J Neurooncol (2012) 109:439–447
DOI 10.1007/s11060-012-0919-z

TOPIC REVIEW

Steroid psychosis: a review for neurosurgeons

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Received: 21 March 2012 / Accepted: 19 June 2012 / Published online: 5 July 2012
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Abstract Steroids are beneficial in neurological illness, but have many serious side effects. Having observed several patients with severe steroid psychoses, which greatly prolonged their hospitalizations, the authors sought to improve understanding of this entity. A literature review was conducted. The incidence of severe psychiatric symptoms was estimated in a meta-analysis of 2,555 patients to be 5.7 % and the incidence of any psychiatric symptoms was 18.6 % in patients receiving >80 mg/day of prednisone (12 mg/day dexamethasone). Dose is not predictive of time of onset, severity, type, or duration of symptoms. Symptoms can develop rapidly following exposure to even low doses and with oral, epidural, or intra-articular administration. Glucocorticoid effects on the brain fall into three categories: genomic, non-genomic, and neurotrophic/neurotoxic and can be permanent. Excessive glucocorticoid exposure may result in decreased production of endogenous neurosteroid molecules, resulting in unopposed glucocorticoid effects. Treatment includes early recognition, steroid withdrawal when appropriate, reduction in stimulation, and medication. Atypical antipsychotics like olanzapine and risperidone may cause fewer dystonic reactions and extrapyramidal symptoms than typical antipsychotics like haloperidol, and therefore, are often recommended as first line treatment. Steroids are powerful medications with many undesirable side effects. They should be used with caution. More research is needed on their effects on the human central nervous system.

Keywords Dexamethasone · Neurosurgery · Psychosis · Side effects · Steroids

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Introduction

Steroids are frequently used in neurosurgical practice. They have been employed in the treatment of vasogenic edema associated with brain tumors, spinal cord injury, aseptic meningitis, bacterial meningitis, aneurysmal subarachnoid hemorrhage, inflammatory radiculitis, and spinal pain. Further, steroids are often routinely given in the operating room to prevent brain swelling, nausea, etc. Dexamethasone is the most commonly used steroid in neuro-oncology because of its potency (27 times as potent as cortisol per milligram), strong anti-inflammatory activity (30 times that of cortisol), and minimal mineralocorticoid activity (near zero compared to cortisol, see UpToDate for a summary of relative steroid effects [1]). Other steroids with different properties may also be used. Methylprednisolone has been used in trials in patients with spinal cord injury [2], hydrocortisone in pituitary surgery and pituitary replacement therapy [3], and fludrocortisone may be used in fluid and electrolyte disturbances [4]. Time release forms of methylprednisolone and triamcinolone are also used for epidural injections [5].

Their use is so ubiquitous within the field of neurosurgery that it is easy to forget that they are potent medications with numerous side effects. These side-effects include hypertension, hyperglycemia, acne, hair loss, insomnia, immuno-suppression, interference with wound healing, gastric ulceration, weight gain, and aseptic necrosis of the

Table 1 Recommended key articles on steroid psychosis

References	Topic
Boston Collaborative Drug Surveillance Program [1]	Report by the Boston Collaborative Drug Surveillance Program among 718 patients receiving prednisone
Lewis and Smith [42]	Review of 14 previously unreported cases of steroid-induced psychiatric syndromes, 79 cases from the literature and 29 studies of the clinical efficacy of steroids in various medical illnesses
Braunig et al. [89]	A letter to the editor of *Biol Psychiatry* detailing suicide risk after long- or short term administration of glucocorticoids (corticosteroid-induced psychosis)
Sapolsky [79]	A review of the cellular and molecular mechanisms of glucocorticoids on the hippocampus
Warrington and Bostwick [6]	A review of approaches to identifying and managing corticosteroid-induced psychiatric syndromes based on type of symptoms and anticipated duration of corticosteroid treatment
Strous et al. [56]	A review of neurosteroids (role in many psychiatric disorders)
Seeman et al. [87]	The role of dopamine pathways in psychosis
Wolkowitz et al. [12]	A review of mechanisms of steroid activity in the brain

