Lithium in the prophylaxis of unipolar depression: a review[1]

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Unipolar depressive illness is an episodic recurrent disease (Angst *et al.* 1973) with a very high continuing morbidity. The first episode starts commonly around 42 years of age and the episode can last for a period of up to 12 months or more. The episode will then remit and the patient can be symptom-free for a period of several years before it is followed by a further episode in a substantial proportion of patients. Many patients will have multiple episodes; the length of an episode usually does not vary but the interval between the episodes decreases. After 3 or 4 episodes patients can spend a considerable proportion of their lives (on average 30%) with a depressive episode (Coppen *et al.* 1971). The object of prophylactic treatment is to reduce the considerable morbidity of depressive patients with the minimum of undesirable subjective and toxic side effects.

Long-term lithium treatment has been evaluated in two therapeutic situations: first, as a continuation treatment over a period of 6–12 months following recovery from a depressive illness; and secondly, as a prophylactic treatment in patients who have had multiple attacks of depression. There is very good evidence that lithium can greatly reduce the morbidity of patients in both situations.

Lithium as a continuation treatment

Although the immediate response to electroconvulsive therapy (ECT) and antidepressants is good, there is ample evidence that there is a high incidence of relapse in the months following treatment unless antidepressants are given as continuation therapy (Seager & Bird 1962, Imlah *et al.* 1965, Kay *et al.* 1970, Mindham *et al.* 1973, Coppen *et al.* 1978*b*). Perry & Tsuang (1979) in a retrospective study found lithium and tricyclics to be equally effective in reducing subsequent relapses. In a prospective study of lithium continuation therapy following ECT, Coppen *et al.* (1981) studied a group of 38 patients who had responded to ECT. The patients were randomly allocated to receive either placebo or lithium therapy for one year. The patients who received lithium spent significantly less time with a relapse (average 1.7 weeks over the year) than the placebo group (over 7.8 weeks). The difference was particularly marked during the second six months of the study when the lithium patients spent 0.2 weeks with a relapse compared to 5.6 weeks in the placebo group. Lithium thus appears to be a satisfactory continuation therapy after recovery from the acute episode.

Lithium prophylaxis in unipolar depression

The earliest report by Hartigan (1963) was of an anecdotal nature, but the value of such investigations should not be ignored. The first systematic study was reported by Baastrup & Schou (1967). They studied 88 patients with recurrent affective illness of whom 22 suffered from recurrent unipolar depression, who were given lithium for at least one year. The relapse rate during this period was compared with the relapse rate over a similar period before commencing lithium. The average number of depressive episodes was reported to be 1.56 before lithium treatment compared with 0.40 during lithium treatment. Before lithium

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treatment the patients spent 3.88 months per year with an affective episode and this fell to 0.27 months per year during the period of lithium treatment. Other investigations using a similar 'before and after design' also produced similarly encouraging reports (Angst *et al.* 1973, Hullin *et al.* 1972). However, this design was criticized, notably by Blackwell & Shepherd (1968), on the grounds that the evaluations were not blind, that they depended on assumptions about the natural history of the illness which were doubtful, and that the improvement might have been due not to lithium but to spontaneous improvement of the illness.

These early trials led to further studies. Baastrup *et al.* (1970) studied 34 patients with a recurrent depressive disorder who had been on open lithium for at least a year. Matched pairs of patients were allocated at random and under double-blind conditions either to placebo or to continuation with the previous lithium treatment. During the five months of the trial, 9 patients who received placebo relapsed, whereas the patients on lithium all remained well – an outcome that significantly favoured lithium. A placebo controlled study by Hullin *et al.* (1972) also favoured lithium.

Perhaps the most satisfactory trials are the prospective double-blind placebo studies in which patients are randomly allocated to receive either lithium or placebo for a fixed period during which time they are regularly assessed. Relapses are treated by conventional antidepressant measures, but the prophylactic measures are not changed. This enables a sensitive measure of benefit to be obtained either in terms of the time spent with an episode or as the affective morbidity index. The affective morbidity index is a composite measure both of duration and severity of affective episodes (Coppen *et al.* 1973), and is calculated by measuring the area under the curve made by joining all the points representing ratings of severity of affective disturbance at each assessment. Such a measure is invaluable in calculating reduction of morbidity where, as is often the case, there is not a complete abolition of morbidity.

