Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders

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Background   The effectiveness of lithium is being questioned increasingly and requires clarification.

Aims   To assess the effectiveness of lithium treatment in depression and mania, syndromal types I and II, with predominantly mixed or psychotic episodes or rapid cycling, during treatment resumed following discontinuation, and across three decades.

Method   The longitudinal course of 360 patients with bipolar disorder compliant with lithium treatment for at least 1 year and without comorbidity for substance use disorder was reviewed.

Results   Risk of single-episode recurrences, a common index of treatment failure, was similar to that in other reports. Both episode frequency and 'time ill' improved more in type II than type I cases. Reduced morbidity during treatment was similar in patients with mixed or psychotic episodes, or rapid cycling, and in less complex cases. Retreatment yielded minor decrements in response, and there was no tendency for lesser responses in more recent years.

Conclusions   Based on overall affective morbidity, long-term lithium treatment in compliant patients without comorbid substance use disorder, though imperfect, remains effective, even in subgroups of supposedly poor prognosis.

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Lithium opened the modern era of psychopharmacology, following rediscovery of its antimanic effects by John Cade 50 years ago (Hammond, 1871; Cade, 1949; Baldessarini, 1996). Its slowness of onset and limited tolerability when administered aggressively limit its usefulness in the treatment of acute mania. However, since the 1960s, lithium has proved its clinical value for preventing or modifying recurrences of both mania and depression in bipolar manic–depressive disorders. The effectiveness of long-term treatment with lithium to prevent recurrences in manic–depressive disorder is supported by many open studies, and at least 10 controlled, double-blind studies (Goodwin & Jamison, 1990; Alastair & Wood, 1994; Price & Heninger, 1994; Baldessarini et al, 1996). This evidence far exceeds the available support for possible alternatives to lithium treatment, including recently emerging empirical applications of anticonvulsant, antipsychotic or sedative agents. Several of these alternatives have proven, or probable, antimanic activity, but their long-term mood-stabilising effectiveness remains largely untested (Ahlfors et al, 1981; Watkins et al, 1987; Prien & Potter, 1990; American Psychiatric Association, 1994a; Price & Heninger, 1994; Baldessarini, 1996; Baldessarini et al, 1996). Moreover, only lithium has substantial evidence of long-term reduction of suicide risk (Tondo et al, 1998a; Baldessarini & Jamison, 1999; Tondo & Baldessarini, 2001). Increased off-label use of alternatives to lithium may be encouraged by reports emphasising poor outcome in some patients treated with lithium, although the superiority of alternative treatments for such patients also remains unproven. Many of the negative reports about lithium arise from clinical samples from specialised referral centres that may overrepresent diagnostically atypical, comorbid and otherwise complex patients unlikely to respond well to any treatment, or may reflect sub-optimal care encountered within ordinary clinical conditions (Dunner & Fieve, 1974; Dickson & Kendell, 1986; Page et al, 1987; Maj et al, 1989, 1998; Markar & Mander, 1989; Harrow et al, 1990; Tohen et al, 1990; O'Connell et al, 1991; Keller et al, 1993; Guscott & Taylor, 1994; Peselow et al, 1994; Sachs et al, 1994; Gitlin et al, 1995; Goldberg et al, 1995, 1996; Winokur et al, 1995; Gitlin & Altshuler, 1997; Grof, 1998).

Given the recent questioning as to whether lithium remains an effective option in the long-term treatment of bipolar manic–depressive disorder, we reviewed three decades of clinical experience at a private, university-affiliated research clinic that has not selected for complex, atypical or treatment-resistant cases. In response to the literature cited above, we specifically addressed the hypotheses that lithium is more effective:

(a) in bipolar type II than in type I disorder;

(b) in mania than in bipolar depression;

(c) in patients without psychotic features, dysphoric-mixed episodes or rapid cycling;

(d) initial trials than in treatment resumed following discontinuation;

(e) in earlier than in later years of its use.