femoral head (see Table 1 in Warrington and Bostwick [6]). Additionally, steroids may cause behavioral aberration ranging from mild disorientation to frank psychosis, leading to the potential for patient injury [7] or even to the arrest of affected patients [8]. Having observed multiple patients experience steroid psychosis, which greatly prolonged their hospitalizations, a review of this topic was undertaken. We searched the United States National Library of Medicine PubMed database using the search terms: "steroid" AND "psychosis", "steroid" AND "delirium", "steroid" AND "mood disorder", AND "neurosteroids". Articles in peer reviewed journals available through the Oregon Health & Sciences University library system were reviewed and where appropriate and non-redundant, included in this review. A similar search for "steroid psychosis" AND "brain tumor", "glioma", OR "meningioma" did not return any references. See Table 1 for a summary of some important articles.

Case report

A 68-year-old man with no previous personal or family history of psychiatric disease developed a slowly progressive left hemiparesis and left hemisensory deficit. Magnetic resonance imaging revealed a large right central parasagittal mass with surrounding edema consistent with a meningioma. He was started on dexamethasone 4 mg bid and scheduled for surgery approximately 2 weeks later. When the patient presented for surgery, the family reported some new irritability and confusion. For this reason, and following uncomplicated resection of the mass, his dexamethasone dose was not increased. Post-surgery, the man was floridly psychotic. He was unable to sleep, confused, disoriented, and combative. He pulled out his intravenous and arterial lines and his Foley catheter. He was aggressive toward caregivers. He was loquacious and would expound indefinitely on any topic suggested to him by conversation in his room. He perseverated on the idea of already being dead. On the recommendation of a psychiatric consultant, he was started on quetiapine 12.5 mg bid without obvious benefit. Dexamethasone was tapered over 1 week. Within 5 days of steroid cessation, the patient had returned to his baseline personality. Hospitalization amounted to 17 days, most of which was related to the patients psychosis care and not recovery from surgery.

Steroid psychosis

In Harvey Cushing's descriptions of the syndrome now bearing his name, he observed "fits of irritability (alternating) with fits of depression" [9]. In one later report, 83 % of patients with Cushing syndrome met strict diagnostic criteria for an affective disorder [10]. Replacement glucocorticoids became available in 1950 [11] and side effects were soon noted [12]. Reports of major affective side effects began to appear in the early 1950s [13, 14] when steroid side effects were reported to include symptoms such as impairment of memory, concentration, and attention, hypomania, depression, irritability, anxiety, insomnia, fatigue, and overt psychosis [15–19]. Hypomania was more commonly found initially, but depressive symptoms became more common as treatment continued [20]. Wada et al. [21], described 18 patients among 2,069 at risk by virtue of exogenous steroid administration (0.9 %) who met DSM-IV criteria [22] for steroid-induced mood disorder (15) or psychosis (3).

It was noted that psychiatric symptoms in Cushing syndrome correlated with cortisol levels [23, 24] and improved as cortisol levels fell [25]. There are, however, reports of persisting cognitive decline even after normalization of steroid levels or discontinuation of exogenous steroids [26]. It has also recently been recognized that

psychiatric improvement may be fluctuating, delayed, or incomplete [27], possibly due to permanent changes in the central nervous system [27–30]. The first use of the term steroid dementia is credited to Varney et al. [31] who described 6 patients from a group of 1,500 patients (0.4 %) on long term steroid treatment who displayed disturbances of memory, attention, and occupational performance, and who had measurable declines in IQ scores. Symptoms largely remitted 3–11 months after discontinuing steroids in the 4 patients who did not display psychotic symptoms, but did not fully resolve in 2 patients who did suffer from psychosis. In a controlled trial in children, temporary memory disturbances were noted in the 6–8 h period after corticosteroid administration in asthmatic children [32].

