British Journal of Psychiatry (1994), **164**, 208–214

Lithium Prophylaxis of Bipolar Illness
The Value of Combination Treatment

ERIC D. PESELOW, RONALD R. FIEVE, CONSTANCE DIFIGLIA and MICHAEL P. SANFILIPO

Using a longitudinal life-table analysis, we assessed the efficacy of lithium alone, administered within the context of a naturalistic clinical setting, by calculating the probability of patients remaining free of an affective episode (manic or depressive) over a five-year course. In addition, for those who suffered a manic or depressive relapse, we attempted to analyse the subsequent course of patients who suffered a manic/hypomanic or depressive relapse and were then restabilised on lithium plus either a neuroleptic, carbamazepine, or a benzodiazepine, or lithium plus an antidepressant. Lithium alone offered an average 83% probability against an affective relapse after one year, 52% after three years, and 37% after five years. For patients who failed on lithium alone, it appeared that combination treatment offered greater protection against subsequent affective relapse than the initial course on lithium alone.

Bipolar illness is typically a chronic disease entailing an episodic course, whereby psychiatric status alternates between periods of normal functioning and periods of illness. The major conclusive finding regarding long-term preventive drug treatment is that lithium carbonate is generally effective in preventing manic recurrences, and, to a lesser extent, depressive recurrences (Davis, 1976; APA Task Force on Lithium Therapy, 1975). However, despite its superiority to placebo, the average failure rate for lithium was 33% in the above studies. Indeed, the more recent NIMH collaborative study of lithium prophylaxis in affective disorders (Prien *et al*, 1984) noted that only 33% of patients who received lithium as prophylaxis for a bipolar disorder remained entirely free of both manic and depressive relapses over a succeeding 18–24-month period. Accordingly, numerous somatic agents have been frequently added to a lithium regime when lithium alone has failed to prevent a manic or depressive relapse, although this treatment has been investigated in only a few carefully controlled double-blind studies (Prien & Gelenberg, 1989).

The purpose of this paper was twofold. First, we analysed, through the longitudinal life-table method of Fleiss *et al* (1976) and Mantel (1966), the efficacy of lithium alone, administered within the context of a naturalistic clinical setting. This was achieved by calculating the probability of patients remaining free of an affective episode (manic or depressive) over a five-year course while on lithium alone. Secondly, for those who suffered a manic or depressive relapse, we attempted to analyse the subsequent course of patients who suffered a manic/hypomanic relapse and were then restabilised on lithium plus a neuroleptic, carbamazepine, or a benzodiazepine, and the subsequent course of patients who suffered a depressive relapse and were then restabilised on lithium plus an antidepressant, in order to determine whether combination treatment in lithium failures provided better subsequent prophylactic efficacy than on lithium alone.

Method

Medical records were examined for all patients who attended the Foundation for Depression/Manic Depression (New York State Psychiatric Institute) between 1 January 1975 and 1 January 1991 (approximately 1200 patients in all). All patients voluntarily consented to receive treatment and to the recording of clinical data. Patients who were included in the study all met Feighner criteria (Feighner *et al*, 1972) for primary affective disorder, and Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978) and DSM–III criteria (American Psychiatric Association, 1980) for recurrent bipolar illness. All patients had had at least one discrete episode of mania that had resulted in somatic treatment or hospital admission. All patients treated in this out-patient setting were seen at least once a month, and they were rated by the Columbia-Milhauser mood scale, a modified version of the Biegel mania scale (Biegel *et al*, 1971) and the Hamilton Rating Scale for Depression (Hamilton, 1967), with a 7-point global severity scale (1–3 refer to severe, moderate, and mild depression, respectively; 4 refers to euthymia; and 5–7 refer to mild, moderate, and severe mania, respectively) at each visit.

To be included in the study, patients had to have been observed by a psychiatrist and rated as having a euthymic mood for six months while on lithium alone. Once patients were stable on six months of lithium alone, they were considered to have begun prophylaxis. While this time period is arbitrary (Quitkin *et al*, 1978), it is consistent with the work of Angst *et al* (1979), who found that the average

length of time for a manic episode was 4.4 months and the average length of time for a depressive episode was 5.1 months. Unlike some investigators who required only one month of euthymia before assessing prophylaxis (Schou, 1968; Fieve *et al*, 1975; Peselow *et al*, 1982), we felt that six months of euthymia more definitively ensures complete recovery from the current episode, thus, any subsequent manic or depressive episode may be considered to be a new episode rather than a continuation of an old one.

