an exacerbation. Inpatient units and emergency rooms were used as recruitment sites.

2) Other symptoms were significantly reduced, perhaps facilitating test-taking ability.

3) Entering a clinical trial is often associated with clinical improvement. Expectation and enhanced clinical care may contribute.

4) Prior drug therapy may have had an adverse effect on cognition, and study drugs had less adverse effect (3).

5) Practice effects causing improved scores on later test administration (4).

6) Industry-sponsored studies tend to report more favorable effects of drug treatment.

7) Missing data from attrition of subjects may bias observations to the best cases.

The data presented give emphasis to the lack of meaningful cognitive enhancing efficacy of these "atypical" antipsychotic drugs. The authors' interpretation of a significant drug-caused improvement is not compatible with the study design that did not include a comparison group. Other potential causes appear more compelling as explanations for the modest improvement in test scores.

To test an efficacy hypothesis for cognition in schizophrenia, there is a consensus design intended to control for pseudospecific causes of improved cognition (5).

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WILLIAM T. CARPENTER, M.D.
ROBERT R. CONLEY, M.D.
Baltimore, Md.

Dr. Carpenter has served as a consultant to AstraZeneca, Eli Lilly, Cephalon, and Solvay/Wyeth. Dr. Conley has served as a consultant to AstraZeneca, Eli Lilly, Janssen, Johnson and Johnson, and Wyeth.

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Dr. Keefe and Colleagues Reply

TO THE EDITOR: Thank you for the opportunity to clarify our recent article published in the *Journal*. We are grateful that interest in cognitive problems associated with schizophrenia, and how to treat them, has attracted broad attention in the field of schizophrenia research, including from experts in phenomenology and psychopharmacology such as Drs. Carpenter and Conley.

We are happy to report that we agree with Drs. Carpenter and Conley on almost all of the points they have made, although we were somewhat perplexed about the intention of their letter, since we made these points in our article. In fact, of the seven "causal explanations" they raise for the cognitive improvement found with the treatments that we tested, we discussed six in detail. The sole exception was their statement that industry-sponsored studies tend to report more favorable effects of drug treatment. We declined to discuss this important issue in our article because none of the effects we reported were particularly favorable. We repeatedly referred to treatment effects as "modest" and stated that "the amount of cognitive change we report here is consistent with what may be expected from practice effects and placebo effects" (p. 1069). In fact, we discussed in this article and other recent publications (1) that the small improvements found with atypical antipsychotics cannot be distinguished from practice or placebo effects (2) and atypical antipsychotics may even impair some cognitive functions (3). For all these reasons, we certainly do not feel that we have overstated the positive cognitive benefit of atypical medications.

Drs. Carpenter and Conley criticize the design of our study because it only included three antipsychotic treatments and did not include control conditions such as a typical antipsychotic or placebo treatment group. We did not feel the necessity to repeat previous first-episode studies that compared risperidone and olanzapine with haloperidol (4, 5). Our primary aim was to compare the cognitive efficacy of atypical drugs in first-episode patients, which had not been done previously. The inclusion of a fourth treatment with a typical antipsychotic would have required a reduction in the sample size for the other treatments and thus a loss of statistical power. In addition, our perspective at the time the study was designed (prior to the Clinical Antipsychotic Trials of Intervention Effectiveness results [6]) was that treatment with a typical antipsychotic raised ethical questions and was not relevant because of the tiny percentage of first-episode patients who in practice receive typical antipsychotics. The suggestion of treating first-episode patients with placebo in an antipsychotic trial continues to be ethically objectionable to us.

Drs. Carpenter and Conley also raise the question of whether the effect had "clinical importance." First, their letter cites the weak relationship between cognitive improvement and changes in quality of life at 12 weeks. As stated in our article, we feel that it is unwise to emphasize these correlations because it is unlikely that any cognitive benefit or worsening will precipitate changes in functional outcomes in such a short period of time. Surprisingly, Drs. Carpenter and Conley ignore our data from the truer test of the relationship between cognitive change and functional change, which was after 52 weeks of treatment. These correlations were between 0.22

and 0.36, within the range of a medium effect size (7), which is the traditional criterion for clinical importance (7). Thus, we stand by our conclusion that these cognitive changes "may be clinically relevant" (p. 1068). However, as we stated in our article, "interpretation of this relationship is tempered by analyses indicating that symptom change and baseline cognitive scores also predicted the variance in functional outcomes. Thus, cognitive improvement may be a part of a general treatment response that is associated with improved functional outcomes" (p. 1068).

In summary, we do not see substantial differences between the concerns raised by Drs. Carpenter and Conley and our views about the study design and modest treatment effect. We certainly agree with their major point, which we tried to make clear in our article, in that our ability to improve cognition in schizophrenia remains very limited and we cannot, as a field, accept the modest improvement in cognitive test performance that atypical medications provide as satisfactory. We need to redouble our efforts to discover and evaluate new treatment options to improve cognition and functional outcomes in schizophrenia patients. This will be the best way, and probably the only convincing way, to move beyond worries about whether the modest cognitive changes of the level we reported are powerful enough to have "clinical relevance" and are more than what might be attributed to practice and placebo effects.

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RICHARD S.E. KEEFE, PH.D.
Durham, N.C.
JOHN A. SWEENEY, PH.D.
Chicago, Ill.
HONGBIN GU, PH.D.
ROBERT M. HAMER, PH.D.
DIANA O. PERKINS, M.D.
Chapel Hill, N.C.
JOSEPH P. MCEVOY, M.D.
Butner, N.C.
JEFFREY A. LIEBERMAN, M.D.
New York, N.Y.

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Hyperammonemia and Valproic Acid-Induced Encephalopathy

TO THE EDITOR: We read with great interest the thought-provoking clinical case conference by Russell B. Carr, M.D., and Kerrie Shrewsbury, M.D., in the July 2007 issue of the *Journal* describing the difficulty in predicting hyperammonemia-induced encephalopathy. The authors stated that "hyperammonemia occurs at both therapeutic and supratherapeutic concentrations of valproic acid, implying that other factors often influence the development of symptomatic hyperammonemia" (1, p. 1022). We propose that increased free valproic acid levels in the presence of normal total levels might be an unidentified factor that may mediate hyperammonemia as well as valproic acid-induced encephalopathy.

The importance of monitoring free valproic acid levels has been described in several single-case and case-series reports and deserves more systematic research. A high free valproic acid level with a normal total valproic acid level has been described when both valproic acid and aspirin were taken (2). The relationship between free and total valproic acid was shown to be linear when the total valproic acid level was in the lower therapeutic range (r=0.68) (3). However, free fraction of valproic acid increases nonlinearly at higher total valproic acid levels. Similarly, Henriksen et al. (4) found nonlinear increases of free valproic acid above the recommended therapeutic total valproic acid range when protein binding sites were saturated. Using available data from Buchanan and Ponniah (5), Figure 1 demonstrates an exponential increase in free valproic acid with increased concentration of total valproic acid ($7.4 \times e^{0.0035}$, $R^2=0.93$). This exponential relationship shows a stronger fit than the linear relationship noted by Roman et al. (3) (r=0.68 vs. $R^2=0.93$).

Upon valproic acid binding site saturation on albumin, subsequent incremental changes in total valproic acid may cause disproportional increases in free valproic acid. This may play a significant role in adverse effects, particularly when other drugs that might inhibit valproic acid metabolism are also administered (2). We agree with Drs. Carr and Shrewsbury that polypharmacy and malnutrition are among the most likely risk factors for hyperammonemia. Under