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SPECIAL ISSUE

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Lithium in the long-term treatment of bipolar disorders

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Abstract Usefulness of lithium in the prophylaxis of bipolar disorders has been challenged for five major reasons. The authors review the empirical basis of these criticisms and come to the following conclusions. 1. *Lithium efficacy* is high and beyond reasonable doubt in classic manic-depressive illness. Bipolar patients presenting atypical features show a much poorer response rate to lithium. 2. There is no empirical evidence for a *loss of lithium efficacy* over time. 3. There is little evidence for *discontinuation-induced refractoriness to lithium*. 4. *Lithium withdrawal phenomena* are well established but seem to be rather specific to certain subgroups. Withdrawal phenomena seem to be common in atypical bipolar disorder but rare in fully stabilized classic manic-depressive illness. 5. Other factors limiting lithium efficacy in *clinical practice* (e. g., non-compliance) are not specific to lithium. In conclusion, prophylactic lithium does have major drawbacks and there is a clear need for more efficacious alternatives in non-classic bipolars. Compared to existing alternatives, lithium currently is to be considered the golden standard. This status might, however, be challenged by major alternative mood-stabilizers that are presently under clinical investigation.

Key words bipolar disorder · effectiveness · efficacy · lithium · maintenance treatment · mood-stabilizer · review · withdrawal symptoms

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Introduction

After termination of a manic episode, the risk to suffer from a manic or depressive recurrence is at least 90 % (Solomon et al. 1995). The classic medication used to reduce the recurrence risk is lithium. Its prophylactic properties have been studied systematically since the late 1960s in several randomized controlled trials (e. g., Baastrup & Schou 1967). Lithium was considered as golden standard for at least two decades. But although prophylactic lithium is still recommended as first-line treatment in practice guidelines (e. g., APA 1994; Bauer et al. 1999) this status is increasingly challenged by the introduction of other mood-stabilizers such as carbamazepine, valproate and lamotrigine. Further treatment strategies currently under investigation include newer antiepileptics (e. g., gabapentine), calcium-channel blockers (such as nimodipine) and atypical neuroleptics (e. g., clozapine and olanzapine) (Zarate et al. 1995; Sarfati et al. 1996; Tohen u. Zarate 1998, Keck et al. 1998, Tohen et al. 2002). In addition, combinations of mood-stabilizers widely used in clinical practice (Levine et al. 2000) might prove superior to monotherapy in many cases (Freeman and Stoll 1998; Calabrese 2002).

Besides research on new substances, scientific discussion has focused on the intrinsic usefulness of lithium. The criticism regarding the impact of lithium in long-term treatment of bipolar disorder has at least five aspects:

- Lithium efficacy
- Lithium effectiveness in clinical practice
- The possibility of withdrawal phenomena after lithium discontinuation
- A possible loss of efficacy after discontinuation and re-institution of lithium
- A possible loss of efficacy over time

Efficacy of lithium in the prophylaxis of bipolar disorders

It is essential to distinguish conceptually between efficacy and effectiveness. Efficacy is defined as the therapeutic potential of a treatment under optimal conditions (Guscott and Taylor 1994). An efficacy study, typically a randomized controlled trial, is designed to answer the question whether a treatment can work. In contrast, a study in the effectiveness of a treatment strategy investigates the actual results of the treatment obtained under ordinary conditions. Besides efficacy, effectiveness depends on variables such as diagnostic accuracy and patients' compliance (Guscott and Taylor 1994).

The classic randomized placebo-controlled trials to investigate long-term efficacy of lithium were carried out in the 1970s. The results were very clear and resulted in the approval of lithium as prophylactic agent by regulatory agencies. Eight out of ten studies yielded a significant superiority of lithium over placebo. The two remaining studies (Melia 1970 and Dunner et al. 1976) showed a trend in favor of lithium but were lacking statistical power. It has, however, been argued that these early studies would no longer be up to modern methodological standards and that they might simply have "produced spurious results owing to flawed methods" (Moncrieff 1995). Ms. Moncrieff's criticism mainly refers to the discontinuation design used in about half of the studies, to single (instead of double) blindness and to high drop-out rates inducing a bias.

The first critical point is very serious. In the 1970s many studies were conducted as discontinuation trials with a sample of patients on lithium being randomized to either continuation or abrupt discontinuation of lithium treatment. Subsequent studies (Klein et al. 1981; Greil et al. 1982; Suppes et al. 1991) have shown that abrupt lithium discontinuation increases the risk of an early, especially manic, recurrence and this might have inflated the recurrence rates in the placebo groups studied in the 1970s. A close examination of the original data (e. g., Schou 1970) shows, however, that this phenomenon probably was much less pronounced in the early efficacy studies than in the subsequent studies. A possible explication for this difference might be related to different patient groups. Lithium withdrawal reactions seem to be common in atypical bipolar patients and in patients who were not fully stable under lithium, but less common in the classic manic-depressive patients included in the trials of the 1970s (Schou 1998).

