Dr Ghaemi Replies

To the Editor: Dr Rasmussen's letter, despite its not entirely collegial tone, provides an opportunity to expand further on our findings regarding the harm caused by antidepressants in rapid-cycling bipolar disorder.[1] To address the question whether a few patients might have skewed the mean results, we report here, as challenged, distributions of the data.

In subjects randomized to antidepressant discontinuation, the distributions for depressive episodes were similar in the non–rapid cycling vs rapid-cycling groups (22/28 non–rapid cycling subjects vs 7/10 rapid-cycling subjects had 0 or 1 episode; only 3/28 non–rapid cycling subjects vs 1/10 rapid-cycling subjects had 4 or more episodes). In subjects randomized to continue antidepressants, the distributions for depressive episodes in the non–rapid cycling vs rapid-cycling groups were clearly different (15/25 non–rapid cycling subjects vs 1/7 rapid-cycling subjects had 0 episodes; only 1/25 non–rapid cycling subjects vs 3/7 rapid-cycling subjects had 4 or more episodes).

In summary, in all groups except the rapid cyclers maintained on antidepressants, distributions were skewed toward zero, meaning that most patients had few if any depressive episodes. In the rapid-cycling group maintained on antidepressants, the distribution was normal, meaning most patients had 2 to 4 depressive episodes. These are real differences in most study patients, not outliers.

Sample size is always limited in secondary outcomes of partial datasets. We addressed this problem in 2 ways. First, to avoid a common overemphasis on *P* values (as in the letter),[2] which are liable to major false-negative risks with small samples, we emphasized descriptive statistics of effect sizes (number of episodes per year). Second, since we predicted and found that only 25% of the sample would have rapid cycling, we planned a priori, 7 years before the data analysis, to compare the rapid-cycling sample (n = 17) to the much larger non–rapid cycling sample (n = 53). The rationale was that, in such an analysis, large descriptive differences, as described above, would be statistically significant when *P* values were applied (as detailed in the article; namely, an about 3-fold increased rate of depressive episodes in rapid-cycling vs non–rapid cycling subjects continued on antidepressants; mean of 1.29 vs 0.42 depressive episodes per year, $P = .04$).

If these data "make no sense," a solution may be found in study of the standard text in the field,[3] prospective outcome studies,[4] and comprehensive review articles,[5] which clearly describe how in bipolar disorder—including rapid-cycling—depressive episodes are more frequent and lengthy than manic episodes. Our data are consistent with this literature; we observed about 2-fold more depressive versus manic episodes in our rapid-cycling subjects (over 3 years, 12 manic episodes in 6 subjects vs 20 depressive episodes in 13 subjects). Our study confirms the importance of the concept of "cycling" or "recurrence" (not just polarity) as a key aspect of manic-depressive illness—a notion that dates back to Kraepelin.[3] In an illness in which most cycles involve depression more frequently and severely than mania, antidepressants appear to induce not just acute mania, but long-term cycle acceleration with worsening depressive morbidity—a concept about which some of us have published repeatedly for decades.[3,6]

"The great tragedy of science—," Thomas Huxley called it, "the slaying of a beautiful hypothesis by an ugly fact." Lamentably, the antidepressant faith does not fare well in randomized studies of bipolar disorder (or even, to some extent, in major depressive disorder[7]). Our data are not definitive, but they are based on the most valid research design we have, and they are consistent with the only other available randomized data on antidepressants in rapid-cycling bipolar disorder.[3,6] Facts are stubborn, sometimes even tragic, things.

References

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Potential conflicts of interest: Dr Ghaemi has received grant/research support from Pfizer. ***Funding/support:*** The work discussed in this letter was supported by National Institutes of Health grant MH-64189 (Dr Ghaemi).
doi:10.4088/JCP.10lr06489ablu