METHOD

Adult participants with bipolar I (mania and depression) and II (depression and hypomania) disorder meeting DSM–IV (American Psychiatric Association, 1994b) diagnostic criteria for syndromes and episodes were evaluated while undergoing long-term clinical maintenance treatment with lithium carbonate and follow-up at the Lucio Bini mood disorders centre in Cagliari, Sardinia, a Stanley Foundation research centre. Confidentiality was assured, and participants provided written informed consent for analysis and anonymous reporting of information obtained from their clinical and research records (Tondo et al, 1998a,b). Excluded from the study were those exposed to mood-altering drugs other than for brief treatment of breakthrough symptoms ($\leqslant 12$ weeks), those receiving long-term anticonvulsant treatment, those misusing drugs or alcohol during treatment, those treated continuously for less than 12 months and those considered non-compliant with treatment recommendations because of repeated interruptions lasting 2 or more days or self-reduction of dosage.

Clinical assessments made by research psychiatrists (L.T., G.F.) in follow-up visits (four to 12 times per year) were recorded on research data forms and monthly life charts to document treatments given (type, doses and duration of psychotropic agents and their adverse effects), as well as the type, severity and duration of recurrent episodes of affective illness. Demographic data included gender, birth date and educational level, as well as marital and employment status at the start of maintenance treatment. Clinical data included diagnostic type based on most recent assessments, probable presence of psychotic features or mixed mood states in a majority of episodes, relevant family history, age at illness onset, length of first interval between episodes, number and duration of all episodes of mania (or hypomania in type II patients), depression and psychiatric hospitalisation, majority sequence of episode polarities in at least three cycles of illness (mania before depression, or the opposite), presence of a rapid-cycling course (four or more episodes in any year), time from illness onset to the start of regular maintenance treatment (treatment latency), occurrences of suicide attempts or fatalities and doses and average of approximately semi-annual serum concentrations of lithium.

This information yielded annual morbidity rates as manic or depressive episodes, or hospitalisations per year, and proportion (percentage) of time in DSM–IV mania (or hypomania) or depression before and during lithium maintenance treatment. Statistical analysis employed paired t-tests or analysis of variance (ANOVA) (F) for unpaired continuous data; categorical data were compared by contingency tables (χ^2), with defined degrees of freedom (d.f.). Data are means (s.d.) unless stated otherwise. Non-significance (NS) is at $P > 0.05$ in two-tailed tests.

RESULTS

The 360 bipolar (BP) disorder subjects participating in the study included type I (BP-I; $n=218$; 60.6%) and type II (BP-II; $n=142$; 39.4%) cases; women (64.7%) outnumbered men (35.3%); most were 'employed' – working, homemakers, students or retired (81.7%); and a minority had more than 8 years of education (39.4%) or were married (46.4%) at the start of treatment. Patients with 'typical' or non-complex BP-I without prominent psychotic

features or episodes of mixed moods represented a minority of all 360 patients (28.9%); those with mainly psychotic episodes accounted for 27.8% of all cases (45.9% of BP-I cases) and those with predominantly mixed states were the least common BP-I subtype (6.4% of BP-I; 3.89% of all cases). A family history of affective disorder in a first-degree relative was recorded in 56.1% of subjects, with suicidal acts by a close relative in 1.82% of cases, whereas suicide attempts were recorded in 18.3% of probands themselves. Age at onset of first life time bipolar illness averaged 29.2 years; in 63.6% of cases the onset episode polarity was depressive. A regular course of the illness with at least three cycles of the same sequence of mania (M), depression (D) and euthymic interval (I) was found in 74.7% of cases, including a rapid-cycling course in 14.7% of subjects plus another 14.2% with a slower but continuously cycling course. Patients started maintenance lithium treatment after an average of 8.3 years from the onset of bipolar illness, or at 37.4 years of age, and were treated for 6.0 years at moderate average serum lithium concentrations of 0.615 mmol/l, in accord with common international practice aimed at enhancing tolerability and compliance (Jamison & Akiskal, 1983; Maj *et al*, 1986; Baldessarini *et al*, 1997; Tondo *et al*, 1998*b*). This information is summarised in Table 1.

