Lithium in Unipolar Depression and the Prevention of Suicide

Alec Coppen, M.D., D.Sc., F.R.C.P., F.R.C.Psych.(Hon)

Unipolar depression is a severe recurrent illness with high lifetime morbidity and premature mortality due to suicide. Numerous double-blind, placebo-controlled trials have shown that lithium is very effective at reducing relapses when given as maintenance therapy. It is also very effective when given as maintenance therapy after electroconvulsive therapy. It can be given once a day at night, and controlled trials have shown a 12-hour plasma lithium level between 0.5 and 0.7 mmol/L the most effective, with very slight side effects. Long-term studies of lithium maintenance therapy show a suicide rate of 1.3 suicides per 1000 patient years. This is much lower than comparative studies in long-term follow-up of untreated depression, which show about 5.5 suicides per 1000 patient years. Although it is neither feasible nor ethical to carry out double-blind studies on suicide reduction, the massive evidence showing a reduction in morbidity on lithium treatment suggests that systematic long-term lithium treatment of unipolar depression could considerably lower the suicide rate.

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The discovery of lithium for the treatment and prophylaxis of mood disorder is one of the most remarkable in the history of psychopharmacology. The article by John Cade in 1949[1] could have only been published during a very narrow window of time. At the same time Cade published his paper, lithium salts were being explored as a therapeutic measure in the treatment of hypertension as a substitute for sodium chloride.[2] Subsequently, there were numerous reports of deaths by lithium poisoning, a fact that would have discouraged further research in the use of lithium. However, Cade persisted on the basis of a nebulous hypothesis ("Guinea pigs given lithium became very lethargic"); the *Medical Journal of Australia* was brave enough to publish his paper describing 6 cases of patients with manic excitement responding well to his therapy. Without this paper, lithium therapy—with all its marvellous benefits—would never have been born. Even today, no neurochemist could possibly have predicted the profound effect that lithium would have on behavior and mood disorders. Once published, Cade's ideas were taken up by clinicians in many countries, mostly in Europe: Mogens Schou, M.D., and his colleagues in Denmark and British psychiatrists such as Toby Hartigan, D.P.M., and Ronald Maggs, D.P.M. At this time, Jules Angst, M.D.,[3] from Zurich was embarking on extremely influential work showing that all mood disorders, including both bipolar illness and unipolar illness, were recurrent illnesses with devastating effects on the life of the patient and an increased mortality rate. This work has been amply confirmed, and the World Health Organization[4] ranks unipolar major depression as fourth in importance in global mortality and disability, far ahead of any other psychiatric illness.

LITHIUM AS PROPHYLACTIC AND CONTINUATION TREATMENT

This section concentrates on the action of lithium as a continuation therapy after recovery from a depressive illness and as a prophylactic agent in unipolar depression. During an episode of depression that has responded to treatment, patients need further continuation treatment for a considerable period to prevent a relapse of that episode. Most consensus statements[5,6] recommend a period of about 6 months of treatment after clinical recovery. They also emphasize that this is an arbitrary period and that the end of the required continuation period can only be ascertained by trial and error, i.e., by stopping treatment and seeing if the patient relapses. The second phase is prophylactic or maintenance treatment. The consensus statements now recognize that, if patients have had 2 or 3 previous attacks, the chances of a further relapse are so great that long-term maintenance treatment is justified.

In the early 1970s, my research group[7] reported a prospective double-blind, placebo-controlled trial of lithium prophylaxis in 70 patients with recurrent affective disor-

From the MRC Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey, U.K.

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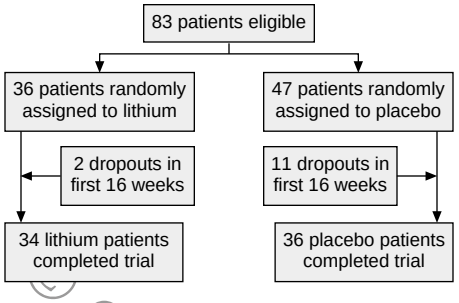
Reprint requests to: Alec Coppen, M.D., D.Sc., F.R.C.P., F.R.C.Psych. (Hon), 5 Walnut Close, Downs Rd., Epsom, Surrey KT18 5JL, United Kingdom.

Figure 1. Intent-to-Treat Sample From 1971 Study[a]



[a]Data from Coppen et al,[7] 1971.

