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 (lamotrigine and valproate) and atypical antipsychotics in acute bipolar depression have been highly informative and conclusive.[3–5]

Moreover, it appears that this meta-analysis[1] 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 trial[7] 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

1. Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis [published online ahead of print October 5, 2010]. *J Clin Psychiatry*. 2010.
2. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004;161(9):1537–1547.
3. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry*. 2009;194(1):4–9.
4. Smith LA, Cornelius VR, Azorin JM, et al. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. *J Affect Disord*. 2010;122(1–2):1–9.

5. Cruz N, Sanchez-Moreno J, Torres F, et al. Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis. *Int J Neuropsychopharmacol*. 2010;13(1):5–14.
6. McElroy SL, Weisler RH, Chang W, et al; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry*. 2010;71(2):163–174.
7. Vieta E. Antidepressants in bipolar depression. *Acta Psychiatr Scand*. 2008;118(5):335–336.
8. Baldessarini RJ, Leahy L, Arcona S, et al. Patterns of psychotropic drug prescription for US patients with diagnoses of bipolar disorders. *Psychiatr Serv*. 2007;58(1):85–91.
9. Vieta E. Case for caution, case for action. *Bipolar Disord*. 2003;5(6):434–435.
10. Nivoli AM, Colom F, Murru A, et al. New treatment guidelines for acute bipolar depression: a systematic review [published online ahead of print June 8, 2010]. *J Affect Disord*. 2010.

Nuria Cruz, MD
Eduard Vieta, PhD
evieta@clinic.ub.es

Author affiliations: Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain. ***Potential conflicts of interest:*** **Dr Vieta** has been a consultant to Almirall, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer Inc, Sanofi-Aventis, Servier, Solvay, Schering-Plough, Takeda, United Bioscience Corporation, Wyeth, Ministry of Science and Innovation, the Stanley Medical Research Institute, and the 7th Framework Program of the European Union. **Dr Cruz** reports no potential conflicts of interest relevant to the subject of this letter. ***Funding/support:*** None reported.
doi:10.4088/JCP.10lr06638