Clinical effectiveness of long-term lithium treatment was evaluated using several measures, including annual rates of recurrent episodes of mania and depression, considered separately or together, and of psychiatric hospital admissions. Overall morbidity was also rated as the proportion of time-at-risk in all affective illness, or in mania or depression. We also considered estimates of mean episode duration. All measures were compared for years of assessment (mainly retrospective) prior to lithium maintenance treatment and years of prospective follow-up during lithium treatment, and reductions of episode frequency or percentage of time ill were computed (Table 2). All measures of morbidity showed significant reductions, including 55.7% fewer episodes per year and 56.5% less time ill during treatment. On average, episode frequency was reduced somewhat more for mania than for bipolar depression (63.6% *v.* 46.4%), but reductions in the proportion of time in mania and in depression were more similar (61.2% *v.* 52.8%). Moreover, the average duration of episodes

was reduced substantially more for depression than for mania (32.4% *v.* 19.4%), in part reflecting the longer duration of depressive episodes compared with manic episodes prior to lithium treatment: 4.84 *v.* 3.14 months (Table 2). The majority of patients showed substantial reductions in episode frequency and the proportion of time ill; 28.9% had no new episodes of

Table I Sample characteristics ($n=360$)

Characteristic	Percentage or mean
Demographic factors (% of cases)	
Women	64.7
Educated > 8 years	39.4
Employed[1]	81.7
Married[2]	46.4
Family history (% of cases)	
All mood disorders	56.1
Bipolar	29.4
Unipolar	29.7
Suicide	1.82
Suicidal acts (% of cases)	18.3
Onset episode (% of cases)	
Depressive	63.6
Manic	36.4
Diagnostic types (% of all cases)	
Bipolar I[3]	60.6
typical	28.9
psychotic	27.8
mixed	3.89
Bipolar II	39.4
Course (% of cases)[4]	
M–D–I	30.5
D–M–I	15.3
RC	14.7
Continuous non-RC	14.2
Erratic	25.3
Onset and treatment latency, years (mean (s.d.))	
Onset age	29.2 (12.0)
Age at lithium start	37.4 (14.2)
Latency: onset to lithium	8.30 (8.23)
Lithium maintenance (mean (s.d.))	
Duration of treatment (years)	6.00 (5.03)
Serum lithium concentrations (mmol/l)	0.615 (0.137)

1. Working, homemaker, student or retired.
2. In a stable relationship.
3. Characterised by majority of episodes.
4. Depression (D) or mania (M) (hypomania in type II) before a euthymic interval (I), followed by mania or depression in a majority of cycles before lithium; rapid cycling (RC): ⩾four episodes in any year before lithium maintenance.

Table 2 Morbidity before and during lithium maintenance

Measure	Before	During	Reduction (%)
Annual rates (mean (s.d.))			
Episodes	1.83 (2.14)	0.81 (1.11)	55.7
Manias[1]	0.99 (1.48)	0.36 (0.53)	63.6
Depressions	0.84 (1.03)	0.45 (0.84)	46.4
Hospitalisations[2]	0.33 (0.86)	0.06 (0.22)	81.8
Morbidity (% of time (s.d.))			
Total illness	45.7 (30.6)	19.9 (21.8)	56.5
Mania/hypomania	20.9 (22.3)	8.11 (12.8)	61.2
Depression	24.8 (22.5)	11.7 (16.7)	52.8
Episode duration (months (s.d.))			
Mania/hypomania	3.14 (2.03)	2.53 (1.95)	19.4
Depression	4.84 (4.16)	3.27 (2.55)	32.4

1. Mania in type I, hypomania in type II.
2. Hospitalisation rate refers to 178 (49.4%) patients with at least one hospitalisation before lithium treatment, which lasted an average of 7.13 ± 5.62 years in this subgroup. All paired $t \geqslant 3.60$; all $P < 0.0001$.

