REVIEW ARTICLE

Drug Safety 2000 Feb; 22 (2): 111-122
0114-5916/00/0002-0122/$20.00/0

Corticosteroid-Induced Adverse Psychiatric Effects

Incidence, Diagnosis and Management

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Contents

Abstract

Reports of corticosteroid-induced adverse psychiatric effects began to appear in the literature soon after the introduction of these medications in the 1950s. Unfortunately, early studies relied on informal classification and measurement procedures and tended to utilise nonspecific descriptive terminology (such as 'steroid psychosis'). A growing number of contemporary investigations have begun to address these problems. However, the literature remains surprisingly undeveloped from a pharmacoepidemiological perspective, consisting largely of case reports and case series.

The objective of this review is to summarise published data concerning corticosteroid-induced adverse psychiatric effects. A clinical perspective will be adopted since opportunities to minimise the impact of corticosteroid-induced adverse effects tend to present themselves most readily within the sphere of clinical management.

Some of the psychiatric adverse effects of corticosteroids are mild, and not necessarily clinically significant. However, several serious psychiatric syndromes can be caused by corticosteroids: substance-induced mood disorders (with depressive, manic and mixed features), substance-induced psychotic disorders and delirium. While certain clinical groups may be at greater risk of corticosteroid-induced adverse psychiatric effects, corticosteroid-induced psychiatric toxicity is remarkably unpredictable.

The literature regarding prevention and treatment of corticosteroid-induced adverse psychiatric effects is poorly developed. As a result, the emphasis of this review is on clinical and epidemiological evidence linking specific adverse effects to corticosteroid medications. However, clinical reports do provide some practical guidance for prevention and treatment, and these are summarised as well. A variety of pharmacological strategies for treatment and prevention have been proposed. Education and support also appear to be important, and perhaps neglected, aspects of management.

The literature concerned with corticosteroid-induced adverse psychiatric effects dates back over 40 years. Early reports consisted of detailed descriptions of individual cases[1-4] and the observations and conclusions of these early authors have sometimes been restated uncritically in reviews of this literature. Sometimes, reviewers have cited the opinions of previous reviewers, who in turn based their conclusions on the clinical observations of early authors. An objective of this review is to examine this literature from a more critical perspective. However, case reports will not be excluded from the review in situations where they represent the only available information. Levels of evidence associated with various associations and clinical strategies are summarised in table I.

Historically, certain authors have questioned whether corticosteroids cause psychiatric adverse effects at all.[5] A recent meta-analysis of randomised controlled trials has provided firm confirmation that they can.[6] This issue is, therefore, not addressed further in this review. Furthermore, while Cushing's syndrome is associated with psychiatric effects[7-10] and presents its own unique clinical challenges,[11] this review is exclusively concerned with the psychiatric adverse effects of exogenous corticosteroids.

In a 1952 case series and review, Rome and Braceland[12] proposed a classification for corticosteroid-induced psychiatric adverse effects consisting of 4 grades of symptom severity. This classification system has been widely used and has been endorsed by Kershner and Wang-Cheng.[13] However, corticosteroid-induced psychiatric adverse effects can occur in a variety of qualitatively distinct forms, with distinct clinical implications, and a 'scaling' of such disturbances along a single axis of severity can no longer be justified. The use of unitary nominal categories, as implied by the term 'steroid psychosis,' is an alternative, but this approach has been widely criticised on the grounds that it lacks specificity.[14-16]

An alternative approach to classification is offered by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).[17] Here, classification is based on the predominant features of the clinical syndrome displayed. The DSM-IV approach is employed wherever possible in this review.

1. Classification of Corticosteroid-Induced Adverse Effects in the DSM-IV

Corticosteroid-induced mood disturbances are classified in DSM-IV as substance-induced mood disorders (with an associated specification of depressive, manic or mixed features). Other disturbances, characterised by psychotic symptoms such as delusions or hallucinations, and associated with

impairments in reality testing (but without prominent cognitive or affective features), may be classified as a substance-induced psychotic disorder. According to the DSM-IV classification, corticosteroid-induced confusional states should be classified as delirium. Delirium is characterised by a disturbance of consciousness with deficits in attention, other cognitive impairments and perceptual disturbances such as transient delusions, hallucinations and illusions.

