative memory requires conscious recollection in contrast to reflexive/implicit memory, which is not dependent on conscious awareness. Much evidence supports declarative memory as a hippocampal-dependent process.^{25,26}

During acute, high-dose corticosteroid therapy, two studies reported changes in cognition in addition to the mood symptoms described above (Naber *et al.*¹⁵ in adults, and Bender *et al.*¹⁸ in children). Naber *et al.*¹⁵ reported a decline in declarative memory and some improvement in tasks not related to declarative memory (e.g., Trails A) following 8 days of corticosteroid therapy. Bender *et al.*¹⁸ reported a decline in declarative memory in children who were receiving high versus low doses of corticosteroids. Similarly, Keenan *et al.*²⁴ reported poorer performance on a paragraph recall test at weeks 1 and 12 in adults with systemic disease receiving prednisone therapy compared to untreated controls.

Numerous studies have examined memory in healthy control subjects given corticosteroids. Wolkowitz *et al.*²⁷ reported increased errors of omission on a verbal memory task in healthy controls given a single dose of 1 mg of dexamethasone or 5 days of prednisone at 80 mg/day. Newcomer *et al.* reported reductions in paragraph recall, a test of declarative memory, in controls given dexamethasone for 4 days as compared to placebo.²³ Seven days after the last dose of dexamethasone, the controls showed a return to normal performance on the memory test. Newcomer *et al.* later reported a reversible and dose-dependent impairment in declarative memory with high-dose hydrocortisone (160 mg/day = 40 mg prednisone equivalents) but not low-dose hydrocortisone (40 mg/day = 10 mg/day prednisone equivalents) administration.²² The findings from these studies suggest that a decline in declarative memory occurs quickly and is observed with either synthetic corticosteroids or hydrocortisone.

Working memory, the cognitive mechanism that allows for the storage and manipulation of a limited amount of information for a brief period of time, is related to dorsolateral prefrontal cortex functioning and has been shown, like declarative memory, to be sensitive to the effects of corticosteroids.²⁸⁻³⁰ Lupien *et al.* reported a decline in performance on a working memory task, but not a declarative memory task, in a group of 40 healthy controls 45 min after an intravenous (IV) infusion of hydrocortisone or placebo.²⁹ These findings suggest that working memory may be more sensitive than declarative memory to the very acute effects of corticosteroids. In addition, Young *et al.* reported that 10 days of hydrocortisone administration at 40 mg/day in healthy volunteers was associated with changes in spatial working memory.³⁰

Several studies have used functional imaging to examine the impact of corticosteroids on the human brain (Table 1). Ganguli *et al.* found that IV hydrocortisone infusion of 5 μ g/kg/min for 60 min (21 mg total for a 70 kg person)

was associated with increased regional cerebral activity in the right hippocampus but decreased regional cerebral activity in the left hippocampus of eight healthy controls.³¹ de Leon *et al.* reported that an IV hydrocortisone bolus (35 mg) reduced hippocampal glucose metabolism compared to placebo in elderly controls.³² de Quervain *et al.* used positron emission tomography (PET) imaging to examine task-related changes following administration of a single dose of cortisone (25 mg) or placebo to 14 healthy controls using a within-subject crossover design and showed that cortisone administration was associated with a significant reduction in task-related regional cerebral blood flow in the posterior medial temporal lobe.³³

Studies in patients with seizures also suggest a reduction in regional cerebral blood flow³⁴ and glucose metabolism³⁵ with corticosteroid administration. One of these studies included a control group of three patients without seizures who were given hydrocortisone 15mg/kg/day for 1 month.³⁴ These controls with cerebello-opsomyoclonic syndrome showed a decrease in mean cerebral blood flow following hydrocortisone therapy. Thus, the available data suggest that corticosteroid administration is associated with decreased regional cerebral blood flow or metabolism.

A postmortem analysis of patients receiving corticosteroids for 2 days to 4 months at the time of death found evidence of apoptosis, but not widespread neuronal loss or histological changes, in the hippocampus of three out of nine of the patients receiving exogenous corticosteroids and one out of 16 controls.^{36,37} Since exposure to corticosteroids was generally brief, this study does not address the effects of long-term exposure on the hippocampus.

