Review Article

A critical appraisal of lithium's efficacy and effectiveness: the last 60 years

Grof P, Müller-Oerlinghausen B. A critical appraisal of lithium's efficacy and effectiveness: the last 60 years.
Bipolar Disord 2009: 11 (Suppl. 2): 10–19.

The history that depicts the evaluation of lithium's efficacy presents an interesting contrast: on the one hand, conviction that, of all psychotropic drugs, lithium has the best demonstrated efficacy; on the other hand, repeated attempts to question it. Those contesting lithium's stabilizing abilities have argued from several angles, for example that the proof was methodologically incorrect or insufficient, that the number of responders is small, or that the response is poor in practice and does not last. But there is a good explanation for this paradox. While the early challenges to lithium's value in recurrent mood disorders reflected mainly that psychiatry had not yet developed a methodology suitable for testing long-term efficacy, more recent questioning has resulted mostly from retesting its efficacy and effectiveness in a substantially broadened bipolar spectrum, outside the classical diagnosis. Lithium, however, continues to stabilize very well the patients suffering from typical bipolar disorder—the condition for which its efficacy was originally demonstrated. More recently, lithium has also proven to dramatically reduce suicidal behavior and mortality and to augment markedly the efficacy of antidepressants in unresponsive patients.

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Key words: antisuicidal action – bipolar disorders – effectiveness – efficacy – lithium – long-term treatment

Received 5 January 2009, revised and accepted for publication 10 March 2009

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The history of evaluating the usefulness of stabilizing lithium in mood disorders has unfolded in two separate directions. One large stream focused on proving the efficacy. For scientific purposes, the most important evidence has come from randomized, double-blind, placebo-controlled, group trials backed up by large mirror-image studies. For practicing clinicians, often most convincing have been the stories of their individual patients who suffered from frequently recurrent bipolar illness for many years, experienced a number of hospitalizations, and then, on adequate lithium treatment, remained illness-free for many years.

And then there has been the other stream, again and again doubting, questioning, and attacking the gathered evidence. Most objections have reflected the methodological complexities of testing maintenance treatment: the capricious and largely unpredictable natural history of mood disorders, greatly fluctuating compliance with medication, often short or sporadic follow-up of patients, and so on. Some opposition was more basic, coming from the antimedication doctrine (1). Both the positive and negative positions are reflected in this paper.

The benefits of lithium treatment can be utilized in several psychiatric and medical disorders: for example, as a mood stabilizer, antimanic agent, antidepressant, and an augmenter, hematopoetic, or antithyroid substance (2). We will focus here on two types of efficacy that are unique to lithium's actions and so far have not been reproduced, at least not to the same extent, with other medications: long-term stabilization of typical, episodically recurring, mood disorders and lasting antisuicidal action.

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

Long-term stabilization

Proving that lithium exhibits stabilizing power for recurrent mood disorders has had an evolution marked by controversies. When, in 1967, Baastrup and Schou (3) proposed lithium for prophylactic treatment of bipolar disorders, psychiatry was largely unprepared for such a task and the methodology needed for testing the efficacy against recurrences had not been developed. An understanding of the capriciousness of clinical course was missing, yet that notion is essential in order to assess correctly future recurrence risk. The span of bipolar diagnosis reflected clinical experience, but was not yet based on systematic epidemiological studies, and therefore was open to flux and changes that followed. In addition, the differences between efficacy in clinical trials and effectiveness in clinical practice were also not appreciated.

The story that ensued, and tells about the testing lithium's stabilizing efficacy, has been conveyed more fully before (4–6), in various contexts, and the reader will also find more in this journal issue. Here we will only summarize it in capsule form in order to support our main points. Preceding it were trials corroborating the antimanic effect of lithium observed by Cade in 1949 (7) and demonstrated by Schou et al. in 1954 (8), and the pioneering work with lithium in Australia by Gershon, Trautner, Noack, and Coats (9, 10), which created the essential base for the subsequent safe testing and use of lithium. Already at that early point Gershon and colleagues (11) pointed out a relative specificity of benefit in typical cases and to a disappointing activity in atypical ones, so much so that in schizophrenic and schizoaffective cases, neuroleptics were superior to lithium. This important issue was often overlooked later.