The DSM-IV syndrome-based classification system offers important clinical advantages to clinicians in the area of differential diagnosis. Rather than a nominal distinction concerning whether a patient experiences a 'steroid psychosis,' a clinical evaluation can be guided by a coherent differential diagnosis. If clinical features suggest delirium, then the work-up will be distinct from that of, for example, a depressive syndrome. In the former case, a set of potentially dangerous aetiologies need to be evaluated urgently. In the latter case, the differential diagnosis will include a broad array of other conditions that could account for depression: an adjustment disorder, a major depressive disorder, a mood disorder caused by a general medical condition (e.g. multiple sclerosis), bereavement, a family problem, etc.

2. Adverse Psychiatric Effects of Corticosteroids

The association of corticosteroid treatment with depressive and manic syndromes is relatively well documented, although there remains a need for additional prospective studies in the various clinical populations where corticosteroids are used so that the frequency and severity of these disturbances within specific populations can be more clearly elucidated. The literature concerned with delirium is poorly developed, consisting only of case reports.[15] However, given the capacity of almost any drug to contribute to the aetiology of delirium, a contributing role for corticosteroids is not in dispute. The literature indicates a consensus that other psychotic disorders may also be induced by corticosteroids, but the published evidence documenting this is scant, consisting only of case reports.[18,19]

Table I. Corticosteroid-induced adverse psychiatric effects from the perspectives of incidence, prevention and management

	Clinical problem	Level of evidence[a]
Incidence	Substance-induced mood disorder, with depressive features	Prospective Pharmacoepidemiological studies
	Substance-induced mood disorder, with manic features	Prospective Pharmacoepidemiological studies
	Delirium	Clinical case reports
	Substance-induced psychotic disorder	Clinical case reports
Prevention (pharmacological strategies)	Lithium	A single quasi-experiment Clinical case reports
	Antidepressant medications	Clinical case reports
	Antipsychotic medications	Clinical case reports
	Anticonvulsant medications	Clinical case reports
Management (pharmacological strategies)	Lithium	Clinical case reports
	Antipsychotic medications	Clinical case reports
	Sedative-hypnotic medications	None[b]
	Antidepressant medications	Clinical case reports[c]

a Level of evidence refers to the highest level of methodological sophistication in studies supporting an association or intervention. From lowest to highest, these levels were rated as: (i) no evidence; (ii) case reports and clinical observations; (iii) formal epidemiological or clinical studies.

b A single case report described the successful use of clonazepam, but a relationship of the patient's symptoms to corticosteroids was clinically unclear.

c Some describing beneficial effects, some describing adverse effects of treatment.

2.1 Substance-Induced Mood Disorder with Depressive Features

Two cross-sectional epidemiological studies have evaluated associations between corticosteroids and depressive symptoms in clinical samples,[20,21] and one in a community sample.[22] Each study reported higher depressive symptom ratings in corticosteroid-treated participants. These studies confirmed that, as a group, individuals under treatment with corticosteroids have elevated levels of depressive symptoms.

There have been relatively few prospective studies of the propensity of corticosteroids to induce depression. One study[23] followed a series of general medical inpatients who were not depressed at the time of their admission to hospital during the course of their treatment. Those treated with corticosteroids were approximately 3 times as likely to develop elevated depressive symptom levels during their admission as were control patients. These changes were evident within 5 days of exposure to corticosteroids, confirming that corticosteroid-induced depressive symptoms can have a rapid onset.

In contrast to the association between corticosteroids and depressive symptoms, the potential association between corticosteroids and depressive disorders remains poorly documented. In psychiatric terms, high ratings on depressive symptom rating scales and diagnoses of depressive disorders are not clinically equivalent. For example, those experiencing sleep and appetite disruption in isolation will display elevations on most depression rating scales, but could not be diagnosed with substance-induced mood disorder on the basis of these symptoms alone.

