chosen the wrong drugs at an improper dose to emphasize the importance of the *5-HTR$_{2A}$* polymorphism (pharmacodynamics) against an enzyme polymorphism (pharmacokinetics).

There is a growing body of evidence that the consideration of pharmacokinetics can improve antidepressant or antipsychotic pharmacotherapy with regard to efficacy and safety. While reading the article, my clinical colleagues had the impression that pharmacokinetics is of little or no importance. However, the truth is that in many cases, genetics contribute only partially—and sometimes only to a small extent—to pharmacokinetics.

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Drs. Murphy and Schatzberg Reply

TO THE EDITOR: We appreciate Dr. Härtter's comments on our finding that the *CYP2D6* genotype had no effect on the efficacy or tolerability of paroxetine or mirtazapine. He asserts that a difference would not be expected between *CYP2D6* genotype groups at a 40 mg/day dose of paroxetine but that an effect would be apparent had we used a lower dose. However, all paroxetine-treated patients received 20 mg/day of this medication for 2 full weeks. There were no significant differences between the *CYP2D6* genotype groups in patients receiving 20 mg/day of paroxetine.

Dr. Härtter questions the role of *CYP2D6* in the metabolism of mirtazapine. Stormer and colleagues (1) reported a significant role for *CYP2D6* in the metabolism of mirtazapine. Furthermore, Kirchheiner et al. (2), who presented dosing guidelines for many antidepressants based on *CYP2D6* genotypes, recommended additional research on the impact of *CYP2D6* polymorphisms on mirtazapine.

Dr. Härtter considers it "wrong" to study the effects of *CYP2D6* genetic variation on paroxetine treatment outcomes. However, as he notes, there is ample support for the role of *CYP2D6* in the metabolism of this medication. In addition, Kirchheiner and colleagues (2) recommended major reductions in paroxetine dosing in *CYP2D6* poor metabolizers. We found no support for these recommendations.

Dr. Härtter states there is growing evidence that consideration of pharmacokinetics can improve psychotropic efficacy and safety. Actually, the relevance of cytochrome enzymes to clinical psychiatry has been debated for a number of years without resolution. One reason for this continuing controversy is the paucity of prospective pharmacogenetic outcome data from well-designed clinical trials. We believe that our study was the first in psychiatry to actually test prospectively the role of the *CYP2D6* genotype on clinical outcomes by using two widely prescribed medications and a statistically meaningful group size.

Finally, we agree with Dr. Härtter that pharmacokinetic considerations can be important in certain clinical settings, but our data indicate that pharmacokinetic variation due to the *CYP2D6* genotype should not be a major concern for clinicians during monotherapy with paroxetine or mirtazapine. It is possible that complex interactions may occur between concurrently administered *CYP2D6* substrates and inhibitors and that these interactions may be affected by the *CYP2D6* genotype. However, we found no such interactions between the *CYP2D6* genotype and concurrent medications that affected paroxetine or mirtazapine outcomes. We noted that our results may not apply to other medications, and we hope there will be additional prospective pharmacogenetic trials with other antidepressants.

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Untreated Depression and Hippocampal Volume Loss

TO THE EDITOR: In their retrospective study of 38 women, Yvette I. Sheline, M.D., et al. (1) reported that reduction of hippocampal volume was significantly correlated with lifetime number of untreated days depressed. There was no significant correlation of "hippocampal volume loss" with lifetime number of treated days depressed. Their key conclusion was that "antidepressants may protect against hippocampal volume loss associated with cumulative episodes of depression" (p. 1517). These claims are tenuously based and are subject to serious reservations.

The small, unrepresentative study group and the retrospective design permit no general conclusion about protective antidepressant drug effects on the hippocampus in major depression. There is also no preclinical basis for such speculation. The authors tried to claim such a basis by reference to a preclinical study of the agent tianeptine (2). They misled readers in stating, "Animal studies have shown antidepressants to protect against stress-induced decrease in neurogenesis with preservation of hippocampal volume during a social stress paradigm" (p. 1518). The cited study of social stress in tree shrews (2) examined no standard antidepressant agents. Tianeptine is not an accepted antidepressant agent. Placebo-controlled trials of its antidepressant efficacy are scarce (3), and its primary action is opposite to that of the antidepressant drugs that block monoamine membrane transporters. Functionally, tianeptine and fluoxetine have very different

acute interactions with stress effects on hippocampal physiology (4) and opposite effects in behavioral pharmacology testing after long-term administration (5). In a chronic restraint stress model with rodents (6), fluoxetine does not possess the protective effect of tianeptine against dendritic atrophy in the hippocampus. In the tree shrew, social stress model, clomipramine has some protective activity similar to tianeptine (7), but it is a safe bet that none of the patients of Dr. Sheline and colleagues was treated with that drug. The authors lack a coherent preclinical case for their speculation, and what they proffer is misleading.

