

Adverse Consequences of Glucocorticoid Medication: Psychological, Cognitive, and Behavioral Effects

Lewis L. Judd, M.D.

Pamela J. Schettler, Ph.D.

E. Sherwood Brown, M.D., Ph.D.

Owen M. Wolkowitz, M.D.

Esther M. Sternberg, M.D.

Bruce G. Bender, Ph.D.

Karen Bulloch, Ph.D.

John A. Cidlowski, Ph.D.

E. Ronald de Kloet, Ph.D.

Laurence Fardet, M.D., Ph.D.

Marian Joëls, Ph.D.

Donald Y.M. Leung, M.D., Ph.D.

Bruce S. McEwen, Ph.D.

Benno Roozendaal, Ph.D.

Elisabeth F.C. Van Rossum, M.D., Ph.D.

Junyoung Ahn, B.S.

David W. Brown, M.D.

Aaron Plitt, B.A.

Gagandeep Singh, M.D.

Glucocorticoids are the most commonly prescribed anti-inflammatory/immunosuppressant medications worldwide. This article highlights the risk of clinically significant and sometimes severe psychological, cognitive, and behavioral disturbances that may be associated with glucocorticoid use, as well as ways to prevent and treat these disturbances. An illustrative case

vignette is presented describing a patient's experience of cycles of manic-like behavior and depression while on high-dosage prednisone, with long-term cognitive disorganization, vulnerability to stress, and personality changes. Severe neuropsychiatric consequences (including suicide, suicide attempt, psychosis, mania, depression, panic disorder, and delirium, confusion, or disorientation) have been reported to occur in 15.7 per 100 person-years at risk for all glucocorticoid courses, and 22.2 per 100 person-years at risk for first courses. The majority of patients experience less severe but distressing and possibly persistent changes in mood, cognition, memory, or behavior during glucocorticoid treatment or withdrawal. Although prediction of such effects is difficult, risks vary with age, gender, dosage, prior psychiatric history, and several biological markers. Key mechanisms thought to underlie these risk factors are briefly described. Recommendations are given for identifying individual risk factors and for monitoring and managing adverse neuropsychiatric effects of glucocorticoids.

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Glucocorticoids are a commonly prescribed class of medication used to suppress the immune system and decrease inflammation. Since their introduction in the 1950s, they have come into use as an effective treatment for a wide range of medical conditions, including back pain, allergies, rheumatic diseases, gastrointestinal disorders, ophthalmic conditions, dermatological conditions, asthma, chronic obstructive pulmonary disease, systemic lupus erythematosus, and cancer, as well as to prevent transplant rejection. In the United States alone, 44.3 million prescriptions for oral glucocorticoids are written annually (1).

Use of Glucocorticoids and Prevalence of Severe Neuropsychiatric Events in Adults

In the United Kingdom, the Health Improvement Network (THIN) database contains electronic medical records from

over 400 general practices. In this large patient population, Fardet et al. (2) found that 8.5% of patients age 18 or older who were in the system from 1989 through 2008 received any oral glucocorticoid prescription, including 2.3% who received long-term glucocorticoid treatment (lasting ≥ 3 months). Between 1989 and 2008, the prevalence of long-term oral glucocorticoid prescriptions at any given time rose 34%, from 0.59% to 0.79%.

Recent reviews of neuropsychiatric effects of glucocorticoids in clinical populations have been based largely on individual case or case-series reports (3, 4). In a case-series study of 80 consecutive patients completing their first lifetime glucocorticoid therapy (at a mean of 42 mg/day of prednisone for 3 months), 52.5% of patients developed one or more mood-related conditions (5). These included irritability (25.0%), euphoric hyperactivity (12.5%), anxiety or depression (11.3%), or a manic episode (3.8%). A major psychiatric disorder occurred soon after initiation of

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A patient experiences unexpected symptoms during treatment with prednisone after renal biopsy.

