Corticosteroids are widely used in modern medicine but can result in troubling psychiatric side-effects. Physicians and other medical professionals should be aware of the potential for these side-effects, possible means of prevention, and efficacious treatments. Herein, we review adult case report data published during the past quarter-century on adverse corticosteroid-induced psychiatric effects, and present a case of corticosteroid-induced psychotic depression. PubMed and PsychLit databases were searched using the terms ‘corticosteroids’, ‘steroids’, and the generic names of corticosteroid medications with terms for psychiatric symptoms or syndromes, including psychosis, mania, hypomania, depression, apathy, anxiety, panic, depersonalization, delirium, confusion, hallucinations, delusions, paranoia, cognitive impairment and dementia. Fifty-five cases and a number of clinical trials investigating the incidence and treatment of these psychiatric symptoms and syndromes were identified. Data on incidence, drug dose, risk factors, course of illness and treatment (when present) were tabulated. We conclude that the cumulative data indicate that psychiatric complications of corticosteroid treatment are not rare and range from clinically significant anxiety and insomnia, to severe mood and psychotic disorders, delirium and dementia. While tapering or discontinuation of the corticosteroid treatment may remedy these adverse side-effects, psychotropic medications are often required because of the medical necessity of the corticosteroid or the severity of the psychiatric symptom. Further studies are needed to better understand the deleterious psychiatric effects associated with corticosteroids.

Key words: corticosteroids, delirium, mood, anxiety, psychosis.
aggressive behavior\textsuperscript{21} (including attempted murder\textsuperscript{22}), insomnia and agitation with clear consciousness, depersonalization; and, isolated cognitive impairments (impaired attention, concentration, memory and word-finding difficulties).\textsuperscript{14,17,23–26} In addition, the existence of a reversible, corticosteroid-induced dementia has been confirmed.\textsuperscript{27–30} Rarely, corticosteroids have been abused for their euphoria-producing effects, producing drug dependency.\textsuperscript{31–33} The term ‘psychosis’ has been variably applied to many of these clinical presentations, without distinguishing, for example, mania or psychotic depression from delirium.

Corticosteroid-induced cognitive deficits in the absence of psychotic symptoms commonly involve declarative or verbal memory.\textsuperscript{34–40} Similar reversible deficits in declarative memory have been reported in Cushing’s disease and are greater in more severe cases.\textsuperscript{41–45} suggesting that excess endogenous and exogenous corticosteroids produce similar cognitive impairment. Reversible cognitive deficits and mood symptoms have been reported in healthy control subjects after administration of prednisone,\textsuperscript{40} dexamethasone,\textsuperscript{47,48} and cortisol.\textsuperscript{38} By contrast, a small \((n = 10)\) double-blind, placebo-controlled, crossover-design study utilizing prednisone 0.5 mg/kg/day in SLE patients with mild symptoms who had not received corticosteroids for at least 6 months demonstrated beneficial effects on cognition, mood and SLE symptoms.\textsuperscript{44}

In older patients, corticosteroid-induced dementia has been misdiagnosed as early Alzheimer’s disease and can occur in patients who have not experienced a steroid psychosis and are free of mood symptoms.\textsuperscript{45} Deficits occur in memory, attention, concentration, and mental speed and efficiency, and in severe cases, formal IQ is substantially reduced.\textsuperscript{28,45} Occupational performance is diminished, but the patients do not appear ‘manifestly demented, amnestic, or disoriented, or... toxic or intoxicated’ (p. 372).\textsuperscript{45}

**INCIDENCE OF PSYCHIATRIC SYMPTOMS AND SYNDROMES**

Almost 40 years ago, The Boston Collaborative Drug Surveillance Program\textsuperscript{46} reported ‘psychiatric reactions’ in 1.3\% of 463 patients treated with 40 mg/day or less of prednisone, 4.6\% of 175 patients dosed with 41–80 mg/day, and 18.4\% of 38 patients receiving doses higher than 80 mg/day. A decade later, Lewis and Smith\textsuperscript{12} reported a weighted average 5.7\% incidence of severe psychiatric symptoms across 13 studies involving 2555 patients treated with corticosteroids. A subsequent review by Steiffel et al.\textsuperscript{6} of major psychiatric symptoms in cancer patients treated with high-dose corticosteroids noted a 5–10\% incidence. In contrast to patients with other medical conditions, cancer patients seemed more likely to develop delirium rather than affective syndromes, and these authors postulated that this difference may arise from the patients’ frequent medical complications, from the co-administration of narcotics, and from the neurological effects of the cancers themselves. Nishimura et al.,\textsuperscript{47} reviewing 139 treatment episodes in 135 patients with SLE but without current overt central nervous system manifestations, observed 14 cases (10.1\%) of new-onset DSM-IV disorders, primarily manic episodes \((n = 9, 6.5\%)\).

