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# Editorial

## Perspectives on the pharmacological treatment of bipolar disorder

Lithium has been the gold standard in the pharmacological management of bipolar patients for many years.[1] Due to its high efficacy in the acute and prophylactic treatment of the illness, there was not much emphasis on the development of newer medications to treat this severe mental illness in past decades. The availability of lithium as a treatment has seemed to be the definite remedy, obviating the need of other medications for bipolar patients.

In the 1970s and 1980s, preliminary studies on the anticonvulsant medications carbamazepine and valproate as mood stabilizers and potential treatments for bipolar disorder were reported. More convincing evidence of their efficacy came from larger multicenter double-blind placebo controlled studies, which has only become available over the past decade. In the US, divalproex was approved by the Food and Drug Administration (FDA) for treating bipolar mania in the 1990s as a result of a pivotal study that documented its efficacy in the treatment of acute mania.[2]

In recent years, there has been mounting evidence that lithium is either not effective or not well tolerated in a sizeable group of bipolar patients (in some studies up to 40% or 50%).[3] As a result, there has been a growing interest in examining new candidate medications for treating this disease. New drugs, such as lamotrigine and olanzapine, have recently been tested and become available.[3] Gabapentin was tested in controlled studies but mostly with disappointing results. Other promising medications such as topiramate, zonisamide, and levetiracetam are currently being investigated.

In the management of mania unresponsive to a single mood stabilizer, there is often need to use combination strategies of two mood stabilizers, or regimens that would include other agents, such as atypical antipsychotic agents.[3] There is a considerable lack of controlled studies that would directly compare alternatives for this challenging clinical entity. Among other agents, calcium channel blockers (verapamil and nimodipine) have been studied, but there is limited controlled evidence in support of their efficacy. The utilization of atypical antipsychotics has recently been an area of considerable interest, particularly when in combination with mood stabilizers. The atypical antipsychotic agent olanzapine was recently approved in the US by the FDA for treating acute mania. These studies, in combination with preliminary findings in support of the efficacy of other atypical antipsychotics such as risperidone, suggest that these agents, either as monotherapy or in combination with mood stabilizers, are promising alternatives for the management of bipolar disorder.

The management of bipolar depression is often a major clinical challenge. Most of the residual impairment in bipolar patients is generally related to the depressive phase of the disease. The anticonvulsant lamotrigine has good efficacy in the treatment of bipolar depression, as indicated by a large double-blind controlled study.[4] Atypical antipsychotics may have antidepressant properties, and could possibly be useful in the management of depressive symptoms in bipolar disorder. Recently, the use of combination strategies of an atypical antipsychotic agent, such as olanzapine, added to an antidepressant drug has been proposed. Preliminary data available from a double-blind controlled study on the combination of olanzapine and fluoxetine in the treatment of bipolar depression are very promising, as they suggest good efficacy and safety. Despite evidence that some specific antidepressant agents, e.g., SSRIs or bupropion, may induce mania to a lesser extent than other antidepressant drugs, systematic investigation of the comparative risk of mania induction with various treatment alternatives currently available requires further study.

Rapid cycling patients are generally the hardest-to-treat bipolar patients. Some patients seem to benefit from newer treatments to a larger extent than more traditional ones. As it currently stands, the combination of mood stabilizers that would include some of the newer agents, e.g., valproate or lamotrigine, may often be the most adequate treatment for rapid cyclers. Even though polypharmacy should be avoided, available findings and clinical experience in this patient group suggest that combination strategies are generally necessary.

Developments in clinical neurosciences, allied to improved tools in genetics, brain imaging, cognitive neuropsychology, and neuropharmacology have raised one's hopes to achieve a better understanding of causation of this illness.[5] When the in-

volved brain mechanisms will be elucidated, more meaningful diagnostic classifications will be possible, and more specific targets for drug development will become available. Such progress will very likely result in improved ways of treating this severe psychiatric illness, which may well allow effective early intervention and possibly illness prevention.

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## References

1. Gershon S, Soares JC. Commentary: current therapeutic profile of lithium. *Arc Gen Psychiatry* 1997;54:16-20.
2. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. *JAMA* 1994;271:918-24.
3. Soares JC. Recent advances in the treatment of bipolar mania, depression, mixed states, and rapid cycling. *Int Clin Psychopharmacol* 2000;15:183-96.
4. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 1999;60:79-88.
5. Neumaier JF, Dunner DL. Toward a pathophysiology of bipolar disorder. In: Soares JC, Gershon G, editors. *Bipolar disorders - basic mechanisms and therapeutic implications.* New York: Marcel Dekker; 2000. p. 545-53.