A married 50-year-old Caucasian woman began experiencing depression, intense fatigue, malaise, weight gain, and swelling of her lower extremities. She sought medical treatment and was found to have pedal edema, azotemia, and proteinuria. A renal biopsy showed acute focal and segmental glomerulosclerosis that was typical in its presentation. Because of the renal biopsy, the patient was started on a cycle of prednisone, beginning with 70 mg/day and tapering by 5 mg per week until the dosage was 10 mg/day. At 10 mg/day, the proteinuria returned, and the nephrologist decided to initiate another cycle of prednisone, with the same starting dosage and tapering schedule. Once again the proteinuria returned when the dosage reached 10 mg/day, and the patient underwent a third cycle of prednisone, with the same result. During this time, the patient was intensely anxious, and her nephrologist prescribed alprazolam in escalating doses up to 4 mg per day, which suppressed her anxiety. After the third course of prednisone failed to ameliorate the glomerulosclerosis, the patient was started on 100 mg/day of cyclophosphamide, to continue until her urine was free of protein. She was treated with cyclophosphamide for approximately 4 months, at which time she was free of proteinuria and was asymptomatic. She was discharged from treatment and has remained asymptomatic, with continued monitoring every 3 to 6 months.

Three days after starting the first prednisone cycle, the patient became, as she described it, “higher than a kite.” She recalls being unable to sleep, lacking impulse control, and being inappropriately humorous. Her mind was flooded with unrelated thoughts, and her thinking became so disorganized that she was unable to drive. She had marked memory problems and required multiple reminders, including some pinned to her clothes, for various responsibilities and appointments. Her physician had explained that she might become “hyperactive” during prednisone treatment, but she was not prepared for the magnitude and extent of the changes she experienced during in the first cycle, nor for the depression that occurred during the first taper period and those in the other two treatment cycles. When her depression became severe, she sought treatment on her own from a psychiatrist, who prescribed bupropion, which successfully treated the depression. Throughout the three treatment cycles, the patient’s thinking remained disorganized, with memory difficulties and memory loss. These symptoms persisted for approximately 12 months, diminishing over time to the point that she was able to return to work and begin driving again. The patient continues to report experiencing memory problems, some loss of cognitive clarity, and a greater vulnerability to overreacting to stress.

glucocorticoid therapy in six patients, five of whom required hospitalization. Fardet et al. (6) used the THIN database to analyze the incidence of five serious neuropsychiatric outcomes (depression, mania, panic disorder, suicide or suicide attempt, and delirium, confusion, or disorientation) during the first 3 months of a course of oral glucocorticoid treatment in 261,272 patients compared with an age- and gender-matched group with the same underlying medical condition but no glucocorticoid therapy. The overall incidence of these five outcomes was 15.7 per 100 person-years of glucocorticoid exposure for all glucocorticoid courses, with an incidence of 22.2 per 100 person-years at risk for first courses, 14.0 for second courses, and 11.7 for third or later courses. Table 1 presents the hazard ratio for onset of specific neuropsychiatric disorders for patients taking a first course of glucocorticoid compared with the matched unexposed population. Glucocorticoid treatment was associated with a sevenfold higher risk of suicide or serious suicide attempt and with markedly higher risks of the other severe neuropsychiatric conditions examined.

Effects of acute glucocorticoid treatment on mood have also been reported in smaller prospective studies of changes within patients (7, 8) or healthy volunteers (9), while effects of long-term glucocorticoid treatment on mood have emerged from studies of changes within patients (10) and between treated and untreated patients with comparable

illness severity (11). Numerous case studies have focused on the effects of acute glucocorticoid treatment on cognition, including difficulty with concentration, declarative memory, working memory, abstraction, and analysis (12, 13). Although generally thought to remit fully and quickly after glucocorticoid discontinuation (14), severe cognitive disturbances have occasionally been reported to persist for an extended period afterward (15). Cognitive impairments in patients have also been found in prospective studies of change associated with acute glucocorticoid treatment in children (16) and adults (7) and in longer-term treatment in adults (10), as well as studies of acutely (17) and chronically (18–20) treated patients compared with untreated patients with similar underlying illness severity. Cognitive effects of acute glucocorticoid treatment have been studied in medically and psychiatrically healthy adults (21), including in small double-blind placebo-controlled studies (22–27).