Although a modern efficacy study would strictly avoid rapid discontinuation of lithium, we are far from being able to avoid the other major problems. To establish efficacy, Ms. Moncrieff asks for a double blind placebo controlled trial with adequate statistical treatment of drop-out patients. It seems, however, unlikely that blindness can be kept in a majority of patients over a study period of at least six months to both, the patient and the treating physician (Marini et al. 1976; Watkins et al. 1987; Oxtoby et al. 1989; Double 1996). Similarly, drop-out rates are usually higher in the placebo group and the bias thereby introduced is difficult to eliminate. In contrast to Ms. Moncrieff we think that a well conducted randomized controlled trial is meaningful even if the drop-out rate is substantially higher in the placebo group or if it has not been conducted in a double-blind manner. We hence agree with most authors that the prophylactic efficacy of lithium is well established (e. g., Maj 2000, Pies 2002). This is supported by recent data from a large placebo-controlled trial (lamotrigine vs. placebo vs. lithium) showing lithium to be significantly superior to placebo ($p = 0.003$; Bowden et al. 2003).

Effectiveness of prophylactic lithium in clinical practice

Several naturalistic and epidemiologic studies in the 1980s and 1990s failed to confirm effectiveness of lithium in clinical practice (e. g., Dickson and Kendell (1986); Markar and Mander (1989); Harrow et al. (1990)). The most obvious reason for the discrepancy between the naturalistic studies and the data from the controlled trials from the 1970s is non-compliance. A very substantial number of bipolar patients does not regularly take the prescribed medication (Shaw 1986; Maj et al. 1998; Schumann et al. 1999) and this clearly decreases the response rates. It is unlikely that this phenomenon selectively affects patients treated with lithium. In our own study (Kleindienst and Greil 2002) the drop-out rate under carbamazepine was significantly higher than under lithium. It must be emphasized that any prophylactic treatment of bipolar disorder will probably fail for non-compliance unless the patient is convinced about the treatment. Similarly, it is essential that treatment is supported by the patients' relatives. Finally, the patient is much more likely to be compliant if well informed and actively involved in all treatment decisions.

Another major factor that might explain the discrepancy between the excellent results in the 1970s and the disappointing results during the following decades is a change in the sample populations studied (Gershon and Soares 1997). The diagnosis of bipolar disorder has been substantially extended. What is diagnosed as bipolar disorder today is a substantially larger and much more heterogeneous group than the manic-depressive patients studied in the early 1970s (Akiskal et al. 2000; Stoll et al. 1993). Studies in prediction of response to prophylactic lithium did show that lithium is highly efficacious in classic manic-depressive patients, but not in patients with atypical features such as mood-incongruent delusions (Maj et al. 1986; Greil et al. 1998). In conclusion, "the perceived changes in lithium effectiveness, with decreased effectiveness rates, seem to be primarily attributed to a change in the sample population studied" (Gershon and Soares 1997). As a consequence, only a minority of patients with the diagnosis of bipolar disor-

der according to current diagnostic systems fully respond to prophylactic lithium.

Major drawbacks of lithium in clinical practice

Besides prophylactic effectiveness, the usefulness of lithium in clinical practice was challenged for several disadvantageous phenomena. Lithium is a potentially toxic substance with a narrow therapeutic window and was reported to be related to severe side effects such as nephrogenic diabetes insipidus and to teratogenic effects such as floppy infant syndrome. In clinical practice, lithium showed, however, a low rate of severe side effects (Johnson 1998; McIntyre et al. 2001), teratogenity (Cohen et al. 1994; Altshuler et al. 1996) or suicidal intoxication (Kaschka 1997). In well informed and motivated patients lithium generally proved to be a safe therapy and criticism has moved to other points of concern such as the possibility of withdrawal effects.

As mentioned above, the phenomenon of severe withdrawal effects including psychotic states is well established but seems to affect primarily atypical bipolar patients. Whenever feasible, lithium discontinuation should be done slowly as a slow tapering of lithium is clearly associated with a lower relapse rate (Baldessarini et al. 1997). It is unclear whether withdrawal reactions are specific to lithium or whether they also affect other mood-stabilizers after their long-term use.

