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The prophylactic efficacy of lithium – transient or persistent?

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Abstract It has been reported recently that the prophylactic efficacy of lithium is a transient phenomenon in many patients. Other studies suggest sustained efficacy against affective recurrences for many years. As this issue is of major therapeutic relevance, published literature considering changes in lithium efficacy over time has been reviewed. The present review includes a critical evaluation of the data and the methodology which yielded these controversial results. Considering the published data discussed in this review, the balance of evidence does not indicate a general loss of lithium efficacy in the prophylaxis of major affective disorders. A supposed persistence of the prophylactic effects in general does not, however, exclude the reappearance of affective recurrences after years of successful treatment in individual cases. Possible reasons for this phenomenon are discussed.

Key words Depression · Bipolar disorder · Lithium · Prophylaxis · Efficacy

Introduction

Lithium efficacy in the long-term treatment of recurrent mood disorders is discussed controversially in many respects. Some authors have questioned the long-term effectiveness of lithium in general (Moncrieff 1997). Other authors (Guscott and Taylor 1994; Schou 1993, 1999) emphasise the relevance of compliance, adequate dosage, and symptomatology. They argue that low response rates in some studies are due to under-dosing, non-compliance, and the inclusion of patients who are unlikely to respond to lithium. In a recent study (Greil et al. 1998), lithium was highly efficacious in patients with a "classical" bipolar symptomatology, but not in patients with "non-classical" features such as mood incongruent psychotic delusions or comorbidity. Schou (1993) argues that lithium is not a panacea but highly effective when patients are carefully selected according to the clinical picture and their presumed compliance. But even for patients who are likely to be compliant and initially responsive to lithium, the long-term efficacy has been questioned. In a couple of publications, two distinct phenomena affecting the long-term use of lithium are discussed: refractoriness, which seems to be induced by lithium-discontinuation, and a gradual loss of efficacy over time. Discontinuation-induced refractoriness is described as resistance to lithium therapy after lithium prophylaxis was discontinued and resumed (Post et al. 1992; Coryell et al. 1998). Gradual loss of efficacy is defined as a recurrence under an initially effective maintenance treatment without interruption of the prophylactic treatment (Post et al. 1993; Maj et al. 1996). These two patterns of non-response may involve very different neurobiological mechanisms (Post et al. 1993) and should be considered separately. This article focuses on the latter phenomenon. It provides a critical evaluation of the literature on the loss of prophylactic efficacy of lithium during continued treatment, and a reanalysis of the largest clinical trial that prospectively investigated changes in lithium efficacy over time (Coryell et al. 1997).

Evaluation of the published data

Patients who have suffered from recurrences after initial response to lithium prophylaxis have been described for at least 20 years (see Table 1). In recent years, this topic has been addressed more systematically by several investigations, including two prospective studies with large case numbers (Maj et al. 1989; Coryell et al. 1997).

Maj et al. (1985, 1989) have prospectively examined the long-term outcome of 68 bipolar and 79 unipolar pa-

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Table 1 Literature on changes in lithium efficacy over time