Neuropsychiatric effects during glucocorticoid discontinuation have also been reported from case studies (28). Again using THIN data, Fardet et al. (29) analyzed the incidence of five severe neuropsychiatric outcomes among 21,995 adult patients during withdrawal from 1 to 3 years of oral glucocorticoid therapy, counting only new episodes present during but not prior to withdrawal. Incidence rates per 100 person-years at risk during the withdrawal period were 11.1 (95% CI=10.0, 12.3) for depression; 3.9 (95% CI=3.3,

4.6) for delirium, confusion, or disorientation; 0.4 (95% CI=0.2, 0.7) for mania; 0.4 (95% CI=0.3, 0.7) for panic disorders; and 0.03 (95% CI=0.01, 0.20) for suicide or serious suicide attempt.

Risk Factors for Severe Neuropsychiatric Outcomes of Glucocorticoid Therapy

Fardet et al. (6) found that women were more likely than men to develop depression during initiation of oral glucocorticoid treatment, while men were more likely to develop mania or delirium, confusion, or disorientation. The risk of depression, mania, and delirium, confusion, or disorientation increased with age. Patients ages 18 to 50 had the highest risk of suicidal behavior, and those from 18 to 30 had the highest risk of panic disorder. Risk for depression, mania, panic disorder, or suicide attempt during glucocorticoid treatment increased for patients with past histories of these conditions, contrary to findings from some earlier studies (30). Experiencing a specific psychiatric disorder during glucocorticoid therapy increased the risk of recurrence of that disorder during subsequent glucocorticoid exposure. The risk for each of these disorders increased with the magnitude of the initial daily dose (in prednisone equivalents). This is consistent with an early case-series study of 676 patients showing an incidence of acute psychiatric reactions of 1.3% for patients receiving a daily equivalent of <40 mg of prednisone (low dosage), 4.6% for those receiving 41–80 mg/day (high dosage), and 18.4% in those receiving >80 mg/day (very high dosage) (31). In a large U.S. managed care population, the incidence of mood-related problems with long-term glucocorticoid use was also found to vary with dosage (32). Risk varies with timing. Early during a course of glucocorticoid treatment, especially a first course, patients often experience an idiosyncratic and unpredictable set of labile and manic or hypomanic symptoms unrelated to the underlying illness, whereas depressive symptoms are more common during long-term glucocorticoid treatment and are sometimes severe even at relatively low dosages (30, 33). Other risk factors are not well established at this time.

Risk factors identified for five severe psychiatric outcomes during withdrawal from long-term glucocorticoid therapy in an analysis of the THIN database (29) included an elevated risk of delirium, confusion, or disorientation for patients age 80 or older. A past history of depression or of delirium, confusion, or disorientation significantly increased the risk of that condition during withdrawal from long-term glucocorticoid therapy. Compared with short-acting glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone, deflazacort), long-acting glucocorticoids (e.g., dexamethasone, betamethasone, triamcinolone) significantly increased the risk for withdrawal-induced depression (hazard ratio=1.92; 95% CI=1.07, 3.46; $p=0.03$) and delirium, confusion, or disorientation (hazard ratio=4.96; 95% CI=2.60, 9.49; $p<0.001$).

TABLE 1. Risk of Five Severe Neuropsychiatric Outcomes Associated With First Course of Oral Glucocorticoid Prescription, Compared With Unexposed Adult Population Matched for Age, Gender, Practitioner, and Underlying Medical Condition^a

Neuropsychiatric Outcome	Adjusted Hazard Ratio	95% CI
Suicide or suicide attempt	6.89	4.52, 10.50
Delirium, confusion, or disorientation	5.14	4.54, 5.82
Mania (nonpsychotic)	4.35	3.67, 5.16
Depression (nonpsychotic)	1.83	1.72, 1.94
Panic disorder	1.45	1.15, 1.85
>5 neuropsychiatric outcomes	2.26	2.15, 2.37

^a Data From Fardet et al. (6), analysis of records for adult patients in the U.K. Health Improvement Network (THIN) medical database for the period 1989–2008. The overall estimates of incidence rates of five severe neuropsychiatric outcomes of oral glucocorticoid therapy are low because the authors did not analyze psychotic bipolar disorder or depression, generalized anxiety disorder, or other severe neuropsychiatric outcomes.