Table 3 Percentage of cases at levels of improvement during lithium maintenance

Level of improvement	Percentage of patients	
	Episodes/year	Time ill (%)
None	27.2	21.4
0–49%	13.3	14.2
50–99%	30.6	35.5
100%	28.9	28.9
All levels	100.0	100.0

Table 4 Clinical factors: morbidity during lithium maintenance

Variable	Time ill (% (s.d.))
Diagnostic type[1]	
Bipolar I	22.0 (22.0)
Bipolar II	16.5 (21.0)
Bipolar I subtypes	
Typical	23.9 (24.2)
Psychotic	19.9 (19.5)
Mixed	23.3 (22.1)
Polarity sequence	
M–D–I	17.7 (15.7)
D–M–I	19.2 (21.4)
Cycling rate	
RC	22.0 (23.8)
Non-RC	19.5 (21.4)

1. For diagnostic type, by analysis of variance [1; 358 d.f.]; $F = 5.57$, $P = 0.02$; no other difference is significant. D, depression; M, mania; I, euthymic interval; RC, rapid cycling.

mania or depression during lithium maintenance treatment, and about a quarter of patients showed no improvement (Table 3).

Affective morbidity, as reflected in the proportion of time ill during lithium treatment, was significantly lower in BP-II than in BP-I, as we reported previously based on an analysis that included many of the present subjects (Tondo *et al*, 1998b). However, there were only minor, non-significant, differences among typical, psychotic and mixed-episode types of BP-I patients, between those with a majority of polarity sequences starting with mania or depression and in those with rapid cycling in any year prior to starting lithium maintenance treatment (Table 4).

In addition, several factors were significantly associated with a superior treatment response, as defined by at least a 75% reduction in the proportion of time ill before treatment *v.* time ill during lithium maintenance – the approximate median level of improvement (Table 5). These factors were:

(a) older age at onset of bipolar illness;

(b) a shorter interval between first and second life time episodes;

(c) greater morbidity before lithium therapy (as episode frequency or proportion of time ill, yielding a greater contrast to morbidity during treatment);

(d) a shorter latency period between illness onset and the start of lithium treatment (associated with greater pretreatment morbidity);

(e) a shorter recovery time for the episode associated with the start of lithium treatment;

(f) a longer stable interval between the end of this index episode and the first recurrence during lithium treatment;

(g) requirement for less lithium (lower mean serum concentration).

Other factors that were not significantly related to improvement quality based on the preceding definition were gender ($\chi^2 = 1.15$); family history of affective illness ($\chi^2 = 0.31$); more than 8 years of education ($\chi^2 = 0.60$); polarity of first life time episode ($\chi^2 = 2.26$); age at starting lithium ($F = 1.51$); and marital status at the start of lithium treatment ($\chi^2 = 2.21$). However, there was a slightly higher proportion of employment (working, homemaker, student or retired) at the start of lithium treatment in superior responders (86.2% *v.* 77.1%; $\chi^2 = 4.97$, $P = 0.026$). A median split for high ($n = 181$) *v.* low ($n = 179$) improvement in percentage time ill was also used for a logistic regression analysis. A higher percentage of improvement was significantly associated with the following factors in rank order: longer first interval on lithium, shorter recovery of first episode on lithium, shorter time before starting lithium and more episodes per year before lithium (overall model: $\chi^2 = 91.2$, $P < 0.0001$) (Table 5).

A subgroup of patients ($n = 85$) discontinued lithium in a non-experimental fashion, experienced a recurrence, and then returned to lithium maintenance for at least another year. During these repeat lithium treatment trials, patients showed only minor and non-significant increases in annual rates of recurrence or in the proportion of time ill compared with their first long-term trial, and hospitalisation rates were non-significantly less frequent during retreatment.