Author	Study design	Diagnosis	Author's comment on changes in lithium efficacy
Dotti and Bernini (1979)	Series of cases reports	Manic-depressive illness	"In some cases, lithium seems to lose its efficacy after several years of 'successful treatment'" (p. 295)*
Felber (1979)	Retrospective, 23 months of lithium treatment on average	Monopolar depressive, monopolar manic, bipolar affective and schizoaffective disorder	"A positive association between treatment success and the duration of treatment was found." (p. 67)*
Maj et al. (1985, 1989)	Prospective, 7 years of lithium treatment	major depression and bipolar disorder (DSM-III)	"Overall, the results ... confirm that lithium retains its prophylactic efficacy in the long term" (p. 537) "in some patients recurrences may reappear, after years of successful treatment" (p. 537)
Nilsson and Axelsson (1989)	Prospective, 7 years of lithium treatment	Major depression and bipolar disorder (DSM-III)	"Depressive symptoms significantly increased during the 7-year follow-up period" (p. 387)
Post et al. (1993)	Case series and a single case report	Lithium-refractory affective disorders	"34.9% (of the patients) ... presented either an initial complete or partial response to lithium, then a gradual loss of efficacy over time " (p. 72)
Koukopoulos et al. (1995)	Retrospective, 12.2 years of prophylactic treatment on average	Bipolar I, bipolar II, unipolar depressive	"7 cases of good response ... became poor responders after an average of 10 ... years of lithium treatment" (p. 140) "(13) patients after an average of 10 years of poor response showed an excellent and long lasting response" (p. 140)
Berghöfer et al. (1996)	Retrospective, 8.2 years of lithium treatment on average	Unipolar, bipolar affective or schizoaffective disorder	"There was no indication of a loss of the prophylactic effect in ... patients ... who had been treated for a minimum of 10 years" (p. 349)
Coryell et al. (1997)	Prospective, 96 weeks	Mania, schizoaffective mania or major depression with history of either mania or schizoaffective mania (RDC)	"The apparent transience of lithium prophylactic effects ... may reflect important, physiological differences between relapse and recurrence." (p. 281) "Lithium may be effective in the prevention of relapses but not in the prevention of recurrences." (p. 286)

*Translated by the authors

tients under prophylactic lithium treatment. The total follow-up of seven years was divided into two treatment periods. Period I comprises the first two years; period II is a long-term study of the 43 bipolar and 36 unipolar responders who had been stable on lithium for the first two years. Of 49 patients who completed study period II, 14 suffered from a relapse or recurrence. This corresponds to an average annual failure rate of 6.5%. The average annual failure rate during study period I was 32%. Although these relapse rates during period I and II are not directly comparable because the drop-outs and failures during period I lead to a selection bias, these results can be seen as an indication that in general "lithium retains its prophylactic efficacy in the long term" (Maj et al. 1989, p. 537). However, four patients who have been evaluated as compliant had three or more episodes which occurred during the last two years of period II after a stable period of at least five years. This observation indicates that "in some patients recurrences may reappear after years of successful treatment" (Maj et al. 1989, p. 537). Patients with affective recurrences after several years of an apparent response to prophylactic lithium treatment have also been reported by Koukopoulos (1995). Out of the 129 poor responders described in this study, 7 patients had previously shown good response for an average of 10 years. On the other hand, 13 patients showed an excellent and long lasting response after an average of 10 years of poor response.

Berghöfer et al. (1996) systematically examined the recurrences in 86 patients over a period of 8.2 years on average. They found that in patients who had been treated for at least 10 years the duration of depressive episodes and the severity of manic episodes were lower for years 6–10 as compared to years 1–5. The average morbidity index, however, did not change substantially during the observation period. In total, their "data suggest that the effect of regular lithium prophylaxis remains constant over a period of up to 10 years in monopolar and bipolar patients" (p. 353). These results are in line with Felber (1979) who found that the reduction of affective episodes was more pronounced in patients treated for 42–48 months than in patients who were on lithium for 6–12 months.

On the other hand, Nilsson and Axelsson (1989) reported an increase in psychopathology in $n = 37$ patients with major affective disorders who were continuously treated with lithium. A high percentage of the patients developed depressive symptoms during the follow-up period of 7 years. Various reasons for this phenomenon are discussed, e.g., natural aggravation of the underlying illness and a changed treatment policy aiming at a serum level within the lower therapeutic range.

The study of Post et al. (1993) examined the case histories of 66 patients who were refractory to prophylactic lithium treatment. They report that about one third of these patients initially showed at least partial response to

