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Innovation in the Treatment of Bipolar Depression

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The treatment of depression in patients with bipolar disorder is fundamental to the management and prognosis of this condition. Despite multiple adequately powered, randomized, placebo-controlled studies that demonstrate that antidepressants added to mood stabilizers are no more effective in bipolar illness than placebo,[1–3] and are potentially problematic,[4,5] the use of antidepressants in patients with bipolar illness remains controversial.[6] The confusion derives, in part, from studies showing that antidepressants added to antipsychotics (in type I patients), or used as monotherapy (in type II patients), are effective acutely.[7–9] Continued widespread use of antidepressants in bipolar depression[10] is probably emblematic of the lack of effective alternatives in a disorder in which depression is the predominant mood.[11–13] This unmet need has become fertile ground for a small flowering of innovation in psychiatry. For example, sub–antipsychotic doses of second-generation antipsychotics are being repurposed for bipolar depression.[14,15]

In this issue, Calabrese and colleagues[16] present data for another novel option for the treatment of bipolar depression. Armodafinil, and modafinil before it, have been shown in randomized, placebo-controlled studies[17] to be safe and effective in the acute treatment of bipolar depression when added to a mood stabilizer. The true value of these studies extends beyond the value of yet another option for depressed patients with bipolar illness. While the mechanisms of action of armodafinil and modafinil are not known, they do not alter serotonin. Rather, they appear to augment signals of dopamine and histamine.[18,19] As such, they are the only available prohistamine antidepressant agents used in bipolar illness. Thus, Calabrese and colleagues' article is introducing a new class of antidepressant treatment for bipolar disorder.

Despite the importance of the study, it has clear problems. The effect size was small, and the reason for that is not clear. Armodafinil's separation from placebo occurred late in the study. It is clear that additional studies are needed to confirm these data and clarify the optimal dose. Furthermore, maintenance studies are required to ensure that the destabilization of the illness that happens with antidepressants does not happen with armodafinil. Ongoing development of these agents, by providing a safe and effective alternative to antidepressants, may ultimately make antidepressant avoidance less controversial in the treatment of bipolar depression.

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