One case-control study has reported that the odds of exposure to corticosteroids were reduced in medical inpatients with clinical diagnoses of a depressive disorder,[24] implying a protective effect. However, this study used clinical diagnoses recorded in an electronic administrative database to identify cases and controls. This data source may be inaccurate, and associations may have been masked by misclassification bias. Nevertheless, Arana et al.[25] reported a statistically significant advantage of dexamethasone over placebo in the treatment of major depressive disorder. Ambiguities resulting from the differences between depressive symptom ratings and depressive disorders will need to be resolved by prospective studies using primary data sources.

An aetiological role for corticosteroids in episodes of substance-induced mood disorder with depressive features is supported by a large number of clinical case reports[2,26-29] and a single study by Naber et al.[30] These authors prospectively evaluated 50 ophthalmological patients undergoing short term corticosteroid treatment. They reported that 5 of these patients developed an organic mood disorder of the depressed type. Unfortunately, as this study was uncontrolled, there was no standard of comparison against which to evaluate the reported frequency. The emergence of depression during withdrawal from corticosteroids is discussed in section 2.6.

2.2 Substance-Induced Mood Disorder with Manic Features

Manic episodes are among the most important manifestations of corticosteroid-induced psychiatric toxicity. In one study, corticosteroid medications were judged responsible for 54% of cases of organic mania seen by a psychiatric consultation-liaison service.[31] Naber et al.[30] reported that 13 out of the 50 participants in their study developed manic-like episodes compared with 5 who developed a depressive syndrome. None of these episodes were severe and none were associated with psychotic symptoms. While the study of Naber et al.[30] was uncontrolled, the reported incidence clearly exceeds expectation for ophthalmological populations.

The tendency for hypomanic or manic symptoms to occur during treatment, and for depressive episodes to occur after discontinuation of treatment was a prominent feature of a series of three cases described by Sharfstein et al.[32] Each individual in this series was taking prednisone at a dosage of at least 50 mg/day on alternate days, and each developed a syndrome reminiscent of rapid cycling bi-

polar disorder. Another study evaluated mood changes in 18 female patients with systemic lupus erythematosus treated with alternate-day corticosteroid regimens, but at a much lower dose level (mean 13.9mg).[33] There were no significant changes in mean depressive symptom scores when the 'on' days were compared with the 'off' days. Minden et al.[34] retrospectively investigated 50 patients with multiple sclerosis treated with prednisone or corticotropin (adrenocorticotropic hormone). Of these, 9 developed mood elevation, with 1 episode evolving into a full-blown manic episode.

Fishman et al.[35] described 2 patients, each with a past history of corticosteroid-induced mania, who developed manic episodes after single regional injections of corticosteroids into the celiac plexus. Another reported case involved the use of inhaled beclomethasone, albeit at a higher dosage than is usually recommended,[36] and there are several reports of manic symptoms emerging in the context of treatment with inhaled budesonide.[37,38] One reported case described a persisting bipolar disorder that was apparently precipitated by corticosteroid treatment,[39] although a coincidental onset of the bipolar disorder is an alternative explanation in such circumstances.

2.3 Delirium

No formal studies have investigated the frequency of delirium in corticosteroid-treated patients. Stiefel et al.[16] believed that delirium was a particularly common form of neuropsychiatric toxicity in corticosteroid-treated cancer patients, but the literature contains case reports describing the occurrence of delirium in a variety of other clinical circumstances.[15] Delirium is characterised primarily by deficits in the area of attention, and is aggravated by excessive sensory stimulation. In view of this, the deficits in attention[40] and 'sensory flooding'[41] described in association with corticosteroid administration may aggravate, or perhaps precipitate, delirium that is related to other aetiologies. The literature also contains reports of delirium occurring after corticosteroids have been discontinued, or dosages decreased.[42,43]

Delirium tended to be a neglected category in early case reports. Hall et al.[41] failed to differentiate corticosteroid-induced delirium from other forms of 'steroid psychoses' in a widely cited case series. These observations have had a great impact on the subsequent literature, especially the observation that four participants treated with tricyclic antidepressants had a dramatic deterioration in their symptoms. According to Hall et al.,[41] these individuals experienced agitation, impaired concentration, an increase in sensory flooding and a more severe degree of organic impairment than others in the study. This introduces the possibility that these individuals may have experienced a worsening of delirium as a result of the use of the strongly anticholinergic tricyclic antidepressants (amitriptyline and imipramine) in clinical use at that time, rather than any general tendency for antidepressant medications to aggravate corticosteroid-induced psychiatric disturbances.

