Steroid psychosis: a review

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Abstract

This review is built upon a time-framed perspective to unfold the growth of evidence and the shifting of focus from primary affective short-term reactions to later findings of cognitive deficits and possible permanent impairment linked to steroid treatment. An incidence related to dosage has been documented and delirium and withdrawal symptoms have been reported in later studies. A hypothesis of sensitization process with multiple course of steroids has been proposed with the reporting of recurrent cases. The issue of individual risk appears unsettled while management of psychiatric reactions to steroids has shifted toward prophylactic use of lithium. © 2003 Elsevier Science Inc. All rights reserved.

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1. Introduction

For the last half-century, corticosteroids have been widely used and prescribed for a variety of systemic diseases. Cortisone was first made available commercially in July 1950 [1] and the first reports about psychiatric side effects came out the same year [2]. As early as 1952–53, psychiatric symptoms associated with the clinical use of corticosteroids have been documented and detailed [3]. These first observations dealt with psychological response [1], psychiatric risk [4] and mental disturbances [3,5] associated with corticosteroid therapy. The understanding of the nature of such psychiatric reactions awaited further observations and research. The aim of the present review is to unfold the building of such evidence through a time-framed perspective of cumulative observations and hypotheses.

Such an approach is both useful and relevant to examine the unfolding of evidence and the interplay of clinical findings and working assumptions. Data retrieved for the construction of the review were obtained from two main sources: aggregated references taken from recent reviews and a Medline search covering the past fifteen years. The paper is a blend of recent selected data and a re-examination of earlier observations. It is not meant to cover all available data. The review is divided into three parts: early reports (1950–70); first-generation reviews and later reports (1970–83); and second-generation reviews and recent reports (1983–2002).

2. Early reports: 1950–1970

Two sets of material make up the initial mapping of the field: seminal articles on the psychiatric effects of corticosteroid treatment (1950–54) and various papers reporting on cohorts of patients with chronic diseases under corticosteroid treatment and providing information about psychiatric side effects. Early papers focused on the outline of symptomatology and natural history of psychic reactions to corticosteroid treatment. To establish a clear relation, cases were selected so that none had a past history of psychiatric illness, none had any endocrinologic problem and none had any other factor suggesting a toxic psychosis related to some other drug or medical condition. Affective symptoms were noted: mood elevation, euphoria, feeling of well-being and insomnia [1]. Symptoms were not related to overdosage and previous tolerance to steroid treatment was found not predictive of later reactions. Finally, complete recovery was reported.

Clark [3] excluded patients “exhibiting only euphoria of slight or moderate degree” as “the increased joviality and optimism have been seen in nearly all cases” (p. 205). Clinical findings included affective distress both depressive and hypomanic, with disturbances of speech, from mutism to press of speech; depersonalization, derealization and distortion in body image were also noted along with insomnia,
emotional lability and impaired memory. Further observations of more complicated cases extended the clinical profile. In thirteen additional cases reported by Clark [5] three were found to have a serious depressive reaction, seven displayed paranoid features and hallucinations, while only two were manic and one had a cerebral tumor. The notion of toxic psychosis was put forward even though the classic features of such conditions—desorientation and confusion—were found not characteristic of psychoses associated with corticosteroid treatment. Patients with a history of previous psychotic episodes were not found to be more liable to a steroid psychosis although the course of such reactions could be longer in those cases should it happen. Finally, the duration and severity of the steroid psychosis were not greater in those patients who broke down early and under small dosage of hormone. Symptoms were not attributed to toxic deliria (p. 215), drug withdrawal (p. 214) or drug dosage (p. 214). Caution was advised with patients having a past history psychiatric illness. Lewis and Fleminger [4] reported observations that did not support that caution.

These early reports put forward two hypotheses to explain such observations: a reprieve from painful invalidism and a relief from symptoms of systemic toxicity [1]; hence it was thought that such psychological response was a reaction to a better physiological state. Either hypothesis emphasized a mediated psychological reaction to corticosteroid treatment as such psychic changes could not be "commonly associated with demonstrated metabolic changes" (p. 147).

