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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Benzodiazepines Versus Antidepressants for Panic Disorder

TO THE EDITOR: Steven E. Bruce, Ph.D., et al. (1) suggested that despite current practice guidelines, benzodiazepines are being used more frequently than selective serotonin reuptake inhibitors (SSRIs) to treat panic disorder. One possible explanation for this discrepancy is that some physicians are prescribing benzodiazepines as needed for patients who experience infrequent panic attacks. (I can offer only anecdotal evidence drawn from working with dozens of physicians in emergency rooms and psychiatric and general/family medicine settings.) I would argue that this approach is reasonable because these patients only need to take a benzodiazepine periodically rather than having to take an SSRI every day for at least a year (according to APA recommendations [2]). The obvious advantages of this regimen are its lower cost and less frequent side effects. The disadvantage, many would argue, is that periodic use of benzodiazepines can escalate into physical dependence and abuse (2). However, this argument is based somewhat on myth because there are "no data to suggest that long-term therapeutic use of benzodiazepines by patients commonly leads to dose escalation or recreational abuse" (3).

Although I have suggested that there may be a place for the first-line use of benzodiazepines for the treatment of panic disorder, there are some circumstances in which I would argue that SSRIs should be the first-line treatment. For example, there is some evidence that patients with comorbid substance-related disorders are more inclined to abuse prescribed benzodiazepines; therefore, they may benefit from a treatment regimen that involves SSRIs (2). Another population that would clearly benefit from SSRIs are patients with comorbid major depression. Also, patients with frequent panic attacks may benefit from the prophylactic effect of regular use of SSRIs, rather than the symptom control that would be garnered by a benzodiazepine taken after the onset of panic symptoms.

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TO THE EDITOR: A recent study by Dr. Bruce et al. reported that "Despite efforts aimed at increasing the use of SSRIs in patients with panic disorder (e.g., APA's practice guideline for panic disorder, Food and Drug Administration approval of particular SSRIs for the treatment of panic disorder), only a modest increase in their use was found" (p. 1432). Benzodiazepines were found to be the most commonly used medications for panic disorder.

This statement and the findings bring up several questions. One of them is, how much are we all under the influence of the pharmaceutical industry? Who is making the greatest effort to use SSRIs, originally categorized or miscategorized as antidepressants, for anxiety disorders? Certainly the pharmaceutical industry is. Should we ignore the response of the market—i.e., in spite of all the more or less scientific evidence—that benzodiazepines are liked and considered effective, efficacious, and well tolerated by patients with anxiety disorders and their physicians? Benzodiazepines have been found to be effective in the treatment of various anxiety disorders (a review of the evidence is beyond the scope of this letter), and some of them have also been approved by the Food and Drug Administration for the treatment of panic disorder (e.g., alprazolam). During the treatment of panic disorder, many clinicians have found benzodiazepines useful in various situations, including breakthrough panic anxiety and fear of flying, and only when needed. Certainly, benzodiazepines have disadvantages, namely, the physiological dependence potential. Nevertheless, SSRIs have also several disadvantages (mentioned by Dr. Bruce et al.), and it is questionable whether they have the most favorable balance of efficacy and adverse effects for the treatment of panic disorder.

Each new product undergoes the process of reevaluation, at times a sobering one, after its initial enthusiastic use. SSRIs are no exception. They appear to have more problematic adverse effects than originally thought and observed. Also, as noted by Dr. Bruce et al., no large controlled comparison study has been conducted to examine the superiority of SSRIs over benzodiazepines for the treatment of panic disorder. Maybe the time for such a large study has come.

In the meantime, we should treat our patients with whatever is helping them the most. And we should also ask, along with Healy (1), "In contrast to other areas of business, do pharmaceutical corporations follow what the markets dictate, or like other corporations, can they shape the marketplace into which they sell their products?"