The use of the six-month normothymic period was important because it allowed all patients to have a common starting-point, despite the fact that they entered the analysis at various intervals over a 15-year course. Thus, a patient who entered our facility on 1 January 1976, was stable for the succeeding six months, and suffered a depressive relapse on 1 January 1978 had exactly the same course as someone who entered on 1 January 1983, was stable for the succeeding six months, and suffered a depressive relapse on 1 January 1985; that is, both failed in their 18th prophylactic month.

Once patients were stable on lithium alone (maintaining blood levels of 0.5–1.4 mmol/l) for six consecutive months, they were followed until one of three possible outcomes:

(a) *termination well* – if the patient remained well until 1 January 1991 (the end of the study evaluation), *or* the patient requested discontinuation of medication, *or* the patient discontinued medication at our discretion, *or* the patient was terminated because of side-effects or other medical problems
(b) *failure* – if the patient was rated as depressed or hypomanic/manic by the above global rating scales by both a nurse and a psychiatrist, *and* the existing symptoms were of such severity that the patient met RDC or DSM–III criteria for a hypomanic/manic or major depressive episode *and* the patient now required either hospital admission or additional pharmacotherapy (lithium plus a neuroleptic, carbamazepine, or a benzodiazepine, or lithium plus an antidepressant)
(c) *drop-out*.

An important complication of this study was that it was impossible to know whether a patient dropped out as a treatment success (dropped out while still euthymic) or a treatment failure (dropped out because of an affective episode). As reported and conceived by Fleiss *et al* (1976), the study drop-outs were handled in two distinct ways. One assumption was that all drop-outs failed (had a hypomanic/manic or depressive episode) in the month they dropped out. Fleiss *et al* considered this to be the pessimistic result as it gave the lowest probability of remaining free of an affective episode. The other way to handle drop-outs assumed that all drop-outs left well, giving the optimistic result or highest probability of remaining free of an affective episode. This method allows for the extreme ranges of probability with the true probability of remaining free of an affective episode lying between the pessimistic (worst possible) and optimistic (best possible) results. For a complete description of calculations for the life-table and procedures for making statistical comparisons between life-tables from different samples, see Fleiss *et al* (1976).

The decision to give patients lithium alone was based on clinical grounds, such as previous favourable response to lithium, or the fact that lithium alone is the preferred treatment for recurrent bipolar disorder (Davis, 1976; APA Task Force on Lithium Therapy, 1975). As previously noted, all patients were stable on lithium for six consecutive months before entry into the analysis. This criterion indicated that they had responded to that particular treatment (lithium) for a specific time period (six months), and allowed us to assume that they would continue to do equally well on the same treatment over longer time periods.

In all, 305 patients on lithium alone (Table 1) were included in the analysis and assessed for one of the above outcomes (termination well, failure, or drop-out). Of the group that failed (had an affective relapse), 83 were restabilised on lithium in combination with an additional agent, and their second course was compared with the initial course on lithium alone. The decision as to which additional agent was to be added to lithium varied. Patients who suffered a manic relapse received lithium in combination treatment with either a neuroleptic, carbamazepine, or a benzodiazepine. Those who suffered a depressive relapse received lithium in combination treatment with an antidepressant (a tricyclic, MAOI, or fluoxetine). The choice of which class or subclass of drug to use adjunctively with lithium after a manic or depressive relapse was also based on clinical grounds. Clinical factors used in determining treatment were history of acute response – i.e. a patient responding to lithium plus a neuroleptic acutely (in which case the treatment was used again) – or sensitivity to side-effects of one agent in which case another agent was used. Thus, a severe tremor or other Parkinsonian symptom on neuroleptics might have necessitated the use of lithium plus carbamazepine or a benzodiazepine as prophylaxis. Patients who were treated successfully after a second consecutive six-month period were considered to have begun a second prophylactic period. As with the first prophylactic period analysis, this indicated that since they had responded to that particular treatment for six months they would continue to do equally well on it over longer time periods. Thus, our clinical expectation, or bias, in this non-randomised evaluation as to choice of treatment was based on the hope of achieving the best possible result for the patient within the clinical setting.

In all, 36 patients on lithium alone who suffered a manic/hypomanic relapse were restabilised on lithium plus a neuroleptic, carbamazepine, or a benzodiazepine, and 43 patients who suffered a depressive relapse were restabilised on lithium plus an antidepressant (Table 2). For the purpose of this analysis, we will compare 'manic prone' patients on combination treatment or lithium alone with 'depression-prone' patients on lithium alone or lithium plus various antidepressants.