Coppen *et al.* (1971, 1979) reported a highly significant reduction of morbidity in unipolar depressives in a prospective double-blind placebo controlled trial in which 11 patients received lithium and 17 patients received placebo over a $2\frac{1}{4}$-year period. The percentage of time spent with a depressive episode was 4.7% in the lithium group and 30% in the placebo group. The affective morbidity index was 0.12 in the lithium patients compared to 0.60 in those who received placebo. All these differences were statistically significant. No patient in the lithium group required ECT but almost half the patients in the placebo group required one or more courses.

Fieve *et al.* (1975) randomly treated 29 unipolar recurrent depressive patients with either lithium or placebo for periods of up to 4 years. The mean number of depressive periods per patient was 0.59 in the lithium group compared with 1.60 in the placebo group. Depressive episodes that did occur in the lithium group were significantly less severe than those that occurred in patients receiving placebo.

Lithium versus antidepressants

There are now numerous studies which demonstrate that lithium is either superior or equivalent to long-term therapy with antidepressants. Prien *et al.* (1973) studied 78 unipolar patients followed for a period of up to 2 years treated by either imipramine, lithium or placebo. They found both lithium and imipramine superior to placebo but no differences between the two active treatments. Quitkin *et al.* (1978) studied 27 patients treated by lithium or imipramine or placebo. They found lithium but not imipramine superior to placebo.

Coppen *et al.* (1976, 1978*c*) compared the prophylactic action of maprotiline and mianserin with lithium. In both studies, lithium was found to be superior to both maprotiline and mianserin, which is cogent evidence for the prophylactic action of lithium as neither drug is likely to be inferior to a placebo. One criticism of these studies was that since the patients were already attending a lithium clinic prior to starting the trial, a bias existed favouring lithium because these patients were known to be lithium responders. However, the annual dropout rate of patients from this clinic for failure to respond to lithium is less than

5% of a sample of unipolar patients commencing lithium, so this is not a likely source of error.

A recent study reported by Glen (1981) was a double-blind prospective study of lithium, amitriptyline or placebo in a prospective study in unipolar depression. Again, both lithium and amitriptyline were superior to placebo.

There is thus considerable evidence that lithium is an effective prophylactic treatment in recurrent unipolar depression. Any patient who would benefit from a prophylactic treatment should be carefully considered for long-term lithium treatment.

Indications for commencing prophylaxis in unipolar depression

A crucial decision for the clinician is when to start lithium prophylaxis. A detailed and profound discussion of this topic was published by Angst (1981). He analysed the course of the illness in 159 unipolar patients and decided that it would be desirable to start prophylaxis if the patients were likely to suffer 2 further attacks (in addition to the present one) in the subsequent 5 years. He examined numerous criteria to see which identified those patients at risk. His conclusions were surprisingly simple. He found that if the patient had had one episode or more in the previous 5 years in addition to the present one, then he was likely to have 2 further attacks in the following 5 years. He also reported that at least 40% of unipolar patients would require prophylactic treatment. Of course, more than one episode in the previous 5 years would be a very strong indication for starting prophylactic therapy. He could find no good criteria for discontinuing lithium therapy which, in the present state of knowledge, should be continued indefinitely.

Selection of patients and prediction of outcome

Coppen *et al.* (1979) examined different variables said to have a bearing on the outcome of lithium prophylaxis. Sex, age at start of lithium therapy, age of onset, number of years on lithium therapy, number of previous episodes, family history of affective disorders and red blood cell lithium concentration, all had no relationship to outcome. Neuroticism, as measured by the Eysenck Personality Inventory (Eysenck & Eysenck 1964), was correlated with a relatively poor response to lithium. More recently we have found (unpublished) that patients classified as having neurotic depression had a worse prognosis than those classified as having endogenous depression on the Newcastle Diagnostic Scale (Carney *et al.* 1965).

Regime and dose

This varies very much from centre to centre. In our own regime, used in all our investigations since 1969, lithium carbonate as a sustained-release tablet (Priadel, Delandale Laboratories, Canterbury) is given once a day in the evening. The dose is adjusted to give a plasma level of 0.8–1.2 mmol/l in 12 hours after the evening dose. To obtain such levels on a twice-daily dosage entails giving a higher daily dosage of lithium (Perry *et al.* 1981). The minimum plasma level to obtain a satisfactory prophylaxis has not yet been ascertained. Jerram & McDonald (1978) suggest that patients may be maintained at a lower serum level of 0.4 mmol/l (on a twice-daily dosage). Recently, Sashidharan *et al.* (1982) showed that patients with a favourable outcome had spent significantly less time at serum levels above 0.9 mmol/l than those who had a recurrence of affective episodes. This, they argued, may be due to a recognition by the clinician of high-risk patients and the prescription of higher lithium doses in an attempt to prevent relapses. However, we suggest that the question of the optimum dose of plasma level for a particular regime awaits the results of long-term double-blind prospective dosage-response studies which we and other laboratories are now undertaking.