Mechanisms of Neuropsychiatric Effects

The main endogenous glucocorticoid, cortisol, plays a vital role in regulating glucose metabolism, inflammation, immune activity, and a wide range of homeostatic functions linked to the stress response. It also has important effects on emotional arousal, memory, and cognition, as well as on essential aspects of fetal development and aging. Cortisol is the end product of the hypothalamic-pituitary-adrenal (HPA) axis: Stress causes hypothalamic secretion of corticotropin-releasing factor, which stimulates the release of corticotropin from the anterior pituitary and the subsequent release of cortisol (hydrocortisone) from the adrenal glands. Within cells, cortisol facilitates or inhibits the expression of genes, with a U-shaped dose relationship (34, 35), and also has rapid nongenomic effects, which in turn provide feedback to the hypothalamus (36–40). These actions are mediated by two distinct receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). MRs are important for appraisal processes and the onset of the stress reaction, while GRs terminate the stress response and promote recovery, memory, and adaptation. A balance between GRs and MRs in the brain and body is crucial for homeostasis and health. Synthetic glucocorticoids used in clinical treatment preferentially activate pituitary GRs while causing profound suppression of adrenal cortisol secretion, depleting the body and brain of endogenous cortisol (12, 41, 42). Hence, synthetic glucocorticoids can still activate glucocorticoids in the brain while depleting cortisol from MRs. Extreme imbalance between GRs and MRs caused by exogenous glucocorticoids may underlie cognitive impairment, disturbed emotions, and other central dysregulation experienced by many individuals during glucocorticoid therapy (43).

At prolonged high dosages, glucocorticoids impair brain function in several ways. In animal models, glucocorticoids have been shown to decrease branching of dendrites and sprouting of axons in some brain regions, impairing recovery from various forms of neuronal damage (44–46). In

addition, glucocorticoids decrease glucose availability in the hippocampus, decrease neurotrophic factors in the hippocampus and neocortex, significantly diminish postnatal neurogenesis (47–52), and attenuate the synaptic strengthening that is essential for memory formation (38).

Impact on Mood

Although widely studied, the exact nature of the relationship of cortisol to depression remains unclear (12). High levels of cortisol and glucocorticoid resistance at the level of the pituitary and brain GRs are commonly observed. High cortisol levels inhibit brain-derived neurotrophic factor (BDNF), which is important for maintaining neural architecture in key brain regions such as the hippocampus and prefrontal cortex. Low BDNF levels in these areas may contribute to the development of depression and anxiety (53).

Impact on Memory, Cognition, and Behavior

Glucocorticoid effects on concentration, recall, abstraction, and analysis (sometimes referred to as “steroid dementia” when extreme and protracted) may be due partly to dysfunction in neural circuits in the hippocampus and the prefrontal cortex (12, 54), both of which contain high concentrations of MRs and GRs (44). Working memory is dependent on the prefrontal cortex and is involved in temporary storage of information necessary to carry out cognitive tasks like learning and reasoning (55, 56). Declarative memory, which is involved in explicit recall of verbal information, facts, and events, is dependent on the hippocampus (57, 58). Deficits in these functions can be attributed to the effect of prolonged glucocorticoid exposure on GRs or MRs in the hippocampus, reduction of hippocampal volume (59), or elevated glutamate accumulation in that area (60). Declarative memory impairment has also been associated with reduced blood flow in the medial temporal lobe during glucocorticoid therapy (21).