Results

Table 1 assesses the course of the 305 lithium-treated patients after six months of euthymia. By the longitudinal

https://doi.org/10.1192/bjp.164.2.208 Published online by Cambridge University Press

Table 1
Patient course during six-month intervals

Interval (months)	Starting interval well	Terminated well in interval	Dropped out in interval	Failed in interval	Probability of remaining well	
					Pessimistic result (%)	Optimistic result (%)
Lithium alone						
1-6	305	4	22	15 (6 M, 9 D)	87.79	94.86
7-12	264	8	18	14 (6 M, 8 D)	76.99	89.57
13-18	224	18	14	14 (6 M, 8 D)	66.96	83.54
19-24	178	20	10	17 (8 M, 9 D)	56.20	74.83
25-30	131	6	4	11 (4 M, 7 D)	49.46	68.30
31-36	110	7	4	10 (4 M, 6 D)	42.96	61.76
37-42	89	4	3	7 (4 M, 3 D)	38.13	56.70
43-48	75	6	4	6 (4 M, 2 D)	32.83	51.84
49-54	59	10	1	3 (2 M, 1 D)	30.40	48.93
55-60	45	8	1	2 (1 M, 1 D)	28.18	46.51
Total at 5 years	34	91	81	99 (45 M, 54 D)		

M = manic relapse; D = depressive relapse.

Table 2
Combination medication given to patients on lithium alone

Patients who had manic relapse
Lithium plus neuroleptics ($n = 16$)
- Haloperidol ($n = 3$; average prophylactic dose 10 mg/day)
- Perphenazine ($n = 4$; average prophylactic dose 16 mg/day)
- Chlorpromazine ($n = 3$; average prophylactic dose 250 mg/day)
- Thioridiazine ($n = 3$; average prophylactic dose 200 mg/day)
- Fluphenazine ($n = 2$; average prophylactic dose 10 mg/day)
- Thiothixene ($n = 1$; average prophylactic dose 15 mg/day)

Lithium plus carbamazepine ($n = 13$) (average prophylactic dose 650 mg/day)
Lithium plus benzodiazepines ($n = 7$)
- Lorazepam ($n = 2$; average prophylactic dose 3 mg/day)
- Clonazepam ($n = 5$; average prophylactic dose 2.6 mg/day)

Patients who had depressive relapses
Lithium plus tricyclics ($n = 23$)
- Imipramine ($n = 6$; average prophylactic dose 175 mg/day)
- Amitriptyline ($n = 5$; average prophylactic dose 150 mg/day)
- Desmipramine ($n = 4$; average prophylactic dose 150 mg/day)
- Nortriptyline ($n = 6$; average prophylactic dose 75 mg/day)
- Doxepin ($n = 2$; average prophylactic dose 125 mg/day)

Lithium plus MAOI ($n = 13$)
- Phenelzine ($n = 8$; average prophylactic dose 45 mg/day)
- Tranylcypromine ($n = 5$; average prophylactic dose 20 mg/day)

Lithium plus fluoxetine ($n = 7$) (average prophylactic dose 30 mg/day)

life-table analysis, the average probability of remaining free of an affective episode on lithium alone was 83% after one year (pessimistic–optimistic range 77.0–89.5%), 52% after three years (pessimistic–optimistic range 43.0–61.8%), and 37% after five years (pessimistic–optimistic range 28.2–46.5%). Overall 99 patients were observed to have suffered an affective relapse (45 hypomanic/manic and 54 depressed). A total of 125 patients remained entirely well on lithium alone, 34 of the patients remaining free of an affective episode for more than five years. Eighty-one patients were well as long as they were followed, but later dropped out of treatment.

Table 2 shows the medication regime of patients who failed on lithium alone and were then restabilised on lithium combination treatment. Thirty-six patients who had a manic relapse on lithium alone were restabilised on lithium plus neuroleptics ($n = 16$), lithium plus carbamazepine ($n = 13$), and lithium plus benzodiazepines ($n = 7$). Forty-three patients who had a depressive relapse on lithium alone were restabilised on lithium plus antidepressants (tricyclics, $n = 23$; MAOI, $n = 13$; fluoxetine, $n = 7$).

Table 3 shows the subsequent course of the patients who failed on lithium alone with a manic episode. Over a five-year course (mean (s.d.) 35.56 (25.2) months), there were 14 affective relapses (six manic, eight depressed) in patients on lithium plus combination treatment. Fifteen patients remained entirely well on the combination treatment and seven dropped out. Overall, 21 of the patients remained euthymic longer on the lithium-antimanic combination than lithium alone, two remained euthymic for exactly the same time on both treatments, and nine remained euthymic longer on lithium alone than on the lithium-antimanic combination. Four other patients who had failed on lithium after 16, 20, 34, and 38 months, respectively, and were then stable on the lithium-antimanic combination for shorter periods of time (15, 15, 28, and 28 months, respectively) were not included in the analysis because they had not come to a conclusion (relapse or drop-out) on the second treatment and were thus not on the combination treatment long enough to allow comparison with the lithium-alone course.