Psychiatric Symptoms during Chronic Corticosteroid Exposure

In addition to the above described effects of short-term corticosteroid therapy,

TABLE 1. Neuroimaging Studies in Patients Taking Corticosteroids

Study	Sample	Design	Findings
Brown <i>et al.</i> , 2004 ⁵¹	17 patients	MRI on patients after mean 9 years on mean of 15 mg/day	↓ hippocampal volume, ↓ temporal lobe n-acetyl-aspartate in corticosteroid-treated patients
Okuno <i>et al.</i> , 1980 ⁴⁹	15 children with infantile spasms or Lennox syndrome	CT scans after 4 weeks of ACTH	11/15 (73%) with cerebral atrophy reversible 4 weeks after stopping ACTH
Bentson <i>et al.</i> , 1978 ⁴⁸	15 adults with autoimmune diseases	CT scans after 6 months to 5 years of corticosteroids	Cerebral atrophy that controlled with corticosteroids dose and was visible in 2/15 after stopping corticosteroids
Wilner <i>et al.</i> , 2002 ⁵⁰	37-year-old woman with heart transplant	MRI after 5 years of corticosteroids	Hippocampus atrophy
Ganguli <i>et al.</i> , 2002 ³¹	8 schizophrenia patients 8 healthy controls	PET after 60 min infusion of hydrocortisone (~21 mg)	↑ regional cerebral activity left hippocampus in schizophrenia ↓ regional cerebral activity left hippocampus controls
de Leon <i>et al.</i> , 1997 ³²	8 Alzheimer's patients 7 elderly controls	PET after 35 mg hydrocortisone	↓ hippocampus glucose metabolism health groups
de Quervain <i>et al.</i> , 2003 ³³	14 healthy controls	PET after 25 mg cortisone or placebo	Cortisone associated with ↓ task-related rCBF in medial temporal lobe
Brown <i>et al.</i> , 2008 ⁵²	15 patients on corticosteroids 13 controls	MRI in patients on long-term corticosteroids and controls	↓ amygdala volume in corticosteroid-treated patients compared to controls
Coluccia <i>et al.</i> , 2008 ⁵⁵	13 patients on chronic corticosteroids and 11 controls	Neurocognitive testing and MRI	Acute memory effects that resolved day after corticosteroid dose. No hippocampal volume differences

numerous studies indicate effects of chronic corticosteroid treatment. Bolanos *et al.*³⁸ conducted structured clinical interviews for the DSM-IV (SCID) on 20 patients receiving long-term corticosteroid therapy (mean of 9 mg/day for a mean of 11 years) and found that 55% had a lifetime corticosteroid-induced mood disorder (50% depressive, 5% manic) and 5% had a corticosteroid-induced anxiety disorder (panic). Scores on the HAM-D, BPRS, ISS-ACT (self-reported mania), ISS-Perceived Conflict (general symptoms), and ISS-Depression were higher, whereas ISS-Well-being scores were lower, and YMRS scores were similar in corticosteroid-treated patients

compared to 14 controls with similar medical conditions not taking corticosteroids.

Gift *et al.*³⁹ assessed symptoms of depression in 20 patients with chronic obstructive pulmonary disease, receiving 20–40 mg/day of prednisone in the hospital after receiving 2–5 mg/day prior to hospitalization for 30–74 days, and in a control group of 20 patients with similar respiratory symptom severity not receiving corticosteroids. The prednisone-treated group had significantly higher scores on the Beck Depression Inventory and the Depression Scale of the Brief Symptom Inventory than the controls. Manic symptoms were not assessed in this study.

These two studies suggest that depressive symptoms may be more common and severe than manic symptoms during long-term corticosteroid therapy at relatively low dosages. This is consistent with data in animals, suggesting that chronic corticosteroid administration may provide a model for depression.⁴⁰ However, self-rated, but not clinician-rated, manic symptoms were also elevated in the corticosteroid-treated group in the Bolanos *et al.* study,³⁸ and manic symptoms were not assessed by Gift *et al.*³⁹

Neurocognitive Symptoms and Neuroimaging during Chronic Corticosteroid Exposure

Animal data suggest that exposure to high levels of corticosteroids in stress paradigms or through corticosterone administration are associated with changes in the brain. Repeated restraint stress or daily injections of corticosterone for 21 days is associated with decreased numbers of dendritic branch points and reduced apical dendrite length in the rat hippocampus.^{41,42} Hippocampal changes are also reported in some,^{43–45} but not all,⁴⁶ studies in primates exposed to corticosteroids.