In the older literature, psychotic symptoms were reported in 58\% of the 55 cases reviewed by Ling et al.\textsuperscript{14} Nearly 72\% of their 55 cases included mood symptoms. In the review by Lewis and Smith,\textsuperscript{12} ‘disturbances in reality testing’ were reported in 71\% of the 79 cases (which included 44 of the 55 cases from the review of Ling et al.\textsuperscript{14}), but only 14\% (11/79) had ‘a psychotic disorder without evidence of significant mood changes or features of a delirium.’ Depression was present in 32/79 (40.5\%), mania in 22/79 (27.8\%), a mixed state in 6/79 (7.6\%) and delirium in 8/79 (10\%) of the sample. A review by Sirois\textsuperscript{48} reporting on steroid ‘psychosis’ published between 1970 and 1983, before publication of the current edition of the American Psychiatric Association’s DSM-IV-TR, found a syndromal breakdown of 35\% mania, 28\% depression, 12\% mania and depression, 13\% delirium, and 11\% psychosis.

A number of more recent publications support the conclusion that symptoms of hypomania or mania are the most common psychiatric adverse effect of corticosteroid treatment.\textsuperscript{12,13,18,20,47,49} Some recent studies have suggested, however, that the risk of depression increases with prolonged or chronic exposure.\textsuperscript{48,50–52} Patients who experience corticosteroid-induced depression during one treatment course may experience drug-induced mania in a subsequent course, and vice versa.\textsuperscript{53}

Appenzeller et al.\textsuperscript{54} report episodes of acute psychosis meeting DSM-IV criteria in 17.1\% (89/520) of SLE patients followed for periods of from 4 to 8.8 years. Corticosteroid-induced psychoses accounted for 31.5\% (28/89) of the cases of psychosis (a 5.4\%
incidence in the entire sample), of whom 10 (35.7%) had more than one psychotic episode.

Gift et al.\textsuperscript{55} found significantly greater self-reported depression scores in 20 patients with chronic obstructive pulmonary disease receiving 20–40 mg/day of prednisone for 10–14 days than in 20 not receiving corticosteroids, but did not include any measure of hypomanic/manic symptoms. Swinburn et al.\textsuperscript{56} in a study of 20 similar patients given 30 mg/day of prednisolone, found only a small reduction in anxiety and depression after 3 days of prednisolone (before lung function improved) and no significant mood change after 2 weeks of treatment.

**ONSET OF PSYCHIATRIC SYMPTOMS**

Early studies\textsuperscript{12,14,26} suggested and later studies\textsuperscript{13,39,57} confirmed that the psychiatric side-effects of corticosteroid treatment have a rapid onset. Lewis and Smith\textsuperscript{12} reported a median time to onset of 11.5 days; 39% of cases had onset during the first week and 62% within 2 weeks. Hall et al.\textsuperscript{26} noted that 86% of patients with psychiatric side-effects developed these symptoms within 1 week of starting treatment. Ling et al.\textsuperscript{14} reported that the psychiatric sequelae of corticosteroid treatment generally occurred within 2 weeks. In a study of 50 ophthalmic patients receiving high-dose corticosteroids, Naber et al.\textsuperscript{13} reported development of psychiatric symptoms within 3 days of initiating corticosteroid treatment (when present). Another study by Nishimura et al.\textsuperscript{47} found a mean of 12.5 days for onset of symptoms in their 14 cases, noting a range of 2–28 days after starting treatment. Lastly, a study of healthy subjects by Wolkowitz et al.\textsuperscript{19} reported onset of psychiatric sequelae within 5 days of corticosteroid administration.

The corticosteroids dexamethasone and betamethasone have half-lives of 36–54 h.\textsuperscript{58} As a result, they may accumulate and induce psychiatric symptoms that begin after the last dose has been given.\textsuperscript{9,10}

**CORRELATION BETWEEN DOSE AND OCCURRENCE OF PSYCHIATRIC SYMPTOMS**

The early study of the Boston Collaborative Drug Surveillance Program demonstrated the striking dose–response correlation of corticosteroids. Similarly, Chan et al.\textsuperscript{59} reported psychosis in 8% of patients receiving prednisone 90 mg/day compared to 3% of patients receiving 30 mg/day. The more recent literature confirms that the likelihood of inducing psychiatric symptoms follows a dose–response correlation. Nishimura et al.\textsuperscript{47} noted that all 20 SLE patients who developed psychiatric symptoms (primarily hypomania, mixed states or depression) were receiving at least 40 mg/day of prednisolone. An additional 97 patients receiving these doses did not develop psychiatric symptoms. Wada et al.\textsuperscript{18} describing 18 patients who developed mood disorders or psychosis after receiving 30–60 mg/day of prednisone-equivalent, also reported a strong association with dose, although they noted that some patients had a recurrence of depression or mania related to psychosocial stressors rather than to dose changes or to resumption of corticosteroids. Appenzeller et al.\textsuperscript{54} reported that all patients with corticosteroid-induced psychosis were taking prednisone 0.75–1.0 mg/kg/day, which translates into total doses as high or higher than those just noted.