The same period produced various reports about cohorts of patients with selected chronic problems treated with corticosteroids. The data collected from these reports are difficult to assess and use at face value for two reasons: the uneven level and the incidental aspect of provided information. For instance, a case-control study [6] of pulmonary patients concluded that a previous psychiatric history does not indicate a particular risk (p. 575). However, two thirds of the patients received very low dosage (less than 10 mg of Prednisone daily) and, though the numbers are small, a breakdown of cases with a 2x2 table shows that patients with a past psychiatric history have at least a fivefold incidence of psychiatric reactions to corticosteroid treatment. As these early studies are not meant to provide a specific evaluation of the psychic reactions, most of them (as reported in Table 2, Brown and Suppes [7] (p. 242) do not carry such item of information as whether the patient had a psychiatric history. The clinical description of psychiatric symptoms also wants in accuracy. But two controlled studies [8,9] showed a greater frequency of psychosis in patients treated with corticosteroids than when given other drugs for the same diseases, supporting the regular higher incidence of psychosis associated with such treatment in any population. Two additional studies [10,11] about rheumatoid arthritis patients suggested a female predominance in psychiatric reactions to corticosteroid treatment.


First-generation reviews came out about 25 years after the first observations of psychiatric symptoms associated with corticosteroid treatment. The more influential are those of Hall [12] in 1979 and of Lewis & Smith [13] in 1983 that is taken as a cutting point. Both reviews added 14 new cases each to the 65 odd cases (79 with those of Hall) retrieved by Lewis in the literature. Basic data were expanded to map a more elaborate clinical profile of such psychiatric reactions.

**Incidence** was found to vary. Out of 29 studies of the clinical efficacy of corticosteroid treatment in medical conditions, Lewis calculated a weighted incidence of 5.7%, with no difference between reports before 1960 and later ones. As found earlier, such studies showed a greater frequency of psychoses in patients treated with steroids than those given other drugs for the same disease, ulcerative colitis [8,9] and lupus nephritis [14].

#### 3.1. Symptomatic profile

Two clinical profiles (Table 1) came out from the 130 cases tabulated for this review: an affective profile and a toxic-organic profile. For the sake of clarity, all cases available within the three time slots were lumped together here, including 79 collated by Lewis in the literature, 14 additional provided by Lewis [13], and 37 new cases retrieved for this review [Villareal [15], Wada [16], Wada [17], Sharfstein [18], Stoudemire [19] and Finkenbine [20]. Table 1 shows the relative frequency of both types.

The affective profile includes mania, depression, and mania and depression; these comprise 75% of cases. Psychotic (hallucinations) symptoms are often associated, up to half the cases. Mania is more frequent than depression.

### Table 1

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N.</th>
<th>%</th>
<th>Lr</th>
<th>Lc</th>
<th>V</th>
<th>W1</th>
<th>W2</th>
<th>Sh</th>
<th>St</th>
<th>F</th>
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<tr>
<td>mania</td>
<td>.47</td>
<td>(35%)</td>
<td>22</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>depression</td>
<td>.37</td>
<td>(28%)</td>
<td>32</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>mania &amp; depression</td>
<td>.15</td>
<td>(12%)</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>delirium</td>
<td>.17</td>
<td>(13%)</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>—</td>
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<tr>
<td>psychosis</td>
<td>.14</td>
<td>(11%)</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

Lr = Lewis’ review; Lc Lewis’ cases; V = Villareal; Wada1 = Wada 2001; Wada2 = Wada 2000; Sh = Shafstein; St = Stoudemire; F = Finkenbine
Early lead signs for affective symptoms are mainly insomnia, distractibility and excitation; and later, hyperactivity, euphoria, pressured speech and irritability might be present, while apathy and mutism will appear for depression. The toxic-organic profile of delirium and psychosis makes for 25% of cases. Early lead signs for the toxic-organic profile include confusion, perplexity, agitation; hallucinations, delusions and thought impairment are present in full-blown psychosis.

3.2. Clinical course

Median onset of psychiatric symptoms after the start of steroid treatment is an unsettled aspect: 3–4 days as reported by Hall [12] and 11 days as reported by Lewis [13]. Inspection of Lewis’ fourteen cases shows a bimodal pattern: an early onset (about 4 days) similar to the data from Hall in seven cases, and a late onset, about 3 weeks into the treatment, in seven cases. Drug dosage and clinical profile are not discriminant for time of onset. Duration of symptoms is ill-defined in the literature and the use of the mean as a measure is misleading. Data from Lewis’ cases show a difference according to the clinical profile. Delirium lasts a few days, psychosis around a week, mania about 2–3 weeks and depression longer. But the numbers are small and only rough estimates and the severity of symptoms within each group is not discussed. Moreover, although the toxic-organic profile makes for 6 out of 14 cases, Lewis reports that 50% of patients were found to recover within 2 weeks and 90% within six weeks. Outcome is complete recovery in over 90% of cases. Hall’s data show that half cases improved within 4 days, half in about two weeks. A tail-off period of a few additional days were needed in some patients while others had their symptoms abated quicker. There is no indication in Hall’s data that the toxic-organic group improved faster than the affective group.

