What is the best treatment for bipolar depression?

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One of the challenges facing clinical psychiatry is how to treat bipolar depression effectively.[1] Surprisingly, its neurobiology and rational decisions about its treatment remain somewhat of a mystery. Recent findings have even called into question the role of traditional antidepressants in bipolar depression when other classes of drugs may be more effective first-line treatments for this illness.[2] Setting aside the thorny question of whether antidepressants induce manic switches or rapid cycling, it seems worthwhile to consider recent clinical studies and try to make sense of their implications for the neurobiology of bipolar depression.

Treating bipolar depression with antidepressants remains a popular option in clinical practice and published guidelines. Most clinicians choose the drug or class of drugs, usually selective serotonin reuptake inhibitors and bupropion, that is most effective and best tolerated.[1] However, the recently published results from the STEP-BD project found no benefit to adding an antidepressant (paroxetine or bupropion; $n = 179$) compared with placebo ($n = 187$) to a mood stabilizer in a large naturalistic sample of patients with bipolar I and II disorders.[2] This intriguing finding certainly questions whether antidepressants, a common intervention for bipolar depression, are effective in the treatment of this remarkably disabling and difficult-to-manage condition.

Practice guidelines and clinical consensus support the use of mood stabilizers such as lithium or anticonvulsants either as monotherapy or add-on therapy for bipolar depression.[1] In general, this treatment is not considered to be highly effective for bipolar depression because symptoms often improve slowly or incompletely. When lithium is included as a comparator in maintenance trials for new potential mood stabilizers, results show it is effective in the prevention of manic relapses, but limited in the prevention of relapses into depression.[3]

I have had a long interest in bipolar depression. In a proof of principle study, my research colleagues and I questioned whether adding a second mood stabilizer could treat depressive symptoms as effectively as adding an antidepressant, and we were surprised to see that both treatments had such a similar effect.[4] A recent meta-analysis of the treatment of bipolar disorder showed that valproate had a surprising ability to prevent depressive relapses, and at least a few studies have suggested the drug may be an effective treatment for acute depressive symptoms in bipolar disorder.[1,5] In light of the recent data suggesting that antidepressants may have little effect when added to a mood stabilizer, this treatment option might warrant reconsideration and further study. To make the situation even less clear, at least one anticonvulsant, lamotrigine, lacks antimanic properties, and although it is an adequate antidepressant agent in bipolar depression, it is not as effective in the treatment of major depressive disorder.[6] Carbamazepine has fallen out of favour with many clinicians owing to adverse effects and complicated drug interactions; however, in my experience, it can be a very useful agent for the treatment of bipolar depression.[1] Taken together, traditional mood stabilizers, including anticonvulsants, are potentially effective treatments for bipolar depression.

The increasing acceptance of atypical antipsychotics as mood stabilizers was first based on their proven ability to treat acute mania and, more recently, on their effectiveness in the treatment of bipolar disorder and their acute antidepressant effects. Olanzapine has been shown to have acute antidepressant effects in bipolar disorder either alone or in combination with fluoxetine.[7] Although quetiapine has been established for some time as an agent with antidepressant effects in bipolar disorder, some recent data have shown even more impressive effects. Two studies involving close to 1500 depressed patients with bipolar I and II disorders compared quetiapine with placebo and either lithium or paroxetine.[8,9] In both studies, quetiapine was reported to be more effective in reducing depressive symptoms compared with placebo or the other agent after an 8-week trial. Interestingly, neither lithium nor paroxetine was more effective than placebo. Although few would have argued with the results for lithium before the publication of the STEP-BD results,[2] the lack of apparent effect of paroxetine found in that study was an unexpected outcome. Nonetheless, atypical antidepressants are emerging as effective treatments for bipolar depression.

Historically, we have extrapolated from the mechanism of

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action of psychotropic drugs to construct or validate neurobiologic models of psychiatric disorders. Do these results suggest that monoaminergic mechanisms are less important in our understanding of bipolar depression than of unipolar depression? Do the surprisingly encouraging results for anticonvulsants suggest that we should look more closely at either GABAergic (quite popular at one time) or glutamatergic hypotheses for bipolar depression? Since lamotrigine has not been shown to be effective in unipolar depression, this may indeed support such a change in our thinking. Finally, although the effects of atypical antipsychotics offer new options for a phase of bipolar disorder that is difficult to treat, they limit our understanding of the neurobiology of the disorder even further. Theories on the antidepressant effects of antipsychotic medications have ranged from modulating dopamine and serotonin to sharing metabolite properties with other antidepressants to demonstrating intracellular mechanisms for antidepressants and lithium. In sum, it is hard to find a parsimonious and elegant explanation for the emerging effectiveness of these drugs in bipolar depression.

It is encouraging to see so many new findings in a previously moribund area of psychiatric research. Although these encouraging clinical data may raise more questions than they answer, they may point to the need to discard older models of the neurobiology of psychiatric disorders, to be open to new data and to explore new treatments.

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