Many reports of psychosis in patients with Cushing syndrome can be found in the literature [33, 34]. Steroid psychosis constitutes a variable constellation of symptoms, not all psychotic, and includes delirium, confusion, insomnia, emotional lability, depression, mania, sensory flooding, and suicide ideation [6, 12, 16, 35]. This terminology has been criticized as too non-specific and some prefer using DSM-IV [22] terminology such as mood disorder, delirium, or substance-induced psychotic disorder [35]. The incidence of psychosis with administration of exogenous steroids also appears to be dose related. The Boston Collaborative Drug Surveillance Program reported that the incidence of psychiatric symptoms was 18.6 % in patients receiving >80 mg/day of prednisone, 4.6 % in patients receiving 41–80 mg/day, and 1.3 % in those receiving <40 mg/day [15]. This would correspond to doses of dexamethasone, the most commonly used steroid in neurosurgery, of >12, 6–12, and <6 mg/day. However, dose does not seem predictive of time of onset, severity, type, or duration of symptoms [6, 13, 14]. Symptoms can develop rapidly following exposure to even low doses of steroids [36]. Symptoms have been reported with oral administration, epidural administration [8], or intra-articular injections [37, 38].

There is enormous variation in susceptibility to these effects between individuals and within individuals over time [12]. It was long ago suggested that there may be a predisposition to steroid-induced psychiatric symptoms due to pretreatment personality factors [39, 40] or a potentiation of usual stress responses [41]. The incidence of severe psychiatric symptoms is quite variable, but was estimated in a meta-analysis of 2,555 patients from 13 uncontrolled series to be about 5.7 % [42]. Patients who have experienced a previous psychiatric reaction to steroids may be at higher risk for recurrence with psychotic features [43, 44], but this has not been confirmed in some reports [16, 45]. A history of previous psychiatric illness was thought to be a risk factor at one point [40, 46, 47], but subsequent studies indicate that this does not necessarily predict a susceptibility to steroid-induced psychiatric symptoms [19, 48–50]. Females may have a slightly higher risk of steroid-induced psychiatric symptoms, even after correcting for a higher incidence of steroid requiring medical conditions among women [51]. Symptoms may occur at any time after initiating or even after cessation of steroid treatment, but most develop in the first days or weeks of treatment [16, 42].

Mechanisms

The effects of dexamethasone and other glucocorticoids are likely complex and diverse. Neuronal cell death in the amygdala [52], alterations in cortical dendritic spines [53], and changes in level of nerve growth factor (NGF) expression in the septal nuclei [54] are but a few of the changes attributed to glucocorticoids. Glucocorticoid effects on the brain are thought to fall into three categories: genomic, non-genomic, and neurotrophic/neurotoxic [12]. Genomic effects result from alteration of gene expression and thereby protein synthesis, and therefore take hours to days to occur. These account for the majority of glucocorticoid effects, especially for exogenous steroid molecules.

Non-genomic effects are mediated by direct action at cell surface receptors and occur in seconds to minutes. There is now increasing evidence that steroids affect the surface of cells and alter ion permeability and the release of neurohormones and neurotransmitters [55]. Cell surface receptors may respond both to exogenous and to endogenous steroid molecules. The brain is now thought to be capable of synthesizing endogenous steroid molecules [56]. These molecules are synthesized within the central nervous system from cholesterol or from circulating steroid molecules [57]. Neurosteroid synthesis occurs within or outside of the mitochondria of several cell types, including neurons, oligodendrocytes, astrocytes, and Schwann cells [56, 58]. Neurosteroids include pregnenolone, pregnenolone sulfate, progesterone, dehydroepiandrosterone (DHEA), DHEA sulfate, tetrahydro-deoxycorticosterone, and allopregnanolone [12, 56]. In contrast to the putative site of action of exogenous steroids on genomic expression, these neurosteroids, in addition to some genomic effects, perhaps at the progesterone receptor [59], may influence neuronal excitability and receptor activity via membrane-bound ligand gated ion channel receptors, particularly at the gamma-aminobutyric acid A receptor [GABA (A)-R], but also at *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, glycine, serotonin, nicotinic acetylcholine, and sigma type-1 receptors (see Table 1 in Strous et al. [56]) [56, 59–61]. For example, DHEA-S, the most abundant steroid molecule in the human body, exerts potent inhibitory