Table 1. Global Assessment Scores in Lithium Maintenance Trials: All Patients[a]

	Rating Scale Scores			
Treatment Group	1	2 or 3	4 or 5	p Value
Lithium, N	21	5	10	< .0005
Placebo, N	1	8	38	

[a]Data from Coppen et al[7] intent-to-treat analysis. Global assessment rating scale: 1 = no conspicuous affective disturbance, 2 = moderate improvement compared with the previous 2 years, 3 = slight improvement compared with the previous 2 years, 4 = no change from morbidity of previous 2 years, 5 = worse than previous 2 years.

ders, including unipolar depression (N = 26) and bipolar illness (N = 39) who completed more than 16 weeks of treatment. In this investigation, carried out in 4 centers, patients were randomly assigned to receive either lithium or placebo tablets but were then able to receive any other treatment the clinicians thought appropriate. Both the unipolar and bipolar patients who were treated with lithium were significantly improved at the end of the study as compared with the placebo-treated patients. In unipolar patients, the total percentage of time ill was significantly less for the lithium-treated than the placebo-treated patients.

Recently, I updated the results so they could be examined in an intent-to-treat analysis of the original 83 patients who were randomly assigned to receive lithium (N = 36) or placebo (N = 47; Figure 1). While the original article contained many measures of morbidity, including the number of inpatient and outpatient episodes and courses of electroconvulsive therapy (ECT), only the global assessment, which is based on a 5-point scale (Tables 1 and 2) is shown in the intent-to-treat analysis. The subgroup of patients with unipolar depression (N = 34) who were treated with lithium (N = 14) were significantly better at the end of the study than the placebo-treated patients (N = 20) with unipolar depression ($p < .005$). Both the original results and the intent-to-treat analysis suggest that the response was very greatly improved by lithium in unipolar and bipolar patients. The results in unipolar patients are comparable with those in studies of maintenance antidepressant treatment of depressed patients,[8] which are generally conducted in patients who have responded to antidepressant medication, but we know that only a limited proportion of patients respond to antidepressant treatment in the first place. A recent comprehensive review puts the response rate as low as 50% on active drug treatment compared with 32% on placebo therapy.[9]

Table 2. Global Assessment Scores in Lithium Maintenance Trial: Unipolar Patients[a]

	Rating Scale Scores		
Treatment Group	1 or 2	3, 4, or 5	p Value
Lithium, N	10	4	< .005
Placebo, N	3	17	

[a]Data from Coppen et al[7] intent-to-treat analysis.

Table 3. One-Year, Placebo-Controlled Trial of Lithium Continuation Therapy in Patients With Major Depressive Disorder[a]

		Number of Weeks as Inpatients or Day Patients, Mean ± SE		
Treatment Group	N	First 6 Months[b]	Second 6 Months[c]	1 Year[d]
Placebo	20	2.4 ± 1.1	5.6 ± 1.7	7.8 ± 2.4
Lithium	18	1.5 ± 0.8	0.2 ± 0.2	1.7 ± 0.8

[a]Data from Coppen et al,[10] 1981.
[b]No significant difference between placebo and lithium.
[c]$p < .01$ between placebo and lithium.
[d]$p < .02$ between placebo and lithium.

My colleagues and I[10] studied lithium continuation therapy following ECT in 38 patients with major depressive disorder randomly assigned to receive either lithium or placebo following clinical recovery. During the next year, placebo-treated patients spent a mean ± SE number of 7.8 ± 2.4 weeks as an inpatient or day patient as compared with lithium-treated patients, who spent 1.7 ± 0.8 weeks as an inpatient or day patient (Table 3). The results are significantly ($p < .05$) better in the lithium group compared with the placebo group. Lithium patients spent less time ill during the second 6-month period compared with the first 6 months; this trend is completely reversed in the placebo group. In fact, the results indicate that ECT accompanied by lithium was a very effective form of treatment for this group of severely depressed patients.