Olsen et al.\textsuperscript{60} found a significant correlation between mood lability and prednisone dose in mg/kg during a 6-week taper from 40 mg/d to zero in 32 patients with alopecia areata. Naber et al.\textsuperscript{13} used the Profile of Mood States scale, a European psychiatric symptom scale developed by the Association of Methodology and Documentation in Psychiatry, a semi-structured interview and a battery of neuropsychological tests to study the psychological and cognitive effects of methylprednisolone or fluocortolone (50–300 mg/day to start, tapered to 18–100 mg/day by day 8) in 50 ophthalmologic patients, all of whom were initially free of psychiatric disorders. Although 36% (18/50) developed DSM-III-R mania (n = 13) or depression (n = 5) during treatment, the authors found no correlation between the daily dose of steroid and the daily ratings of mood symptoms. No patient developed psychosis, delirium or severe cognitive deficits.

In almost all of the cases of corticosteroid-induced dementia located in the present search of the literature, the corticosteroid dose has been at least 60 mg/day of prednisone-equivalent. Varney et al.\textsuperscript{55} reported one case in which dementia was documented 2 weeks after the prednisone dose was reduced to 20 mg/day after a 4-month course of 100 mg/day; irregular improvement occurred over the following 24 months, while prednisone was continued at 20 mg/day.
OTHER RISK FACTORS

Other than dose, no strong predictors of risk have emerged. However, psychiatric risk may be increased by drugs that increase circulating levels of corticosteroids. Clarithromycin, for example, is an inhibitor of the cytochrome P450 enzyme (CYP) 3A4 that metabolizes prednisone’s biologically active metabolite, prednisolone. Finkenbine and Gill reported a case of mania induced by adding clarithromycin to prednisone; the mania resolved over 5 days when both drugs were stopped. Finkenbine and Frye report a case of psychotic paranoia that required the addition of olanzapine, plus a prednisone taper and the discontinuation of clarithromycin, which was followed over the next 6 days by a clearing of the paranoia.

Nishimura et al., studying 135 patients with systemic SLE, found cerebral spinal fluid/serum albumin ratio (a marker of blood–brain barrier damage) to be a significant risk factor for corticosteroid-induced psychiatric disorder (odds ratio 33.3). Chau and Mok, studying 92 SLE patients, of whom 5% experienced a corticosteroid-induced psychosis or mania, found that hypoalbuminemia distinguished those who suffered this side-effect from those who did not. Appenzeller et al. reported that after multiple regression analysis, hypoalbuminuria (odds ratio 2.2) was the only variable significantly associated with corticosteroid-induced psychosis in their series of SLE patients.

Some earlier studies, but not all, reported a higher prevalence of steroid-induced psychiatric problems in women. In part, the higher prevalence may have reflected their greater propensity to seek medical care, more common experience of certain psychiatric disorders, such as major depression and most anxiety disorders, or the higher prevalence of certain medical disorders, such as SLE in women; the female preponderance persisted in one study (2) even after cases of SLE were excluded.

A previous history of psychiatric disorder does not seem to increase the risk of an adverse psychiatric reaction. Early studies reported that prior episodes of steroid-induced psychiatric symptoms may or may not be followed by recurrence during future treatment courses and that risk does not appear to be associated with a particular age group. Nothing in the modern literature contradicts these findings.

PATHOPHYSIOLOGY

The pathophysiological mechanisms giving rise to the psychiatric symptoms associated with corticosteroid treatment remain unclear. Speculations regarding these mechanisms are discussed elsewhere and include corticosteroid effects on dopaminergic and cholinergic systems, decreases in serotonin release, and toxic effects on hippocampal neurons or on other brain regions.