3.3. Patient factors

According to Lewis, age appears not significant (39.6 yr in cases and 42.7 yr in controls) and is related to the underlying medical pathology to be treated. Distribution of cases by sex shows that twice as many female as men are found to have psychiatric reactions to corticosteroid treatment. In the 130 cases collated for this review, data about 115 (Villareal’s data are incomplete) show 77 females and 38 males, a 2/1 ratio. It may only imply that more women are affected with diseases that require steroid treatment. Lewis tried to check this point; first by excluding systemic lupus erytematosus and rheumatoid arthritis patients where the F/M ratio is around 9/1 and 3/1, respectively, resulting in a 60/40 F/M ratio; second by reviewing clinical trials where the incidence by sex was reported resulting in a 19.7% to 3.3% female to male ratio in such studies. The incidence of psychiatric reactions to corticosteroid treatment according to the underlying medical conditions to be treated is not significantly higher than the expected one in ulcerative colitis, rheumatoid arthritis, lymphoma. However, patients with SLE do have a higher incidence of corticosteroid-induced psychiatric symptoms. History of psychosis during previous steroid treatment does not predict later relapses with further treatment [12, 13]. Where relapses occurred the clinical profile was different from first reactions [12]. Data about history of psychiatric illness unrelated to corticosteroid treatment show that 7 out of 55 cases (12%) where information is available (41 retrieved by Lewis and his own 14 cases) have such a history. As no data are available for controls neither Hall nor Lewis found it significant, confirming earlier findings by Lewis and Fleminger [4] in 1954.

3.4. Treatment factors

Lewis’ review confirmed the increased incidence of psychiatric reactions to steroid treatment with increasing average daily doses of prednisone. The observation first made in 1972 by the Boston Collaborative Drug Surveillance Project [21] was confirmed in the collated cases retrieved by Lewis, as well as studies by Sergent [22], Rosenberg [23], and Hall [12] as 77% of patients with psychiatric reactions had been receiving doses greater than 40 mg/day. However, the dose-response effect could not be demonstrated to apply to earlier onset of symptoms or longer duration of such reactions. Lewis examined data about 17 cases that had had a previous course of corticosteroid treatment. There was no evidence that the presence or absence of a psychiatric disturbance during the initial course predicted the response to a subsequent course. Contrary to early reports, Lewis [13] further reported that a small percentage of patients have persistent symptoms. He first reported that one of 14 patients had a mild permanent impairment of cognitive function.

3.5. Management

Tapering of corticosteroid dosage and administration of psychiatric drugs for symptom relief were the two main options (13, p. 327). Lewis found that tapering only brought recovery in 92% of 36 patients, neuroleptics only brought recovery in 84%, and 100% of 8 patients managed both ways recovered. Psychiatric drugs used for symptom relief included neuroleptics and tricyclic antidepressants. Tricyclic antidepressants used in patients with depressive reactions worsened the condition that was reversed with phenothiazines [12]. Dosage of neuroleptics used to bring improvement had to be ascertained case by case. Some patients improved rapidly with low dosage while others needed higher dosage for a longer period. Most patients improved in the first three days with a tail-off period to bring complete recovery (12, p.232). In 1979, Falk [24] used lithium as prophylaxis for corticosteroid-induced psychosis with beneficial effects.

A new set of second-generation reviews came out about twenty years later (1998–2000) by Brown [7,25] and Patten [26]. At this time, approximately ten million new prescriptions for corticosteroids were issued each year in the United States [25]. Additional aspects of psychiatric reactions to corticosteroid treatment are now described and discussed: long-term deficits, cognitive impairment, withdrawal symptoms; prevention of such reactions are proposed. Recent reviews pay more attention to the quality of evidence provided by various sources of information.