effects at gaba-ergic receptors [56] and DHEA protects hippocampal neurons from glutamate toxicity [62, 63], suggesting that DHEA/DHEA-S may have protective effects in cerebral ischemia [56]. Many neurosteroids bind the GABA-A receptor with affinities equal to or much higher than benzodiazepines and barbiturates [59], suggesting a strong role for neurosteroids in anxiolytic and anxiogenic activity, including post-traumatic stress disorder [56]. Neurosteroids may have roles in development, neuro-protection, gender differences, sleep, the effects of alcohol, eating disorders, and in psychiatric disease [56].

Excessive glucocorticoid exposure may result in decreased production of neurosteroid molecules, resulting in unopposed glucocorticoid effects [12]. Neurosteroid molecules may interact with cortisol in complex ways. For example, DHEA may have anti-glucocorticoid effects [62] and the ratio of cortisol to DHEA may correlate with some psychiatric symptoms [64]. Age related declines in DHEA and DHEA-S may make the brain more sensitive to circulating cortisol activity [65], although the aging nervous system does appear to remain responsive to the protective effects of steroids [66], interestingly, in contrast to haloperidol, a typical antipsychotic, increases in some neurosteroid levels are seen with treatment with the so-called atypical antipsychotic medications clozapine and olanzapine [56].

Neurotrophic or neurotoxic effects may also be exerted by glucocorticoids, depending upon concentration and duration of exposure [12]. At normal physiologic levels, glucocorticoids permissively sustain the viability of cells in the dentate gyrus [67–71]. High or prolonged exposure to supra-physiologic doses, glucocorticoids can decrease pyramidal cell dendritic branching and axonal sprouting, impair recovery from damage, and potentiate ischemic and convulsive neuronal damage [12, 68, 72–74]. In animal models, chronic exposure to steroids results in dendritic atrophy in hippocampal CA3 neurons and in pyramidal cell loss [75]. In some cases of less severe stress, these changes appeared to be reversible. Similarly, humans with Cushing syndrome have hippocampal volume loss, which may be reversible if the disease remits [75]. While changes in dendrites may be reversible, neural cell death may not be [76]. Glucocorticoids have also been shown to decrease hippocampal glucose utilization and insulin signaling [77], in turn rendering neurons vulnerable to excitotoxic amino acids, calcium toxicity, and free radical damage [12, 71, 78]. This cascade can lead to proteolysis of the cytoskeletal protein spectrin and accumulation of abnormally phosphorylated tau microtubule protein [79]. Glucocorticoid toxicity also leads to decreased hippocampal and neocortical expression of neurotrophic factors, diminishing neurogenesis and impairing the response to brain damage [12].

Reversible deficits in declarative memory are common in normal volunteers given brief courses of steroids [80]. Because of the prominent memory disturbances, the neocortex and hippocampus are thought to be involved in steroid related cognitive impairment [18, 81]. These areas known to contain large numbers of glucocorticoid receptors [71] and cortisol does cross the blood brain barrier [71, 78]. Sapolsky [76, 79] has put forth the hypothesis that excessive exposure to steroids due to exogenous administration or because of chronic stress results in the down-regulation of glucocorticoid receptors in hippocampal neurons. Subsequent glucocorticoid resistance may result in altered neurotransmitter levels, such as decreased serotonin activity and increased dopaminergic activity, which might contribute to psychiatric symptoms [12, 82].

Dexamethasone is actively excluded from the brain at low doses, but not the pituitary gland [83]. It does not, at low doses, therefore, replace endogenous cortisol but rather administration may actually lead to decreased glucocorticoid receptor activity in the brain [84]. This can lead to lowered serotonergic activity and increased dopaminergic activity, both potentially linked to psychotic symptoms. There is some evidence that dexamethasone may have a higher risk of adverse psychiatric effects than other corticosteroids [85].