RESULTS OF OUR REVIEW OF CASES

The following review of the adult case report data on corticosteroid-induced psychiatric side-effects targets those published since the last major review of this kind in 1983 by Lewis and Smith, with the goal of ascertaining whether recent experience with corticosteroids has produced new conclusions regarding the clinical pictures and their management. We searched the PubMed and PsychLit databases by combining the search terms ‘steroids’, ‘corticosteroids’ and the generic names of corticosteroid steroid medications with terms for psychiatric symptoms or syndromes including psychosis, mania, hypomania, depression, apathy, anxiety, panic, depersonalization, delirium, confusion, hallucinations, delusions, paranoia, cognitive impairment and dementia. Our search produced 55 cases along with a number of trials investigating the incidence and treatment of these conditions. Our review focuses on the nature of these adverse events, their incidence, correlation to drug dose, risk factors, course and treatment; we also summarize the findings from earlier studies and reviews.

A caveat is that case reports are likely to be influenced by publications bias – more dramatic or consequential symptoms or syndromes are more likely to be written up and accepted for publication. Thus, the analyses we present are unlikely to represent accurately the milder symptoms that may occur or the true population incidence rates of more serious reactions. Still, our analyses may provide value to the clinician treating such patients.

Our search produced 55 cases with the following syndromes: hypomania/mania; depression; delirium; subsyndromal symptoms, such as hallucinations and agitation/anxiety, and panic disorder. Of these cases, 34 (61.8%) were psychotic, that is, had hallucinations and/or delusions coupled with impaired reality testing or lack of insight. Suicidal ideation was present in 22 cases (40%), of whom half were psy-
chotic and half not; one patient committed suicide. In addition, the search produced three cases of steroid-induced reversible dementia confirming the 1984 observations of Varney et al. and six cases of psychoses apparently induced by rapid steroid discontinuation. The dementia cases were atypical of psychoses apparently induced by rapid steroid discontinuation. Earlier case series analyses could not be ruled out, the results of our analysis largely resemble those of Appenzeller et al. and our findings indicate similar mean recovery times for delirium (several days), depression (4 weeks) and hypomania/mania (3 weeks). Without distinguishing various syndromes, Appenzeller et al. noted a median time to recovery of 13.3 ± 5.2 days in SLE patients suffering corticosteroid-induced psychoses. Some patients were treated with psychotropic drugs and some recovered simply by virtue of corticosteroid discontinuation.

**CASE REPORT**

The following case illustrates the difficulty that may be experienced in treating corticosteroid-induced depression, particularly when medical stressors continue and the corticosteroid cannot be quickly reduced. It also illustrates the need in such cases for prolonged use of psychotropic treatment, and the ultimate good prognosis. The authors received informed consent to publish her case.

Mrs S, an 85-year-old widowed, socially active woman with no prior psychiatric history, developed temporal arteritis with abrupt and permanent loss of vision in her right eye and blurred vision in her left. Subsequently, she began oral prednisone...
Table 1. Summary of identified cases (n = 55)