4.1. Clinical aspects

The area of affective responses to corticosteroids has gained scant additional evidence. Comparison has been made with excessive endogenous corticosteroids in Cush- ing’s syndrome patients; over half of these cases were found to be depressed and about 30% had manic symptoms, some antedating the depressive symptoms [27, 28]. Simple euphoria, as distinct from hypomania, was regarded as a reduction of dysphoria secondary to clinical improvement subsequent to corticosteroid treatment. However, Swinburn [29] showed that mood improvement preceded improvement in physiological measures in a series of patients with chronic obstructive airway disease, suggesting a primary effect on mood. Brown [30] also recently showed that mood changes were not correlated with improvement in airway obstruction in asthma patients. The association of psychotic symptoms to affective ones remain an unsettled question. Some investigators like Naber [31] found none in a series of ophthalmologic patients while early reports by Clark [5] described the association as frequent. Wada [16] studied patients with recurrent corticosteroid mood disorders and reported subacute onset, predominance of mania and more frequent accompanying psychotic symptoms than those found in single episode cases. Brown [30] found that mild mood changes occurred early (3–7 days) into the treatment and returned to baseline 10 days off prednisone, in the context of a short course (14 days) of treatment in asthma patients.

Cognitive deficits have been reported associated with either short-term (Naber [31]) or long-term (Keenan [32]) steroid treatment. The specific deficit is memory impairment of the declarative (verbal) type, and is related to involvement of the hippocampal areas (Wolkowitz [33], p.1301). That impairment may be reversed with the reduction or withdrawal of corticosteroids (Newcomer [34]). However, Varney [35] reported on six cases where “steroid dementia” lasted many months and recovered very slowly from their memory deficits. Four of these patients had not developed an acute “steroid psychosis”; the two other cases showed intellectual impairment after the steroid psychosis had resolved.

Delirium has been also reported but confusing evidence still shadows proper ascertainment of such reaction as associated with corticosteroid treatment. The evidence is based only on occasional case reports and the following confounding variables are present: 1) the general clinical state: reported in cancer patients (Stiefel [36]) where the toxic state or concurrent treatment is not given; 2) reported as a withdrawal syndrome (Campbell [37], Baloch [38]); 3) reported as corticosteroid-induced (Stoudemire [19]) in an addicted patient; and 4) could be considered as part of an acute psychotic reaction in a severely ill patient (Clark [5], Case 6). Patten [26] suggested also that some of the cases described by Hall [12] as worsening with tricyclic antidepressants treatment of the steroid psychosis might be occurrence of a worsening delirium aggravated by the anticholinergic effects of such drugs. The four cases of delirium in Lewis’ series are not explicitly described. The symptomatic configuration of delirium needs therefore further detailed global clinical assessment.

Withdrawal symptoms have been reported with cessation of corticosteroid therapy, basically with long-term treatment. As early as 1951, Freyberg [39] had described a corticosteroid withdrawal syndrome characterized by fatigue, anorexia, discouragement and depression in 20% of patients with rheumatoid arthritis. Wolkowitz [40] reported on two cases with depersonalization, fatigue and decreased energy. Dixon [41] had given earlier (1980) a clear outlook of the condition. He gave evidence of three types of withdrawal: type 1 is linked with biochemical evidence of HPA (hypothalamic-pituitary-adrenocortical) function; type 2 is associated with a recrudescence of the symptoms of the disease for which corticosteroids were prescribed; type 3 is defined as the true drug dependence, whether physical or psychological. The symptomatic psychiatric pattern of steroid withdrawal is diverse: delirium (Campbell [37]), mania (Venkatarangam [42]), and depression (Wolkowitz [40]).

4.2. Patient factors

There are very few leads in the literature to identify individuals at risk for steroid psychosis. According to Patten [26], there are no studies providing clear evidence that a previous history of psychiatric disorder increases the risk of psychiatric adverse effects of steroid treatment. Data provided by early studies stood still. However, Brown [30] in a recent study of asthmatic patients suggested “that psychiatric history might predict mood responses to corticosteroid treatment” (p.59). Subjects (N=16) with a history of depressive disease had a significantly smaller increase in mania (as measured by scale and not clinically), a few days into the treatment, as opposed to subjects (N=10) without such history. Also, 50% of subjects (N=6) with a history of posttraumatic stress disorder had a worsening of depressive aspects (measured by scale). Wada [16] studied nine patients with recurrent corticosteroid-induced mood disorders. None had previous psychiatric episodes, all had their first episode as a result of steroid treatment, and none had a
family history of psychiatric disorder. But a bipolar mood disorder seemed to have been activated by corticosteroid treatment as later non steroid-induced episodes occurred. All but two had at some later point episodes unrelated to steroid therapy. Seventeen of the manic bouts occurred after an increase in corticosteroid dosage while only 3 of 11 episodes were corticosteroid-induced. It appears as if steroid treatment triggered in these patients a genuine bipolar mood disorder. This would be consistent with Pies’ observation [43] of a persistent bipolar illness after corticosteroid administration. Three of these patients had Systemic Lupus.