It has also been discussed whether lithium might become ineffective in patients who discontinue prophylactic lithium as some of these patients did not respond to re-institution of lithium (Post et al. 1992; Maj et al. 1995; Tondo et al. 1997). As pointed out by Coryell et al. (1998) it is very difficult to draw firm conclusions from the published literature as important confounding factors such as variation in clinical course, and the difference between acute and prophylactic treatment have not been controlled. Hence, it is not clear whether lithium discontinuation results in lithium resistance. If so, discontinuation-induced refractoriness does not seem to be very frequent (cf. the data published in Tondo et al. 1997 and in Coryell et al. 1998).

Another possible drawback discussed in the literature is loss of efficacy over time. According to the study by Corryell et al. (1997) lithium might prevent relapses for about half a year and lose its preventive effects thereafter. A re-analysis of this study shows, however, that the data do not contradict the hypothesis of persistent lithium efficacy (Kleindienst et al. 1999). The remaining literature on the topic suggests that in general lithium efficacy persists over many years and is not a transient phenomenon (Kleindienst et al. 1999). This does not exclude the possibility of multiple recurrences after several years of stability under lithium in some cases (Post et al. 1993; Maj et al. 1989). This phenomenon of "late non-response" seems to affect a minority of patients and is most convincingly explained by an increasing severity of bipolar illness over time (Maj 2000).

Alternative mood-stabilizers

Currently, carbamazepine, valproate and lamotrigine are the best studied alternative mood-stabilizers. The only study comparing carbamazepine to placebo showed a non-significant trend in favor of carbamazepine (Okuma et al. 1981). Studies comparing the prophylactic efficacy of carbamazepine and lithium found the substances to be generally equally efficacious. The only exception is the study by Watkins et al. (1987) which found lithium to be superior. Besides a global comparison of carbamazepine and lithium, the results of the MAP study give clear indications regarding differential efficacy of lithium and carbamazepine. In n = 171 patients diagnosed as bipolar according to the broad criteria of DSM-IV carbamazepine was equally efficacious as lithium (Kleindienst and Greil 2002). The results were in favor of lithium when the diagnosis was closer to classic manic-depressive illness, i. e., in patients diagnosed as bipolar I or as bipolar according to ICD-9 (Greil et al. 1997; Greil and Kleindienst 1999). Lithium was clearly superior in the subgroup of patients with a "classical" presentation, i. e. in bipolar I patients without mood-incongruent delusions and without psychiatric comorbidity. In contrast, carbamazepine tended to be superior in the large group of "non-classical" patients (Greil et al. 1998).

The indication of valproate as a prophylactic agent in bipolar patients has been tested in one large randomized trial (Bowden et al. 2000). No significant difference between valproate, lithium and placebo was found in time to recurrence to an affective episode. As this study is lacking statistical power because of the exclusion of severely ill patients, it is difficult to draw definite conclusions (Bowden et al. 1997). The results tended, however, to be in favor of valproate as this substance did have an edge over placebo and also over lithium on some secondary measures. Prophylactic efficacy of valproate is also supported by a few open-label studies (McElroy et al. 1987; Calabrese and Delucchi 1990) and case reports (Juckel et al. 2000).

Prophylactic lamotrigine in bipolar disorder has been investigated in two double-blind placebo-controlled randomized trials. In the first study (Calabrese et al. 2000), lamotrigine was superior to placebo on most outcome measures in n = 324 rapid-cycling bipolar patients. In the second study, lamotrigine demonstrated superiority over placebo in extending time to any affective episode (Calabrese et al. 2001; Bowden et al. 2003). This study also included a lithium comparator group and showed significant superiority of lithium over placebo in a well designed modern study.

Great efforts are currently made to carry out large-scale maintenance studies to prove efficacy of further putative mood-stabilizers such as olanzapine. Preliminary results on prophylactic olanzapine are very encouraging and strongly suggest olanzapine might be an efficacious mood-stabilizer (Tohen et al. 2002).

There has been continued discussion whether lithium is equally effective in preventing depression and mania (e. g., Bowden 2002). The direct empirical evidence is stronger for the manic pole of the illness with several studies showing lithium to be significantly superior to placebo in preventing mania (e. g., Cundall et al. 1972; Prien et al. 1973; Stallone et al. 1973; Calabrese 2001). Further evidence suggests that lithium also prevents depressive recurrences in bipolar patients. Significant superiority over placebo in one study (Baastrup 1970) is corroborated by a couple of underpowered studies showing a clear trend in favor of lithium (e. g., Cundall et al. 1972; Persson 1972) and several studies showing lithium to prevent depression in unipolar depression (e. g., Persson 1972; Coppen et al. 1978; Kane et al. 1982; Greil et al. 1996). The latter studies give strong indirect support for lithium preventing bipolar depression, especially as many of the patients formerly diagnosed as unipolar would be considered to belong to a bipolar spectrum according to recent research criteria (Angst 1998; Greil and Kleindienst in press). When reviewing the results on the four large-scale studies comparing prophylactic antimanic and antidepressive effects of lithium with carbamazepine (Kleindienst and Greil, manuscript in preparation), valproate (Bowden et al. 2000), lamotrigine (Bowden et al. 2003; Calabrese et al. 2001) and olanzapine (Tohen et al. 2002) the results might be summarized as follows. In *prevention of depressive episodes* lithium seems to be equally efficacious as carbamazepine, valproate and olanzapine. Lamotrigine might have an edge over lithium, though the difference between the substances was small and far from statistical significance ($p = 0.36$). In *prevention of mania*, olanzapine was significantly superior to lithium (Tohen et al. 2002). Carbamazepine and valproate were similarly efficacious as lithium and lithium might have an edge over lamotrigine ($p = 0.09$).