In rats given a single intraperitoneal dose of dexamethasone, significant increases in dopamine (DA) levels were seen in the hypothalamus and nucleus accumbens of the dexamethasone treated rats when compared with saline treated rats [86]. There was no significant effect of dexamethasone on DA levels in frontal or striatal brain areas. In the dexamethasone treated rats, a significant increase in serotonin (5-HT) was observed in the hypothalamus; a significant decrease in 5-HT was observed in the frontal cortex. Animal models of psychosis from a wide array of causes, including steroid exposure (but also illicit drugs, brain injury, ethanol, medial temporal lesions, etc.), strikingly all lead to dopamine super-sensitivity and increase in the high affinity states of dopamine D2 receptors (D2 high) by 200–400 % [87].

Treatment

Management algorithms for steroid-induced psychiatric symptoms are based on case reports and a few small series only [6]. Reducing environmental stimulation may be of benefit [6]. Asking patients and families about psychiatric symptoms is important, as patients may be reluctant to reveal these symptoms [6, 88]. Assessment for suicide risk may be appropriate for some patients [42]. Braunig et al. [89] found that among 150 patients with steroid psychosis, 26 had suicidality, 15 had suicide ideation, 8 had attempted suicide, and 3 had succeeded in ending their lives. If discontinuing steroids is acceptable, delirium may improve

within a few days, psychosis within a week or 2, and depression, mania, or mixed affective states within 6 weeks [6]. It should be noted that in rare cases, steroid withdrawal can precipitate mania [90] or delirium [91].

For patients who cannot stop steroids or for whom a taper is necessary, pharmacotherapy may be of benefit. A number of different agents have been tried with some benefit, including lithium [92–97], chlorpromazine [98], valproic acid [99–101], gabapentin [102], carbamazepine [103], lamotrigine [104], fluoxetine [105], sertraline [106, 107], venlafaxine [108], typical antipsychotics like haloperidol or phenothiazines [103, 109–111], and atypical psychotics such as olanzapine or risperidone [102, 112–114].

In a prophylactic trial of lithium in patients receiving corticotrophin for multiple sclerosis, none of the 27 patients treated with lithium developed psychiatric symptoms, but in an historical control group of 44 identically treated patients, 6 (14 %) became psychotic [94]. Serum lithium levels were targeted to the 0.8 to 1.2 meq/L range. One patient who had to withdraw from ACTH treatment 4 times because of psychotic reactions was able to tolerate the medication while on lithium. Lithium has a narrow therapeutic index and must be monitored closely to prevent side effects such as ataxia, blurred vision, and tremor [48, 94], all of which could be mistaken for neurological problems related to a neurosurgical illness. Lithium toxicity can also be increased by alterations in serum sodium level [115], a definite risk in patients with brain pathology, which can lead to disturbances in sodium balance.

The mechanism of action of lithium is not yet clearly known, but it seems to have both neurotrophic and neuroprotective effects in various diseases and stressors, and against glutamate excitotoxicity [116]. The benefits of lithium are slow in onset and not immediately reversed when it is discontinued, suggesting alterations in gene expression and signaling pathways are involved in its actions [116]. Inhibition of activated glycogen synthase kinase 3 (GSK-3), an enzyme the activity of which is involved in the pathophysiology of many neurodegenerative diseases, seems to be fundamental to the beneficial effects of lithium [116, 117]. Glutamate mediated excitotoxicity seems to be reduced both by effects on calcium influx mediated by NMDA receptors and by altered phosphorylation of the receptor itself [116]. Lithium may also induce expression of the anti-apoptotic protein Bcl-2 [118], brain derived neurotrophic factor (BDNF) [119], vascular endothelial growth factor (VEGF) [116], and heat shock proteins [116]. Blockade of BDNF activity prevents lithium's neuroprotective effects [116]. Lithium has also been shown to prevent the impairment of neuronal progenitor cell proliferation induced by glutamate and by steroids [120]. Neurosteroids may be involved in the activity of lithium [121]. Patients receiving lithium for treatment of bipolar disorder show less gray matter volume loss [122] and higher *N*-acetyl-aspartate (NAA) levels than controls [123].