First observations indicating a long-term benefit of lithium were reported by Hartigan (12) and Baastrup (13). In 1967, a Danish open, nonblind, prophylactic trial provided the first systematically collected evidence of stabilizing action (3). The study employed an interesting mirror design which involved a successfully treated group of 88 manic-depressive patients who experienced recurrent episodes before they were started on lithium—the first systematically collected evidence of lithium's stabilizing action. The difference between the expected and developed recurrences during lithium treatment was statistically highly significant. Furthermore, Angst et al. (14) gathered supportive evidence from a mirror design study of 250 patients. Laurell and Ottosson (15) performed similar analyses on data from natural course and illustrated the usefulness of mirror design for testing the pharmacological reduction of recurrences.

Blackwell and Shepherd (16) challenged the validity of such observations. They felt that the findings resulted from observer bias and the suggestive power of the psychiatrists, and that due to the trend toward the mean, patients selected for frequent episodes during recent years must be presumed to have fewer episodes during the following years. In hindsight, it was fortunate that the controversy about the findings generated a heated debate, as it forced the Danish group to put aside their ethical concerns about using placebo control in newly stabilized patients. As a consequence, in 1970, Baastrup et al. (17) published a double-blind discontinuation trial that proved their point. After discontinuation, about half of the patients on placebo became ill again, but none on lithium. A series of randomized, placebo-controlled trials ensued which confirmed the Danish findings (e.g., 18-20).

Using the gathered data, Schou and colleagues (21) also tested the presumptions on which Blackwell and Shepherd had based their criticism. He compared recurrences in patients in whom lithium treatment was changed to placebo blindly and in patients who stopped taking lithium on their own initiative. The results were similar, demonstrating that observer bias and suggestion were not strong enough to influence the relapse rate.

In concert, these observations generated much enthusiasm and in the ensuing years were backed up by a series of double-blind trials with different designs: randomized, double-blind trials of fresh patients [''start designs'' (18, 19, 22)], double-blind discontinuation of treated patients (23), and double-blind crossover (22). Unlike the recent maintenance trials of atypical neuroleptics that used enriched designs, the efficacy of lithium was proven in a straightforward manner. Thus, the findings appear more rigorous, providing impressively low number-needed-to-treat (NNT) values (average 2.3) and large effect sizes. It is also worth noting that the benefit of lithium was proven in an untraditional way, outside of the usual stream driven by the pharmaceutical industry.

After a slow start in Australia and then Europe, the treatment attracted attention and spread around the world. The accumulated evidence of lithium efficacy became so convincing that lithium became approved for stabilizing, long-term treatment in many countries. Its use took hold and spread rapidly even in Great Britain and the United States, where the use of lithium was initially shunned. Because of earlier fatal toxicity problems in dietary use, there was an understandable resis-

tance to lithium therapy in America (24), but several enthusiastic investigators in the United States (e.g., S. Gershon, N. Kline, F. Goodwin, R. Fieve) quickly added to the growing knowledge.

Lithium use expanded over a large part of the world. Clinical experiences inspired nonclinical research in many fields and international cooperation in psychiatry was initiated in order to resolve quickly new, challenging questions about longer-term treatment. The successful demonstration of lithium efficacy has also left a positive mark on the methodology of clinical trials. With maintenance lithium came also emphasis on and enthusiasm for longitudinal studies, maintenance treatment, and the development of detailed methodologies of long-term trials (25, 26). For a number of years lithium became the preferred stabilizing agent in bipolar disorder.

Doubts and criticisms

Notwithstanding this solid evidence, the efficacy of lithium stabilization has been repeatedly questioned. Time and again, the view has been expressed that the prophylactic effect of lithium has not been satisfactorily demonstrated. These attacks coincided with the fact that over time, the use of long-term lithium moved from high praise to relative disrepute, particularly in North America, where valproate and other compounds were replacing lithium in spite of weak or even absent evidence of their efficacy. Yet the following examples show that the criticisms have been based mostly on wrong assumptions, misunderstandings, and inappropriate patient selection.

Lithium's stabilizing efficacy has not been proven

As summarized above, the double-blind controlled trials from the 1970s to the 1980s found lithium salts to be a mood stabilizer, effective in prophylaxis of manias and depressions.

