CNS Spectrums (2013), **18**, 175–176. © Cambridge University Press 2013
doi:10.1017/S1092852913000448

EDITORIAL

Controversies in treating bipolar depression

Appearing in this issue of *CNS Spectrums* are several articles on bipolar depression.[1–6] Until recently, this condition took a backseat to its clinical cousin, unipolar depression, both in terms of development of new treatments and in terms of clarifying how to treat on the basis of evidence-based data. Now, the treatment of bipolar depression is recognized as an area of great unmet need, and unfortunately, controversy. Practicing evidence-based medicine for this condition is therefore difficult, especially in children and adolescents where large randomized trials are either rare or nonexistent, as pointed out by DeFilippis and Wagner.[1] Thus, it is entirely unclear whether the classical bipolar agents lithium or lamotrigine are robustly effective in bipolar depression on the basis of evidence-based data, either in children/adolescents,[1] or even in adults both in data from the U.S. perspective[2] or from the European perspective.[3]

Randomized controlled trials in bipolar depression mostly include bipolar I patients and mostly exclude those patients who are more common and perplexing in clinical practice, namely bipolar II patients, NOS (not otherwise specified), and mixed depression (full syndrome depression with subsyndromal mania of the new DSM5). Furthermore, most trials are of monotherapies, whereas in the real world, most patients receive combination therapies. Perhaps this is why the gap between evidence-based practice and practice-based evidence for the treatment of bipolar depression is a yawning one and filled with controversy.

For example, should bipolar II, NOS, and mixed depression patients be treated with the same drugs that have been found to be effective in bipolar I depressed patients? There is almost no evidence to address this question. Also, should lamotrigine be a first-line agent for bipolar depression despite the negative results from randomized controlled trials? Published guidelines answer this question by giving the nod to firstline treatment of bipolar depression with lamotrigine in spite of the lack of solid evidence from randomized controlled trials (see Cerullo and Strakowski[2] and Musetti et al[3]). Practice-based medicine has also endorsed lamotrigine for acute bipolar depression and not just for the prevention of depressive recurrences as approved by the FDA. The article by Mitchell et al[4] proposes an explanation for why the therapeutic actions of lamotrigine in bipolar depression, which are apparent in clinical practice, may have been missed in various evidence-based trials: namely, because the clinical benefits may be confined to improvement in depressive cognition and psychomotor slowing, and not in insomnia, low energy, or anxiety.

Another area where guidelines and clinical practice differ from the evidence of randomized controlled trials in bipolar depression is in the use of lithium and divalproex, where their robust actions in mania are matched only by equivocal evidence-based data that support their efficacy in bipolar depression.[1–3] By contrast, guidelines and clinical practice nevertheless use these agents second line for the treatment of bipolar depression, and it seems that some patients do indeed benefit.

The story of atypical antipsychotics in bipolar disorder is a fascinating one, starting from evidence of efficacy of essentially all of these agents in acute bipolar mania, and progressing in recent years to proven efficacy in bipolar depression for some but not all atypical antipsychotics.[2,3] It appears that there is a class effect for all atypical antipsychotics in acute bipolar mania,[7] although not all agents are formally FDA approved. On the other hand, there does not appear to be a class effect for these same agents in the treatment of acute bipolar depression.[2,3] That is, robust actions of quetiapine seem to be replicated only by lurasidone. Lurasidone is not discussed in the articles in this issue,[2,3] since the large-scale randomized controlled trials of lurasidone in bipolar depression have only been presented in poster form, and as of this date are unpublished and yet are awaiting imminent FDA approval for bipolar depression. Olanzapine is approved for bipolar depression, but only in combination with fluoxetine, a curious observation given the controversy in using antidepressants for bipolar depression.[2,3] Studies of aripiprazole, ziprasidone, and other agents are not robustly positive in bipolar depression, possibly because of clinical design issues, but possibly also due to the differing and perhaps less robust mechanisms of antidepressant action for these agents compared to quetiapine or lurasidone.[7]

Stimulants and dopamine agonists are other agents where data are sparse and where controversy persists in bipolar depression. Although amphetamine, methylphenidate, modafanil, armodafanil, and dopamine agonists such as pramipaxole or ropinirole all have some clinical trial evidence for efficacy in bipolar depression, none has reached the level of FDA approval and all are second-line agents in various treatment guidelines. Curiously, these agents may cause less induction of mania or rapid cycling than antidepressants, but there are few large-scale studies and no head-to-head studies of stimulants with antidepressants to answer this question.[2,3,7]

Not mentioned in the articles published here[1–6] is a positive, large-scale, multicenter, randomized controlled trial of armodafanil add-on to atypical antipsychotics for bipolar depression, only presented so far as an unpublished poster. A second such trial failed, and as of this date, the results of a third trial are awaited, and if positive, would probably lead to submission to the FDA for approval.

Finally, antidepressants: They work. They don't work. They work, but they cause mania, rapid cycling, or loss of efficacy. Who knows? Incredibly, many prescription audits still find that the most common treatment of bipolar depression is antidepressants, as clinicians often may treat the symptom (depressed mood), not the disorder (bipolar as opposed to unipolar disorder). Even treatment guidelines for bipolar disorder are not clear on how and whether to use antidepressants in bipolar disorder, and differ one from another, and change over time, with some guidelines shunning antidepressants and others allowing combination treatment third line after several other agents fail.[2,3] No guideline suggests antidepressant monotherapy in bipolar depression.

Two other articles in this issue of *CNS Spectrums* suggest the way of the future for bipolar depression, namely targeting glutamate systems.[5,6] Blocking glutamate NMDA (N-methyl-d-aspartate) receptors with ketamine and similar drugs may be effective not only for bipolar depression, but also for suicidal thoughts and for treatment-resistant unipolar depression.[5]

So, it is good to take stock now of the controversies regarding treating bipolar depression as addressed in the articles within this issue of *CNS Spectrums*, as new data have been generated and practice guidelines are ever-changing. There remain both huge unmet needs and insufficient data in this field. In some ways, clinical practice is leading the way, and the evidence has not yet caught up with practice. Stay tuned, as bipolar depression is a rapidly evolving area of psychiatry with great hope for better treatments and better data to come hopefully soon.

Stephen M. Stahl
Editor-in-Chief
CNS Spectrums, Department of Psychiatry
University of California–San Diego, San Diego California
and
Department of Psychiatry, University of Cambridge
Cambridge, UK

Reference

1. DeFilippis MS, Wagner KD. Bipolar depression in children and adolescents. *CNS Spectr*. in press.
2. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr*. in press.
3. Musetti L, Del Grande C, Marazziti D, Dell'Osso L. Treatment of bipolar depression. *CNS Spectr*. in press.
4. Mitchell PB, Hadzi-Pavlovic D, Evoniuk G, Calabrese JR, Bowden CL. A factor analytic study in bipolar depression, and response to lamotrigine. *CNS Spectr*. in press.
5. Cateno-Dell'Ossa M, Gagiolini A, Rotella F, Baroni S, Marazziti D. Glutamate system as target for development of novel antidepressants. *CNS Spectr*. in press.
6. Stahl SM. Mechanism of action of ketamine. *CNS Spectr*. in press.
7. Stahl SM. *Stahl's Essential Psychopharmacology*, 4th ed. Cambridge, UK: Cambridge University Press; 2013.