A one-sample t-test was performed on the difference in time to relapse between patients on lithium alone and the subsequent lithium-antimanic combination treatment. For the group that suffered an initial manic episode, the mean difference for the entire group was 12.63 months in favour of the lithium-antimanic combination, as compared with

https://doi.org/10.1192/bjp.164.2.208 Published online by Cambridge University Press

Table 3
Course on combination treatment for patients who relapsed with manic episode on lithium alone

Combination	Remained well	Relapsed		Total	Drop-outs
		Manic relapse	Depressive relapse		
Lithium plus neuroleptic ($n=16$)	6 (37.5%)	1 (6.3%)	6 (37.5%)	7 (43.8%)	3 (18.8%)
Lithium plus carbamazepine ($n=13$)	6 (46.2%)	3 (23.1%)	1 (7.7%)	4 (30.8%)	3 (23.1%)
Lithium plus benzodiazepines ($n=7$)	3 (42.9%)	2 (28.6%)	1 (14.3%)	3 (42.9%)	1 (14.3%)
Total ($n=37$)	15 (41.7%)	6 (16.7%)	8 (22.2%)	14 (38.9%)	7 (19.4%)

Table 4
Course on combination treatment for patients who relapsed with depressive episode on lithium alone

Combination	Remained well	Relapsed		Total	Drop-outs
		Manic relapse	Depressive relapse		
Lithium plus tricyclics ($n=23$)	9 (39.1%)	2 (8.7%)	9 (39.1%)	11 (47.8%)	3 (13.1%)
Lithium plus MAOI ($n=13$)	6 (46.2%)	3 (23.1%)	3 (23.1%)	6 (46.2%)	1 (7.7%)
Lithium plus fluoxetine ($n=7$)	3 (42.9%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)
Total ($n=43$)	18 (41.9%)	6 (14.0%)	13 (30.2%)	19 (44.2%)	6 (14.0%)

lithium alone, with 95% confidence levels on the mean ranging from 5.0 to 20.3 months. This indicates a clear advantage of the lithium-antimanic combinations over lithium alone. The Wilcoxon matched-pairs, signed-rank test for related samples was done because of the non-random distribution of this related sample, and the Z value corrected for ties was highly significant ($Z=-2.95$, $P=0.0044$).

Table 4 shows the subsequent course of the patients who failed on lithium alone with a depressive episode. Over a subsequent five-year course (mean (s.d.) length of time followed 35.74 (29.5) months), there were 19 affective relapses (six manic, 13 depressed) in patients on lithium plus combination treatment. Eighteen patients remained entirely well on the combination treatment and six dropped out. Overall, 28 of the patients remained euthymic longer on the lithium-antidepressant combination than lithium alone, one remained euthymic for exactly the same time on both treatments, and 11 remained euthymic longer on lithium alone than on the lithium-antidepressant combination. Three other patients who had failed on lithium alone after 26, 34, and 46 months, respectively, and who were then stable on the lithium-antidepressant combination for shorter periods of time (25, 15, and 8 months, respectively) were not included in the analysis because they had not come to a conclusion (relapse or drop-out) on the second treatment and were thus not on the combination treatment long enough to allow comparison with the lithium-alone course.

A one-sample t-test was performed on the difference in time to relapse between patients on lithium alone and those on the subsequent lithium-antidepressant combination treatment. For the group that suffered an initial depressive episode, the mean difference for the entire group was 17.23 months in favour of the lithium-antidepressant combination, as compared with lithium alone, with 95% confidence levels on the mean ranging from 6.7 to 27.8 months. This indicates a clear advantage of the lithium-antidepressant combination over lithium alone. The Wilcoxon matched-pairs, signed-rank test corrected for ties was highly significant ($Z=2.56$, $P=0.0104$).

Discussion

The life-table method has been used in medical research to determine the short- and long-term probabilities of mortality in several diseases (Kramer, 1969; Lew & Seltzer, 1970). Fleiss *et al* (1976) reported that the life-table is the best method for longitudinal studies because it allows all data on patients to be included in the analyses regardless of the length of follow-up. Thus, the life-table method provides a precise estimate of a given outcome, which in this study was the time to one affective (hypomanic/depressive) episode. By incorporating all available data, the probability ranges (pessimistic–optimistic) of the life-table method offer a more precise and therefore more valid index of actual outcome rates than many other statistical methods.