4.2.1 Treatment factors

Various aspects in the administration of corticosteroid treatment have been studied to look for ways of preventing the occurrence of psychiatric complications. Although it has been suggested (Brown, [7]) that chronic long-term corticosteroid treatment may increase depressive symptoms while acute corticosteroid therapy might be associated with mania, the data provided by Wada [16] do not support this position nor Lewis’ review which presented 6 out of 17 patients who had recurrent episodes during other courses of steroid therapy. Hall [12] reported also two recurrent episodes but the information provided is unclear. Whatever the symptomatic profile, the potential risks of multiple courses of steroid treatment have not been explored. Already in 1953, Clark [5] had reported that 5 of 13 patients had tolerated a previous course of steroid treatment without complications and became psychotic during a subsequent course of treatment with comparable or even smaller doses; two of these cases were quite ill from a medical standpoint. Brown [7] suggested that “if a sensitization process of increased symptoms with multiple course of steroids is observed, this could model a phenomenon hypothesized to occur in bipolar patients, in whom having multiple episodes appears to lower the threshold for future episodes.”

Various modes of corticosteroid administration were studied in relation to behavioral abnormalities. Some early studies suggested that alternate-day corticosteroid therapy reduced the incidence and severity of somatic toxic effects; it was hypothesized that the benefit would also apply to psychiatric reactions. Although this regimen is the treatment of choice for long-term maintenance on steroid therapy, as to mimic the circadian cycle of cortisol and minimize the HPA axis suppression, Sharfstein [18] reported on three patients who displayed a rapid type of bipolar cycling when exposed to such treatment, being excited and agitated on prednisone days and depressed and lethargic on alternate days. Glynne-Jones [44] had proposed divided daily doses to prevent or reduce the severity of steroid psychosis, and claimed that subsequent change to enteric-coated prednisolone led to the return of a normal state. That last assumption had been challenged by Tomson [45] on grounds that such mode of administration leads to unintended dose reduction due to variability of absorption. But the hypothesis suggests that peak plasma level may be a factor in such reactions.

More recently, drug interaction during corticosteroid therapy has received attention. Finkenbine [20] reported on a case of mania due to prednisone-clarithromycin interaction. Such effect was accounted for by the antibiotic’s ability to inhibit cytochrome systems (CYP450 for hydroxylation, CYP3A4 for oxidation) responsible for the metabolic clearance of prednisolone with possible elevation of the plasma levels of the corticosteroid. It should be noted however that delusional delirium has been reported with the administration of clarithromycin [46]. Studies [47,48] of corticosteroid pulse therapy, iv high-dose methylprednisolone, have not reported more frequent psychiatric complications, but Wada [16] suggests its use in patients with recurrent steroid-induced mood disorders might be associated with a rapid manic flare-up.

4.3. Management of psychiatric reactions to corticosteroids

The classic stand is to try to taper steroid treatment and administer phenothiazines (Lewis [13], p.327). Hall [49] had reported earlier that patients given tricyclic antidepressants did not respond well and worsened their clinical psychiatric condition. The observation still stands. Trials have been made to prevent psychiatric reactions to steroid psychosis by lithium prophylaxis. Earlier also, Falk [24] had reported that none of 27 patients given such treatment during corticosteroid therapy developed a psychotic reaction; in a control group of 44 multiple sclerosis and retrobulbar neuritis patients not given lithium 6 cases of affective psychoses occurred. Goggans [50] and Siegal [51] reported similar results. However, in clinical practice quite a few diseases treated with corticosteroids provoke renal dysfunction, also corticosteroid-induced changes in sodium balance might increase the risk of lithium intoxication. Wada [16] advocated the use of mood stabilizers in such occurrence, carbamazepine or valproate, as does Abbas [52]. But carbamazepine has the capacity to decrease serum concentrations of prednisolone [52]. A study [53] reported on the beneficial effect of fluoxetine, a serotonin reuptake inhibitor (SSRI), on corticosteroid-induced depression. While olanzapine [54] and risperidone [55] have been used in the symptomatic treatment of psychic reactions to corticosteroid treatment, its use appears limited to subacute cases. Up to now haloperidol remains a widely used neuroleptic to control most psychotic reactions to steroid therapy because its versatile mode of administration (po;sc;im;IV) makes it easier to adjust to both acute and subacute clinical situations.