Similarly, the proportion of fully protected patients experiencing no recurrences during lithium treatment also showed only minor losses during secondary retreatment. The proportions of time ill during initial treatment and later retreatment were very similar in the BP-I and BP-II groups considered separately (Table 6).

Finally, to evaluate whether there was a secular loss of long-term benefits of lithium, we compared the improvement among patients who started taking lithium in the 1970s, 1980s and 1990s. There was

Table 5 Clinical factors: quality of improvement associated with lithium maintenance treatment

Variable	Superior (n=181)	Inferior (n=179)	F test	P
Onset age (years (s.d))	30.9 (12.8)	27.4 (11.0)	7.99	0.005
First euthymic interval (months (s.d.))[1]	16.7 (45.5)	35.2 (66.2)	9.64	0.002
Episodes/year before treatment (s.d.)	2.14 (2.24)	1.52 (1.87)	7.66	0.006
Percentage time ill before treatment (s.d.)	53.2 (31.3)	38.2 (28.1)	22.8	<0.0001
Latency: onset to treatment (years (s.d.))	7.31 (8.02)	9.30 (8.34)	5.35	0.021
Index recovery (months (s.d.))[2]	2.21 (1.86)	4.15 (4.90)	24.8	<0.0001
First on-lithium interval (months (s.d.))[3]	45.4 (44.7)	13.6 (23.9)	70.5	<0.0001
Serum lithium concentration (mmol/l (s.d.))	0.57 (0.11)	0.66 (0.14)	50.5	<0.0001

Response is rated superior or inferior by per cent improvement in the proportion of time ill being above or below the approximate median of 75%; for analysis of variance, d.f.=1; 358; for χ^2, d.f.=1. A multiple logistic regression with superior response based on percentage of time ill showed: longer first interval on lithium > shorter index recovery on lithium > shorter time before starting lithium > more episodes per year before lithium (overall model: χ^2=91.2, P<0.0001).
1. Months between end of the first and start of the second lifetime episodes.
2. Months to recovery from episode at which lithium started.
3. Months from end of index episode at start of lithium to start of first recurrence during lithium maintenance.

Table 6 Comparisons of initial and repeat lithium maintenance treatment trials

Measures on lithium	Initial	Repeat	Statistic
Duration (years (s.d.))	4.90 (3.98)	4.42 (3.49)	t=0.77
Episodes/year (s.d.)	0.842 (1.172)	0.959 (1.243)	t=0.67
Percentage of time ill (s.d.)	17.0 (22.0)	22.8 (25.4)	t=1.71
Hospitalisations/year (s.d.)	0.091 (0.315)	0.057 (0.158)	t=1.02
Having no recurrences (%)	30.6	25.9	χ^2=0.46

Subjects were 85 patients with bipolar I or II disorder. By paired t-tests (84 d.f.) or χ^2 (1 d.f.), all comparisons are not significant. Also, there were no significant differences in percentage of time ill during first and second lithium trials in bipolar disorder type I (16.3±17.4% v. 20.4±22.7%) or type II patients (18.1±27.6% v. 26.2±29.0%) considered separately.

no indication that morbidity (as a proportion of time ill per year) increased in later years; rather, the percentage of patients with no new episodes during treatment tended to increase non-significantly over the three decades studied (Table 7).

DISCUSSION

The findings presented here indicate substantial levels of improvement in a large sample of consecutive and clinically heterogeneous patients with BP-I and BP-II unselected for outcome, but requiring treatment and observation for at least a year during lithium maintenance treatment. These patients were followed systematically over a total average of 14.3 years, including 8.3 years before and 6.0 years during lithium treatment used as monotherapy for maintenance, with only brief supplementation during acute recurrences. Beneficial effects of this long-term lithium treatment included reduction of episode

