Antidepressants in Acute Bipolar Depression: An Inconclusive Meta-Analysis

To the Editor: We read with interest the meta-analysis by Sidor and MacQueen on antidepressants in bipolar depression,1 which apparently yielded different conclusions from a previous meta-analysis on the same topic.2 In our opinion, though, the newer meta-analysis is at least as inconclusive as the previous one, and the changes introduced in the selection of the trials has just caused a P < .05 to now be P = .06.

The reality is that placebo-controlled trials for depressive episodes in the frame of bipolar disorder have no commercial interest to drug companies owning antidepressants because clinicians assume that a drug that works in unipolar depression should necessarily also work in bipolar depression. In fact, from a cross-sectional perspective, the diagnostic criteria are the same. This has had an impact on clinical trial quality. On the contrary, drugs that are not assumed to work in bipolar depression may be commercially attractive to be tested in this indication, and, hence, clinical trials and meta-analyses conducted for anticonvulsants (laminotrigine and valproate) and atypical antipsychotics in acute bipolar depression have been highly informative and conclusive.3–5

Moreover, it appears that this meta-analysis1 assumed a priori that all the included trials would have similar underlying effect sizes, given that a fixed-effects model was preferred over a random-effects model, which would be much more realistic and reliable, in view of the heterogeneity of the trials.

The efficacy and safety of antidepressants in bipolar depression are still a matter of debate.6 In support of their lack of efficacy, as suggested in this meta-analysis, the EMBOLDEN II trial7 reported negative findings for paroxetine, whereas quetiapine did separate from placebo. This study was published in 2010 and therefore was not included in the meta-analysis, but in our opinion it is the most compelling study indicating the lack of efficacy of an antidepressant in bipolar depression. It could be argued that the dose of paroxetine was too low (20 mg/d) and that not all antidepressants are the same.

Switch and remission rates did not add much to the meta-analysis. Again, the limited quality of the studies made the meta-analytic approach inconclusive.

In summary, given the limitations of the currently available evidence base, we believe that no meta-analysis will solve the question of whether antidepressants are efficacious and safe in bipolar depression. Only well-designed and -powered placebo-controlled trials may shed light on this clinically crucial question. If no private sponsor is likely to conduct them, perhaps public funding should solve the question, given the public health relevance of the problem: antidepressants are still the most widely prescribed drugs for bipolar disorder.8 Meanwhile, we support a “case for caution” approach,9 prioritizing other options as indicated in the most recent guidelines for bipolar depression.10

References


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