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SPECIAL ISSUE – EDITORIAL

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Is lithium still the gold standard in the treatment of bipolar disorders?

Given the fact that lithium's efficacy is well proven in both the prophylactic treatment of bipolar disorders and the acute treatment of mania, and also that there is some evidence for its efficacy in the acute treatment of bipolar depression, lithium seems to be the only drug currently available that fulfils the criteria for a mood stabiliser in the stricter sense: a drug that is effective in all phases of bipolar disorders. However, in the last decade the importance of lithium has been questioned in depth in the context of the development of other modern mood stabilisers from the group of antiepileptic drugs. Criticism was very sound and especially for some North American experts the situation culminated in the view that the traditional mood stabiliser lithium should generally be replaced by modern mood stabilisers to control several efficacy and safety problems. In Europe this was seen as an unexpected challenge because lithium was considered the leading drug in the field of bipolar disorders, especially in their prophylactic treatment, and in several European countries it was the first rank treatment, although the limitations were recognised and the search for other alternatives was seen as an important task. Before the rise of modern mood stabilisers and atypical antipsychotics, lithium was the most frequently investigated substance in the acute treatment of bipolar disorders, although studies were not always of the highest methodological level. In view of the doubts about sufficient efficacy of lithium expressed in recent years from various sides, and a stronger focus on safety limitations, as well as the simultaneous availability of newer treatment alternatives, the following series of papers aims to review critically the knowledge about lithium and its position in the treatment of bipolar disorders.

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In the context of such a critical review, aspects concerning the changes to the disorder concept through the broadening of the bipolar spectrum must also be considered carefully, especially in the sense that the results of the older studies refer only to the core feature of bipolar disorders and cannot be directly extrapolated to the modern diagnostic situation. This might explain why some clinicians have the impression that nowadays lithium does not always appear to be as effective as previously, and that in recent clinical trials using lithium as the standard comparator it showed lower efficacy than expected. Apparently lithium is especially indicated in the core syndrome of bipolar disorders but has efficacy problems in atypical features of bipolar disorders.

Lithium is the classic medication used to reduce the recurrence risk of bipolar disorder. In the late 1960s and 1970s several randomised controlled trials studied its prophylactic properties (Bastrup & Schou 1976). For at least two decades thereafter lithium was considered to be the gold standard for bipolar disorders. However, although lithium is still recommended as the first line prophylactic treatment in bipolar disorders in several guidelines (e. g. American Psychiatric Association 1994; Bauer et al. 1999), this status is being increasingly challenged by the introduction of other mood stabilisers such as carbamazepine, valproate and lamotrigine. Recently there has been increasing interest in atypical neuroleptics in the indication of bipolar disorder, and the available data are very promising. Besides research on new substances, the scientific discussion has focussed on the intrinsic usefulness of lithium. The criticism about the impact of lithium in the long-term treatment of bipolar disorders has mainly focussed on the following aspects: problems of efficacy, especially the problem of sufficient efficacy in atypical bipolar disorders and the fact that lithium is apparently more effective in the prevention of manic than depressive episodes, safety problems related to problems of compliance and effectiveness in clinical practice, the risk of withdrawal phenomena after lithium discontinuation, and the possible loss of efficacy after discontinuation and over time.

A closer look at the published evidence indicates that the prophylactic efficacy of lithium in bipolar disorder is supported by a large and strong database, whereby a more detailed inspection of the published database indicates that at least some efficacy depends on the subtype of bipolar illness. Lithium seems to be highly efficacious in classical manic-depressive illness, but not in patients with non-classical features, e. g. mood incongruent delusions. In conclusion, lithium should still be seen as the gold standard in the prophylactic treatment of bipolar disorders but there is an urgent need for alternatives that prove to have superior efficacy in the large group of non-classical bipolar patients.

The need for alternative treatment strategies is also underscored by the drawbacks of lithium in clinical practice. Long-term treatment with lithium carries the risk of unwanted adverse events such as tremor and weight gain. The use of lithium is further complicated by its narrow therapeutic range and the risk of withdrawal phenomena when rapidly discontinued.

Cade first described the antimanic efficacy of lithium over fifty years ago. Although his studies did not comply to modern methodological standards, it was still the first time that psychiatrists were given an effective drug treatment for mania. Extensive further studies followed in the subsequent decades, especially by Schou, so that by the beginning of the 1970s lithium treatment of bipolar patients had become established in acute antimanic therapy (Goodwin, Zis 1979; Schou 1997). Even before initiation of the discussion about the switch risk of antidepressants, the acute antidepressive efficacy of lithium continued to be investigated in smaller studies (Adli et al. 1998). However, due to the lack of commercial interest by pharmaceutical companies, large, controlled studies that could be expected to give conclusive evidence for acute antidepressive efficacy according to the methodological standards applied today were never performed. As to antimanic treatment, in the meantime lithium has delivered placebo-controlled proof of efficacy in trials with new potential antimanic compounds, in which it was used as a standard comparator drug in a placebo-controlled, three-arm approach.

An additional point should be mentioned with respect to the acute treatment of bipolar depression, that is the efficacy of lithium augmentation therapy in refractory depression. This refers not only to bipolar but also to unipolar depression. Nevertheless this seems to be a very important aspect showing the enormous potential of lithium.

Another important point is the fact that lithium apparently has antisuicidal effects which go beyond its relapse prophylactic properties in bipolar depression and also in unipolar depression. Given the high risk in both bipolar and unipolar disorders of death by suicide, its prevention seems to be a very important outcome criterion of long-term treatment of affective disorders. Strong evidence has been accumulated during the last decade that lithium prophylaxis can prevent suicidal acts and reduce the excess mortality of patients with affective disorders (Baldesserini et al. 2001).

Lithium continues to represent an important approach in bipolar disorders, not so much due to its good efficacy in the acute treatment of mania and a certain efficacy in the acute treatment of bipolar depression, but particularly because of its relapse prophylactic and antisuicidal properties. As long as the newer substances fail to demonstrate the same efficacy, also backed up by an accumulated wealth of experience from many years in these two areas, lithium remains the primary choice, especially for the long-term treatment of bipolar disorders. Lithium can also still have a relevant position in the acute treatment of mania, although in severe and especially psychotic mania co-medication with a neuroleptic is indicated. Even more so can lithium be seen as an option for the acute treatment of bipolar depression, although at least in more severe cases co-administration of antidepressants is indicated. However, the same is also true for other mood stabilisers in the indication of acute mania or acute bipolar depression so that lithium does not seem to be disadvantageous compared to the other mood stabilisers.

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