In a trial of mianserin versus lithium, 41 patients[11] with unipolar affective illness manifested by at least 3 depressive episodes were allocated to receive either lithium or mianserin over 1 year. Lithium was superior to mianserin in terms of receiving ECT ($p < .025$) or being admitted to hospital ($p < .005$). In an intent-to-treat analysis, in which dropouts were treated as relapses, a significant ($p < .01$) advantage remained for lithium patients. Side effects were similar in both groups, with a mean side effect score of 8.4 in lithium patients compared with 7.2 in the mianserin group. However, since all patients had been initially stabilized on lithium treatment, there could have been a re-

Table 4. Affective Morbidity Index Scores for All Patients Before and During the Trial Period[a]

Plasma Lithium Level During Trial (mmol/L)	N	Affective Morbidity Index Scores, Mean ± SEM		Change (%)
		Pretrial	During Trial	
0.45–0.59	20	0.14 ± 0.04	0.09 ± 0.03	–33.8
0.60–0.79	33	0.26 ± 0.05	0.18 ± 0.03	–33.3
< 0.79	53	0.22 ± 0.04	0.14 ± 0.02[b]	–33.6
> 0.80	19	0.24 ± 0.06	0.24 ± 0.05	+ 0.3

[a]Reprinted from Coppen et al,[12] 1983, with permission.
[b]Significant ($p < .02$) reduction from pretrial morbidity.

Table 5. Affective Morbidity Index Scores for Unipolar Patients Before and During the Trial Period[a]

Plasma Lithium Level During Trial (mmol/L)	N	Affective Morbidity Index Scores, Mean ± SEM		Change (%)
		Pretrial	During Trial	
0.45–0.59	15	0.17 ± 0.05	0.11 ± 0.03	–31.3
0.60–0.79	22	0.32 ± 0.07	0.21 ± 0.04	–35.4
< 0.79	37	0.26 ± 0.05	0.17 ± 0.03[b]	–34.2
> 0.80	12	0.26 ± 0.09	0.31 ± 0.06	+16.7

[a]Reprinted from Coppen et al,[12] 1983, with permission.
[b]Significant ($p < .05$) reduction from pretrial morbidity.

bound effect in these patients. Nevertheless, as Schou has pointed out, there can be no rebound without a "bound."

Dosage and Regimen

It is surprising how many reports on lithium fail to mention the frequency of administration or even the dosage used. All work reported by my research group used a once-daily dosage regimen with a sustained-release salt of lithium carbonate given at night. This schedule enabled the 12-hour plasma lithium level to be readily measured without the patient having to remember to omit the dose. In our trials, the lithium concentration in plasma was always measured before the patient was seen by the doctor, so problems with dosage could always be addressed immediately.

We investigated the optimum dose[12] of maintenance lithium over a period of 1 year in 49 unipolar patients and 23 bipolar patients. Patients were randomly allocated either to be maintained on their usual dose of lithium or to have a 25% or 50% reduction in this dose. In no patient was the plasma lithium level allowed to fall below 0.45 mmol/L.

The results are shown in Tables 4 and 5. The patients with reduced plasma lithium levels, surprisingly, had a decrease in morbidity, but patients with levels above 0.80 mmol/L showed no significant change. Unipolar patients with plasma lithium levels below 0.80 mmol/L had significantly ($p < .02$) lower morbidity than those with levels above. Bipolar patients with reduced lithium plasma levels during the trial experienced a 30% reduction in morbidity. Patients receiving the lower dose had a low average side effect score of 6.6, very similar to scores found in healthy subjects.[13] Of particular interest is the tremor score, as tremor is one of the more troublesome side effects of lithium treatment: this dropped by a significant ($p < .005$) 25%. Thyroid-stimulating hormone levels in patients with the lower lithium levels were significantly ($p < .05$) lower than in the patients with higher levels. The study recommended the use of a single daily dose with a sustained-release lithium preparation and the maintenance of a 12-hour plasma lithium level of about 0.6 mmol/L for prophylactic treatment.

Apart from this very conclusive dosage reduction trial, my colleagues and I have data on 103 patients who were studied for 11 years. The cohort consisted of 67 unipolar patients, 30 bipolar patients, and 6 schizoaffective patients. They were receiving the higher lithium dose, which produced a plasma lithium level of 0.8 to 1.2 mmol/L, for 5 years when their dosages were adjusted downward in the subsequent 6 years. Affective morbidity decreased on lower dose[14] that produced a plasma lithium level of 0.6–0.79 mmol/L during the latter period, in both unipolar and bipolar patients.

The above brief review of the work of my colleagues and me shows that maintenance low-dose lithium is an effective therapy in unipolar depression. I have not attempted to review the enormous amount of evidence that has now accumulated in the area. However, Davis and his colleagues[15] have done so and have found that the efficacy of maintenance lithium is very high in unipolar depression. In 8 maintenance lithium studies for unipolar depression, they reported a significant advantage for lithium versus placebo ($p < 3 \times 10^{-9}$).