In healthy subjects, acute glucocorticoid administration is associated with functional changes in several brain regions: decreased activity in the left hippocampus (61), reduced hippocampal glucose metabolism (48), and reduced cerebral blood flow in the posterior medial temporal lobe (21). In patients with asthma or arthritis, long-term glucocorticoid exposure is associated with smaller hippocampal volume and lower levels of temporal lobe *N*-acetylaspartate (a marker of neuronal viability) compared with patients with the same conditions but with minimal lifetime glucocorticoid exposure (19). Atrophy of the right amygdala, which is important for regulation of mood and anxiety, was correlated with duration of prednisone treatment in this sample (62).

Recommendations for Glucocorticoid Prescribers and Patients

Although our focus here is on their adverse neuropsychiatric effects, glucocorticoids have revolutionized the

treatment of many medical conditions, and they are sometimes the only effective treatment available for severe and life-threatening illnesses. It should be noted, too, that many patients experience none of the side effects described here. That said, glucocorticoids in any form—oral, topical, inhaled, or parenteral—have the potential to disrupt HPA axis function and should be prescribed only if there is no effective non-glucocorticoid treatment for the medical condition (63). In one study, HPA axis dysfunction occurred in two-thirds of 143 asthmatic children treated with inhaled corticosteroids; in one-third of those affected, adrenal suppression persisted after central function recovered (64). The more potent topical glucocorticoids can also suppress the HPA axis (65). If glucocorticoid treatment is required, the safest and most effective one should be used based on current evidence-based guidelines for the patient’s age group, medical condition, and risk factors. Some concomitant medications also impose special requirements (66).

Educating patients about possible side effects and the need to report them is essential (67). Patients have individual levels of susceptibility to severe neuropsychiatric effects of glucocorticoid therapy, which can vary over time and stem from genetic and background factors at all levels

of glucocorticoid regulation. Patients under age 6 (34) and the elderly (18) appear to be at greater risk for cognitive and memory disturbances. The risk for adverse neuropsychiatric effects may be elevated based on an individual’s

past psychiatric history or response to previous courses of glucocorticoid treatment (4, 29), although the data have not always supported such an association (30). While gender, age, dosage, and duration of treatment influence risk, it is not currently possible to predict which patients will experience adverse neuropsychiatric effects during a given course of glucocorticoid therapy. Therefore, all patients should be considered to be at risk and should be monitored during glucocorticoid treatment and withdrawal, and for some time afterward, for signs of changes in mood, memory, thinking, or behavior.

The most appropriate first-line treatment for severe glucocorticoid-induced neuropsychiatric adverse events is dosage reduction or discontinuation. Recommended taper schedules need to be followed, especially after long-term glucocorticoid treatment. Patients need to be closely monitored for signs of new or increased depression or delirium or confusion during this time. If these occur, the patient should be checked for adrenocortical insufficiency, which can be resolved by readministering or increasing the dosage of the glucocorticoid (29). When severe problems with mood, memory, cognition, or behavior occur during glucocorticoid treatment or withdrawal, the prescribing physician should consider consulting with or referring the patient to a knowledgeable psychiatrist or

Educating patients about possible side effects and the need to report them is essential.

a psychiatrist experienced in treating patients with these problems.

Preliminary evidence about medications that may help prevent or treat glucocorticoid-induced neuropsychiatric symptoms comes from case studies, a limited number of clinical trials, and animal studies. These studies point to several recommendations.