5. Discussion

The clinical aspect of psychiatric reactions to corticosteroid treatment has gained more depth with fifty years of
observations. Despite the bimodal pattern described in this review, the clinical presentation of cases is often less clear-cut and more changing in actual clinical conditions. The frequent reference in many reports to psychotic symptoms in manic or depressive cases begs finer description. The term “steroid psychosis” covers a large span of predominantly acute psychiatric syndromes; its usefulness lies in stressing the potential of corticosteroids to produce psychic symptoms. At this point, a larger three-level clinical frame could be proposed for such reactions; first level: a mild, non-pathological and subclinical euphoria, as Swinburn’s study supports Clark’s early reports about such a general, non-specific and frequent occurrence; second level: a full-blown reversible acute or subacute reaction of psychiatric proportions along the bimodal pattern already described; and third level: as suggested by Wada’s study of recurrent cases, a bona fide bipolar disorder induced by a course of corticosteroid treatment, liable to relapses without corticosteroid induction.

Steroid psychosis still presents many unsettled clinical aspects. Modes of onset and recovery need a more accurate description. Clinical reports deal equally with acute and subacute onsets. There is no evidence that any of the two main clinical profiles pertain to a specific mode of onset. More research about individual risks is called for to examine the possibility that mode of onset is bound to different susceptibility. Rapid recovery after tapering of corticosteroids is another obscure clinical aspect. But for Lewis’ review, data about the use of only one single mode of management (tapering or neuroleptics) are lacking. Isolated case reports might be biased toward the publication of long-lasting and difficult cases rather than swift and self-abating side effects of medical treatment. Complete recovery used to be the paradigm. Two factors call for a reconsideration of this paradigm: the expanding literature about the cognitive effects of corticosteroids and some reports of persistent bipolar disorders following corticosteroid treatment. Both point to a small proportion of cases with long lasting changes. A related aspect is the impact the duration of corticosteroid treatment, whether acute burst or chronic administration, might have on the onset of clinical psychiatric reactions; data are lacking.

The issue of individual risks wants further research. Indicators of such risks are scarce, and frequently reduced to two: history of psychiatric illness and previous course of corticosteroid treatment. Both appear unreliable but recent research suggests that the long held idea about past psychiatric illness as not significant is in need of reexamination. The issue of sensitivity to recurrent reactions is also poorly understood.

Much attention has been paid during the last period (1983–2002) to the prevention or prophylaxis of such reactions. Two areas have been explored: lithium prophylaxis and modulation of corticosteroid administration. So far no study has disproved the beneficial effect of lithium prophylaxis for long-term corticosteroid administration. Whether the practice should be a standard is unsettled. There is no clear evidence at this time that a specific mode of corticosteroid administration will reduce the incidence of psychiatric complications, either those geared at peak plasma level (divided daily dose or pulse therapy) or those aimed at the circadian rhythm model (alternate day dosage).

Recent research has shown changing paradigms both in methods and research assumptions. Many recent studies have used research-oriented scales for measuring psychiatric aspects. There is no discussion of the clinical relevance of the scales to the actual management of patients. Research assumptions have moved from a psychosomatic stand (the mediation of psychological status through physiological changes) to some chemical engineering related to corticosteroid administration. Accrued gain in clinical accuracy of the main medical treatment has not carried over a better understanding of psychiatric complications. This suggests the necessity of a twofold approach to such clinical problem: detailed case histories and clinical trials. The first are needed to document unsettled clinical questions and account for many confounding variables such as previous corticosteroid courses, general clinical status, concurrent administration of other drugs, premorbid information about personality. While case histories are needed to account for the complexity of clinical parameters, clinical trials can only address simple questions to be resolved one by one. As such trials are mainly geared towards the main treatment information about steroid psychosis is too often only incidental or collateral. Hence anecdotal evidence attributed to clinical reports might apply as well to many clinical trials, unless specifically designed which is difficult, and does not mean absence of relevant qualitative information. Clinical reports are necessary for hypothesis making, clinical trials necessary for hypothesis testing. The problem is that hypotheses are more easily supplied than proved. It is thus puzzling but understandable to find that many questions and hypotheses raised by the very first seminal studies in the early 1950s are still not answered adequately.

References