Several studies have examined cognition in humans receiving long-term corticosteroid therapy. Keenan *et al.*²⁴ reported decreased performance on a declarative memory task in 25 patients with systemic disease receiving a mean of 16.4 mg/day of prednisone therapy for at least 1 year compared to 25 untreated controls. Memory test performance was not related to prednisone dose or duration. Bermond *et al.* examined memory in a group of 52 patients with renal transplants receiving prednisone at a mean dose of 10.6 mg/day for a mean of 98 months and found below-average performance on some aspects of declarative memory that correlated with mean prednisone dose.⁴⁷

Early reports using computerized tomography suggested general brain atrophy during corticosteroid therapy (Table 1).^{48,49} More re-

cently, Wilner *et al.* reported hippocampal atrophy and impairment in cognitive tests after 5 years of corticosteroid therapy.⁵⁰ Brown *et al.* reported poorer performance on the Rey Auditory Verbal Learning Test (RAVLT; a measure of declarative memory), the Stroop Color Word Test (a measure of working memory), smaller hippocampal volume, and lower levels of temporal lobe N-acetyl aspartate (a marker of neuronal viability) in 17 asthma and arthritis patients receiving a mean of 15.2 mg/day of prednisone for a mean of 92 months compared to a control group of 15 patients with similar medical histories but minimal lifetime corticosteroid exposure (Table 1).⁵¹ A trend toward a significant correlation was found between current prednisone dose and right hippocampal volume. Atrophy of the right amygdala also correlated with duration of prednisone treatment in this patient sample compared to controls.⁵² A follow-up assessment was conducted in six of these corticosteroid-treated patients and six controls for a mean of 4 years after the initial assessment.⁵³ Psychiatric symptoms and neurocognitive function remained relatively stable over time, with the exception of depressive symptoms, which increased in the corticosteroid-treated patients.

Hajek *et al.* conducted neurocognitive testing in 14 patients for a mean of 6 days after starting corticosteroids with reassessment for a mean of 73 and 193 days later.⁵⁴ Magnetic resonance imaging (MRI) was also obtained in nine of the patients (Table 1). A trend toward a decrease in declarative memory performance and an improvement in attention and working memory was observed between the initial and day 73 assessments. No changes in hippocampal volume were found.

Coluccia *et al.* examined memory and hippocampal volume in 13 rheumatoid arthritis patients taking a mean of 7.5 mg/day of prednisone for a mean of 64 months and in 11 controls (Table 1).⁵⁵ Prior to a declarative memory task, the prednisone-treated patients received their usual dose of prednisone, and the controls received a 5 mg dose. Using a crossover

design, the next day, both groups either received prednisone or a placebo prior to the testing of retention and administration of a new list of words. Acute prednisone therapy was associated with a decline in delayed recall in both groups. However, chronic prednisone therapy (delayed recall after the chronically treated patients received placebo prior to recall testing) did not affect recall. Hippocampal volume did not differ between groups.

Taken together, the available literature suggests consistent findings of deficits in declarative memory with chronic corticosteroid use. The hippocampal volume data are mixed with one study showing differences and two studies finding no significant between-group differences. The study with positive findings examined patients on higher corticosteroid dosages and longer duration of treatment than the other studies. The findings of Coluccia *et al.*⁵⁵ and the correlation between memory and hippocampal volume with current corticosteroid dose suggest that the effects of corticosteroids on the hippocampus are due to acute rather than cumulative effects of the medications. If true, then the lack of change in hippocampal volume in the Hajek *et al.*⁵⁴ study may be a result of a decline in hippocampal volume that occurred during the approximately 6 days of corticosteroid exposure prior to the initial MRI. More research is needed to understand the timeframe and mechanism of the effects of corticosteroids on the human hippocampus.

Corticosteroid Abuse or Dependence

Case reports suggest that patients sometimes abuse corticosteroids. Like other potential substances of abuse, corticosteroids have been shown to produce, as discussed above, euphoric effects in some people and withdrawal symptoms upon discontinuation. Stoudemire *et al.* reported the case of a 40-year-old woman with chronic lung pulmonary disease who developed disorientation, disorganized speech, and fea-

tures of abuse, including dose escalation and even theft of corticosteroids.⁵⁶ Although abuse typically involves high-dose systemic corticosteroids, there is one report of abuse resulting in Cushingoid features with the use of dexamethasone nasal spray for the treatment of asthma.⁵⁷ Brown reported that eight out of 11 cases of corticosteroid abuse in the literature had a psychiatric history (particularly depressive symptoms) and four out of 11 had a history of drug or alcohol abuse or dependence.⁵⁸

