Does lithium save lives?

Russell T. Joffe, MD

Co-editor-in-chief, *Journal of Psychiatry & Neuroscience*, and Dean, New Jersey Medical School, University Heights, Newark, NJ.

In a recent retrospective cohort study, Goodwin et al[1] reported that the risks of suicide attempts and of mortality associated with suicide were significantly lower for patients with bipolar disorder treated with lithium as compared with divalproex sodium. Specifically, they showed that death due to suicide was almost 3 times less likely and suicide attempts almost 2 times less likely when patients with bipolar disorder were treated with lithium as compared with divalproex. Their data on carbamazepine were consistent with those for divalproex, although their findings were of a preliminary nature. In an interview associated with publication of this report, Dr. Goodwin, a pre-eminent scholar and author in the field of bipolar disorder, remarked that his study was the first to demonstrate that a psychotropic drug "saved lives." This is an extraordinary statement considering that it is almost 50 years since the modern era of psychopharmacology began with the introduction of chlorpromazine, and more than 30 years since the introduction of lithium as the first treatment for bipolar disorder.

The Goodwin study is not the first to note the potential antisuicide effect of lithium. Other studies have noted and documented this, and there has been discussion about whether lithium may have a specific beneficial effect on propensity to suicide, independent of its mood-stabilizing effects.[2] Notwithstanding the cautions about the methodology employed in the study conducted by Goodwin et al, it is the first to demonstrate convincingly an advantage of lithium over divalproex and, consistent with earlier studies,[3] a potential advantage of lithium over carbamazepine in antisuicide effects. It should also be noted that the Goodwin study is the first to compare the effects of 2 treatments; earlier studies used no treatment as the comparison group.[2]

The clinician's choice of pharmacologic treatment for bipolar disorder involves an implicit cost–benefit calculation for each option available. To date, for a variety of reasons, divalproex has superseded lithium as the first choice for the acute and prophylactic treatment of bipolar disorder. Lithium has generally been relegated from a first-line to an alternative treatment. Thus, the Goodwin study and Goodwin's subsequent comments give us pause. Reduced mortality or "saving lives" has never been an expectation imposed on psychotropic agents, in general, or on treatments for bipolar disorder in particular. The Goodwin data may not provide the definitive answer about lithium compared with other mood stabilizers in reducing mortality, but it does potentially raise the bar in setting standards for outcome in treatment trials involving bipolar disorder. Lithium does generally have a less favourable side-effect profile than other treatments for bipolar disorder, particularly divalproex sodium, but if it indeed uniquely reduces long-term mortality, its restoration to first-line treatment for bipolar disorder requires serious consideration.

Suicidal behaviour is a serious consequence of mood disorders, both bipolar and unipolar. In general, patients with mood disorders have a risk of death by suicide that is 9–20 times greater than that of the general population. As mood disorders are chronic and recurrent, mortality rates should be a key efficacy measure in

Correspondence to: Dr. Russell T. Joffe, Dean, New Jersey Medical School, 185 S. Orange Ave., University Heights, Newark NJ 07103-2714; fax 973 972-7104; joffe@umdnj.edu

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treatment studies, as is the case in all other branches of medicine where diseases have high mortality rates. Psychiatry should demand no less. All treatments for bipolar disorder should be rigorously evaluated for their potential antisuicide effects. This applies also to the antipsychotic drugs that are being used more commonly for acute and prophylactic treatment of bipolar disorder, and to clozapine, which has documented antisuicide effects in patients with schizophrenia.[4]

A voluminous literature documents the acute antidepressant efficacy of various agents in the treatment of unipolar depression in the last 50 years, and in particular in the last 20 years since the evaluation and introduction of new-generation antidepressants. There is a less extensive literature on the long-term efficacy of antidepressants, and very little attention has been paid to a potential reduction in mortality as an outcome measure in treatment studies of unipolar disorder. A vigorous debate has arisen, as exemplified by Healy and Whitaker[5] and Lapierre[6] in this journal, about whether selective serotonin reuptake inhibitors may enhance the risk of suicide. While not diminishing the importance of that debate, the opposite issue should also be addressed. The obvious question for future research is whether antidepressants, in general, and selective serotonin reuptake inhibitors, in particular, reduce mortality from suicide in depressed subjects with unipolar disorder. In the last few years, there has been an increasing refinement of the outcome measures for the efficacy of antidepressants. Differences between response and remission have rightly received increased attention, and quality of life, as well as symptomatic improvement, has been included as a key outcome measure. The Goodwin study suggests that raising the bar and including reduced mortality may be necessary in order to truly evaluate the utility and importance of antidepressants.

Unipolar disorder and bipolar disorder are extraordinarily disabling illnesses that have very high mortality rates. As in any other branch of medicine, serious psychiatric illnesses that cause high mortality should have treatments available that both reduce suffering and increase survival. Rigorous evaluation of all of these dimensions of outcome will not only serve our discipline well but will also be of great value and benefit to our patients. Goodwin's study is an important step along this path.

Competing interests: Dr. Joffe has received fees from Abbott Laboratories for continuing medical education.

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