triguing new evidence that only some hippocampal neurons are affected in schizophrenia (4, 5). Pathology in a subpopulation of hippocampal neurons could remain undetected with the study design of Ms. Walker et al.

Second, the fact that the photographic images of brain slices, but not the histological preparations, revealed smaller hippocampal volume in schizophrenia is intriguing. The histologically defined volume estimates included only the cell-containing regions, whereas the volume estimates derived from photographic images included adjacent tissue as well. Ms. Walker et al. interpreted this as evidence for changes of the parahippocampal gyrus to strengthen their argument that isocortical but not allocortical structures of the medial temporal lobe are abnormal in schizophrenia. However, an alternative explanation seems more likely: the tissue adjacent to the cell-containing regions that is reduced in volume in schizophrenia is the hippocampal white matter, which cannot be distinguished easily from hippocampal gray matter on unstained brain slices. A decrease of white but not gray matter volume and normal total number of all subpopulations of hippocampal neurons is exactly the finding of the only other stereological study of the hippocampus in schizophrenia (6).

It seems that the study by Ms. Walker et al. provides further evidence for a subtle abnormality of the hippocampus in schizophrenia, possibly leading to a disconnection of the hippocampus from isocortical modules in the frontal and temporal lobes.

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A Mood Stabilizer With Risperidone or Haloperidol for Mania

TO THE EDITOR: We read with great interest the article by Gary S. Sachs, M.D., and his colleagues (1). They compared the efficacy of a mood stabilizer in combination with placebo, haloperidol, or risperidone in the treatment of acute mania. The authors concluded that risperidone and haloperidol were equally efficacious as adjuncts and more efficacious than a mood stabilizer alone. The validity of this study can be criticized on the grounds of use of a placebo arm, the selection of patients, and improper random assignment and blinding.

The use of a placebo arm remains a highly controversial issue from an ethical point of view and has been addressed in the Declaration of Helsinki. It states that the patients in a study should "be assured of the best proven diagnostic and therapeutic method," even in the control group (2). This clearly implies that a placebo should not be used as a control when superior existing treatment is available. It can be argued that existing studies of combination therapy in acute mania, several published treatment guidelines, and the widespread accepted use of combination treatment among our colleagues support the opinion that a mood stabilizer with an antipsychotic is the best treatment available to date. We, therefore, suggest that it might have been more relevant to omit the placebo group and compare the efficacy of a mood stabilizer in combination with a variety of different antipsychotics. After all, as Hill pointed out in 1963 (3), the key point is how a new treatment compares with existing treatment rather than whether it is better than nothing.

The clinical relevance of this study can be criticized on the basis of the selection of patients. The issue of selection of patients for randomized controlled trials is controversial and has been addressed in the Consolidated Standards of Reporting Trials (CONSORT) guidelines (4). This state that all patients assessed for a trial must be accounted for and recommends the inclusion of a diagram that explains the outcome for every patient involved in the trial (4). In the study in question, the information about recruitment of the subjects is lacking. We do not know how many subjects were initially assessed, how many subjects were excluded, and the reasons for exclusion. The information regarding the participation rate and the response rate has implications for generalizability and future research.

Ensuring that random assignment of patients to intervention groups is achieved is vital in eliminating the introduction of allocation and confounding bias to a trial. The authors did not describe the method of random assignment or concealment, although the CONSORT guidelines states that this information should be clearly reported. It has been reported that studies that use poor or unclear concealment compared with those that conceal appropriately may give a higher estimate of treatment effect (4). In the absence of adequate information on random assignment, this raises the possibility of allocation bias in the present trial.

Haloperidol causes marked extrapyramidal side effects, which can easily render investigators unblind. We question, therefore, whether the investigators really were blind to treatment. It has been found that trials that are not double blind yield larger estimates of treatment effect than trials in which the authors specify double blinding (5).

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To the Editor: Dr. Sachs et al. conducted a 3-week double-blind, randomized, placebo-controlled study of risperidone or haloperidol augmentation of a mood stabilizer in bipolar patients with a current manic (N=123) or mixed (N=33) episode. They found that the antipsychotic drugs conveyed benefits in patients with mania but not in those with mixed illness. From my experience, the latter finding is hard to accept. I suggest that it arose because the authors did not examine early benefits with antipsychotic drugs and/or used insensitive measures to assess treatment gains.

With reference to the former possibility, the authors compared treatment gains at the 3-week endpoint but not, for instance, during the first week; this is not a trivial issue because every additional day that a patient is disturbed adds to the risk of illness-related harm to the self or environment. With reference to the latter possibility, the authors did not examine whether nonviolent self- and environment-damaging acts resulting from impaired judgment were reduced by antipsychotic augmentation. If the sizes of individual groups were too small for analysis, the drug groups could have been combined to determine whether antipsychotic treatment, per se, is helpful early or otherwise during a mixed episode.

Of note, if the authors are right that risperidone or haloperidol augmentation of mood stabilizers is unhelpful in mixed illness, then olanzapine augmentation may be worth considering. Tohen et al. (1) found that olanzapine attenuated both manic and depressive symptoms and that the gains were greatest in valproate-treated patients with mixed illness.

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Traffic Accidents and Friday the 13th

To the Editor: A recent article in the *Journal* by Simo Näyhä, M.D., Ph.D. (1), is of interest. However, there is clearly an error in the interpretation of the data. The national cause-of-death files of Finland provided information on deaths due to traffic accidents, but no distinction was made in the article between the day of the accident and the day of the death. It is highly likely that many of the people who died on Friday the 13th due to a traffic accident were actually injured before that day. Therefore, the main conclusion drawn in the article—namely, that women are more prone to having a fatal traffic accident on Friday the 13th than on other days of the year—may be false. On the other hand, it would still be valid to conclude from the findings that women who have been in a traffic accident are more prone to die on Friday the 13th than on other days. If so, then superstition could be having an effect on the vital bodily functions of women rather than on women's behavior in traffic.

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Dr. Näyhä Replies

To the Editor: I thank Dr. Smith for his comments. Some of the women who died on Friday the 13th were, of course, injured some days previously. This would not invalidate my argument. It is sufficient that in some proportion of the cases, the accident and the death occurred on the same day. During the 1970s, 75% of the people killed as a result of traffic accidents in this country died at the scene of the accident or en route to the hospital (1), and an additional proportion died in the hospital on the same day. The percentage of more or less immediate deaths may have declined now because of improved emergency services, but more recent data are difficult to come by. In Denmark, where distances are short, 68% of the persons who died in traffic in 1986–1991 were dead upon arrival at the emergency unit, and 88% died within the first day (2). Comparable proportions of quick deaths in this case would be sufficient to provide a sound basis for the conclusion reached in my article.

The suggestion that superstition-related anxiety might cause a degradation in vital bodily functions is interesting but would presuppose a higher risk due to Friday the 13th in older age groups than in younger ones. A reanalysis of female deaths broken down into the age bands of 15–34, 35–54, 55–74, and ≥75 years showed risk ratios of 2.51 (95% confidence interval [CI]=1.45–4.36), 1.26 (95% CI=0.59–2.70), 1.32 (95% CI=0.74–2.36), and 1.36 (95% CI=0.54–3.44), respectively. Since an elevated risk was more typical of young women who have less driving experience, an explanation based on driving errors would seem more likely.

Possible flaws, listed in the article, include deaths of passengers, who obviously cannot be part of the causal chain, and it is also difficult to see why drivers (men or women) beset by this superstition would select women as their victims. Dr. Smith presents an additional problem that cannot be solved without a large study linking accidents to subsequent deaths. So far, any explanations must remain speculative.

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