Psychiatric Symptoms during Corticosteroid Withdrawal

Patients undergoing extended corticosteroid therapy frequently develop withdrawal symptoms that can include depression and fatigue, which are sometimes, but not always, associated with hypothalamic-pituitary-adrenal axis suppression.^{59,60} Other psychiatric symptoms reported during corticosteroid dose reduction or discontinuation include mania⁶¹ and delirium.^{62,63} Psychiatric disturbances during switches from systemic to inhaled corticosteroids in asthma patients are also reported.⁶⁴ Withdrawal-induced psychiatric symptoms have been shown to resolve with re-administration of corticosteroids.^{59,62}

Risk Factors for Corticosteroid-induced Psychiatric Symptoms

Corticosteroid Dose

Psychiatric side effects with corticosteroids have been shown to be dose dependent. The Boston Collaborative Drug Surveillance Program (BCDSP) examined psychiatric symptoms in 676 patients free of psychiatric disease prior to steroid treatment.⁶⁵ Severe psychiatric symptoms were uncommon (1.3%) at doses less than 40 mg of prednisone daily, but increased to 18.4% at doses above 80 mg of prednisone

daily, strongly suggesting that these symptoms are dose dependent. Olsen *et al.* found that mood change/emotional lability was the only systemic side effect that significantly correlated with mg/kg prednisone dose.⁶⁶

Gender

It is not clear whether gender is a risk factor for psychiatric symptoms during corticosteroid therapy. Ling *et al.* suggested that women are more likely to have psychiatric symptoms than men.⁸ Boye Nielsen *et al.* reported that 10% (all women) of a group of patients receiving corticosteroids for rheumatoid arthritis developed “mental disturbances.”⁶⁷ However, the preponderance of case studies involving women may be due to a greater prevalence in women of diseases that require corticosteroid therapy. Reports by Naber *et al.*¹⁵ and Hayreh and Watson⁶⁸ found no significant gender differences in psychiatric symptoms. Brown *et al.* reported that men had greater increases than women in a self-rating of depression, while no differences were found on a clinician-rated depression measure.¹⁶ Thus, based on the current data, it is not clear whether gender plays a role in vulnerability to psychiatric symptoms with corticosteroids.

Psychiatric Illness

Lewis and Fleminger studied 12 patients with psychiatric disorders treated with a mean of 2680 mg ACTH or 5560 mg cortisone over 5.5–7.5 weeks and observed little change in psychiatric symptoms.⁷ Brown *et al.* reported that lifetime depression or current HAM-D scores >15 were associated with improvement in mood during prednisone therapy, while three of six patients with post-traumatic stress disorder (PTSD) had increases in HAM-D scores of ≥ 17 points and two of six patients reported re-experiencing symptoms.¹⁶ Bremner *et al.* reported that patients with major depressive disorder (MDD)⁶⁹ or PTSD⁷⁰ were less sensitive to the acute deleterious effects of corticosteroids

on memory than controls. Thus, the available data do not support that a history of a psychiatric disorder is associated with the development of psychiatric symptoms during corticosteroid therapy.

Other Medications

Brown *et al.* reported that increases in manic symptoms and decreases in depressive symptoms during acute prednisone therapy were associated with the lifetime number of prior corticosteroid courses.¹⁶ In a study examining the effects of two prednisone exposures over a short period of time, Brown *et al.* reported no change in mood but a significant decline in some aspects of declarative memory in controls following 3 days of prednisone at 60 mg/day.²¹ However, when a second course of the same dose and duration of prednisone was administered 11 days later, an attenuated and nonsignificant change in declarative memory was observed. These findings suggest that for a period of time after corticosteroid exposure, the brain may be relatively less sensitive to the declarative memory effects of these medications. Kuhlmann and Wolf reported that women taking oral contraceptives were less sensitive to the effects of corticosteroids on declarative memory than controls.⁷¹

Treatment of Psychiatric and Cognitive Symptoms with Corticosteroids

Psychiatric and cognitive symptoms associated with corticosteroids generally resolve with medication discontinuation.^{14,16,18,23} Some patients, however, require chronic corticosteroid therapy necessitating the use of pharmacotherapy. The mechanism of psychiatric symptoms, such as mania, depression, and psychosis, with corticosteroids is not clear. However, prednisone administration is associated with decreases in cerebral spinal fluid levels of corticotropin, norepinephrine, beta-endorphin, beta-lipotropin, and somatostatin-like immunoreactivity.¹⁷ In animal models,

