Corticosteroids are generally believed to induce a wide range of psychological changes. Textbooks of therapeutics, psychiatry and endocrinology record that administration of corticosteroid drugs or adrenocorticotrophin most commonly result in a high incidence of mood elevation, cheerfulness and optimism. Less frequently there is frank euphoria, irritability, insomnia, increased motor activity and hypomania. A smaller percentage of patients, particularly those on high doses of corticosteroids, become anxious or depressed and apathetic, while a still smaller percentage develop psychoses with hallucinations, delusions and features of depersonalization (Goodman and Gillman, 1980; Kolb and Brodie, 1982; Kaplan, Freedman and Sadlock, 1980; Reichlin, 1981).

These beliefs are based on case reports which started to appear shortly after the introduction of corticosteroids as therapeutic agents. Many report psychotic reactions after starting corticosteroid treatment (Borman and Schmellenberg, 1951; Clark, Quarton and Cobb, 1953). Euphoric and depressive responses are also described (Rome and Brancel, 1952), and such reports have continued to appear (Baloch, 1974; Sharma and Gajwani, 1973; Kauffman et al., 1982). However, evidence that corticosteroids are directly linked to psychological change based on such case reports is insufficient. A causal role for corticosteroids is suggested if the mental disturbance appears shortly after starting the drug and remits on stopping. Unfortunately such case reports are invariably complicated by the use of psychotropic drugs to control symptoms. Furthermore, most reports have been of the steroid-induced psychoses which are relatively easy to recognize and characterize. Even if a causal connection is established here it does not apply to the much commoner and more subtle changes in mood which are said to occur but which are much more difficult to quantitate.

An early study (Rome and Brancel, 1952) stressed the variety of psychological abnormalities seen and divided corticosteroid-induced mental changes into mood elevation, euphoria, psychoneurosis and psychosis. Five patients were described who were thought to have such steroid-induced changes—all of whom had had previous major psychiatric abnormalities. However, a causal link between introduction of steroids and worsening of psychological state is far from clear in this study, frequently quoted in subsequent literature, as insufficient detail is provided. Lewis and Fleminger (1954) tested the hypothesis that a previous psychiatric history was a necessary condition for the development of a steroid psychosis when treating 12 patients (eleven with rheumatoid arthritis and one with systemic lupus erythematosus) with an unequivocal history of mental disturbance with cortisone (maximum dose 100 mg/day), for concomitant organic disease. Patients were observed and underwent psychological testing for 6 weeks, received placebo for 10 days, and then received cortisone for 5.5-7.5 weeks. Cortisone was then withdrawn. All improved as regards symptoms of arthritis initially, and all except one relapsed on cortisone withdrawal. All had mental improvement in parallel with physical improvement. As pain and disability subsided, gloom and depression lifted, and returned when relapse occurred. The authors of this detailed study concluded that mood change was generally the result of symptom relief and that corticosteroids had no direct euphoriant effect. They also suggested that psychiatric history was not a contra-indication to steroid therapy.

Subsequently, larger studies have investigated various aspects of possible corticosteroid-induced mental change and give some indication of the frequency of such changes. In 240 in-patients on corticosteroids a correlation between dose, serum albumin and incidence of side effects was found. Ten patients (2.4%) developed psychoses (Lewis et al., 1971). In another report of 718 consecutive in-patients on cortico-steroids, 21 (3%) patients developed acute psychological changes (Boston Collaborative Drug Surveillance Program, 1972). None of these patients were thought to be emotionally unstable before corticosteroid treatment. Eight had inappropriate euphoria, and 13 became psychotic, of whom
two were depressed and six were manic. All remitted when corticosteroids were stopped or reduced although psychotherapeutic drugs were used in the 13 psychotic patients. The mean dose of prednisolone in patients with psychological side effects was 59 mg/day whereas that of the whole group studied was 32 mg/day. There was a significant relation between dose and incidence of mental change. Of 463 patients on less than 40 mg prednisolone/day, the incidence was 1.3%; of 175 patients on 41–80 mg/day, the incidence was 4.6% and of 38 patients on greater than 80 mg, 18.4%. However, it could be said that patients requiring very high doses of corticosteroids obviously have serious organic disease which itself carries a high incidence of psychiatric complications when compared with mild or moderate disease and perhaps the incidence of psychosis is surprisingly low in the patients requiring such high doses. This point is developed by Kaufman et al. (1982) who emphasize the difficulty of distinguishing between toxic psychosis induced by steroid drugs, delirium associated with severe organic disease, the direct effect of organic disease on the central nervous system from metastatic neoplasm, vasculitis, hypoxia or electrolyte disturbance, and coincidental functional psychosis. The incidence of psychosis in the Boston study (Boston Collaborative Drug Surveillance Program, 1972) agrees with that of Hall et al. (1979) who found that 5% of patients taking more than 40 mg prednisolone/day became psychotic between 2 and 23 days (mean 6 days) after starting treatment.