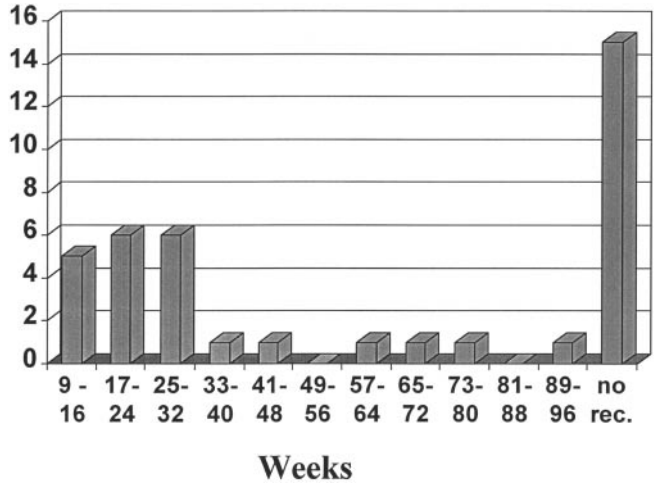

Fig. 1 Number of recurrences in the group without lithium prophylaxis according to Table 2 in Coryell et al. (1997), $n = 38$ (four patients were lost during follow up)

lithium and a gradual deterioration of psychopathology. An evaluation of these results is difficult as patients and methods are not extensively described. According to Post et al. (1993, p. 74) this case series suggests "that a subgroup of initially good responders to lithium may eventually develop tolerance during long-term prophylaxis".

Coryell et al. (1997) prospectively investigate whether the relapse-preventing potential of lithium in bipolar patients is a transient phenomenon or whether lithium provides sustained prophylactic effects. For this purpose, a group of patients treated with lithium prophylaxis ($n = 139$) was compared to a group without lithium ($n = 42$) in a naturalistic setting. Comparisons were carried out by survival analyses for weeks 9 to 96 after recovery. The analyses were done separately for weeks 9–32 and for weeks 32–96. Survival analyses for the second interval (weeks 32–96) included those patients who did not relapse during the first interval. Lithium was significantly superior for the first interval, but for the second interval, no clear-cut difference between the lithium group and the no-lithium group was found. Referring to these results, the authors argue that "the apparent transience of lithium prophylactic effects is unexplained and may reflect important, physiological differences between relapse and recurrence" (p 281).

An alternative interpretation of these results is, however, possible. As can be seen from Fig. 1, the sample investigated seems to be rather heterogeneous regarding the risk to suffer from a recurrence. Many patients without prophylactic lithium relapse within the first 32 weeks. For those patients who did not relapse during the first interval, the risk seems to be rather low. As a consequence, it is likely that the patients who enter the second interval are at a much lower risk than those patients who relapsed from weeks 8 to 32. Lithium has proved to prevent relapses in many patients at risk (e.g., Coppen et al. 1971; Stallone et al. 1973; Prien et al. 1973). This relapse-preventing property of lithium may lead to an overrepresentation of high-risk patients at the end of the first interval in the lithium group as compared to the no-lithium group. As a consequence, a low-risk sample in the no-lithium group would be compared to a sample with a higher risk in the lithium group for the weeks 32–96. This might lead to a substantial bias in favor of the group without lithium prophylaxis for the second part of the observation period (weeks 32–96).

Model calculations

In order to test the alternative interpretation of the data presented by Coryell et al. (1997), model calculations have been carried out. The model calculations are based on the empirical data and methodology presented in Table 2 and the figures of the publication by Coryell et al. (1997). These data are, however, not sufficient for model calculations and additional assumptions had to be made. Altogether, the model calculations are based on the following assumptions:

1. A lithium group of 139 patients and a group of 42 patients without lithium prophylaxis are observed for 11 time intervals of 8 weeks. The interval length of 8 weeks is chosen according to Coryell et al. (1997), Table 2.

2. Both groups comprise high-risk and low-risk patients. The proportion of high-risk patients is 50% in both groups. This assumption is made according to Coryell et al. (1997), Table 2: About 50% of the patients in the group without lithium prophylaxis suffer from an early relapse/recurrence within the first 32 weeks. The risk for these patients seems to be very high. The interval specific probabilities of recurrence of the patients who survive the third interval seems to be rather low (see also Fig. 1 of the present publication). The probabilities for a treatment failure in the high-risk and low-risk group are estimated from the no-lithium group (Coryell et al. 1997, p. 286) by using a minimum chi square estimation. The goodness-of-fit criterion (chi-square measure) is defined as follows:

$$\sum_{i=1}^{3} \frac{(n_i - np_i(\pi_1, \pi_2))^2}{np_i(\pi_1, \pi_2)} \stackrel{!}{=} \min(\pi_1, \pi_2)$$