<table>
<thead>
<tr>
<th>Symptomatic category</th>
<th>Sex</th>
<th>Age</th>
<th>Underlying disease(s) or condition</th>
<th>Prednisolone dose or prednisolone dose equivalent (p.d.e.)/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferris et al. 2003²</td>
<td>Female</td>
<td>62</td>
<td>Undergoing parotidectomy</td>
<td>160 mg (p.d.e.)</td>
</tr>
<tr>
<td>Ismail et al. 2002²</td>
<td>Female</td>
<td>64</td>
<td>Asthma</td>
<td>30 mg</td>
</tr>
<tr>
<td>Ito et al. 2003³</td>
<td>Female</td>
<td>37</td>
<td>Acute myeloid leukemia</td>
<td>50 mg</td>
</tr>
<tr>
<td>Jenkins et al. 1994⁴</td>
<td>Male</td>
<td>42</td>
<td>Meningioma</td>
<td>106.7 mg (p.d.e.)</td>
</tr>
<tr>
<td>Terao et al. 1994⁵</td>
<td>Male</td>
<td>18</td>
<td>Systemic lupus erythematosus</td>
<td>15 mg</td>
</tr>
<tr>
<td>Terao et al. 1997⁶</td>
<td>Female</td>
<td>24</td>
<td>Systemic lupus erythematosus</td>
<td>50 mg</td>
</tr>
<tr>
<td>Terao et al. 1997⁶</td>
<td>Female</td>
<td>66</td>
<td>Polyarteritis nodosa</td>
<td>60 mg</td>
</tr>
<tr>
<td>Wada et al. 2000⁷</td>
<td>Female</td>
<td>31</td>
<td>Systemic lupus erythematosus</td>
<td>30 mg</td>
</tr>
<tr>
<td>Wyzyński et al. 1993⁸</td>
<td>Female</td>
<td>46</td>
<td>Sjögren’s syndrome</td>
<td>156.3 mg (p.d.e.)</td>
</tr>
<tr>
<td>Yoshimura et al. 2001⁹</td>
<td>Male</td>
<td>70</td>
<td>Pneumonia</td>
<td>100 mg</td>
</tr>
<tr>
<td>Yoshimura et al. 2001⁹</td>
<td>Female</td>
<td>50</td>
<td>Pneumonia</td>
<td>80 mg</td>
</tr>
<tr>
<td>Hypomania/mania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benyamin et al. 2008¹⁰</td>
<td>Male</td>
<td>67</td>
<td>Chronic neck pain</td>
<td>100 mg (p.d.e.)</td>
</tr>
<tr>
<td>Bloch et al. 1994¹⁵</td>
<td>Male</td>
<td>26</td>
<td>Multiple sclerosis</td>
<td>30 mg</td>
</tr>
<tr>
<td>Brown et al. 1999¹⁵</td>
<td>Female</td>
<td>21</td>
<td>Asthma</td>
<td>30 mg</td>
</tr>
<tr>
<td>Brown et al. 2001¹⁵</td>
<td>Female</td>
<td>43</td>
<td>Behçet’s disease</td>
<td>30 mg</td>
</tr>
<tr>
<td>Cerullo et al. 2006¹⁶</td>
<td>Male</td>
<td>69</td>
<td>Unidentified cancer</td>
<td>Not reported</td>
</tr>
<tr>
<td>d’Orban 1989¹⁷</td>
<td>Male</td>
<td>26</td>
<td>Undergoing maxillary osteotomy</td>
<td>60 mg (p.d.e.)</td>
</tr>
<tr>
<td>Finkenbine et al. 1997¹⁸</td>
<td>Female</td>
<td>30</td>
<td>Sinusitis</td>
<td>30 mg</td>
</tr>
<tr>
<td>Franco et al. 2000¹⁹</td>
<td>Male</td>
<td>59</td>
<td>Post-stroke cardiac transplantation</td>
<td>20 mg</td>
</tr>
<tr>
<td>Ginsberg et al. 2001¹⁹</td>
<td>Female</td>
<td>59</td>
<td>Asthma</td>
<td>35 mg</td>
</tr>
<tr>
<td>Hong et al. 2006¹⁹</td>
<td>Female</td>
<td>48</td>
<td>Sheehan’s syndrome</td>
<td>15 mg</td>
</tr>
<tr>
<td>Johnson et al. 1996²⁰</td>
<td>Female</td>
<td>36</td>
<td>Asthma, pregnancy</td>
<td>20 mg</td>
</tr>
<tr>
<td>Kato et al. 2005²¹</td>
<td>Female</td>
<td>46</td>
<td>Systemic lupus erythematosus</td>
<td>40 mg</td>
</tr>
<tr>
<td>Lopez-Medrano et al. 2002²²</td>
<td>Female</td>
<td>20</td>
<td>Systemic lupus erythematosus</td>
<td>60 mg</td>
</tr>
<tr>
<td>Lopez-Medrano et al. 2002²²</td>
<td>Female</td>
<td>21</td>
<td>Systemic lupus erythematosus</td>
<td>30 mg</td>
</tr>
<tr>
<td>Lundberg et al. 2000²³</td>
<td>Male</td>
<td>32</td>
<td>Hodgkin’s lymphoma</td>
<td>100 mg</td>
</tr>
<tr>
<td>Mauzyk et al. 2010²⁴</td>
<td>Female</td>
<td>31</td>
<td>Systemic lupus erythematosus</td>
<td>60 mg</td>
</tr>
<tr>
<td>Preda et al. 1999²⁵</td>
<td>Female</td>
<td>41</td>
<td>Nephritis</td>
<td>40 mg</td>
</tr>
<tr>
<td>Siddique et al. 2005²⁶</td>
<td>Male</td>
<td>52</td>
<td>Liver transplant</td>
<td>225 mg (p.d.e.)</td>
</tr>
<tr>
<td>Viswanathan et al. 1989²⁶</td>
<td>Male</td>
<td>38</td>
<td>Post-renal transplant</td>
<td>15 mg</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Female</td>
<td>40</td>
<td>Dermatomyositis</td>
<td>60 mg</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Female</td>
<td>19</td>
<td>Minimal-change nephrotic syndrome</td>
<td>30 mg (p.d.e.)</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Female</td>
<td>21</td>
<td>Dermatomyositis</td>
<td>50 mg</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Female</td>