As such, the common clinical belief that antidepressants are contraindicated in all forms of corticosteroid-induced psychiatric toxicity may have been overstated. Two recent reports[44,45] describe the successful use of antidepressant medications in patients who experienced episodes of depression in response to corticosteroid treatment (see section 4).

2.4 Substance-Induced Psychotic Disorder

Adverse effect data from clinical trials has provided evidence of 'psychoses' in corticosteroid-treated patients, however, the description of the nature of the disturbance is often very scant, leaving some question as to the clinical features of the disturbance described.[46-48] Several case reports described the emergence of psychotic symptoms, apparently in the absence of attentional and cognitive difficulties that would indicate delirium.[18,19] Some such disturbances have apparently been induced by inhaled corticosteroids,[49] emphasising that even low levels of systemic exposure can potentially lead to serious adverse effects.

Many of the reported 'psychotic episodes' have manic features, such as irritability or pressure of speech,[18,49] and may actually have met DSM-IV criteria for a substance-induced mood disorder, with mixed features. The category of corticosteroid-induced psychotic disorders seems to be particularly poorly documented in the existing literature, which is surprising in view of the widely held clinical belief that psychotic episodes can be induced by corticosteroids. Additional research into this category of toxicity is urgently needed.

2.5 Miscellaneous Adverse Psychiatric Effects

A complicating factor in evaluating the literature concerned with subclinical psychiatric adverse effects is the reality that alterations in mood and behaviour are common accompaniments of adjustment to illness, and also that organically-induced mood disturbances are frequent in conditions such as systemic lupus erythematosus and multiple sclerosis. A series of investigations by Wolkowitz[50] avoided this source of confusion by studying the impact of prednisone at a dosage of 80 mg/day on 12 healthy volunteers. Of these volunteers, nine were observed using unstructured logs to experience emotional or behavioural alterations of a subclinical nature: depression, mood elevation, irritability, anger, insomnia, excessive talkativeness, an inability to filter out distracting information (sensory flooding), and increased appetite.

Euphoria (as an isolated symptom, as distinct from the occurrence of hypomania or mania where there are associated features such as rapid speech, insomnia and agitation) has frequently been reported in association with corticosteroid use.[26,51] Cameron et al.[52] reported a decrease in depressive symptoms, without the emergence of euphoria in 8 medical inpatients treated with prednisone. Hence, a reduction in dysphoria (as opposed to induction of euphoria) may be an effect of corticosteroids. The occurrence of euphoria is not necessarily severe, such that a common clinical question concerns whether it is really excessive, or whether it can be regarded as an expected reaction to clinical improvements secondary to the corticosteroid treatment.[26,51]

Swinburn et al.[53] demonstrated that mood improvement preceded improvement in physiological measures in a series of patients with chronic obstructive airways disease, suggesting a primary rather than secondary effect on mood. Euphoria is not necessarily a clinically significant adverse effect in the sense of necessitating dosage reduction or discontinuation of the corticosteroid treatment.[44,52] However, mood elevation can contribute to a pattern of abuse or overuse of corticosteroid medications.[15,54-56]

Additional case reports have implicated corticosteroids in causing catatonia,[57,58] panic attacks (in the context of a substance-induced mood disorder),[44] and reversible dementia.[59] Bell[40] commented that cases with features of dementia may in reality be depressive disorders manifesting as pseudo dementia.

While few studies of corticosteroid-induced psychiatric adverse effects have been controlled, several controlled studies have been conducted in children. In one of these, Suess et al.[60] reported temporary mnemonic effects (impaired visual memory and paired associate learning) in the 6 to 8 hour period following corticosteroid administration in asthmatic children. Bender et al.,[61] using individuals as their own controls, documented mild memory impairments in hospitalised asthmatic children treated with high doses (40 to 80mg prednisone equivalents) of corticosteroids.