While some reports have asserted benefit from tricyclic antidepressants such as doxepin [92, 124], imipramine [125], and amitriptyline [103], or with fluoxetine [105], other reports have noted exacerbation of symptoms with these agents and recommend they not be used [103, 124]. A review of treatment options from 1992 [126] found that low doses of neuroleptics led to improvement in 24 of 29 patients (83 %), but only a third had responded within 3 days, 60 % within 1 week, and 80 % by 2 weeks, a long period of time for hospitalized neurosurgical patients requiring intensive care unit (ICU) care or close supervision. More recently, olanzapine was found to be effective in 11 of 12 outpatients with steroid-induced manic symptoms [112]. Risperidone has been reported to be useful in 3 children with steroid psychosis [127] and also by other reports [114]. So called atypical antipsychotics like olanzapine and risperidone may cause fewer dystonic reactions and extrapyramidal symptoms than typical antipsychotics like haloperidol, and therefore, are often recommended as first line treatment [6]. The theoretical basis for use of risperidone comes from its putative mechanism of action of 5HT2 antagonism and blockade of the dopamine D2 receptor [128, 129].

For completeness, it should be noted that intrinsic steroid activity such as in Cushing's disease presents other opportunities to block steroid effects. Wolkowitz et al. [12] proposed 12 sites at which the problems associated with excessive glucocorticoid activity could be ameliorated (see Fig. 2 Wolkowitz et al. [12]). In Cushing's disease, pharmacologic lowering of cortisol levels or blockade of glucocorticoid receptors has been utilized in the treatment of major depression. In a review of 11 studies, 67 % of patients showed a meaningful antidepressant response [130]. A recent Cochrane review also noted improvements in non-psychotic depression with mifepristone, ketoconazole, and metyrapone, but based upon current evidence could state only that such treatment was promising but unproven [131]. It has been postulated that anti-glucocorticoid treatment exerts its beneficial effect by increasing serotonin sensitivity [132] or by increasing levels of neurally active steroids such as tetrahydro-11-deoxycortisol and tetrahydro-deoxycortisone rather than by decreasing cortisol levels [133] (see above discussion on neurosteroids).

Conclusions

Steroid psychosis is a variable and unpredictable event occurring in about 5.7 % of patients with elevated endogenous steroid levels or with exposure to exogenous steroids. The risk of psychosis is likely to be dose related, but

dose is not predictive of time of onset, severity, type, or duration of symptoms. Patients who have experienced a previous psychiatric reaction to steroids may be at higher risk for recurrence with psychotic features. A history of previous psychiatric illness does not necessarily predict a susceptibility to steroid-induced psychiatric symptoms. Females may have a slightly higher risk of steroid-induced psychiatric symptoms. Asking patients about the presence of psychiatric symptoms is important, as some patients may be reluctant to report them at a time when intervention might avoid a psychotic episode. Assessment of suicide risk should be undertaken in patients experiencing steroid related psychiatric symptoms.

Treatment options include cessation or tapering of steroids and dampening of environmental stimulation. Atypical antipsychotic agents such as olanzapine and risperidone are currently recommended as first line pharmacotherapy. With current information, tricyclic antidepressants should be avoided in patients with steroid-induced psychiatric symptoms. Lithium prophylaxis can be considered in patients at risk who will require prolonged courses of high dose steroids, but toxicity may limit the widespread us of lithium in neurosurgical patients. Further research into the role of neurosteroids in brain function may open new avenues for avoidance and treatment of steroid psychosis.

Steroids may exert severe and long lasting toxic effects on the human brain. The prolonged or repeated use of high doses of exogenous steroids, whether orally, intravenously, or epidurally, should not be undertaken without careful consideration of the potential harm this may cause.

Acknowledgments The authors thank Shirley McCartney, Ph.D., for professional assistance with the manuscript.

Conflict of interest None.

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