<td>23</td>
<td>Ulcerative colitis</td>
<td>26.67 mg (p.d.e.)</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Female</td>
<td>47</td>
<td>Systemic lupus erythematosus</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Male</td>
<td>68</td>
<td>Intractable nephrotic syndrome</td>
<td>15 mg</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Male</td>
<td>53</td>
<td>Systemic lupus erythematosus</td>
<td>40 mg</td>
</tr>
<tr>
<td>Wada et al. 2000²⁷</td>
<td>Male</td>
<td>42</td>
<td>Kidney transplant rejection</td>
<td>666.7 mg (p.d.e.)</td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahmad et al. 1999³⁶</td>
<td>Female</td>
<td>55</td>
<td>Chronic obstructive pulmonary disease</td>
<td>60 mg</td>
</tr>
<tr>
<td>Artukoglu et al. 2007⁷⁷</td>
<td>Female</td>
<td>32</td>
<td>Biopsy for humeral mass operation</td>
<td>53.33 mg (p.d.e.)</td>
</tr>
<tr>
<td>Benazzi et al. 1997³⁸</td>
<td>Female</td>
<td>70</td>
<td>Systemic lupus erythematosus</td>
<td>5 mg (p.d.e.)</td>
</tr>
<tr>
<td>Galen et al. 1997³⁹</td>
<td>Male</td>
<td>26</td>
<td>Facial osteotomies</td>
<td>666.7 mg (p.d.e.)</td>
</tr>
<tr>
<td>Jenkins et al. 2000⁴⁰</td>
<td>Male</td>
<td>93</td>
<td>Renal cell carcinoma</td>
<td>133.3 mg (p.d.e.)</td>
</tr>
<tr>
<td>Koh et al. 2002³⁹</td>
<td>Male</td>
<td>40</td>
<td>ER-breathing difficulty</td>
<td>82 mg</td>
</tr>
<tr>
<td>Mada et al. 2009¹⁰⁰</td>
<td>Female</td>
<td>72</td>
<td>Adrenal insufficiency</td>
<td>12.5 mg (p.d.e.)</td>
</tr>
<tr>
<td>Okishiro et al. 2009¹⁰¹</td>
<td>Male</td>
<td>67</td>
<td>Pulmonary emphysema</td>
<td>13.33 mg (p.d.e.)</td>
</tr>
<tr>
<td>Silva et al. 1995¹⁰²</td>
<td>Male</td>
<td>45</td>
<td>Dental operation</td>
<td>100 mg (p.d.e.)</td>
</tr>
<tr>
<td>Stoudemire et al. 1996¹⁰³</td>
<td>Female</td>
<td>40</td>
<td>Chronic obstructive pulmonary disease</td>
<td>40–100 mg</td>
</tr>
<tr>
<td>Panic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charbonneux et al. 1997¹⁰⁴</td>
<td>Female</td>
<td>31</td>
<td>Erythema multifforme</td>
<td>5 mg</td>
</tr>
<tr>
<td>Raskin et al. 1984¹⁵</td>
<td>Female</td>
<td>35</td>
<td>Hirsutism</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dargen et al. 1997¹⁰⁵</td>
<td>Male</td>
<td>72</td>
<td>Rheumatoid arthritis</td>
<td>74 mg (p.d.e.)</td>
</tr>
<tr>
<td>Gallenari et al. 2008¹⁰⁶</td>
<td>Male</td>
<td>64</td>
<td>Hypertension</td>
<td>40 mg (p.d.e.)</td>
</tr>
<tr>
<td>Paranoia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finkenbine et al. 1998¹⁰⁷</td>
<td>Male</td>
<td>50</td>
<td>Emphysema</td>
<td>20 mg</td>
</tr>
</tbody>
</table>
60 mg/day. While tapering down to 40 mg/day 1 month later, she developed significant depressive and psychotic symptoms that resulted in her hospitalization for apparent steroid-induced psychosis. The psychosis resolved several weeks later and the patient was discharged, but continued to become increasingly depressed. Her depressive symptoms were marked anhedonia, apathy, and poor concentration, and she was disheveled in appearance with poor grooming and loss of function. Although her prednisone dose was lowered to 10 mg/day, she continued to decline. Four months later, after making suicidal statements and becoming assaultive toward her 24-h caregiver, she was hospitalized again, this time for almost 2 months. She was severely depressed, hopeless, nihilistic, with delusional guilt, visual hallucinations, poor insight and self-neglect. In hopes of saving the remaining vision in her left eye, methotrexate was added to her prednisone 10 mg/day. She was stabilized and discharged on olanzapine 7.5 mg alternating with 10 mg q.h.s., bupropion XL 300 mg/day, duloxetine 90 mg/day, benztrapine 0.5 mg q.h.s., and lorazepam 0.5 mg bid p.r.n. Two weeks later upon follow up, Mrs S was neatly groomed and cheerful. She denied depressed mood, anhedonia and suicidality. In the following months, her mood remained stable and she resumed social activities while continuing her hospital discharge medications. Olanzapine and duloxetine were gradually decreased, while bupropion, benztrapine and lorazepam were discontinued after 4 months.