While claiming later that lithium's stabilizing efficacy has not been proven, Moncrieff (1) directed her criticism at discontinuation trials and lithium's side effects. She felt that the evidence of a long-term lithium action bestowed by several discontinuation trials was invalid. The rise of the recurrences after discontinuation of lithium was, in her view, only a rebound precipitated by withdrawal of lithium, not by the removal of stabilization. Moncrieff relied on a report by Suppes et al. (27) that studied the rapid increase of manias after abrupt discontinuation of lithium. While impressive, Suppes's mostly retrospective observations were not applicable to the lithium studies Moncrieff criticized. In the discontinuation trials carried out more than 20 years earlier (17, 23), the patients were diagnosed according to the narrow, restrictive ICD criteria for classical bipolar illness; those patients showed no evidence of withdrawal rebound on lithium discontinuation (21, 28). In bipolar patients from that era, the interruption of lithium during remission led to the re-emergence of recurrences at a rate similar to that experienced by those same patients before they started lithium. Neither was there evidence of withdrawal rebound in a number of other, mostly European, discontinuation studies where patients were diagnosed similarly according to the narrow diagnostic criteria (29–32).

But during the 1980s, and particularly the 1990s, the diagnostic practice changed quickly. New, very broad DSM criteria were used increasingly and markedly expanded bipolar diagnoses. Consequently, epidemiological observations started finding bipolar illness 5–10 times more frequently than previously (33, 34). Lithium was then administered to a ''bipolar'' population much broader than patients who participated in the early lithium trials. Many such patients respond qualitatively differently. They benefit often from antipsychotic and antiaggressive effects of lithium (e.g., 35, 36) and on lithium withdrawal exhibit rebound of overactive episodes, a phenomenon well known with antipsychotics. Thus, Moncrieff was wrong because her critique was incorrectly mixing qualitatively different early and more recent data.

Furthermore, Moncrieff speculated, while presenting no pertinent evidence, that the recognition of lithium side effects compromised the blindness of the trials. However, in trials such as that of Coppen et al. (18), the clinicians made their guesses as to whether the patient was on lithium or placebo, but they did not succeed in identifying which was which. The only example to which Moncrieff referred was not applicable to the issue.

Lithium is not effective and not useful in clinical practice

Several naturalistic and retrospective studies performed in clinical settings and open practice reported much lower response rates than reported in the 1970s. For instance, Symonds and Williams (37) reported increased readmission rates for manias, despite lithium becoming widely used in Great Britain. Mander (38) reported that many patients have similar rates of relapse, regardless of whether or not they were prescribed lithium at the time of discharge. Markar and Mander (39) were

unable to find a difference in bipolar outpatients started on lithium compared with those treated without lithium.

These and similar reports were disconcerting observations challenging the effectiveness of lithium in various settings—not, however, the efficacy of lithium, a distinction to be kept in mind. Efficacy can be assessed only in correctly selected patients who actually comply with adequate, properly monitored treatment.

And evidence shows that for such patients who comply and for whom lithium was proven efficacious—the subgroup of bipolar patients defined in a classical, Kraepelinean way—lithium remains highly efficacious and relatively specific mood stabilizer (40–42). There is substantial consensus about the clinical profile of these lithium-responsive patients (43–47).

The efficacy of stabilizing lithium is limited to a small group of patients

The illustration of this common misconception comes from Goldberg (48), who felt that use of lithium in bipolar disorder is very limited because only "a small group" of patients responds. But "a small group" is a relative concept.

Certainly, a private psychiatrist who treats primarily problems arising from marital discord and work-related conflict will see only a small number of potential lithium responders. In fact, any psychiatrist who has not been shown a single lithium-treated patient during his training—as has recently been the case in a number of psychiatric departments—will probably hesitate to use lithium, and may not ever see a lithium responder. However, in a wider practice, observations indicate that the proportion of bipolar patients stabilizing on lithium is distinctly larger than those given neuroleptics or antiepileptics (49).This is true even when bipolar spectrum disorder is diagnosed quite broadly. The lithium-responder group will enlarge further in mood disorder setups where for one third of patients lithium stabilization may turn out to be the best choice.

Larger populations of lithium-treated patients have been available in a number of facilities (e.g., 40, 41, 50). We, for example, currently follow over 300 excellent responders to lithium monotherapy: bipolar and recurrent unipolar disorder patients that we have accumulated in collaboration over the years. Finally, when one estimates, from various studies carried out over the past 40 years, the number of patients who need long-term stabilization and would respond preferentially to lithium, it may conservatively be up to two patients per 1,000 in population. This proportion would correspond to about 800,000 people in North America and 12 million globally—not a negligible "small group," especially given the terrible impact of unstable bipolar illness on lives of individuals, their families, and society, and considering that we don't have an effective substitute treatment for lithium in such patients and indications.

