

Something Borrowed, Something Blue: Why is Bipolar Disorder an Orphan?

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Bipolar disorders (bipolar I disorder and bipolar II disorder) occur in up to 4% of the population,^{1,2} frequently begin in the mid to late-teens,^{3,4} and cause chronic disability.⁵⁻⁷ Bipolar I disorder and bipolar II disorder are characterized by recurrent and chronic symptoms with associated multiple psychiatric and medical comorbid conditions,^{1,2} as well as excess and premature mortality and suicide.⁸⁻¹⁰ Bipolar disorder has been listed among the top 10 causes of disability worldwide⁷ and is estimated to cost about \$70 billion/year in 2008 dollars.^{11,12} Yet, since the advent of lithium over 60 years ago, not a single medication has been specifically developed for bipolar disorder. Every modern medication approved or studied for bipolar disorder has been derived from existing anticonvulsants,¹³⁻¹⁸ antipsychotics,¹⁹⁻²² antidepressants,²³ wakefulness medications,²⁴ and anticholinergic agents,²⁵ all approved for other disorders. Thus, the paradox exists that one of the most common psychiatric disorders is an orphan. One possible reason for the lack of specific drug development could be the perceived success of lithium.

Lithium recently enjoyed the 60th anniversary of its formal debut into psychiatry.²⁶ John Cade

published his remarkable study in 1949 and it is worth reading for Cade's insightful observations.^{27,28} Through the work of Morgans Schou,²⁹ Sam Gershon,^{30,31} and others, the clinical database for the efficacy of lithium grew. It took until the early 1970's for lithium to enter the market in the United States, partially because of toxicity concerns left over from its use as a salt substitute. Lithium continues to be one of the mainstays of bipolar treatment and is recommended by multiple treatment guidelines.³² Paradoxically, its use has been declining while studies of the mechanisms of action of lithium and lithium response are starting to unlock important clues to bipolar pathophysiology.³³⁻³⁶

Another problem in the bipolar field that may have blocked drug development comes from the surprising controversy in the use of antidepressants. On one hand, a meta-analysis strongly supported the use of antidepressants with anti-manic medications for bipolar depression.³⁷ On the other hand, the largest placebo-controlled study of an antidepressant added to a mood stabilizer found no benefit from bupropion or paroxetine, and no short-term harm with switching from depression to mania.²³ Thus, the problem

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is that bipolar depression may (or may not) be responsive to antidepressants. As an alternative to antidepressants, studies have shown the efficacy of a combination of olanzapine and fluoxetine²¹ or quetiapine.³⁸ The problem here is that we lack effectiveness studies that include a broad, representative bipolar population and integrate tolerability, attrition, and efficacy. Only by conducting effectiveness studies will we know how these treatments perform in the real world.

Where does this leave the bipolar orphan? It might be time to consider that while people with bipolar disorder can become psychotic, bipolar disorder is not schizophrenia. While depression is a prominent component of bipolar disorder, antidepressants may not be the answer. While bipolar patients have mood episodes, it is insufficient to just treat the episodes; they have a chronic disorder and we need to find new treatments to improve the course of the disorder. It is time to develop drugs specific to bipolar disorder, informed by our growing understanding of pathophysiology and genetics. Then we won't have to borrow and be so blue. **CNS**

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