The precision of its probability ranges (pessimistic–optimistic) enhances the validity of the life-table method. Other studies using this method (Quitkin *et al*, 1981; Kane *et al*, 1982) have handled drop-outs by comparing their clinical status at the visit before drop-out with their baseline presentation. In these studies, drop-outs were recorded as having terminated in 'euthymic' status because they were well as long as they were followed and were euthymic

https://doi.org/10.1192/bjp.164.2.208 Published online by Cambridge University Press

at their last visit. Handling data in this fashion is equivalent to our optimistic result. However, since the reasons that patients drop out are often impossible to ascertain, it is incorrect to assume that a final favourable evaluation before drop-out can automatically be applied to the way the patient responded to treatment. The use of pessimistic–optimistic (or worst case–best case) range provides the exact probability range of a given outcome and one that is totally independent of bias.

A review (Fieve & Peselow, 1983) of many of the cited studies on lithium prophylaxis for bipolar disorders (Baastrup *et al*, 1970; Melia, 1970; Coppen *et al*, 1971: Cundall *et al*, 1972; Hullin *et al*, 1972; Persson, 1972; Fieve & Mendlewicz, 1972; Prien *et al*, 1973*a*,*b*; Stallone *et al*, 1973; Fieve *et al*, 1973; Coppen *et al*, 1976; Fieve *et al*, 1976) noted that lithium was superior to placebo in preventing manic and depressive relapses over a subsequent 6-month to 3-year course. Although the study designs varied, if one combined the above studies, one would note an affective (manic or depressive) relapse rate of 37.3% (101/271) on lithium and 75.5% (194/257) on placebo ($P<0.001$). In the studies that specifically reported manic relapses (Baastrup *et al*, 1970; Cundall *et al*, 1972; Persson, 1972; Fieve & Mendelwicz, 1972; Prien *et al*, 1973*a*,*b*; Stallone *et al*, 1973; Fieve *et al*, 1973, 1976), the cumulative manic relapse rate was 16.5% (54/204) on lithium and 64.4% (130/202) on placebo ($P<0.001$). In the studies that specifically reported depressive relapses (Baastrup *et al*, 1970; Cundall *et al*, 1972; Persson, 1972; Prien *et al*, 1973*a*,*b*; Fieve *et al*, 1973, 1976), the cumulative depressive relapse rate was 16.6% (31/187) on lithium and 33.9% (61/180) on placebo ($P<0.001$).

Despite this clear evidence, many patients still do not respond favourably to lithium alone as a prophylactic agent. Indeed, it has been noted (NIMH Division of Clinical Research, 1989) that the poorer outcome for lithium alone reported in the Prien *et al* (1984) study as compared with earlier studies may have been due to differences in patient samples; that is, earlier studies may have included a higher proportion of 'classic manic depressives' who were lithium responders. Today, such classic responders are probably treated satisfactorily in the community and are not generally referred to research centres such as universities and our facility. Instead, referrals to research centres may involve a greater proportion of patients who have failed on lithium alone, and who thus need adjunctive or other treatment for their recurrent affective disorders. In fact, a study comparing the efficacy of lithium and carbamazepine in acute mania and for prophylaxis (Small *et al*, 1991, p. 915) noted that "monotherapy alone with either drug was not sufficient for the majority of manic patients who were referred for tertiary care".

Although combination treatment is frequently used to prevent manic breakthroughs, few controlled trials have evaluated these modalities in the long-term prophylaxis of affective disorders. Despite some efficacy of neuroleptics in acute mania (Chou, 1991), no double-blind parallel-design studies have evaluated the long-term efficacy of neuroleptics in recurrent mania. Two mirror-image studies (Kielholz *et al*, 1979; Ahlfors *et al*, 1981) suggest that the long-acting antipsychotic flupenthixol decanoate can decrease the frequency and severity of affective relapse in bipolar patients, although a placebo-controlled, two-year crossover study found that a lithium-flupenthixol decanoate combination is not superior to lithium-placebo in diminishing affective relapse in bipolar patients (Esparon *et al*, 1986). Some studies suggest that benzodiazepines, particularly clonazepam, are useful in acute mania (Chouinard, 1983), but there are no long-term data to substantiate the effectiveness of a benzodiazepine in combination with lithium in the prophylaxis of bipolar illness. In fact, the one open study of this question had negative results (Aronson & Shukla, 1989).