A subsequent commentary on this paper[62] offered the interpretation that corticosteroid-treated patients had more commission and fewer omission errors on vigilance tasks, possibly indicative of a higher arousal level, and 'hair trigger' button pushing. The data were not strongly supportive of this,[63] but the interpretation is an interesting one because it suggests the clinical phenomenon known as sensory flooding, a frequently reported aspect of corticosteroid-induced mental disturbances in adults.[41,64] In adults, increased rates of commission errors were also reported by Wolkowitz et al.,[65] but not by Newcomer et al.[66]

The literature also contains several reports of behavioural disturbances, often of an aggressive nature, in young children being treated for asthma with inhaled corticosteroids.[38,67] Psychiatric adverse effects of corticosteroids may manifest differently in children and adults. The literature suggests that learning impairments and behavioural disturbances such as argumentative behaviour and irritability[68] may be relatively more prominent in children.

2.6 Withdrawal Effects

Depressive syndromes, sometimes complicated by psychotic features have been reported during corticosteroid withdrawal,[69] and the idea of depressive symptoms emerging after dosage reductions or discontinuation of corticosteroids is central to reports of corticosteroid abuse and dependence.[15,54-56] Corticosteroid withdrawal may also account for depressive symptoms emerging during the switch from systemic to inhaled corticosteroids.[70]

3. Avoidance of Corticosteroid-Induced Adverse Psychiatric Effects

In this section, the literature concerned with the avoidance of corticosteroid-induced adverse psychiatric effects is reviewed. The literature is not definitive in supporting the efficacy of any specific preventive strategy. A variety of clinical strategies have been proposed, however.

3.1 Identifying Individuals at Risk

Potentially, the identification of individuals at high risk of corticosteroid-induced psychiatric disturbances could facilitate prevention by avoidance of corticosteroid treatment in those individuals. Unfortunately, the literature does not confirm any strong predictors of corticosteroid-induced psychiatric disturbances in individual patients. There are no studies providing clear evidence that a previous history of psychiatric disorder increases the risk of psychiatric adverse effects. One study evaluated a series of overtly mentally ill patients treated with cortisone or corticotropin,[71] and reported only minor psychiatric disturbances.

Some authors have dismissed the possibility that a history of mental illness should be regarded as a contraindication for corticosteroid treatment, and have also asserted that a single corticosteroid-induced disturbance should not be regarded as a contraindication for future treatment.[72] It is worth noting, however, that some case reports described individuals who experienced recurrent psychiatric disturbances when challenged with corticosteroids.[73] Few data are available for identifying clinical groups at increased risk of corticosteroid-induced adverse effects. Based on the observation that adverse effects tend to occur at higher dosages, it is plausible that factors influencing biologically relevant unbound concentrations of prednisolone may increase the vulnerability to toxic effects if these are not countered by dosage adjustments.

According to 1 review of pharmacokinetic data, lower dosages should be considered in the elderly, in patients with liver failure, chronic renal failure, transplanted kidneys and those taking estrogen-containing oral contraceptives or ketoconazole.[74]

A review by Lewis and Smith[75] summarised studies published prior to 1983, including clinical trial adverse effects data. These data were used to evaluate the impact of gender on the risk of psychiatric disturbances. A marked female preponderance was observed, which persisted after exclusion of individuals under treatment for systemic lupus erythematosus. Such a conclusion is somewhat tenuous, however, because of the lack of detailed clinical information. For example, the available data precluded a determination of whether the female preponderance was restricted to clinical syndromes such as depressive disorders that are more common in women generally.[76]

3.2 Dosages and Timing of Administration

The Boston Collaborative Study[77] provided strong prospective evidence of a dose-response relationship: psychiatric reactions occurred in 1.3% of hospitalised patients receiving 40mg of prednisone per day or less, in 4.6% of individuals re-

ceiving 41 to 80 mg/day, and in 18.4% of patients receiving more than 80 mg/day. Hence, doses exceeding 40mg may be associated with an elevated risk of adverse events. One clinical trial of prednisone (with or without minoxidil) in the treatment of alopecia areata reported a statistically significant correlation between mg/kg exposure to prednisone and emotional lability.[78] Case reports suggest, however, that adverse effects can also rapidly follow exposure to very low dosages.[19] Glynne-Jones et al.[79] reported 2 cases where psychiatric toxicity was apparently avoided by dividing the daily dose. These authors speculated that lower peak plasma concentrations were responsible for this.