TREATMENT OF CORTICOSTEROID-INDUCED PSYCHIATRIC SYMPTOMS

The literature on the treatment of corticosteroid-induced psychiatric symptoms is limited to multiple case reports and a few small trials. These provide clinical guidance, but require larger double-blind, placebo-controlled trials to meet the standard of evidence-based medicine.

Many authors emphasize the importance of educating patients and their families about the risks of corticosteroid-induced psychiatric side-effects and of seeing patients soon after these drugs are begun, since these adverse effects may have rapid onset. The common occurrence of suicidal ideation (and less often, suicidal behaviors) must be kept in mind and preventive measures considered. When psychiatric symptoms occur, contributions of the underlying medical condition(s), other drugs or treatments, withdrawal from drugs such as alcohol and benzodiazepines, medical complications, such as infections, metabolic derangements or paraneoplastic syndromes, and contributions of psychosocial stressors, including the illness itself, will have to be taken into account and managed.

As has often been pointed out, treatment of corticosteroid-induced psychiatric symptoms should start whenever possible with dose reduction or stopping the drug. Without specifying the diagnoses associated with particular drugs, Lewis and Smith report that simply tapering the corticosteroid dose to zero resolved the psychiatric symptoms in 94% of 36 cases. Appenzeller et al. reported that simply tapering off the drug was effective in half their cases. Warrington and Bostwick cite endocrine experts who recommend tapering the corticosteroid dose to 40 mg/day of prednisone equivalent when discontinuation is not possible, followed as quickly as is safe by a taper to a physiological dose of 7.5 mg/day. The possibility of inducing psychiatric symptoms by tapering too quickly must be born in mind. Even slow taper, however, has led to the onset of depression in patients who were euthymic on prednisone, with the depression lasting 6–8 weeks after completing the taper.

Corticosteroid-induced hypomania, mania and mixed mania have been successfully treated with a typical antipsychotic or mood stabilizer, most often haloperidol, haloperidol plus lithium, risperidone, quetiapine, olanzapine, olanzapine with valproate, carbamazepine, lithium, lamotrigine plus clonazepam, clonazepam alone in a case where lithium had been ineffective. In some cases a combination of an antipsychotic and a benzodiazepine has been required. In a 5-week, open-label trial of olanzapine 2.5–20 mg/day (mean 8.5 mg/day) for mania or mixed mania symptoms secondary to corticosteroids, Brown et al. observed marked improvement in 11 of 12 outpatients; one patient withdrew for lack of efficacy. Renal function must be considered when contemplating the use of lithium and potential drug interactions are always a consideration.

Corticosteroid-induced depression has responded to lithium alone, lithium added to mianserin, amitriptyline, intravenous clomipramine, fluoxetine, venlafaxine, and, low-dose fluvoxamine.
Psychotic depression has responded to electroconvulsive therapy and to combinations of sertraline, risperidone and lorazepam, or paroxetine, risperidone and lorazepam. In the 1970s, Hall et al. recommended against the use of tricyclic antidepressants after observing increased mood lability or symptoms consistent with delirium in some patients; others have also reported poor response. Selective serotonin reuptake inhibitors may be preferable due to their lower side-effect profile. Prednisolone, the active metabolite of prednisone, may increase plasma levels of fluvoxamine, so that smaller-than-usual antidepressant doses may be utilized.

Corticosteroid-induced delirium, like delirium of other causes, may respond to haloperidol or an atypical antipsychotic, although the addition of other agents, such as a benzodiazepine may be necessary.

In one case, corticosteroid-induced panic disorder with agoraphobia responded within 2 weeks to tranylcypromine 20 mg/day coupled with behavioral therapy. In a second case, these symptoms responded within an unspecified interval to fluvoxamine and supportive psychotherapy.

As noted earlier, corticosteroid-induced dementia resolves much more slowly following drug discontinuation than do other syndromes and may leave residual cognitive decrements. Although improvement may be apparent 1 month after discontinuation, deficits in learning and memory may persist for 6 months or more. Symptoms may also remit despite continued corticosteroid treatment. A patient who experienced a manic psychosis on 125 mg/day of cortisone had symptoms of impaired memory, attention and concentration 1 week after recovery while euthymic on 1 mg/day of dexamethasone, but normal mental status when examined 9 months later, despite being maintained in the interim on 0.5–1.5 mg/day of dexamethasone. Interestingly, memantine, used in treating Alzheimer’s disease, has been reported in a double-blind, crossover trial of modest size to decrease adverse effects of corticosteroid treatment on declarative memory. A small, double-blind, placebo controlled study also suggested improvement in declarative memory as a result of treatment with lamotrigine, although the drug was not well-tolerated.