Further attempts to establish a causal relationship between corticosteroids and psychological disturbance have been made by making retrospective surveys of steroid-treated patients and comparing the incidence of psychosis with that in a control group of similar patients not on steroids. Clearly this approach is problematical as presumably there are good reasons why the study group is on steroids, and the control group is not. The most likely of these is that the steroid-treated group has more severe disease which carries a higher incidence of psychological complications anyway. Marx and Barker (1967) found that six of 50 (12%) patients with ulcerative colitis developed acute psychotic reactions while on steroids whereas only two of 80 (2.6%) patients not taking steroids developed psychoses. Such small differences barely reach statistical significance and do not support the general conclusion that steroid therapy can induce psychoses, particularly as the control group was not matched for disease severity, age or sex. Smyllie and Connolly (1968) compared the incidence of serious psychosis between two groups of patients with respiratory disease who were matched for age, sex, disease and psychiatric history. Ten of 550 (1.8%) patients treated with corticosteroids developed psychosis whereas 16 of 499 (3.2%) patients not treated with corticosteroids developed psychosis. The authors of this study which involved comparatively large numbers of patients conclude that the risk of psychosis was not increased by steroids. However the majority of their patients were on the equivalent of 20 mg or less of prednisolone/day.

Cordess, Felstein and Drachman (1981) studied the mental state of 72 patients with neuromuscular disorders, 39 of whom were on alternate day prednisolone (mean daily dose 35 mg; 65 mg and 5 mg on alternate days). They measured mental state using the General Health Questionnaire. The corticosteroid treated group were less anxious and depressed than the 33 non-steroid treated disease controls and the authors suggested that this might be due to a euphoriant action of the drug, although the control group not on steroids were said to be well matched with the steroid treated group. It is unclear why they were not also on treatment. If they were well matched, but not on steroids they probably had more symptoms and disability resulting in a higher incidence of psychological complaint.

In a prospective randomized study, Cade, Spooner and Schlein (1973) showed that nine of 28 (32%) patients with lupus nephritis taking corticosteroids developed psychoses whereas none of 27 (0%) patients not on steroids did so. However, patients with SLE have a high incidence of psychosis anyway (Stern and Robbins, 1960) and the steroid treated patients in this study received high doses of 60–100 mg prednisolone/day for 6 months. The Boston Collaborative Study (1972), as mentioned above, suggested an increased risk of psychosis for patients on very high doses of corticosteroids.

From these studies several conclusions can be drawn. Firstly there may be an increased risk of psychosis when high doses of corticosteroids are used (Cade et al., 1973; Boston Collaborative Drug Surveillance Program, 1972). Secondly, there is no firm evidence of increased risk when lower doses are used. Thirdly, these studies do not provide information regarding less florid psychological changes and their relation to corticosteroid therapy.

Further evidence for a link between psychological abnormalities and corticosteroids is often cited by considering Cushing's syndrome in which a high incidence of neuroses and psychoses is found (Trethowan and Cobb, 1952). Between 20% and 40% have mental disturbances, depression being the most common (Michael and Gibbons, 1963). Although psychological changes may precede physical change, reactive depression due to change in physical appearance also occurs (Kaplan et al., 1980). Less commonly behavioural disturbances occur with irritability, insomnia, loss of libido, anxiety, emotional...
Do corticosteroids really alter mood?

Corticosteroids, induced directly or indirectly, may produce elevated secretion rates and may produce elevated cortisol secretion which have been observed. Some experiments have suggested that corticosteroids may be used in the treatment of patients who suffer from chronic diseases. However, a wide range of psychological disturbances may occur as a result of corticosteroid treatment. Many other mechanisms for steroid-induced psychological change have been suggested including direct effects on the central nervous system, biochemical and enzyme changes in the brain, and a direct neuropharmacological effect of the drug producing euphoria. There is no convincing evidence for any of these mechanisms which must therefore remain purely speculative.

A different issue that requires separate consideration is the question of mental changes which may occur when corticosteroids are used. Some patients have been reported to become psychologically dependent on corticosteroids to experience a variety of mental disturbances on their withdrawal, including psychotic reactions, depression and agitation.

Conclusion

This brief survey shows that a very wide range of mental disturbances has been attributed to corticosteroids acting by many possible mechanisms, but that the evidence that they really cause psychological change is thin and largely circumstantial. Actual case series are often vague regarding details of criteria for inclusion and methods, if any, of psychological measurement. It can be very difficult to distinguish effects of disease from those of treatment. Resolution of the mental disorder on stopping corticosteroids is suggestive of a causal link, but this does not exclude the possibility of disease-induced psychosis for if it is possible to reduce steroids on the basis of mental disturbance, presumably the underlying disease has improved. Even in cases where psychosis has resolved on stopping corticosteroids, the situation is complicated by the inevitable use of psychotrophic drugs to control symptoms. However, the available evidence suggests that some cases of mental disturbance may indeed result from corticosteroid therapy particularly if a high dosage is used. A wide range of changes have been reported, psychosis, euphoria and depression being the commonest. Perhaps this extreme variability in clinical picture argues against a straightforward causal relationship. A psychiatric history does not seem to predispose to such mental changes.
It is clearly important to know if corticosteroids are genuinely euphoriant as, if they are, part of their beneficial effect in the chronic conditions for which they are used may be due to this rather than to a direct action on the disease process itself. Although corticosteroids have been in use clinically for over a quarter of a century their precise mode of action in the patient as a whole remains unclear although there is much information regarding their effects at a cellular level. There is a need for detailed controlled prospective studies of the effect of corticosteroids on psychological status, in a variety of conditions where they remain standard treatment.

References


(accepted 1 february 1984)
Do corticosteroids really alter mood?

D. M. Mitchell and J. V. Collins

*Postgrad Med J* 1984 60: 467-470
doi: 10.1136/pgmj.60.705.467

Updated information and services can be found at:
http://pmj.bmj.com/content/60/705/467.citation

**Email alerting service**

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/