As described in section 2.2, some studies have reported the emergence of psychiatric symptoms in association with alternate day treatment with corticosteroids.[32,33] On the other hand, Cordess et al.[80] investigated a sample of outpatients with neuromuscular disease, finding that individuals on high-low dose alternating schedules (mean prednisone dose of 65mg) had low general psychopathology scores. The literature also contains case reports of psychotic episodes in the context of pulsed corticosteroid therapy.[47] These reports emphasise that certain individuals may react very badly, or indeed very well, to various dosage schedules.

3.3 Adverse Drug Interactions

The risk of psychiatric corticosteroid-induced adverse effects is apparently dose related.[77] As such, pharmacokinetic interactions involving the metabolism of corticosteroids may, in theory, precipitate adverse reactions. Finkenbine and Gill[81] speculated that inhibition of metabolism of cytochrome P450 (CYP) 3A4 substrates by clarithromycin may have resulted in a manic episode occurring in a patient taking 20mg of prednisone by increasing plasma concentrations of unbound prednisolone (which is oxidised by CYP3A4). However, direct evidence of a pharmacokinetic interaction was not provided. In theory, antidepressants that inhibit CYP3A4, such as nefazodone may increase risk by the same mechanism.

3.4 Pharmacological Preventive Measures

In an early report, Falk et al.[82] described the use of lithium as a preventive strategy for 27 unselected patients receiving corticotropin treatment for multiple sclerosis. These authors reported an absence of clinically relevant mood disturbance in these patients, which contrasted with their previous experience at the same clinic (where a retrospective chart review indicated that 6 out of 44 previous patients treated with the same regimen had developed clinically significant disturbances). This early report has contributed to sustained interest in the use of mood stabilisers to prevent psychiatric toxicity associated with corticosteroid treatment.

Goggans et al.[73] described 1 case where lithium pretreatment may have prevented the recurrence of a psychotic episode associated with manic features in a woman with pulmonary hypertension who required prednisone treatment, a finding echoed by Siegal.[83] Another case report described the successful use of a combination of lithium, protriptyline and haloperidol in preventing the recurrence of a melancholic depressive episode in a 34-year-old woman with ulcerative colitis requiring corticosteroid treatment.[84]

Saklad[85] advised caution with the use of lithium in corticosteroid-treated patients in view of the theoretical risk that corticosteroid-induced changes in sodium balance might increase the risk of lithium intoxication. Careful monitoring of serum concentrations was advised. A need for careful supervision of lithium levels in patients with systemic lupus erythematosus, in view of the possibility of renal impairment, has also been identified.[27] In one case where a relative contraindication to lithium existed, an excellent response to an alternative mood stabiliser, carbamazepine, was reported.[86] However, carbamazepine has the capacity to decrease serum concentrations of prednisolone,[87] probably by enzyme induction. This suggests that corticosteroid dosages may need to be increased in patients taking carbamazepine.[74]

An additional possibility, in view of evidence that corticosteroid adverse psychiatric effects are dose dependent, is that the reported effectiveness of carbamazepine may relate to its capacity to reduce serum levels of prednisolone, in which case increased dosages of corticosteroid medications may partially or wholly offset its therapeutic benefits. This possibility has not yet been evaluated. The literature contains a single report describing the use of chlorpromazine to prevent recurrence of a psychotic episode in multiple sclerosis patients who had experienced psychotic episodes during 2 previous courses of corticosteroid treatment.[88]

The literature contains few data on the role of valproic acid (sodium valproate) as a pharmacological preventive measure. A few case reports suggest possible efficacy,[89,90] but all reported cases have been complicated by the existence of multiple potential aetiologies for the mental disturbances described and the simultaneous use of multiple medications. No empirical studies have evaluated the efficacy of valproic acid for the prevention of corticosteroid-induced psychiatric adverse effects.