For patients who have experienced a corticosteroid-induced psychosis or other severe adverse psychiatric effect, the clinician may wish to attempt a preventive intervention when the steroid is again needed. A number of strategies to prevent psychotic symptoms are described in case reports and one case series, but whether these symptoms would have returned absent these interventions is unknown. Falk et al. treated 27 patients receiving corticotrophin for multiple sclerosis or retrolubar neuritis with prophylactic lithium carbonate (serum levels 0.8 to 1.2 mEq/l) and compared them to a historical control group not receiving concurrent lithium. Psychosis had occurred in 14% (6/44) of the historical control group, but was seen in none of the lithium-treated group. Two patients discontinued lithium for side-effects. Goggans et al. reported that a patient with a history of steroid psychosis had no recurrence during a second course of prednisone 60 mg/day preceded and accompanied by lithium 900 mg/day. In another case, lithium did not prevent the onset of mania with a first course of prednisone, but when prednisone was resumed 3 weeks later with concurrent lithium, the mania did not recur. A woman who had experienced two previous psychotic episodes followed by persistent melancholic depression safely underwent a third steroid course while treated with protriptyline, lithium and haloperidol (administered for only a few days). Bloch et al. reported that a patient who had become psychotic during two prior courses of corticosteroid treatment had no symptoms during a third course (methylprednisolone 1 g tapered to zero over 10 days, followed by prednisone 30 mg/day) so long as chlorpromazine 150 mg/day was co-administered. When it was tapered off, the patient became hypomanic and it had to be resumed. A patient who had experienced a manic episode when treated with prednisone 40 mg/day tolerated two subsequent courses while taking gabapentin 900 mg/day starting 1 day before resuming corticosteroids. In a bipolar patient whose lithium had to be discontinued because of worsening interstitial nephritis, lamotrigine plus clonazepam was effective in treating mania present on hospital admission and in preventing an exacerbation when the patient was placed on high-dose prednisone. Valproate has been reported to prevent steroid-induced psychosis in one case. In a double-blind, placebo-controlled trial of 30 patients, acetaminophen 4000 mg/day did not differ from placebo with respect to change in depressive symptoms.

**DIRECTIONS FOR FUTURE RESEARCH**

Brown and Suppes highlight limitations of the current literature on the psychiatric adverse reactions...
to corticosteroid treatment – most large studies have not included formal psychiatric assessment, most studies that incorporated such assessment were small and, thus, the interpretation and generalization of their results are difficult, and useful, patient-specific risk factors remain unknown. As noted above, the case report literature on which much of our knowledge depends cannot be regarded as definitive.

Wada et al. suggest the individual susceptibility to mania versus depression and other corticosteroid-induced psychiatric symptoms be studied. These authors also note a paucity of information on long-term outcome, on the risk of recurrence of symptoms and on the optimum treatments for corticosteroid-induced psychiatric syndromes.

Given the potential severity and cost of corticosteroid-induced psychiatric side-effects, controlled trials of preventive strategies would be quite useful. In addition, recent advances in genetic mapping could be utilized to help identify a risk-promoting role for particular genes or polymorphisms, although the sample sizes needed are daunting.

CONCLUSION

Psychiatric complications of corticosteroid treatment range from anxiety and insomnia to severe mood disorders, delirium and dementia. The psychiatric symptoms typically come on within 1–2 weeks after starting high-dose corticosteroid steroid treatment and the most common serious adverse event reported is hypomania or mania, though various forms of psychotic syndromes, taken together, are even more common. Hypo-albuminemia appears to be a risk factor worth attending to, as does co-administration of drugs that may slow the metabolism of the corticosteroid, for example, P450 (CYP) 3A4 inhibitors. Although steroid taper or discontinuation can remedy these adverse effects, psychotropic medications are often required, either because of the inability to discontinue the steroid treatment or the severity of the psychiatric symptoms. The psychotropic medication classes that are effective for particular idiopathic psychiatric syndromes also appear to be effective in cases induced by corticosteroid treatment.

Although much remains to learn about adverse psychiatric reactions to corticosteroid treatment, physicians, patients and their families should work together to improve awareness of the limited available knowledge and to stimulate research aimed at improved methods of prevention, recognition and treatment.

REFERENCES


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