Other than lithium, carbamazepine has been the most extensively studied agent in the preventive treatment of bipolar illness. To date, four double-blind studies have been done. Okuma *et al* (1981) reported that carbamazepine is superior to placebo in providing affective prophylaxis over a 12-month period. Three studies (Placidi *et al*, 1986; Watkins *et al*, 1987; Lusznat *et al*, 1988), which involved a total of about 150 patients, revealed that carbamazepine is equal to lithium in preventing affective relapses, yielding an overall 30% relapse rate in both groups. Other open studies have suggested that carbamazepine is an effective prophylactic agent both alone and in combination with lithium in patients who have either failed on lithium alone (Stuppaeck *et al*, 1990) or failed on a lithium-neuroleptic combination (Shukla *et al*, 1985).

For bipolar patients who suffer repeated depressive episodes, lithium-antidepressant combinations are frequently used in long-term maintenance in accordance with the common perception that lithium protects the patient against manic recurrence and the antidepressant protects against depressive recurrences. However, two double-blind studies found that a lithium-imipramine treatment combination has little or no effect in preventing depressive recurrences, as compared with lithium alone (Quitkin *et al*, 1981; Prien *et al*, 1984).

However, the main question in this study is *not* how lithium compares with combination treatment in the general bipolar population, but how effective combination treatment is in lithium non-responders. We do not suggest that combination treatment is more effective than lithium alone in a *general bipolar population*. In using the formula of Mantel (1966) and Fleiss *et al* (1976) to evaluate the entire sample of 305 bipolar patients, we found no difference between combination treatment and lithium alone at any single point during the five-year course when comparing pessimistic with pessimistic and optimistic with optimistic probabilities. We also found no difference between combination treatment and lithium alone in comparing the overall course using all points (see Fleiss *et al* (1976) and Peselow *et al* (1990) for explanations of how these statistical comparisons are made). On the basis of results presented here, we suggest that for patients who have an affective relapse (manic or depressive) on lithium alone, combination treatment may offer greater protection against a subsequent relapse. Since many research centres tend to see more and more of the patients who fail on traditional treatments such as lithium (NIMH Division of Clinical Research, 1985), this issue is by no means unimportant. Indeed, in clinical settings, the use of supplemental antidepressants, neuroleptics, and other agents for breakthrough depressions and manias and for subsequent prophylaxis is common, despite an absence of controlled studies validating this approach (Sachs, 1989). In a survey of 20 lithium clinics, Gitlin & Jamison (1984) noted that approximately 40% of bipolar patients were taking supplemental tricyclics or MAOIs for an acute episode or for prophylaxis. The naturalistic study done here suggests that combination treatment for lithium failures may extend the interval between manic and depressive relapses. Therefore, such a treatment approach is justified.

In summary, within a naturalistic clinical setting, lithium alone offered an average 83% probability against an affective relapse at one year, 52% at three years, and 37% at five years. For the patients who failed on lithium alone, it appeared that combination treatment (lithium plus either a neuroleptic, carbamazepine, or a benzodiazepine for those who suffered a manic relapse, or lithium plus an antidepressant for those who suffered a depressive relapse) offered greater protection against subsequent relapse, as compared with the initial course on lithium alone. Future double-blind, controlled studies of various combination treatments for lithium prophylactic failures are needed to assess the efficacy of this approach in the long-term prophylaxis of bipolar illness.

References

AHLFORS, U. G., BAASTRUP, P. C., DENCKER, S. K., *et al* (1981) Flupenthixol decanoate in recurrent manic-depressive illness. *Acta Psychiatrica Scandinavica*, **64**, 226–237.

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn) (DSM-III). Washington, DC: APA.

AMERICAN PSYCHIATRIC ASSOCIATION TASK FORCE ON LITHIUM THERAPY (1975) The current status of lithium therapy. Report of the APA Task Force. *American Journal of Psychiatry*, **132**, 997–1001.

ANGST, J., FELDER, W. & FREY, R. (1979) The course of unipolar and bipolar affective states. In *Origin, Prevention and Treatment of Affective Disorders* (eds M. Schou & E. Stromgren), pp. 215–226. London: Academic Press.

ARONSON, T. A., SHUKLA, S. & HIRSCHOWITZ, J. (1989) Clonazepam treatment of five lithium refractory patients with bipolar disorder. *American Journal of Psychiatry*, **146**, 77–80.

BAASTRUP, P. C., POULSEN, K. O. S., SCHOU, M., *et al* (1970) Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent depressive disorders. *Lancet*, *ii*, 326–330.

BIEGEL, A., MURPHY, D. L. & BUNNEY, W. E. (1971) The manic rating scale. *Archives of General Psychiatry*, **25**, 256–262.