It is possible to illustrate this continuing problem of insufficient treatment with an example from Germany. The number of potential lithium responders in the population has been estimated at 160,000. Yet, based on the prescription volume of lithium preparations within the National Health Scheme, only about 50,000 people annually do receive lithium. That means that less than one in three patients who should receive lithium are actually prescribed it. This is a deplorable situation in a European country, where lithium traditionally keeps a relatively good position within the psychiatric armamentarium (51, 52).

Lithium loses efficacy over time

Post et al. (53) published case histories of four patients who fared recurrence-free during the first couple of years of initial lithium treatment, but were relapsing later. He interpreted these anecdotes as the "loss of lithium efficacy," in analogy to what one may observe with antiepileptics ("pooping out"). His report attracted much attention. But to interpret such observation correctly, one must ask if the initial, temporary remission was actually due to lithium or if it may have been spontaneous. Just that the patient was diagnosed as bipolar does not guarantee an indication for lithium treatment.

In the initial course of illness, extended remissions have often been observed during the studies of untreated course of bipolar illness (54, 55). For example, some patients experienced the second episode only as late as 15 years after the first one. Furthermore, to conclude that in an individual case lithium lost efficacy, we must first have grounds to feel that lithium actually worked for this patient. This would, first of all, require evidence of active illness—e.g., frequent recurrences—followed by a period of sufficient benefit from lithium, and then by its loss. To lose efficacy, there must first be a demonstrable benefit.

Contrary to the anecdotes by Post et al. (53), systematic studies have shown that, once lithium stabilization is documented, it continues (e.g., 40, 41, 50, 56), even up to 20 years (40), and that it is reproducible after temporary discontinuation (57).

Lithium works effectively only against manias

There is a belief that lithium stabilization works strongly against manias and only very weakly, or not at all, against depressions. This is supported in particular by the absence of antidepressant action observed in several recent maintenance studies where lithium served as comparator with neuroleptics (e.g., 58). However, the data strengthen the position that lithium prophylaxis against depressions depends on patient selection.

There is certainly sufficient evidence that in populations of predominantly classical bipolar disorders, lithium reduced significantly both manic and depressive recurrences, and that it in fact has significant prophylactic efficacy in recurrent depressions (59). However, in other, atypical, bipolar spectrum patients, the effect is qualitatively different, and can be described as counteracting only overactivity (2).

Lithium is not effective as monotherapy

Some investigators concluded that in order to stabilize bipolar disorder, one must use polypharmacy, not lithium monotherapy (60). Indeed, recent maintenance trials with lithium monotherapy in bipolar spectrum disorder patients led to discouragingly poor outcomes, which understandably dissuade clinicians from using lithium. Furthermore, polypharmacy undoubtedly has advantages in acute treatment as well as in patients refractory to long-term monotherapies. However, the pertinent observations indicate that, in general, maintenance polypharmacy does not do demonstrably better than individually tailored monotherapies, but causes substantially more side effects (61). It is particularly combinations including antidepressants that have been seen by clinicians to trigger rapid cycling.

Thus, long-term treatment with one carefully chosen primary stabilizer—tailored to the individual clinical profile and given long enough and in sufficient dosage—appears to be the preferable route for a large percentage of bipolar patients. The idea that a treatment with one stabilizer should be attempted first is also supported by all national and international guidelines.

Antisuicidal effects of lithium stabilization

Mood disorders are often a fatal disease. Suicide-related mortality is, according to numerous studies, markedly increased particularly in patients with manic-depressive disorder. Approximately 15–20% of untreated patients commit suicide, resulting in a lifetime risk that is about 15 times higher than that in the general population (62–65). Therefore, a change in mortality, especially suicide related, should be a robust endpoint evaluating the basic efficacy of antidepressant or mood-stabilizing treatment, and should supplement the reduction of morbidity.

Although antidepressants have been in use for more than 50 years, it is disappointing that no valid data exist to prove a suicide- or mortality-reducing effect of antidepressants (66–68), with the exception of a recent re-analysis of the Zurich cohort (69). Thus far, drug regulatory agencies do not consider improving the death rate as an essential criterion for approval of a new antidepressant or mood stabilizer. This is rather astonishing, since for lithium salts such data do exist.