where

- n = total number of patients without prophylactic lithium ($n = 42$),
- n_1 = number of patients with a relapse/recurrence in weeks 9–32. $n_1 = 0.428n = 18$; 0.428 is the probability to relapse during weeks 9–32. This figure is given by Coryell et al. (1997), p. 286
- n_2 = number of patients with a relapse/recurrence in weeks 33–96. $n_2 = 0.2857(n - n_1) = 7$; 0.2857 is the probability to relapse during weeks 33–96. This figure is given by Coryell et al. (1997), p. 286
- n_3 = number of survivors (no relapse/recurrence in weeks 9–96). $n_3 = n - (n_1 + n_2) = 17$
- π_1 = risk for a high-risk patient to suffer from a relapse/recurrence within an interval of 8 weeks

π_2 = risk for a low-risk patient to suffer from a relapse/recurrence within an interval of 8 weeks

$p_1(\pi_1, \pi_2)$ = total probability to relapse during weeks 9–32 (in the model). $p_1(\pi_1, \pi_2)$ is a function of π_1 and π_2

$p_2(\pi_1, \pi_2)$ = total probability to relapse during weeks 33–96 (in the model). $p_2(\pi_1, \pi_2)$ is a function of π_1 and π_2

$p_3(\pi_1, \pi_2)$ = probability to survive week 96 without recurrence (in the model). $p_3(\pi_1, \pi_2)$ is a function of π_1 and π_2

The choice of the three cells was done according to Coryell et al. (1997), Figs. 1–2 and in order to get relatively reliable estimates of the expected cell numbers $n_1p_1(\pi_1, \pi_2), n_2p_2(\pi_1, \pi_2), n_3p_3(\pi_1, \pi_2)$.

3. Lithium reduces the likelihood for a relapse/recurrence. The efficacy is estimated from the recurrence rates in the first 32 weeks (0.238 for lithium treatment and 0.428 without lithium treatment) given by Coryell et al. (1997), p. 286. For an interval of 8 weeks, the efficacy (reduction of risk) is estimated as

$$\frac{1-\sqrt[3]{(1-0.238)}}{1-\sqrt[3]{(1-0.428)}}$$

4. In contrast to Coryell et al. (1997), it is assumed that lithium efficacy is not transient, but remains unchanged throughout the whole observation period.

Based on these assumptions, the survivor functions for the group without lithium treatment are calculated as follows. At week 8 after recovery, $n = 42$ patients are relapse-free; all patients are at risk: By assumption, 21 patients are at a low risk and 21 at a high risk. Out of these patients, $21\pi_1 + 21\pi_2$ have relapsed at week 16 (π_1 and π_2 are the risks for the high- and low-risk group, respectively). The remaining $42 - (21\pi_1 + 21\pi_2)$ patients are at risk at the end of week 16. The other patients have already relapsed. Out of these $42 - (21\pi_1 + 21\pi_2)$ patients, $n_h = 21 - 21\pi_1$ are at a high risk and $n_l = 21 - 21\pi_2$ are at a low risk. $n_h\pi_1 + n_l\pi_2$ of these patients have relapsed at week 24. $n_h + n_l - (n_h\pi_1 + n_l\pi_2)$ patients are at risk at the end of week 24. This procedure is continued to the end of week 96. The number of patients relapsing in weeks 9–32, weeks 33–96, and of those who survive week 96 according to these model calculations are compared to the respective numbers of patients presented by Coryell et al. (1997). For the lithium group, the survivor functions are calculated in a similar way. The only major difference to the calculations for the no-lithium group is that π_1 and π_2 (the risk for a recurrence for the high and low risk patients, respectively) are multiplied by a constant factor (efficacy, reduction of risk) which has been estimated previously.

Figures 2–3 present the results of model calculations for which it is assumed that lithium efficacy remains unchanged during the whole study period. Besides this assumption, the model is based on the empirical data and methodology of the publication by Coryell et al. (1997).