CHOU, J. C. (1991) Recent advances in the treatment of acute mania. *Journal of Clinical Psychopharmacology*, **11**, 3–21.

CHOUINARD, G. (1983) Antimanic effects of clonazepam. *Biological Psychiatry*, **18**, 451–456.

COPPEN, A., NOGUERA, R. & BAILEY, J. (1971) Prophylactic lithium in affective disorder. *Lancet*, *ii*, 275–279.

———, MONTGOMERY, S. A., GUPTA, R. K., *et al* (1976) A double-blind comparison of lithium and maprotiline in the prophylaxis of affective disorders. *British Journal of Psychiatry*, **128**, 479–485.

CUNDALL, R. L., BROOKS, P. W. & MURRAY, G. L. (1972) A controlled evaluation of lithium prophylaxis in affective disorders. *Psychological Medicine*, **2**, 308–311.

DAVIS, J. M. (1976) Overview: maintenance therapy in psychiatry. II. Affective disorders. *American Journal of Psychiatry*, **133**, 1–13.

ESPARON, J., KOLLOORI, J., NAYLOR, G. J., *et al* (1986) Prophylactic action of flupenthixol with placebo in lithium treated patients. *British Journal of Psychiatry*, **148**, 723–725.

FEIGHNER, J. P., ROBINS, E., GUZE, S., *et al* (1972) The use of research criteria in psychiatry. *Archives of General Psychiatry*, **26**, 57–63.

FIEVE, R. R. & MENDLEWICZ, J. (1972) Lithium prophylaxis in bipolar manic-depressive illness. *Psychopharmacology*, **26**, 93.

———, KUMBARACHI, T. & DUNNER, D. L. (1973) Lithium prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. *American Journal of Psychiatry*, **133**, 925–929.

———, DUNNER, D. L. & KUMBARACHI, T. (1975) Lithium carbonate in affective disorders. A double-blind study of prophylaxis in recurrent unipolar depression. *Archives of General Psychiatry*, **32**, 1541–1545.

———, ———, ———, *et al* (1976) Lithium prophylaxis of depression in three subtypes of primary affective disorder. *Pharmacopsychiatry*, **9**, 100–107.

——— & PESELOW, E. D. (1983) Lithium-clinical applications. In *Drugs in Psychiatry* (vol. 1). *Antidepressants* (ed. G. D. Burrows, T. R. Norman & B. Davies), pp. 277–321. Amsterdam: Elsevier-North Holland Biomedical Press.

FLEISS, J. L., DUNNER, D. L., STALLONE, F., *et al* (1976) The life-table: a method for analyzing longitudinal studies. *Archives of General Psychiatry*, **33**, 107–112.

GITLIN, M. R. & JAMISON, K. R. (1984) Lithium clinics: theory and practice. *Hospital and Community Psychiatry*, **35**, 363–368.

HAMILTON, M. (1967) Development of a rating scale for primary depressive illness. *British Journal of Clinical Psychology*, **6**, 278–296.

HULLIN, R. P., MCDONALD R. & ALLSOP, M. N. E. (1972) Prophylactic lithium in recurrent affective disorder. *Lancet*, *i*, 1044–1046.

KANE, J. M., QUITKIN, F., RIFKIN, A., *et al* (1982) Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar illness. *Archives of General Psychiatry*, **39**, 1065–1069.

KIELHOLZ, P., TERZANI, S. & POLDINISER, P. (1979) The long term management of periodical and cyclical depressions with flupenthixol decanoate. *International Pharmacopsychiatry*, **14**, 305–309.

KRAMER, M. (1969) *Application of Mental Health Statistics*. Geneva: World Health Organization.

LEW, E. A. & SELTZER, F. (1970) Uses of the life-table in public health. *Millbank Quarterly*, **48**, 15–37.

LUSZNAT, R. M., MURPHY, D. P. & NUNN, C. M. H. (1988) Carbamazepine vs lithium in the treatment and prophylaxis of mania. *British Journal of Psychiatry*, **153**, 198–204.

MANTEL, N. (1966) Evaluation of survival data and two new rank order statistics arising from its consideration. *Cancer Chemotherapy*, **50**, 163–170.

MELIA, P. I. (1970) Prophylactic lithium – a double blind trial in recurrent affective disorders. *British Journal of Psychiatry*, **116**, 621–624.

NIMH DIVISION OF CLINICAL RESEARCH (1989) *Report from the NIMH Workshop on the Treatment of Bipolar Disorders*. Bethesda, MD: NIMH.

