The authors' statements regarding the efficacy/tolerability of citalopram in geriatric anxiety disorders may be true, but their published repetitive positive conclusions are not consistent with their evidence. For example, the Results section demonstrated that 11 members of a treatment group of 17 subjects experienced less anxiety than a placebo group. However, 88% of the treatment group were women, and 47% received various doses of lorazepam while they received various doses of citalopram (according to their clinical response). This treatment group was compared to an unmatched placebo group, 65% of whom were men and (only) 24% of whom were administered various doses of lorazepam.

The treatment group experienced more adverse side effects (intolerable sedation, nausea, and fatigue) and had a higher dropout rate than the members of the placebo group, who experienced fewer side effects and had a lower dropout rate. Furthermore, despite random assignment, the placebo group—when evaluated for mean scores for anxiety and depression—was more symptomatic than the treatment group before the initiation of any "treatment," and conversely, the "treatment" group was less symptomatic at baseline on both measures, skewing the statistical endpoint contrasts of "treatment effect."

Design difficulties and the questionable interpretation of results were distorted by graphical analysis. In Table 1, the mean baseline rating of anxiety for the placebo group is 23.1, whereas the corresponding number for the citalopram group is 21.4. However, despite the apparent use of data from Table 1 as the basis for Figure 1, the graphical analysis shows that the subjects taking citalopram began with a higher anxiety score than the placebo group, creating the impression that the citalopram "treatment" group had a more pronounced decrease in anxiety after treatment than it, in fact, did.

The evidence shows that the citalopram group did not tolerate its treatment as well as the placebo group, nor did the authors establish the efficacy of treatment since the groups were not comparable. Unmatched intergroup mean baseline scores for the symptoms of anxiety or depression skewed the statistical analysis, and inaccurate graphical representation of the results distorted the findings. The conclusions of this research effort, funded by Forest Pharmaceuticals and three grants from the National Institute of Mental Health, are misleading and inconsistent with the authors' data.

Reference

1. Lenze EJ, Mulsant BH, Shear MK, Dew MA, Miller MD, Pollock BG, Houck P, Tracey B, Reynolds CF III: Efficacy and tolerability of citalopram in the treatment of late-life anxiety disorders: results from an 8-week randomized, placebo-controlled trial. Am J Psychiatry 2005; 162:146–150

STEFAN P. KRUSZEWSKI, M.D.
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Dr. Lenze and Colleagues Reply

TO THE EDITOR: We are pleased that Dr. Kruszewski took interest in our study, but we respectfully disagree with his assertion that our study conclusions are misleading or inconsistent with our results. Our conclusion was that citalopram was efficacious and well-tolerated in elderly persons with anxiety disorders. We are happy to respond to some of his specific concerns. Dr. Kruszewski notes that the placebo and citalopram groups had unequal gender proportions, with more men in the placebo arm. We commented that this was a limitation, but we also mentioned on page 148 that we controlled for gender and found no change in the significantly higher rate of response to citalopram compared to placebo. Thus, the gender proportions did not appear to account for our efficacy finding.

Dr. Kruszewski also notes that the subjects in both groups also received lorazepam. However, there are two important reasons why it is unlikely that lorazepam co-administration could have accounted for our efficacy finding. First, the subjects were taking low doses (the median dose was 0.75 mg/day for the subjects in the citalopram arm). Second, the subjects were required to have been taking a fixed dose of this medication for at least 2 weeks before their random assignment, with no changes in their dosage during the study, and no subjects were administered benzodiazepines during the trial (they kept taking the medication if they were already taking it to avoid the added confounder of benzodiazepine withdrawal during the treatment study). Thus, the subjects still met entry criteria for significant anxiety symptoms despite taking a low dose of lorazepam.

Dr. Kruszewski states that the citalopram group experienced more adverse side effects and had a higher dropout rate than the placebo group. This is not really correct. In fact, a majority of the subjects in both the citalopram and placebo arms mentioned at least one side effect, and the difference in the proportions who reported any side effects was small and statistically insignificant (χ^2=1.12, df=1, N=24, exact p=0.48; effect size: ϕ=0.18). The difference in dropout rates was also small and insignificant (χ^2=1.13, df=1, N=24, exact p=0.29; effect size: ϕ=0.18). Figure 2 on page 148, with the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale, shows that the subjects who were randomly assigned to citalopram tended to have lower side effect scores during treatment. As a whole, these data support the tolerability of citalopram in this population.

Finally, Dr. Kruszewski notes that the Hamilton Anxiety Rating Scale score and Hamilton Depression Rating Scale score were higher at baseline in the placebo groups, but he fails to state that these differences were not statistically reliable. Moreover, the sizes of the effects were small (for the Hamilton depression scale, effect size: d=0.37) to extremely small (the Hamilton anxiety scale, effect size: d=0.06). In practical terms, a difference of 1.7 points on the Hamilton anxiety scale and 1.1 points on the Hamilton depression scale are not clinically meaningful. Thus, despite Dr. Kruszewski's assertion, we would have been remiss to conclude that the placebo group was more symptomatic than the treatment group before the initiation of treatment. He also notes that the baseline Hamilton depression scale and Hamilton anxiety scale scores were not the same as the week-0 scores in Figure 1 on page 148, which shows the course of symptoms over 8 weeks of treatment. This difference is because the subjects' baseline assessment was not on the same day as their week-0 random assignment. The subjects were assessed at baseline to determine inclusion into the study. As is typical of medication studies, they were again assessed with the outcome measure at week 0 (the day of random assignment). The week-0 Hamilton anxiety scale scores shown in Figure 1 demonstrate that

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-