($p<0.10^{-34}$). 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.