Questions arise also about the statistical analyses. The first rule of statistical analysis is to inspect the distribution of the data. When that is done, it is immediately obvious from Figure 1 that a group of four outliers with deviant low hippocampal gray matter volumes was responsible for the apparent statistical significance found in the entire group. A straightforward, conservative, nonparametric median split analysis of the data for the remaining 34 subjects reveals no association of hippocampal volume with days of untreated depression (χ^2=1.06, df=1, p=0.30, with Yates's correction). No amount of multivariate statistical modeling will overcome this problem. The authors clearly overinterpreted the data. They are also guilty of a logical fallacy when they speak of "hippocampal volume loss" because only by a prospective design can they measure loss of hippocampal volume.

It is common knowledge that investigators will engage in wishful thinking, even to a point of losing objectivity about their cherished hypotheses. Journal reviewers and editors are responsible for detecting such pathologies of scientific thought. The field is not advanced when a weak clinical data set is overinterpreted, along with a positively misleading preclinical rationale to promote a currently popular theory.

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Dr. Sheline and Colleagues Reply

TO THE EDITOR: In his letter, my distinguished colleague Dr. Carroll states that there can be "no general conclusion about protective antidepressant drug effects on the hippocampus in major depression." We agree but note that we did not state such a conclusion; we argued simply that our clinical data are consistent with preclinical studies showing protective effects of antidepressants in the hippocampus. In addition, a recent study (1) showed increases in hippocampal volume after 9–12 months of treatment with paroxetine in patients with posttraumatic stress disorder and provides further support for the possibility that antidepressants are protective of hippocampal volume in anxiety disorders and depression.

Dr. Carroll questions the preclinical work that we cited, stating that the authors have "misled readers" by citing a study of social stress in tree shrews by Czeh et al. (2001), which "examined no standard antidepressant agents. Tianeptine is not an accepted antidepressant agent." This is simply incorrect. Tianeptine is a well-accepted antidepressant commonly used in Europe with demonstrated efficacy in both placebo-controlled and active comparator studies (2, 3). Fluoxetine also has been shown to have neuroprotective effects; with the inescapable shock paradigm, fluoxetine prevented stress-induced cell decreases in the hippocampus (4). Whether tianeptine and fluoxetine have different effects on hippocampal physiology and behavioral pharmacology does not preclude both from protecting against stress-induced cell loss.

Dr. Carroll questions our data analysis, stating that we should have removed four data points in our regression analysis. It is troublesome to label 10% of the study group as "deviant." Moreover, by visual inspection, why the four points below the fitted line, rather than the three above, with the longest days of untreated depression were considered "deviant" by Dr. Carroll is not clear. We agree that 38 is a small group size. However, we point out that this size is large enough to have 80% power to detect a correlation coefficient of 0.42 with a two-tailed 5% significance test. The product moment correlation coefficient is relatively robust to deviations from normal distributions but sensitive to nonlinear association and unequal variances around the line (5), neither of which is evident here. Spearman's rank correlation coefficient, which is not affected by outliers, again demonstrates the robustness of our findings (r_s=–0.48, df=36, p=0.003). Furthermore, it is not appropriate to arbitrarily dichotomize outcomes for the purposes of analysis. It is well known that there is a consequent loss of power (6). Thus, Dr. Carroll's post hoc analysis of our chi-square test data and the finding that it was not significant may reflect his use of an inadequately powered test rather than suggesting a change in our conclusion.

Finally, we agree that we could have said that "lower" hippocampal volumes were associated with duration of untreated depression, but the conclusion would still have been that antidepressants *may* have a neuroprotective effect. To fully establish this effect would require not only prospective studies but randomized clinical trials with a long follow-up. The findings here provide testable hypotheses as well as pilot information to guide the design of such studies.

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