the groups were similar in anxiety severity at the point of random assignment.

Thus, we believe that our conclusions were neither misleading nor inconsistent with the results. Despite the study's limitations owing to the small group size, this is, to our knowledge, the first prospective randomized, controlled study that demonstrates the efficacy of a serotonergic antidepressant medication for late-life anxiety disorders. We are currently confirming and extending the results in a larger clinical trial funded by the National Institute of Mental Health that focuses on late-life generalized anxiety disorder.

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Conclusions Inconsistent With Results With Amphetamines and Divalproex

TO THE EDITOR: In their article, Russell E. Scheffer, M.D., et al. (1) reported in their conclusions and elsewhere positive summary statements that included the following: "Pediatric patients with bipolar disorder and concurrent ADHD [attention deficit hyperactivity disorder] can be safely and effectively treated with mixed amphetamine salts after their manic symptoms are stabilized with divalproex sodium" (p. 58).

These ambitious claims were made by the authors after noting what they suggested to be these limitations of their brief trial: 1) ineffectively low doses of mixed amphetamine salts, 2) a failure to increase the divalproex doses to assess greater possible response, 3) the small group size, 4) a study protocol limited to a single academic center, and 5) a failure to address long-term outcomes and safety.

The authors' statements regarding the efficacy/tolerability of mixed amphetamine salts/divalproex might be true, but their repetitively positive published conclusions are not consistent with their evidence. The announced conclusions, likewise, that appeared in the official publication of APA that reiterated this positive news (2) failed to disclose serious research limitations.

The expressed concerns of Dr. Scheffer and colleagues regarding the limitations of their study, while justified, did not address the serious problems in their research design and reporting:

1. Twenty-five percent of the original subjects (N=40) did not have postrandomization data.
2. At least four individuals in the study became manic, three of whom required hospitalization.
3. The "treatment" period with mixed amphetamine salts was limited to a brief 14 days.
4. An individual could be a positive responder with only one follow-up visit, despite being lost to follow-up thereafter.
5. The 80% positive response rate reported with divalproex was unblinded and open label.
6. The authors failed to disclose which treatment groups experienced "transient" side effects of "low to moderate severity and frequency."
7. At least one person treated with mixed amphetamine salts became manic.
8. The authors included a misleading statement regarding the absence of worsening manic symptoms with treatment, and their Results section failed to provide information about other serious adverse reactions.

Published positive conclusions of this research effort, funded in part by a grant from the Stanley Medical Research Institute to Dr. Rush, are misleading. The *Journal* and *Psychiatric News* must be cautious about favorable generalizations from brief trials whose data from partially unblinded and open-label design do not include results from the research itself that demonstrate serious injuries (e.g., rehospitalizations and induction of mania) as a likely byproduct of the protocol. Representations of preliminary results should not suggest "safety and efficacy" when the data are limited and inconclusive.

References

1. Scheffer RE, Kowatch RA, Carmody T, Rush AJ: Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry 2005; 162:58–64
2. Levin A: Kids with bipolar + ADHD respond to added stimulant. Psychiatr News, Jan 21, 2005, p 46

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Dr. Scheffer and Colleagues Reply

TO THE EDITOR: In reply to Drs. Kruszewski and Paczynski's comments, let us consider each point.

1. The doses of mixed amphetamine salts were not ineffective. In fact, the study revealed efficacy for mixed amphetamine salts for the doses used compared to placebo. It is true that higher doses might have been even more effective.
2. We agree that higher doses of divalproex might have led to even greater benefits, although the doses and serum levels used were associated with a substantial rate of response of 80%.

3 and 4. We agree that the small group size and a study conducted at only one site, by definition, limited generalizability and also recommend replication studies. However, we demonstrated strong statistical significance with the group we used.

5. We agree that longer-term studies are needed to best evaluate long-term safety and outcome.

That 20% of the patients with bipolar disorder could not be stabilized while taking open-label divalproex is not particularly surprising. The response rate of 80% with open-label divalproex was substantial, however, and similar to what has been found in other open-label studies (1). The 14-day treatment with mixed amphetamine salts and placebo was long enough to establish clinical statistical significance. Most patients (23 of 29) did elect open treatment with mixed am-