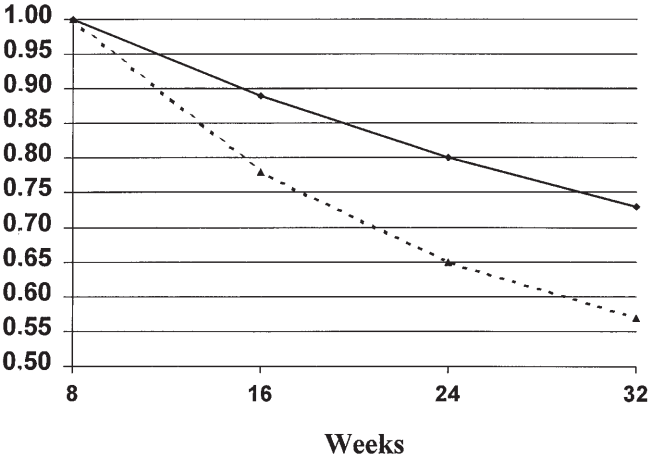

Fig. 2 Expected survivor functions under lithium (——) and without lithium (– – –) for weeks 8–32 (model calculations)

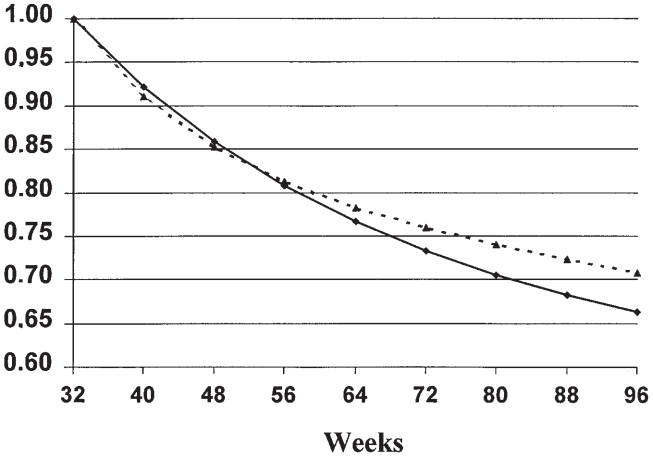

Fig. 3 Expected survivor functions under lithium (——) and without lithium (– – –) for weeks 32–96 (model calculations)

The survivor functions resulting from these model calculations largely correspond to the respective survival curves as presented by Coryell et al. (p. 285): Lithium is clearly superior for the first interval. Thereafter, the curves of the two groups are similar – in spite of the assumption of a persistent efficacy of lithium. Hence, the empirical data do not contradict the hypothesis of sustained efficacy.

Discussion

Recently, it has been suggested by Coryell et al. (1997) that lithium efficacy is a transient phenomenon. A loss of efficacy in lithium prophylaxis would have important therapeutic consequences. Therefore, a critical evaluation of the publication of Coryell et al. (1997) and a review of the literature has been done. Regarding the data presented by Coryell et al. (1997), an alternative explanation is possible. The alternative interpretation of the data does not contradict the assumption of persistent effects in the long-

term treatment with lithium. It is, however, very difficult to draw a distinct conclusion from these data or from the other studies considered in this review.

One major difficulty in the evaluation of long-term efficacy of lithium is that the course of affective disorders is extremely variable (Angst 1980; Post et al. 1986). Hence, if there is no control group, it is unclear whether changes in treatment response after several years of treatment are related to the medication or to the course of the illness. The interpretation is further complicated by the possibility that the use of antidepressant co-medication might increase the frequency of episodes (Kukopulos et al. 1980; Wehr and Goodwin 1987) and affect response to prophylactic lithium (Reginaldi et al. 1981). Other factors such as cocaine abuse, sleep reduction, and jetlag might have similar effects on treatment response (Goodwin and Ghaemi 1998; Wehr et al. 1987).