4. Management of Adverse Psychiatric Effects of Corticosteroids

As with the literature concerned with pharmacological preventive measures, almost all available information concerning the management of corticosteroid-induced neuropsychiatric adverse effects derives from case reports. Generally, treatment efficacy in modern medicine requires confirmation from randomised clinical trials and none have been conducted in this area. While deficient by scientific standards, case reports provide the only available guidance for clinical decision making in this area.

Wyszynski and Wyszynski[45] described 1 patient with Sjögren's syndrome who repeatedly developed severe depressive episodes during or soon after the corticosteroid taper. These episodes responded rapidly (within approximately 7 days) to treatment with fluoxetine at dosages ranging from 10 to 40 mg/day. Another case report has described the successful use of imipramine in the management of corticosteroid-induced depression and panic attacks.[44] Earlier concerns regarding the tolerability of antidepressants in corticosteroid-treated individuals may have been overstated (see section 2.3), but the tolerability of these medications has not been empirically confirmed either. Recently, the successful use of olanzapine in the treatment of a patient with prednisolone-induced mixed mood disturbance has been reported.[91]

Blazer et al.[92] reported primarily favourable responses to electroconvulsive therapy for depressed patients, and to lithium for those displaying manic features. Terao et al.[27,93] have described the successful use of lithium in a series of patients with depressive disorders where clinical observations suggested an aetiological role for the corticosteroids. Lynn[86] subsequently argued that some of these individuals might have had mixed episodes.

Nonpharmacological approaches to management have not been investigated. However, Ismail and Wessely[94] encouraged the application of suicide prevention measures and also suggested that reducing environmental stimuli may be helpful. A concern that patients experiencing adverse psychiatric reactions to corticosteroids may be at especially high risk of suicide was expressed by Bräunig et al.[95] who noted that almost one-third of patients with 'steroid psychosis' at the Bonn psychiatric clinic experienced suicidal ideation. Finally, in circumstances where symptoms emerge during corticosteroid withdrawal, re-initiation of corticosteroid treatment may be a therapeutic option.[69]

Reckart and Eisendrath[96] described a series of 8 volunteers from a chest clinic who had been treated with long term corticosteroids. This case series differed from many other published studies because the volunteers were interviewed about their experiences with corticosteroid treatments, distinguishing this case series from those which have tended to report specific adverse reactions from a clinician-centred perspective. While the individuals reported the expected mixture of mood, anxiety, psychotic and cognitive disturbances (often describing distinctly different reactions to similar courses of corticosteroid treatment), they also

commented that they had rarely been warned of possible psychiatric adverse reactions, that they were fearful of reporting their adverse reactions to their physicians out of fear of being labelled crazy or insane, and that the reactions were much more tolerable when they were made aware that these could be simple adverse drug reactions.

These observations suggest that physicians and pharmacists should be more proactive in discussing the possibility of corticosteroid psychiatric adverse effects, and that doing so may minimise the problems associated with these adverse reactions.

5. Conclusions

Problems arising from the use of nonspecific terminology in the literature have received emphasis in this review, and have been noted by previous authors. The term 'steroid psychosis' could refer to a heterogenous set of circumstances, possibly with very different clinical implications. This term is no longer a clinically useful one. Corticosteroid-induced psychiatric adverse effects can be unpredictable and severe. However, the literature suggests that the application of syndrome-directed conventional pharmacological preventive and treatment strategies are often effective.

Nonpharmacological interventions involving education (particularly the inclusion of psychiatric disturbances with adverse effect information provided to patients) and support may be important, and sometimes neglected, aspects of management. At the system level, the complexity of the diagnostic and therapeutic issues presented by corticosteroids suggests that clinical services using these medications need to have ready access to psychiatric support. Moreover, psychiatrists involved in the management of these disturbances must be highly competent in mental status assessment, and be prepared to deal with relatively complex psychopharmacological issues.

The literature concerned with the prevention and management of corticosteroid-induced psychiatric adverse effects is rudimentary, and essentially contains large amounts of clinical anecdotes regarding prevention and management strategies. While these clinical reports currently provide the only available direction to clinicians in managing these problems, they require validation by formal studies.

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