Surprisingly, lithium is the only compound for which evidence of a suicide-preventing effect has been increasingly accumulated during the last 20 years. And yet, in the current psychiatry, many opinion leaders and treatment guidelines still do not take the findings properly into account (70). A remarkable exception is the guidelines formulated by the World Federation of Societies of Biological Psychiatry (71).

Subsequent to earlier observations that had pointed to a potential suicide-preventive action of lithium (52), two systematic studies were published independently by Coppen et al. (72) and by the International Group for the Study of Lithium-treated Patients (IGSLI) (73). Whereas Coppen's data referred primarily to well-documented, long-term-treated unipolar patients, the large, multicenter IGSLI study comprised data from the whole spectrum of affective disorders (182 unipolar, 440 bipolar, and 171 schizoaffective patients), totaling 5,600 patient observation years. Both studies unambiguously demonstrated a dramatic reduction of the excess mortality expected in untreated patients with affective disorders. In fact, the standardized mortality (SMR) observed in these studies did not differ significantly from that of the general population, even though the mortality specifically related to suicide remained still marginally elevated.

To weaken this finding, it might be speculated that patients willing to accept long-term treatment may exhibit a lower suicide risk. However, a further analysis of the IGSLI material refuted this: at the onset of the treatment period, patients had a twofold increased overall mortality and a 17-fold increased suicide-related mortality compared with the general population. After the first year of lithium treatment, SMR normalized, thus indicating that patients who accept lithium

prophylaxis actually exhibit a high suicide risk (74).

A meta-analysis of the data collected by the late '90s revealed that the risk of suicidal acts in bipolar patients off lithium was 7–8 times higher than in those on lithium (75). A more recent meta-analysis carried out by the Boston group (76) and comprising 31 studies revealed an 80% decrease in the risk of completed and attempted suicide during the treatment of bipolar and other affective disorders, even though the average length of treatment was only 18 months. Furthermore, the findings by Guzzetta et al. (77) support the reports by Coppen and IGSLI that the antisuicidal effect also holds true for patients with recurrent depressions.

Linking regional lithium prescription rates with the Danish suicide register, Kessing et al. (78) added another impressive piece of evidence to the existing data on lithium's antisuicidal effect. There exist also convincing findings from controlled prospective studies. Cipriani et al. (79) reviewed 22 randomized, controlled trials and found that patients on lithium, as compared to other compounds or placebo, were less likely to die from suicide. Additional proof comes from the first controlled trial with lithium versus placebo as an adjunctive treatment in a large sample of high-risk patients. Suicidal events were defined as the endpoint (80). Whereas the number of suicide attempts did not differ between treatment groups, a statistically significant superiority of lithium in terms of completed suicides was observed.

There are several intriguing questions related to the mechanism of the antisuicidal effect of lithium and its potential specificity. First, is the antisuicidal effect coupled directly to the antidepressant effect of lithium? Several reports point to a mechanism separate from lithium's antidepressant action (81). It has been speculated that the antisuicidal effect is associated with the well-proven serotonin-agonistic effect in biochemical terms, and to well-established antiaggressive effect of lithium in clinical terms (82). Second, is the antisuicidal effect of lithium shared by other compounds such as antidepressants, neuroleptics, or mood stabilizers? So far, in various trials using different methodologies, lithium has been shown to be clearly superior to other mood stabilizers in terms of suicide prevention (83–87).

''Does lithium save lives?'' The question raised in an editorial by Joffe (88), can now be answered conclusively: yes, it does, if the treatment is applied and monitored in a rational, careful, and individualized way. While there are negative findings in this respect, such as those from Licht et al. (89), they can most likely be explained by incomplete patient follow-up and insufficient information on patients' compliance with lithium. This saving of lives adds considerably in the favour of lithium when the cost effectiveness of treatment with various mood stabilizers is assessed (90).

Concluding remarks

The evidence of lithium's stabilizing long-term efficacy has had a major impact on psychiatric thinking and practice. Lithium played a major role in starting the psychopharmacology revolution (91) and in overcoming the antipsychiatry movement. It brought fresh life into psychiatry, which previously lived for decades under the influence of psychoanalytic and social movements. In Europe in particular, lithium also helped to restore psychiatry as an essentially medical specialty, e.g., by monitoring carefully lithium blood levels as well as defined somatic functions, such as the thyroid function, in lithium-treated patients. It also illustrated the need for an improved, consensual psychiatric diagnosis and stimulated much, and new, basic research.