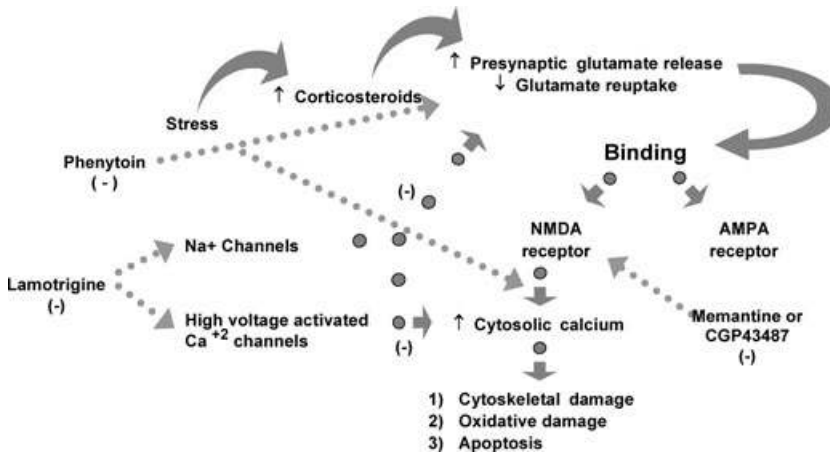


Figure 1. Proposed mechanism for attenuation of the effects of corticosteroids on hippocampal structure and functioning by agents that modulate glutamate.

corticosteroids are associated with increases in glutamate release.^{72–74} Interventions that decrease glutamate release,⁷⁵ act as antagonists at the NMDA receptor,⁷⁶ or enhance serotonin reuptake⁷⁷ prevent hippocampal changes with corticosteroids in animals (Fig. 1).

Relatively little data are available on the treatment or prevention of the CNS effects of corticosteroids in humans. To date, only five controlled intervention trials have been published on the treatment or prevention of corticosteroid-induced psychiatric symptoms or cognitive impairment (Table 2). In the earliest report, Falk *et al.* found that none of 27 patients given open-label lithium carbonate developed severe mood symptoms while receiving corticosteroids, whereas six of 44 patients (14%) not receiving lithium developed mania or depression with psychotic features.⁷⁸

Two more recent prevention trials have been reported in patients receiving short-term prednisone “bursts.” The glutamate release inhibitor and anti-seizure medication phenytoin was associated with a smaller increase than placebo in self-reported manic/hypomanic symptoms, with no differences in depressive symptoms or declarative memory, when initiated concurrently with prednisone at a mean dose of approximately 40 mg/day for approximately 7 days.⁷⁹ Levetiracetam is an anti-

seizure medication that shows neuroprotective properties in animal models of ischemia⁸⁰ and kainic acid-induced toxicity,⁸¹ and decreases in glutamate-induced excitotoxicity in an animal model of seizures.⁸² In a placebo-controlled trial of levetiracetam at 1500 mg/day started at the same time as prednisone (mean dose approximately 40 mg/day or approximately 7 days) for asthma, no significant between-group differences were observed in mood or cognition.⁸³

Two controlled trials have examined medications added to chronic corticosteroid therapy. The glutamate release inhibitor lamotrigine, titrated to 400 mg/day, or placebo was added for up to 24 weeks to prednisone at a mean dose of 14 mg/day for a mean of 65 months.^{83,84} Declarative memory performance, as assessed by the RAVLT, was in the mildly impaired range at base line and showed significantly greater increases in the lamotrigine group compared to the placebo group. Significant changes in hippocampal volume were not observed. Memantine is an NMDA receptor antagonist used for Alzheimer’s disease. A total of 17 patients receiving prescription prednisone at a mean dose of 8 mg/day for a mean of 98 months were given memantine and placebo, titrated to 20 mg/day for eight weeks in a randomized, blinded, crossover design with a

TABLE 2. Controlled Medication Treatment Trials in Patients Taking Corticosteroids