OKUMA, T., INANGA, K., OTSUKI, S., *et al* (1981) A preliminary double-blind study of the efficacy of carbamazepine in the prophylaxis of manic-depressive illness. *Psychopharmacology*, **73**, 95–96.

PERSSON, G. (1972) Lithium prophylaxis in affective disorders. An open trial with matched controls. *Acta Psychiatrica Scandinavica*, **48**, 462–479.

PESELOW, E. D., DUNNER, D. L., FIEVE, R. R., *et al* (1982) Lithium prophylaxis of depression in unipolar, bipolar II, and cyclothymic patients. *American Journal of Psychiatry*, **139**, 747–752.

——, —— & —— (1990) Psychopharmacology in clinical practice: the prophylaxis of unipolar depression. *Lithium*, **1**, 115–123.

PLACIDI, G. F., LENZI, A., LAZZERINI, F., *et al* (1986) The comparative efficacy and safety of carbamazepine versus lithium: a randomized double-blind three year trial in 83 patients. *Journal of Clinical Psychiatry*, **47**, 490–494.

PRIEN, R. F., KLEIT, C. J. & CAFFEY, E. M. (1973*a*) Lithium carbonate and imipramine in the prevention of affective episodes: a comparison in recurrent affective illness. *Archives of General Psychiatry*, **28**, 337–341.

——, CAFFEY, E. M. & KLEIT, C. J. (1973*b*) Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institutes of Health Collaborative Study Group. *Archives of General Psychiatry*, **28**, 420–425.

——, KUPFER, D. J., MANSKY, P. A., *et al* (1984) Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. *Archives of General Psychiatry*, **41**, 1096–1104.

—— & GELENBERG, A. J. (1989) Alternatives to lithium for preventive treatment of bipolar disorder. *American Journal of Psychiatry*, **146**, 840–848.

QUITKIN, F., RIFKIN, A., KANE, J., *et al* (1978) Prophylactic effect of lithium and imipramine in unipolar and bipolar II patients. *American Journal of Psychiatry*, **135**, 570–572.

——, KANE, J., RIFKIN, A., *et al* (1981) Prophylactic lithium carbonate with and without imipramine for bipolar I patients. *Archives of General Psychiatry*, **38**, 902–909.

SACHS, G. M. (1989) Adjuncts and alternatives to lithium therapy for bipolar affective disorder. *Journal of Clinical Psychiatry*, **12** (suppl.), 31–39.

SCHOU, M. (1968) Lithium in psychiatric therapy and prophylaxis. *Journal of Psychiatry Research*, **6**, 67–95.

SHUKLA, S., COOK, B. L. & MILLER, M. G. (1985) Lithium-carbamazepine vs lithium-neuroleptic prophylaxis of bipolar illness. *Journal of Affective Disorders*, **9**, 219–222.

SMALL, J. G., KLAPPER, M. H., MILSTEIN, V., *et al* (1991) Carbamazepine compared with lithium in the treatment of mania. *Archives of General Psychiatry*, **48**, 915–921.

SPITZER, R., ENDICOTT, J. & ROBINS, E. (1978) Research Diagnostic Criteria: rationality and reliability. *Archives of General Psychiatry*, **35**, 773–782.

STALLONE, F., SHELLEY, E., MENDLEWICZ, J., *et al* (1973) The use of lithium in affective disorders. III. A double-blind study of prophylaxis in bipolar illness. *American Journal of Psychiatry*, **130**, 1006–1010.

STUPPAECK, C., BARNAS, C., MILLER, C., *et al* (1990) Carbamazepine in the prophylaxis of mood disorders. *Journal of Clinical Psychopharmacology*, **10**, 39–42.

WATKINS, S. E., CALLENDER, K., THOMAS, D. R., *et al* (1987) The effect of carbamazepine and lithium on remission from affective illness. *British Journal of Psychiatry*, **150**, 180–182.

*Eric D. Peselow, MD, *Research Associate Professor of Psychiatry, Department of Psychiatry, New York University School of Medicine, 550 First Avenue, New York, NY 10010*; Ronald R. Fieve, MD, *Clinical Professor of Psychiatry, Columbia College of Physicians and Surgeons, New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032*; Constance DiFiglia, MD, *Staff Psychiatrist, Foundation for Depression/Manic Depression, 7 East 67th Street, New York, NY 10016*; Michael P. Sanfilipo, MS, *Research Assistant, Department of Psychiatry, New York Veterans Administration Medical Center, 423 East 23rd Street, New York, NY 10010, USA*

*Correspondence: *1322 East 84th Street, Brooklyn, NY 11236, USA*

(First received January 1992, final revision January 1993, accepted May 1993)