

Introduction

Fifty Years of Lithium Use in the Treatment of Bipolar Disorder

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© Although lithium has been used in the treatment of various neuropsychiatric conditions in the past 3 decades, it is particularly beneficial for the acute and long-term treatment of mania and, in some bipolar and unipolar patients, for prophylaxis and treatment of depression. In recent years, however, young physicians have largely ignored the benefits of lithium in favor of anticonvulsant or atypical antipsychotic pharmacotherapy for patients with bipolar disorder. Moreover, while lithium was studied extensively in the past, recent literature shows a paucity of controlled studies of the drug. This Supplement has been compiled to provide a useful update for clinicians and neuroscientists alike on lithium neurobiology and psychopharmacotherapy.

Robert H. Lenox, M.D., and Chang-Gyu Hahn, M.D., Ph.D., begin the series of articles by providing an overview of the mechanism of action of lithium in the brain. They highlight some of the more robust data that not only define the multiple sites of action of lithium but may also lead to new pathways for drug development in the future.

According to Jair C. Soares, M.D., and Samuel Gershon, M.D., the psychopharmacologic specificity of the lithium ion may prove to be useful in elucidating the pathophysiology of bipolar disorder and, ultimately, lead to future drug development. On the basis of their review of new agents, they state that lithium is still the most effective agent for treatment of bipolar disorder if the patient can tolerate the drug.

The differential diagnosis of juvenile-onset bipolar disorder can be complicated by overlapping symptomatology with attention-deficit/hyperactivity disorder, says Jay N. Giedd, M.D. He explores the similarities and differences between the 2 disorders with respect to phenomenology, epidemiology, family history, brain imaging, and treatment response.

Charles L. Bowden, M.D., points out that lithium revolutionized both the treatment and phenomenological study of bipolar disorder. He also notes that lithium is increasingly used in combined treatment regimens, often allowing lower, better-tolerated dosing plus the complementary benefits from drugs with different profiles of action.

In vivo brain imaging techniques offer new access to the previously impenetrable brain compartment for lithium distribution. Clinton D. Kilts, Ph.D. describes the current findings of functional neuroimaging techniques with respect to the pharmacokinetics and pharmacodynamics of lithium.

Trisha Suppes, M.D., Ph.D., and colleagues state that—rather than searching for a unifying theory of bipolar disorder—it may be more productive to define the course of illness by highlighting such factors as findings at the age at onset, psychiatric comorbidity, frequency of episodes, cycle pattern, rapid cycling, mixed symptoms, and precipitants of episodes. Moreover, the way these factors interplay with treatment is now an increasing focus of bipolar research.

The depressive phases of bipolar depression can be quite disabling, with significant associated comorbidity and suicide risk, impairment in functioning, and infringement on quality

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of life. My colleague, Michael T. Compton, M.D., and I review the current evidence for management of bipolar depression, which can be a complicated clinical task. However, the treatment armamentarium is expanding.

Unipolar depression is a severe recurrent illness with high lifetime morbidity and premature mortality due to suicide. According to Alec Coppen, M.D., D.Sc., F.R.C.P., F.R.C.Psych. (Hon), numerous double-blind, placebo-controlled trials have shown that lithium is effective at reducing relapses in patients with unipolar depression when given as maintenance therapy.

An integration of psychotherapeutic techniques with pharmacotherapy has been recommended by the American Psychiatric Association Practice Guideline for the Treatment of Patients With Bipolar Disorder.¹ Barbara O. Rothbaum, Ph.D., and Millie C. Astin, Ph.D., describe the most common psychotherapeutic approaches including psychoeducation, individual cognitive-behavioral therapy, marital and family interventions, individual interpersonal therapy, and adjunctive therapies such as those for substance use.

Side effects of lithium are common but generally benign, says David L. Dunner, M.D., who divides the side effects of lithium treatment into those that (1) occur early in treatment, (2) are late appearing, (3) are related to drug interactions, and (4) are due to lithium toxicity. Early recognition and treatment of side effects are important aspects of lithium pharmacotherapy.

Husseini K. Manji, M.D., F.R.C.P.C., and colleagues note that recent advances in cellular and molecular biology have resulted in the identification of 2 novel targets of lithium's actions. These discoveries may have a major impact on the future use of this unique cation in biology and medicine. They suggest that the use of lithium as a neurotrophic/neuroprotective agent should be considered in the long-term treatment of mood disorders.

In clinical settings, an assessment of suicidal risk must precede any attempt to treat psychiatric illness, cautions Kay Redfield Jamison, Ph.D. She discusses other risk factors for suicide and states that—with the exception of lithium—remarkably little is known about specific contributions of mood-altering treatments to minimizing mortality rates in persons with major mood disorders in general and bipolar depression in particular.

Because suicidal risk is associated mainly with depressive or mixed bipolar episodes, Leonardo Tondo, M.D., and Ross J. Baldessarini, M.D., assert that better protection against bipolar depression is a key to limiting suicidal behavior in bipolar disorder. Their review of 22 studies from 1974 to 1998 yielded 7-fold lower suicide rates for patients who were receiving long-term lithium treatment than for patients who were not receiving lithium or lacked such treatment or for patients after lithium discontinuation.

Clearly, the efficacy of lithium in the treatment of mania and bipolar depression and in converting antidepressant nonresponders is well established. Although the side effect profile is less than optimal, there is little doubt that lithium has literally been a lifesaver for thousands of patients, and further study is in order.

REFERENCE

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder. *Am J Psychiatry* 1994;151(suppl 12):1-36