Yet despite its well-proven efficacy, the use of lithium has to some extent gone into disrepute, particularly in North America. This change happened for a variety of reasons. The repeatedly raised doubts about its benefits might have played some role, but the main reason has been the inappropriate use of lithium in patients with bipolar spectrum disorders and the push from pharmaceutical companies wanting to sell their new and more expensive products, such as atypical neuroleptics and anticonvulsants.

The finding of low lithium effectiveness in clinical routine certainly calls for major changes in practice: better education of clinicians, proper monitoring of lithium treatment, correct selection of patients suited for lithium stabilization, and wider availability of mood disorder clinics. But lithium treatment in settings where typical, classical bipolar patients are treated with standard care continues to report solid lithium effectiveness.

Furthermore, bipolar disorders have a capricious course and the clinician's initial assumptions codetermine outcome. To stabilize with monotherapy, the clinician must choose the right drug and dosage and persist for several months, and the patient must be educated to trust and adhere. These conditions cannot be achieved if the clinician assumes from the beginning that the solution will be polypharmacy: the patient will inevitably end up on it, and the reasoning becomes circular.

There has recently been some renaissance of interest in lithium treatment. This resurgence took

place because of a combination of new factors: a powerful antisuicidal effect of lithium, a putative but intriguing neuroprotective effect of lithium, and finally because the alternative medications—atypical neuroleptics and antiepileptics—are helpful but achieve satisfactory stabilization only in a limited proportion of bipolar patients and with the risk of serious metabolic adverse reactions. In addition, they often require combination with antidepressants or other drugs. Additional interest in lithium may emerge as a result of the recent epidemiological studies indicating that there is a large population of ''pseudounipolar'' patients with recurrent episodes and some of them will require lithium stabilization or may also benefit from lithium as acute antidepressant treatment in unipolar recurrent depressions.

The lithium story, oscillating between remarkable victories and deplorable defeats, in some way reminds one of developments which we have seen in the treatment of other important diseases such as hypertension or type-2 diabetes. In both areas, a plethora of pharmaceutical products have been pushed to the market during the last two decades, partly as true blockbusters, to replace the ''old-fashioned'' standards (diuretics, beta blockers, or insulin and metformin). In the area of hypertension, we have seen the market flooded with various calcium blockers, angiotensin converting enzyme inhibitors, the sartanes, alkirenin, and others. Efficacy was proven in many industry-sponsored studies for each of these compounds. However, a large, independently run trial, i.e., the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (92), showed that the longest-known and cheapest alternative, i.e., the thiazide diuretics, possess the best efficacy and should remain the first choice among all existing options. A similar development took place in the treatment of type-2 diabetes, where most evidence-based independent guidelines nowadays emphasize the benefit of insulin and metformin as first-line treatment, whereas the role of newly introduced compounds such as the glitazones are seen more and more critically, based on a doubtful benefit-risk-cost ratio.

The well-established mortality-reducing effect of long-term lithium that so far could not be demonstrated convincingly for alternative medications raises the intriguing question as to why the reduction of mortality so far has not become one of the primary endpoints, along with reduced morbidity, in critically comparing new and old therapeutic strategies. After all, affective disorders carry a high excess mortality. The augmentation of insufficient response to antidepressant medication is another rather unique ability of lithium; it is well covered elsewhere (93).

We are celebrating 60th anniversary of the official introduction of lithium in psychiatry. What we have learned overall is that lithium offers valuable, unique benefits for psychiatric patients, in particular the stabilization of classical-type bipolar disorder and a possibly specific antisuicidal effect, over and above mood stabilization. To utilize these benefits for our patients, it is necessary, first of all, to use lithium in properly selected patients; second, to teach correct, safe, individual-patient-tailored use of lithium as an obligatory part of education; and third, to integrate the antisuicidal effect of lithium more fully in psychiatric practice and in treatment guidelines and other consensus documents.

Acknowledgement

We want to acknowledge the enormous contribution of the late Professor Mogens Schou, M.D. to the demonstration of lithium's stabilizing efficacy and its benefit-risk ratio. For many years, he single-handedly fought for recognition of lithium as a stabilizing medication and for its acceptance in clinical practice. This paper is dedicated to him and his memory.

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