Lithium and Suicide Prevention

As mentioned earlier, it is now well established that the recurrence of unipolar depression and mood disorders can be significantly reduced by adequate maintenance treatment; it is strange, therefore, that the reduction in suicide rate over the years has been relatively modest.[16] A probable explanation of this modest reduction is that only a proportion of patients with depression are diagnosed, and only a proportion of those patients are treated adequately in terms of dosage and duration. If patients are adequately treated, however, one can make a significant reduction of up to 75% in the suicide rate, as demonstrated by 18-year mortality and suicide rate in a group of 103 patients who attended our mood disorder clinic in 1977.[17]

Sixty-seven patients with unipolar illness, 30 with bipolar illness, and 6 with schizoaffective disorder participated in the study. All patients had severe and recurrent illness. The patients were routinely informed that the effectiveness of prophylactic treatment could only be assessed after a 1-year trial. Patients were treated with lithium and attended the mood disorder clinic, where they received encouragement from the staff and support from the other patients at the clinic. There were few dropouts during the first year of treatment. The standard treatment was sustained-release lithium carbonate given once daily at

Table 6. Patient Characteristics at Baseline[a]

Type	Men, N	Women, N	Mean Age, y	Mean Duration of Lithium Therapy, y
Bipolar	9	21	50.9	5.1
Unipolar	18	49	56.7	4.1
Schizoaffective	3	3	53.6	5.4
All	30	73	54.9	4.5

[a]January 1977.

Table 7. Patient Characteristics at Endpoint[a]

Characteristic	All Patients	Unipolar	Bipolar	Schizo-affective
Alive at end of study				
Completed 18 years	24	12	11	1
Left clinic still on lithium therapy	43	26	13	4
Discontinued	12	10	2	0
Died during study				
While attending clinic	7	5	1	1
Left clinic while on lithium therapy	8	7	1	0
Discontinued before death	9	7	2	0

[a]January 1995.

night, as described earlier. Until 1982 the plasma lithium concentration (measured approximately 12 hours after dosage) was maintained at between 0.8 and 1.2 mmol/L. In 1982, the regimen was changed to maintain patients at a plasma lithium concentration between 0.6 and 0.8 mmol/L. Additional treatments, including antidepressants and neuroleptics, were administered as required. Patients were seen by a psychiatrist at least 4 times per year for general assessment, but when they were ill they were seen more often.

All patients were entered into the National Health Service (NHS) Central Registry, which agreed to notify the clinic of deaths. This is an established method of follow-up in which the endpoint measurement is death. For people who are normally resident in the United Kingdom, the ascertainment of death is assumed to be complete even though the death may have occurred outside the country. Copies of patient death certificates were obtained from the Office of National Statistics. Thus, the mortality of the group could be assessed accurately, even though some patients had left the clinic.

The characteristics of the patients, when recruited in 1977, are shown in Table 6. Twenty-nine percent were men. There was no significant difference in the sex ratio between the 3 types of mood disorder. There was no significant difference in the mean age of the 3 groups, nor were there any differences in the mean length of time the patients had been treated with lithium before recruitment in 1978.

The status of the patients in January 1995 is shown in Table 7. Twenty-four patients were still attending the clinic. Seven patients had died while still attending. Twenty-one patients had definitely stopped treatment for a variety of reasons: 4 because they had developed severe physical illness, 14 because they were dissatisfied with the treatment, 1 because of pregnancy, and 2 because they felt too well to need further treatment. Fifty-one patients left the clinic either because they moved to another part of the country or they wished to continue treatment under their general practitioner.

The patients had been on lithium therapy for many years. After each attendance at the clinic, their general practitioners were informed of their clinical progress and medication, so it was very easy for them to continue treatment. In 1990, the patients who had transferred to their general practitioners were contacted through a postal survey. The results of the survey indicated that over 70% of patients had continued treatment for at least 2 years after their discharge from the clinic.