Study	Sample	Medication	Design	Findings
Falk <i>et al.</i> , 1979 ⁷⁸	71 pts with multiple sclerosis	Lithium (Li) 0.8–1.2 mEq/L	Nonrandomized Open-label Prevention	6/44 (14%) given corticotropin 80 U/day without Li developed mood disorder while 0/27 given Li had mood symptoms
Brown <i>et al.</i> , 2005 ⁷⁹	39 pts with allergy/ respiratory/ rheumatic dz	Phenytoin (PHN) 300 mg/day	Randomized Placebo-controlled Parallel-group Prevention	After ~7 days of prednisone (40 mg/d) PHN group had smaller ↑ in ACT (self-reported manic symptoms) but not on other mood or mania measures
Brown <i>et al.</i> , 2007 ⁸³	30 pts with asthma	Levetiracetam 1500 mg/day	Randomized Placebo-controlled Parallel-group	No difference in mood or cognition after ~7 days of prednisone (40 mg/d)
Brown <i>et al.</i> , 2008 ⁸⁴	28 pts with renal transplant, rheumatic dz	Lamotrigine (LAM) 400 mg/day	Randomized Placebo-controlled Parallel-group Treatment	Up to 24 weeks of LAM associated better declarative memory but no change in hippocampal routine in pts on prednisone (mean 14 mg/day, 65 months)
Brown <i>et al.</i> , 2008 ⁸⁵	20 pts with renal transplant, neuromuscular dz	Memantine (MEM) 20 mg/day	Randomized Placebo-controlled Parallel-group Treatment	8 weeks of MEM associated with improvement in memory in pts on prednisone (mean 8 mg/day, 98 months)

4-week washout period between medications.⁸⁵ Mean mania and depression scale scores were in the normal range, while declarative memory was in the low normal to mildly impaired range. Memantine was associated with a significantly greater change in the Hopkins Verbal Learning Test total words recalled and delayed recall compared to placebo. Changes in mood were not significant.

Several uncontrolled medication trials and numerous case reports and case series have been reported in corticosteroid-treated patients. Brown *et al.* gave lamotrigine, at a mean maximum dose of 340 mg/day, for 12 weeks to 10 patients on long-term corticosteroid therapy.⁸⁶ An analysis of the five completers revealed significant improvement in the RAVLT and Stroop tests and a trend toward significant

improvement in self-rated, but not clinician-rated, depressive symptoms.

Perhaps the most extensively investigated medication for corticosteroid-induced psychiatric symptoms in uncontrolled trials is olanzapine, with a case report,⁸⁷ a case series,⁸⁸ and small longitudinal trial⁸⁹ suggesting its efficacy. Based on case reports, risperidone,⁹⁰ quetiapine,⁹¹ and older antipsychotic “neuroleptics”^{14,92–94} may be useful for treating psychiatric symptoms due to corticosteroids. Case reports also suggest that valproate,^{95,96} carbamazepine,⁹⁶ gabapentin,⁹⁷ clonazepam,^{96,98} and lithium^{99,100} may be associated with improvement in psychiatric symptoms in these patients. A caveat with the use of phenytoin or carbamazepine is that these medications with extended use can induce the metabolism

of corticosteroids, potentially decreasing their efficacy.¹⁰¹

The limited available literature on the use of antidepressants in patients taking corticosteroids is mixed. Hall *et al.* found that tricyclic antidepressants (TCAs), given for depressive symptoms, were associated with increased agitation and psychosis in patients taking corticosteroids.¹⁰² Blazer *et al.* also reported that two patients who developed depression secondary to corticosteroid therapy showed minimal therapeutic response to TCAs.⁹³ However, a more recent report suggested that TCAs may be effective for depression during corticosteroid therapy.⁹⁶ Single case reports also suggest that the newer antidepressants sertraline,¹⁰³ fluoxetine,¹⁰⁴ and venlafaxine¹⁰⁵ are associated with improvement in corticosteroid-induced depressive symptoms. Similarly, Brown *et al.*, in an analysis of data from two clinical trials, did not find a worsening in mood symptoms when newer antidepressants were added to prednisone or when prednisone was added to newer antidepressants.¹⁰⁶

Conclusions

Corticosteroids appear to induce mood symptoms similar to those of bipolar disorder. Psychosis can also occur, but it generally occurs along with prominent mood symptoms. Corticosteroids also have negative effects on declarative and working memory. All of the CNS effects of corticosteroids appear to be dose dependent, but other risk factors are not well established. The most appropriate first line of treatment for these mood or cognitive symptoms is, when possible, dose reduction or discontinuation. Mood symptoms with corticosteroids seem to respond to medications that are effective for bipolar disorder. The effects of corticosteroids on memory seem to respond to the same classes of medications that attenuate the effects of corticosteroids on the hippocampus in animal models. Areas in need of further research include genetic factors in

CNS response to corticosteroids, reversibility of hippocampal atrophy with corticosteroid discontinuation, and human postmortem studies examining hippocampal histology following long-term corticosteroid administration.

Conflicts of Interest

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