Table 7 Historical trends in morbidity during lithium maintenance treatment

Decade	n	Percentage time ill (s.d.)[1]	Episodes/year (s.d.)[2]	Episode-free[3] (%)
1970s	90	16.4 (20.4)	0.860 (1.102)	25.6
1980s	148	18.3 (21.4)	0.829 (1.138)	31.8
1990s	122	18.3 (23.3)	0.751 (1.126)	38.5
Total	360	17.8 (21.8)	0.810 (1.123)	32.5

1. Percentage of time ill during treatment: F[2; 357 d.f.]=0.27, not significant (NS).
2. Episodes/year during treatment: F[2; 357 d.f.]=0.28, NS.
3. Proportion of patients with no recurrences during treatment: χ^2 [2 d.f.]=4.03, NS.

frequency by 56% overall, and by 64% for manias and 46% for depressions. The duration of both manic and depressive recurrent episodes was also reduced (by 19% and 32%, respectively), and, consistent with our previous findings with many of the same subjects, BP-II syndromes benefited somewhat more than BP-I (Tondo *et al*, 1998*b*). The net impact of reduced episode frequency and duration was to yield major reductions in the proportion of time ill during follow-up, by 56% overall, and by 61% for mania and 53% for bipolar depression. Evidently, benefits to overall morbidity (proportion of time ill) reflect reductions in both episode frequency and duration. These gains would not be appreciated by recording the time to occurrence of a new episode, or even by episode-counting alone. Such measures have commonly, but potentially misleadingly, been used to define 'treatment failure' (Goodwin & Jamison, 1990; Baldessarini *et al*, 1996).

The most striking numerical impact of lithium treatment was found for the hospitalisation rate, which fell by 82%. This finding has considerable economic significance, since hospitalisation accounts for a major proportion of direct costs in major psychiatric illness (Wyatt & Henter, 1995; Frankenburg & Hegarty, 1996). Additional economic impact can be expected in the major reduction of overall morbidity, which is likely to limit ability to work or to live independently, and, presumably, premature mortality and loss of income due to suicide or stress-related medical illness (Angst *et al*, 1998; Baldessarini & Jamison, 1999).

It is important to emphasise that only about a quarter of the patients in this study (29%) experienced complete remission from all recurrences of affective illness during maintenance treatment (see Table 3). This level of protection is in keeping with past reports suggesting that full protection is not commonly achieved with lithium or with alternative treatments (Rybakowsky *et al*, 1980; Prien *et al*, 1988; Gelenberg *et al*, 1989; Goodwin & Jamison, 1990; Tohen *et al*, 1990; Keller *et al*, 1993; Koukopoulos *et al*, 1995*a*; Baldessarini *et al*, 1996; Greil *et al*, 1997; Maj *et al*, 1998; Baldessarini & Tondo, 2000). Although perfect prophylaxis was uncommon, at least 60% of patients experienced reductions in episode frequency and in the proportion of time ill by at least one-half (see Table 3). These considerations strongly suggest that requiring complete protection against all recurrences of mania

or bipolar depression as a test of effectiveness of a mood-stabilising agent is unrealistic and, specifically, would tend to lead to underestimates of the substantial, long-term, overall beneficial effects of lithium.

Another difficulty of measuring treatment effectiveness is the risk of artefactual inflation of change scores, or decreases in recurrence rates or the proportion of time ill, such that a higher level of pretreatment morbidity can lead to overestimation of benefit of treatment. For example, the apparent gains found with shorter latency from illness onset to the start of lithium maintenance treatment are probably associated with the need to intervene earlier in more severe illness (see Table 5). This view is supported by the failure to find a relationship between latency from illness onset to the start of lithium maintenance treatment, and clinical status during lithium treatment, in many of the same patients (Baldessarini et al, 1999).