Side effects of lithium therapy

The occurrence of subjective side effects during lithium therapy is well documented (Ghose 1977). Side effects such as thirst, tremor, dryness of mouth, weight gain and passing urine too often have been specifically related to lithium treatment. Subjective side effects have

been investigated in our department, over many years, by asking patients to complete a side-effects checklist (Ghose 1977). Lithium-treated patients had only slightly higher mean side-effects scores than control subjects in the general population, but both groups had significantly lower mean total side-effects scores than drug-free depressed patients (Abou-Saleh & Coppen 1983).

A frequent complaint made by about 50% of patients on lithium was that of poor memory and, indeed, it has been one of the most common side effects reported by several investigations. However, Coppen *et al.* (1978*a*) found no difference in complaints of impaired memory between patients on long-term lithium and patients on tricyclic antidepressants. There was also no association between complaints of poor memory and the duration of lithium therapy.

Effects of lithium on thyroid function

Lithium in therapeutic plasma concentrations produces a transient decrease of thyroxine (T_4) and triiodothyronine (T_3) during the first few weeks of treatment. Consequently, a new equilibrium is established with an increased basal level of thyroid-stimulating hormone and normal thyroid hormone concentrations. Schou (1968) found that 3.6% of his lithium-treated patients had developed euthyroid goitre after periods of 5 months to two years. In our series we have observed an incidence of 4.3% hypothyroidism in patients who received lithium for periods of 1 to 15 years (mean $\pm$ s.e. $= 7.4 \pm 0.3$ years) (unpublished).

Thyroid disorders are not a contraindication to lithium prophylaxis if thyroid function is regularly investigated and thyroid hormones are maintained at normal levels by replacement therapy when necessary.

Effects of lithium on renal function

Hestbech *et al.* (1977) demonstrated lithium-induced chronic nephropathy in post-mortem and renal biopsy specimens from patients on long-term lithium. This report generated much concern and stimulated a good deal of further research into renal function in patients on long-term lithium therapy. The results of these investigations were reassuring (*Lancet* 1979), especially when the appropriate control groups were concurrently investigated (normal controls and patients with affective disorders but never treated with lithium). Coppen *et al.* (1980) found little difference in kidney function between lithium-treated patients and patients with affective disorders who were never treated with lithium. The mean difference was increased urinary volume in lithium-treated patients. All these findings suggest that patients with a urinary volume of 3–4 litres should have their plasma lithium levels reduced.

Recent reports suggest that a once-a-day dosage regime may cause less disturbance to the kidney. Plenge *et al.* (1981) found that the same 24-hour dose of lithium caused more kidney damage when given to rats in their food to maintain a steady level than when given intraperitoneally once a day. Perry *et al.* (1981) found that the same dose given once a day caused a decreased volume compared to the same dose given twice daily. They also made the important point that the daily dose given to maintain a significant 12-hour serum level is greater when the lithium is given twice daily than when it is given once daily.

In physical illness with disturbance of electrolyte control, lithium should be used with great caution. A common drug interaction is with thiazide diuretics, but recently we have shown frusemide to be a safe diuretic to administer during lithium therapy (Saffer & Coppen, unpublished) although, again, caution should be used. We do not recommend lithium prophylaxis during pregnancy.

Most psychotropic drugs and antidepressants can be administered with lithium. If a patient relapses it is important to continue lithium but to add, if necessary, antidepressants such as a tricyclic antidepressant or a monoamine oxidase inhibitor. Caution should be used with neuroleptics (which are only given rarely to unipolar depressives) as there have been reports of interaction between haloperidol and lithium, with the production of an organic brain syndrome (Cohen & Cohen 1974).

Lithium has profoundly changed the management of recurrent depressive illness. The ease with which it is monitored means that compliance and dosage can be satisfactorily regulated. Patients who twenty years ago were constrained by frequent periods of depression with numerous inpatient admissions, can now look forward to a normal life. In our view it represents one of the most remarkable advances in psychiatric treatment.

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