It has been suggested to distinguish between class A and B mood-stabilizers (Calabrese et al. 2002) with class A mood-stabilizers exerting their primary acute and prophylactic effect on the manic pole ("above baseline") and class B mood-stabilizers primarily being efficacious against mood "below baseline". This distinction might become very fruitful when the efficacy profiles of current and upcoming mood-stabilizers become clearer for both a differentiated pharmacotherapy and rational combination therapy. Besides the two major poles of bipolar disorder (mania and depression) we propose two more targets to be considered: suicidality and, in some cases, psychotic features (see Fig. 1). Again, antisuicidal and antipsychotic effects might highly vary between different mood-stabilizers – with some evidence for suicide preventive action of lithium (Greil and Kleindienst, in press) and a superior efficacy of olanzapine and other atypical neuroleptics for the psychotic pole of the disorder.

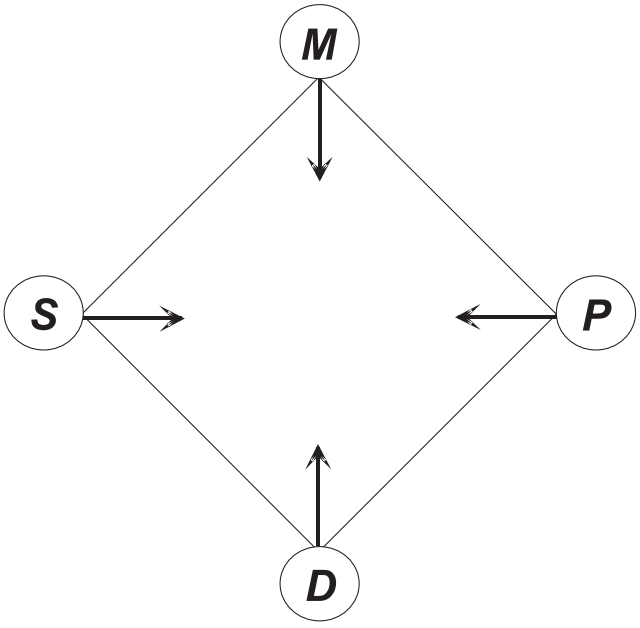

Fig. 1 Major targets for mood-stabilizing drugs: *M* Manic Pole, *D* Depressive Pole, *S* Suicidality, *P* Psychotic Features (Greil and Kleindienst, in press)

Conclusions

Regarding prophylactic efficacy in bipolar disorder, evidence is strongest for lithium. A closer look at the published evidence does, however, indicate that lithium efficacy depends on the subtype of bipolar illness. In classical manic-depressive illness lithium seems to be highly efficacious, but not in patients with non-classical features, e. g., in patients with mood-incongruent delusions. In conclusion, lithium is still to be considered as golden standard, but we urgently need alternatives that prove to be superior in the large group of non-classical bipolar patients. Besides research on new substances a systematic evaluation of combination therapies such as lithium plus lamotrigine or olanzapine plus lamotrigine seems very promising.

The need of alternative treatment strategies is underscored by the drawbacks of lithium in clinical practice. Long-term treatment with lithium is often associated with unwanted adverse events such as tremor and weight gain and implies the risk of lithium intoxication due to its narrow therapeutic range. The use of lithium is further complicated by its narrow therapeutic range and by the risk of withdrawal phenomena when rapidly discontinued. It remains, however, to be established whether rapid discontinuation of alternative mood-stabilizers is less problematic. It may be speculated that we simply have more experience with the use of lithium in clinical practice and hence have discussed more possible drawbacks such as low percentage of complete response, late non-response in initially responsive patients and withdrawal reactions.

Lithium has major drawbacks and only a minority of bipolar patients fully respond to prophylactic lithium.

We urgently need better mood-stabilizers that prove to be superior in both, efficacy studies and in naturalistic trials. But up to now, lithium is still to be considered as the golden standard.

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