($p<0.10^{-34}$). A recent meta-analysis conducted by Geddes et al. (3) indicated a 70% reduction in relapse with antidepressant continuation compared with placebo substitution.

The public gets a biased view from consideration of only the acute data indicating adverse health consequences. Additionally neglected in media coverage are depression data indicating that antidepressants 1) increase neuroprotective factors (such as brain-derived neurotrophic factor) and neurogenesis, 2) protect against hippocampal volume loss, and 3) prevent stress from decreasing brain-derived neurotrophic factor in the hippocampus (4). Episodes of depression are overwhelmingly bad for peoples' lives, cognition, brain function and structure, medical health, and longevity. The more depressions one has, the worse most of these adversities get.

Each depressive episode is associated with decreases in brain-derived neurotrophic factor (in proportion to its severity) and increases in oxidative stress, glucocorticoids, and inflammatory cytokines (4). After every new depressive episode, there is an additional 10% risk of chronicity (failure to recover) (5). All of the many treatment guidelines of which I am aware recommend long-term prophylaxis after two or three prior episodes of depression.

Why are these facts rarely in the news? The media are so anxious to conjure up conspiracies by the pharmaceutical industry that they fail in what used to be their primary mission: to inform the public. Further, rarely mentioned in articles about publication bias are its historical roots, i.e., the Food and Drug Administration requiring only two positive trials and ignoring the number of failed trials and the reluctance of journals to publish articles with negative results.

As clinicians and academicians, we need to better educate our patients and the public. Depression is markedly undertreated in both the short- and long-term, and it is a figurative and literal killer. Moreover, everyone should consider long-term antidepressant prophylaxis after several serious episodes, as suggested by the guidelines. The risks are small and the potential benefits are enormous.

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This letter (doi: 10.1176/appi.ajp.2009.09020209) was accepted for publication in April 2009.

Placebo Effect in Depression

TO THE EDITOR: Drs. Mathew and Charney (1) provided a very informative commentary on publication bias and antidepressant efficacy. They made clear that the modest advantage of drug over placebo in reported clinical trials is reduced when unreported clinical trials are included in data analysis. The robust placebo response, particularly in less severely depressed subjects, deserves emphasis when considering clinical implications. A negative view is that the moderate effect size suggests that the advantages of drug treatment may not be worth the costs in many instances and antidepressant drugs should be more restricted to severe cases. An alternative view is that the placebo effect has substantial clinical benefit. Aspects of the placebo response may be associated with psychosocial therapeutics, but for many patients (e.g., primary care) prescription of antidepressant medication is the only effective means of providing the placebo effect (with whatever additional active drug effect may be present). The critical comparison for efficacy requires placebo, but the critical comparison for clinical effectiveness is a no-treatment control.

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This letter (doi: 10.1176/appi.ajp.2009.09030385) was accepted for publication in April 2009.

Potential Limitations in Generalizing Findings From the TORDIA Study

TO THE EDITOR: In the April 2009 issue of the *Journal*, David A. Brent, M.D., et al. (1) examined predictors of suicidal adverse events in the treatment of selective serotonin reuptake inhibitor (SSRI) resistant depression in adolescents. The authors found that adjunctive use of benzodiazepines in a small patient group (N=10 [3% of the total sample]) was associated with a higher rate of both suicidal and non-suicidal self-injury. They concluded that the disinhibitory effects of benzodiazepines may lead to increased risk-taking behavior. This finding was reiterated in an accompanying editorial (2).

We suggest that this finding in such a small subgroup more likely represents a selection bias. Patients with comorbid anxiety disorders who have a higher risk of suicidal behaviors (3) are more likely to require adjunctive pharmacological treatment. Benzodiazepines may also have been prescribed for high levels of distress or agitation in this subgroup, which would also lead to an increase in self-harming behaviors. Given the small sample size and lack of information about comorbid diagnoses, the authors' conclusion cannot be generalized to the population as a whole.

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This letter (doi: 10.1176/appi.ajp.2009.09050639) was accepted for publication in June 2009.

TORDIA: Unique Opportunity to Explore Half-Life Theory

TO THE EDITOR: Dr. Brent et al. (1) provided excellent detail about self-harm events during the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial. The authors observed that venlafaxine is associated with greater risk of self-harm in adolescents with higher than median suicidal ideation when compared with SSRI treatment. These results are consistent with theory and analysis put forth by myself (2) and others (3) indicating that risks of suicidal ideation/behavior in adolescent antidepressant trials correlate significantly with antidepressant half-life. I would like to request that the authors take advantage of TORDIA's unique data (randomizing to four antidepressants of substantially different half-life) by presenting rates, by individual antidepressant, of self-harm and suicidal adverse events in the total sample and among those participants with higher baseline suicidal ideation.

The antidepressant half-life theory predicts that a general pattern would be observed, i.e., venlafaxine would likely have the numerically highest event rates, paroxetine the next highest, etc. To maximize sample size, I would suggest combining participants receiving a specific antidepressant alone with participants receiving that antidepressant plus cognitive behavior therapy. However, caveats definitely exist. First, with only four medications, any relationship will almost certainly not reach statistical significance, even if suicidality risks rank in perfect register with the medication half-lives (unfortunately reported most consistently for adults, not adolescents). Second, while the Food and Drug Administration (FDA) meta-analysis found that fluoxetine had one of the lowest rates of suicidal ideation/behavior, its rates were similar to those for citalopram (4). For both these reasons, it would be interesting to also compare the rate of self-harm and suicidal adverse events of the combined participants receiving venlafaxine and paroxetine with the combined participants receiving citalopram and fluoxetine. Last, TORDIA might show a different pattern of risk by half-life because, in the FDA meta-analysis (4, p. 122–123), the rate of suicidal events with fluoxetine and citalopram peaked earlier in treatment than with paroxetine, and the TORDIA trial has the highest rates of self-harm early in treatment.

Despite these potential limitations, it is important to our patients that psychiatry continues to investigate whether a small but genuine increased risk of suicidal behavior exists early in antidepressant treatment and, if so, the ultimate biological mechanisms by which such risk occurs (and might be prevented). Exploring the antidepressant half-life theory in the TORDIA sample would be one important contribution.

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Dr. Smith receives grant funding from Forest Research Institute (affiliate of Forest Pharmaceuticals) for an unrelated project.

This letter (doi: 10.1176/appi.ajp.2009.09050601) was accepted for publication in June 2009.

Dr. Brent, Ms. Porta, and Dr. Emslie Reply

TO THE EDITOR: We thank Drs. Moore and Cooney for sounding a note of caution about generalizing from our finding that the use of benzodiazepines was associated with an increased risk of suicidal events and self-injury (1). Their concerns—that the number of participants who received benzodiazepines was small (N=10) and those who received benzodiazepine may have been treated for symptoms that also increased the risk for suicidal events—are valid. We did adjust for baseline differences between those who received benzodiazepines and those who did not, and our findings persisted. Nevertheless, we recognize the importance of being circumspect about drawing strong inferences from these findings. Perhaps it is useful to restate the concerns that we articulated in the Discussion: "The relationship between the use of benzodiazepines and the occurrence of self-harm events must be interpreted cautiously because of the small number involved, the heavy representation of just one site, and non-random assignment" (1, p. 424). As per our conclusion, we simply suggested "the need to re-evaluate the risk and benefits of…anti-