Deaths were ascertained through the NHS Central Registry whether or not the patients had remained in contact with the clinic. By January 1995, 24 patients had died. Twenty-one of the deaths were from natural causes, 2 were from suicide, and 1 was the result of a road traffic accident. One of the patients who committed suicide was being treated at the clinic with lithium at the time of her death. The second suicide occurred in a 55-year-old woman, who had said that she was dissatisfied with the treatment and had defaulted on appointments at the clinic several years earlier. The standardized mortality ratio (SMR) for the whole group was calculated using the age-specific death rates for England and Wales for the midpoint of the period of observation. The expected number of deaths was 25.89, giving an SMR of 0.93. The expected number of suicide deaths was less than 1. The overall suicide rate was 1.3 per 1000 patient years of observation.

In 2 other long-term follow-up studies of lithium-treated patients, patients had been treated for at least 1 year before recruitment and lithium levels were carefully monitored. In the first study, the International Group for the Study of Lithium[18] followed up patients from 4 countries who attended lithium clinics for up to 7 years (5600 patient years). The overall suicide rate was 1.3 per 1000 patient years, the SMR (all causes) was 0.9. The other study[19] involved all mood disorder patients admitted to the main psychiatric hospital in Gothenburg, Sweden, between 1970 and 1991 and who had received lithium for at least 1 year. The suicide rate was 1.5 suicides per 1000 patient years for patients maintained on lithium treatment. For patients who had discontinued lithium, the suicide rate was 7.1 per 1000 patient years. Some caution must be exercised in the interpretation of the figures, since discontinuation did not occur at random. The average suicide rate in these 2 studies and the present study was similar. Combining the 3 studies (11,085 patient years) yielded an average suicide rate of 1.3 per 1000 patient years.

These figures contrast with the reports of suicide rates in long-term studies of patients not given maintenance

Table 8. Long-Term Studies of Mood Disorder Patients: Summary of Studies[a]

Treatment Group	Patient Years	Suicide	Suicide per 1000 Patient Years
Maintenance lithium	11,085	14	1.3
Nonmaintenance treatment	24,224	131	5.4

[a]Data from Coppen et al,[17] 1998.

treatment.[17] Suicide rates between 5.4 and 10.2 per 1000 patient years have been reported with an average for those studies of 5.4 suicides per 1000 patient years (Table 8). These suicide rates among depressed patients, who were not given systematic follow-up, are remarkably similar, despite the differences in methodologies. Moreover, it should be emphasized that in none of the studies were the patients selected, as were the patients in the current study, on the basis of the severity of their illness.

In general, patients given long-term lithium maintenance treatment are selected because of severity and high recurrence rate. The patients involved in the follow-up study reported here had both severe and recurrent disease. It is thus unlikely that the marked decrease in suicide rate in patients receiving lithium was due to selection of patients on the basis of severity. In the present series, the patients showed a high compliance rate—only 14 (14%) discontinued for negative reasons in the 18-year follow-up. In this clinic, compliance was not due to patient selection but to the work of the clinic, with its emphasis on education and careful follow-up. However, careful follow-up without medication is insufficient treatment, as the early placebo-controlled trial showed.

Other reports[17] of long-term lithium maintenance in which the patient did not receive treatment for 1 year or showed poor compliance are difficult to interpret. Poor compliance can be detrimental, as it is possible that discontinuation of lithium in bipolar patients can increase the relapse rate and induce refractoriness to further treatment with lithium.

Maintenance treatment with antidepressants has been shown to be effective when given for periods up to 5 years.[8] There is a limitation with antidepressants, in that at least one third of patients show a poor response to them. Moreover, there are some problems with tricyclic antidepressants, as long-term treatment can cause problems in everyday living because of their side effects, such as marked weight increase, dizziness and drowsiness, interaction with alcohol, and serious toxicity in overdose. These problems are very much reduced with the selective serotonin reuptake inhibitor antidepressants.

Lithium treatment has the advantage that it can be easily measured to ensure proper dosage and compliance and that many other treatments such as neuroleptics or antidepressants can be added. For bipolar patients, lithium—augmented when necessary by neuroleptics—must be the treatment of choice.

There is little doubt that recurrent mood disorders are most easily and satisfactorily treated in a mood disorder clinic. It is especially important that the initial assessment of a patient for long-term treatment be made by a specialist. In the National Health Service setting, the maintenance should be undertaken by a partnership of a mood disorder clinic and a general practitioner.

In conclusion, lithium is as effective in unipolar depression as in bipolar illness. Unipolar depression is woefully undertreated, and as a consequence, many patients are suffering and dying unnecessarily. Doctors, and especially psychiatrists, need to improve systematic long-term treatment. The evidence makes it clear that it is very well worth the effort to improve one's skills in this area.

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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