in the mesolimbic or mesocortical tracts, leading to an improvement in tardive psychosis.

On the other hand, clozapine, in comparison with typical antipsychotics, may not be more efficacious for new-onset schizophrenia because these patients have not been medicated previously and do not have dopaminergic upregulation that can be reversed.

Although this explanation may not be the whole story (for example, clozapine probably also has direct therapeutic effects through the D_2 or other receptors), it is a parsimonious interpretation of these data, and it suggests ideas that can be tested empirically.

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DAVID E. ROSS, M.D.
Midlothian, Va.

Schizophrenia, Syndrome X, and Omega-3 Fatty Acids

TO THE EDITOR: In an interesting study, Martina C.M. Ryan, M.B., M.R.C.Psych., et al. (1) found an increased prevalence of impaired glucose tolerance and insulin resistance in patients with drug-naive, first-episode schizophrenia in relation to healthy comparison subjects. This finding is in line with the results of a recent review showing that features of the metabolic syndrome X are more common in subjects with schizophrenia than in the general population (2). Dr. Ryan and colleagues discussed the influence of diet (1), but we believe that they omitted the possible role of polyunsaturated fatty acids of the omega-3 and omega-6 series, in particular, eicosapentaenoic acid and arachidonic acid. Substantial evidence suggests that impaired polyunsaturated fatty acid metabolism is related to both schizophrenia and the metabolic syndrome X. In recent reviews, low consumption of omega-3 polyunsaturated fatty acid was concluded to be associated with hypertriglyceridemia, cardiovascular disease, and probably also to insulin resistance and type 2 diabetes (3–5). Of interest, lowered omega-3 polyunsaturated fatty acid levels have also been reported in the erythrocytes of drug-naive psychotic patients (6) and in medicated young schizophrenic patients in comparison with normal comparison subjects (7). Furthermore, placebo-controlled trials have found eicosapentaenoic acid to be effective in schizophrenia, depression, and borderline personality disorder (8–10).

We believe that randomized, controlled trials are warranted to test whether supplementation with long-chain omega-3 polyunsaturated fatty acid, such as eicosapentaenoic acid, can improve the symptoms of schizophrenia and prevent the development of features of the metabolic syndrome X in subjects with schizophrenia.

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FRANÇOIS POUWER, PH.D.
RITSAERT LIEVERSE, M.D., M.SC.
MICHAELA DIAMANT, M.D., PH.D.
JOHANNA ASSIES, M.D., PH.D.
Fatty Acids in Diabetes, Depression, and Schizophrenia Study Group
Amsterdam, the Netherlands

Aripiprazole for Acute Bipolar Mania

TO THE EDITOR: The double-blind, randomized, placebo-controlled trial of Paul E. Keck, Jr., M.D., et al. (1) suggests that aripiprazole is effective and safe for acute bipolar episodes—mania and mixed. We consider that careful scrutiny of the methodology and the results of this study are worthwhile before integrating the study results into clinical practice.

The study incorporated patients whose mania was below 4 weeks' duration and excluded those with prior nonresponse to clozapine. Although the authors did not use a duration criterion for mixed affective episode, considering the unique pharmacodynamic properties of aripiprazole, it is unclear why such an exclusion of patients with severe and refractory mania was considered. In this study (1), there seems to be less uniformity in assessing the severity of psychopathology. While manic symptoms were quantified with the 11-item Young Mania Rating Scale (2), the measurement of severity of

depression was performed with a single item of the Clinical Global Impression scale (bipolar version) (3). Because about one-third of the study participants had a mixed affective episode at inclusion and because improvement in depression was an outcome measure, use of a more quantifiable scale to quantify depression, e.g., the Hamilton Depression Rating Scale, could have made efficacy analysis balanced and more meaningful.

Another issue of concern is assessment variations. Although the authors attempted to control the effect of intercentric assessment variations by loading study centers as a covariate in analysis of covariance, which we consider an indirect way of addressing interrater reliability, they failed to address the details of intracentric assessment. Considering that this is a multicentric study, such a description of intracentric assessment variations, if any, is important for interpretation of the results. In this study (1), use of analysis of covariance to control the effect of baseline psychopathology is not adequately justified (1), as there was no mention that baseline psychopathological scores differed significantly between groups. A further issue, under the safety analysis section, the authors could have provided the details (mean dose and pattern) of anticholinergic medication use.

The high attrition rate observed in both groups (79% in the placebo group and 58% in the aripiprazole group) was the main limitation of this study and hinted that the study findings were only preliminary evidence of aripiprazole's antimanic property. Thus, further studies are needed to arrive at a robust conclusion regarding the benefits of aripiprazole in acute bipolar—mania and mixed—episodes.

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KARUPPIAH JAGADHEESAN, M.B.B.S., M.D.
DAVID MUIRHEAD, M.B.B.S., F.R.A.N.Z.C.P.
Broadmeadows, Victoria, Australia

Typical Versus Atypical Antipsychotics

TO THE EDITOR: Stefan Leucht, M.D., et al. (1) concluded their meta-analysis by comparing the difference in relapse rates between atypical and typical antipsychotic agents to that produced by aspirin in preventing vascular events. But this comparison does not support the widespread use of atypical antipsychotics. A year's supply of enteric-coated aspirin costs less than $10 and reduces the risk of fatal or disabling myocardial infarction and stroke by 8% per year. A year's supply of an atypical agent costs thousands of dollars more than a typical agent, but when compared to a typical agent, it reduces the risk of psychotic relapse by 8% per year.

This is not to diminish the impact of psychosis nor does it serve as an argument for reducing expenditures for those with serious mental illness. Rather, it questions whether the billions of dollars currently spent on atypical antipsychotics might not produce a greater reduction in mortality, morbidity, and misery if spent on more robust interventions, such as assertive community treatment or supported employment and adequate housing. Perhaps providing atypical antipsychotic medication to a population that is 85% unemployed, has 10–20 times higher rates of homelessness, 8–10 times higher rates of criminal justice involvement, and 2–3 times higher rates of substance abuse is more like "giving an aspirin" than the authors had intended.

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DANIEL LUCHINS, M.D.
Chicago, Ill.

The Nature of Traumatic Memories

TO THE EDITOR: Ruth A. Lanius, M.D., Ph.D., et al. (1) claimed that the differences they found in brain connectivity between subjects with posttraumatic stress disorder (PTSD) and comparison subjects "may account for the nonverbal nature of traumatic memory recall of PTSD subjects, compared to a more verbal pattern of traumatic memory recall in comparison subjects" (p. 36). This statement would seem to imply that there could be a difference between traumatic and other memory. It is questionable, however, whether responses provoked by reading a script to subjects would permit conclusions about "memory" in the usual sense.

Furthermore, the authors reported that the 11 subjects with PTSD collectively had nine comorbid axis I diagnoses and that five had current nicotine abuse, while their comparison subjects had no such conditions. The authors' failure to control for this factor in their analysis suggests strongly that their conclusions are not legitimate with respect to memory. The predominance of differences in frontal and limbic regions makes it seem far more likely that their results reflect differences in emotional arousal, which is not surprising given the axis I characteristics of their PTSD subjects. Such responses hardly constitute proof of a difference in memory.

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HARRISON G. POPE, JR., M.D.
Boston, Mass.

Dr. Lanius Replies

TO THE EDITOR: I thank Dr. Pope for addressing the issues of the script-driven imagery symptom provocation paradigm as a means of examining memory recall and the influence of comorbid conditions on the results of our functional connectivity study with PTSD patients.

The script-driven imagery symptom provocation paradigm has been a standard and well-established symptom provoca-