Several factors expected to predict poor treatment response had little effect on the proportion of time ill during lithium treatment. These factors include prominent psychotic features (Prien et al, 1988; Keller et al, 1993; Solomon et al, 1995; Kusumakar et al, 1997); mixed states (Koukopoulos et al, 1995b; Goldberg et al, 1998); and rapid cycling (Prien et al, 1974; Dunner & Fieve, 1974, 1977; Koukopoulos et al, 1980; Wehr et al, 1988; Maj et al, 1989; Bauer & Whybrow, 1991; Koukopoulos et al, 1995a; Solomon et al, 1995; Calabrese et al, 1996; Post et al, 1997). In contrast to expectations, diagnostic type, psychotic or mixed BP-I subtypes and rapid cycling were not predictive of inferior benefits, in terms of the proportion of time well or ill during lithium maintenance treatment (see Table 4). Moreover, despite repeated suggestions that such features routinely predict a poor outcome or inferior treatment response, the evidence on which such conclusions are based is much less secure than is sometimes realised.

The sequence of manic and depressive episodes was also not associated with treatment response (see Table 4). This result was not expected in view of previous reports indicating that the sequence of mania before depression and a euthymic interval (M–D–I) is more likely to be followed by successful lithium maintenance treatment than the D–M–I pattern, or depression before mania (Koukopoulos et al, 1980; Haag et al, 1987; Grof et al, 1987; Maj et al, 1989; Faedda et al, 1991; Koukopoulos

et al, 1995a). Our results may reflect the requirement of at least three cycles in which the same sequences of mania and depression were found.

On the other hand, some clinical factors found early in the course of illness (e.g. age at illness onset, and a longer interval between first and second life time episodes) or early in treatment with lithium (e.g. rapidity of recovery from the index episode at the start of lithium treatment, and a longer interval to the first subsequent recurrence) were significantly associated with a better long-term treatment response as indicated by the overall proportion of time ill during treatment (see Table 5).

Finally, we found no evidence of significant degradation of treatment responses during repeated long-term maintenance treatment with lithium (see Table 6) or over decades of following patients at the research clinic from which our sample was drawn. Some reports have indicated that a second treatment trial with lithium following its discontinuation may be less effective than the initial trial (Post et al, 1992; Maj et al, 1995). Our findings, however, agree with those of an earlier study that included many of the same subjects (Tondo et al, 1997), and with another independent study by Coryell et al (1998). The stability of results over three decades accords well with our meta-analysis of studies reported within the same era, in which there has actually been a non-significant trend toward superior responses in more recent times (Baldessarini & Tondo, 2000).

Although the participants in this study were not selected for ability to tolerate or benefit from lithium treatment there is likely to be bias in any naturalistic, clinical sample that is not based on random assignment to treatment. On the other hand, if patients are not treated for prolonged periods with any accepted or investigational agent, it is not possible to assess its effects. It seems likely that reliance on naturalistic or only partially controlled treatment trials will be necessary since blinded, randomised trials for testing of long-term effectiveness over several years are becoming increasingly impracticable (Calabrese & Rapport, 1999). Systematic observations of treatment effects in patients with bipolar disorder for longer than 1–2 years are rare, extremely rare for maintenance treatments other than lithium, and few have been carried out under industrial sponsorship.

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CLINICAL IMPLICATIONS

■ The mood-stabilising effectiveness of lithium is supported by many open trials, and at least 10 controlled and blind studies. The long-term effectiveness of alternative treatments remains largely untested.

■ Lithium treatment was found to be somewhat more effective in type II than in type I bipolar disorder, similar in patients with typical syndromes and those with psychotic or mixed features, with different majority polarity sequences, as well as in rapid-cycling and non-rapid-cycling forms of the disorder.

■ Treatment response did not significantly deteriorate on treatment resumption following discontinuation of lithium, nor across years 1970–1998.

LIMITATIONS

■ The study design was naturalistic and clinical.

■ The requirement of a minimum duration of treatment of 1 year may select for motivated patients, and perhaps those with greater responsiveness to lithium, and would eliminate patients who drop out because of poor initial response or intolerance to lithium.

■ The findings may not be generalisable in ordinary clinical settings.

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