The comparison of the different studies presented in this review is complicated by differences in the study designs and in the samples investigated. Inconsistencies regarding the samples are not only due to differences in the diagnostic systems and inclusion criteria applied, but also to a selection bias: recent studies are more likely to include treatment-resistant, more severely ill patients who are referred to tertiary research centers (Goodwin and Ghaemi 1998). The overrepresentation of patients who do not respond to standard therapy is also a serious drawback regarding generability of the results. As the comparability of the different studies is limited, it is difficult to draw definite conclusions regarding a possible loss of lithium efficacy. When summarizing the pros and cons, there is, however, little evidence to support a general loss of efficacy over time.

Most studies following patients over several years of lithium treatment found sustained or even improved response for a majority of patients (Felber 1979; Maj et al. 1989; Berghöfer et al. 1996). The apparent improvement of lithium efficacy on affective symptomatology which has been reported in some studies and reviews (Schou 1968) should, however, be interpreted very cautiously. Many patients who do not respond adequately might drop out before the end of the observation period and this might result in an unquantifiable overrepresentation of good responders in the samples who have been treated for several years.

As mortality rates are highly increased in affective disorders (Tsuang and Woolson 1978; Goodwin and Jamison 1990; Tondo et al. 1998), a comprehensive evaluation of a treatment strategy should also consider the effectiveness in reducing excess mortality. It is widely accepted that suicidal behavior in patients suffering from a major affective disorder is reduced by long-term treatment with lithium (Coppen 1994; Ahrens and Müller-Oerlinghausen 1997; Goodwin and Ghaemi 1998; Tondo et al. 1998). There is a clear-cut and enduring reduction of suicidal behavior during lithium maintenance as compared to periods before lithium treatment and periods following lithium discontinuation (Ahrens et al. 1993; Müller-Oerlinghausen et al. 1994). The enduring reduction of suicides can, however, not prove persistence of lithium efficacy because the methodological difficulties in interpreting these results are quite similar to those in the evaluation of changes in the rate of recurrences over time. But the data regarding efficacy on suicidal behavior are in line with a persistent lithium efficacy as they do not indicate a loss of the antisuicidal and mortality-reducing effects of lithium.

The supposed persistence of lithium efficacy in general does, however, not exclude that affective symptoms may reappear in some patients who were apparently responsive to lithium for months or even years. This phenomenon has been observed by several authors (Dotti and Bernini 1979; Maj et al. 1989; Post et al. 1993; Koukopoulos 1995; Maj et al. 1996), and is well established. The reasons are unclear. Terms like “lithium tolerance” (Post et al. 1993) suggest that lithium loses its efficacy in a similar way as carbamazepine loses its seizure-preventing properties, but this suggestion remains highly speculative.

Alternative explications consider the course of the illness. The natural course of affective disorders is capricious and tends to become more severe over time (Angst 1980; American Psychiatrie Association 1994). In some cases, the natural aggravation of the underlying illness might outweigh the prophylactic effects of lithium (Nilsson and Axelsson 1989; Koukopoulos et al. 1995; Post and Weiss 1995; Maj et al. 1996). But even if there is no aggravation, one would expect that in some patients several months or even years might elapse before the first episode under lithium occurs. In general, lithium cannot completely eliminate the affective illness but only reduce the likelihood and severity of affective episodes (Baastrup and Schou 1967; Coppen et al. 1971; Persson 1972; Prien 1983; Goodwin and Jamison 1990; American Psychiatric Association 1994), prolonging the average time between two episodes. Hence, it is not surprising that some patients suffer from a recurrence even after several years of apparently successful treatment.

Another explanation of the apparent transience of efficacy in some patients considers side effects that counteract the prophylactic effects of lithium. Lithium may induce a slightly depressed mood in some patients (Dotti and Bernini 1979; Nilsson and Axelsson 1989). Moreover, long-term lithium treatment can cause endocrinologic side effects such as hyperparathyroidism which might engender affective symptoms (Garfinkel et al. 1973; Franks et al. 1982; Brochier et al. 1994). Affective symptomatology caused by side effects might counteract the mood-stabilizing properties of lithium and appear as a “loss of effectiveness” (Brochier et al. 1994, p. 339).

Conclusion

Although affective recurrences appear in some patients after years of an apparently successful treatment, the literature considered in this review does not indicate a general loss of lithium efficacy in the prophylaxis of major affective disorders.

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