Glucocorticoid-induced mania or mixed manic symptoms appear to respond to lithium carbonate (4), olanzapine (68), or phenytoin (69). Sodium valproate has been shown to reverse manic-like symptoms rapidly while allowing glucocorticoid treatment to continue (70). Glucocorticoid-induced depressive symptoms appear to improve with the use of selective serotonin reuptake inhibitors, such as sertraline, fluoxetine, venlafaxine, and low-dosage fluvoxamine, as well as with lithium alone (4), but not tricyclic antidepressants (71). With any indication of underlying bipolarity, mood stabilizers (e.g., lithium, valproate, carbamazepine, lamotrigine) should be used instead of antidepressants, to prevent switch into manic or mixed dysphoric states (72). Glucocorticoid-induced psychotic depression has been shown to be responsive to ECT (4). Glucocorticoid-induced psychosis may be prevented or resolved with atypical antipsychotics alone (4, 30) or with lithium (4, 73), while glucocorticoid-induced delirium appears to respond to haloperidol or atypical antipsychotics (4). Glucocorticoid-induced memory problems in patients have been reduced by prophylactic administration of lamotrigine (74, 75) and by the NMDA receptor antagonist memantine (76). The beta-blocker propranolol has been found to block glucocorticoid-induced memory retrieval deficits in healthy subjects (77).

Close monitoring should be an especially high priority, and evidence-based prophylactic treatment should be considered for patients with a recent history of mood or cognitive disorder. Prophylactic treatment should also be considered for patients with medical conditions such as systemic lupus erythematosus (3), multiple sclerosis (78), and other neurological disorders (79) that are frequently characterized by comorbid mood or cognitive disturbance, since these conditions may increase the risk for new onsets or exacerbations of such problems during glucocorticoid treatment or withdrawal.

Summary and Conclusions

While glucocorticoids are a valuable and sometimes life-saving treatment for many conditions, population data show that their use, particularly in large dosages or for extended periods, is accompanied by a substantial risk of severe adverse neuropsychiatric effects. In this article we have provided recent and compelling data on the prevalence of this risk during glucocorticoid initiation and withdrawal, and we have summarized the key mechanisms by which glucocorticoids are currently believed to be capable of altering mood, memory, cognition, and behavior. Prescribing

physicians and their patients need to operate in close partnership to balance the risks and benefits of initiating glucocorticoid treatment and use the latest evidence-based strategies to minimize, recognize, and treat severe adverse neuropsychiatric effects of glucocorticoids.

Received Sept. 24, 2013; revision received Feb. 7, 2014; accepted Feb. 14, 2014 (doi: 10.1176/appi.ajp.2014.13091264). From the Department of Psychiatry, University of California, San Diego, La Jolla; the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas; the Department of Psychiatry, University of California, San Francisco; the Arizona Center for Integrative Medicine, College of Medicine, University of Arizona, Tucson; the Department of Pediatrics, National Jewish Medical and Research Center, Denver; the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology and Laboratory of Cell Physiology and Immunology, Rockefeller University, New York; the Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, Research Triangle Park, N.C.; the Leiden/Amsterdam Center for Drug Research, Medical Pharmacology, Leiden University, Leiden, the Netherlands; Assistance Publique-Hôpitaux de Paris, University Pierre and Marie Curie, Department of Internal Medicine, Hôpital Saint-Antoine, Paris, France; the Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center, Utrecht, the Netherlands; Division of Pediatric Allergy and Immunology, National Jewish Medical and Research Center, Denver; Anatomy Section, Department of Neuroscience, University Medical Center, Groningen, the Netherlands; and the Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands. Address correspondence to Dr. Judd (ljudd@ucsd.edu).

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Clinical Guidance: Treating Psychiatric Effects of Glucocorticoids

Tapered discontinuation or dosage reduction is the first-line treatment for severe glucocorticoid-induced psychological, behavioral, or cognitive disorders—such as mania, depression, panic disorder, suicidal behavior, or delirium or confusion. Patients should be monitored for depression and cognitive problems during the taper, caution Judd et al. In addition, glucocorticoid-induced mania and depression can be treated with lithium and SSRI antidepressants, respectively. Glucocorticoid-induced delirium appears to respond to haloperidol or atypical antipsychotics. Prophylactic lamotrigine can reduce memory problems, and prophylactic treatment should also be considered for patients with neurological disorders involving mood or cognitive disturbance. Greater risk of glucocorticoid-induced neuropsychiatric problems is associated with higher dosage, long-term treatment, greater patient age, and past history of a neuropsychiatric disorder during glucocorticoid treatment.