The Black Box Warning: Decreased Prescriptions and Increased Youth Suicide?

To The Editor: The article by Robert D. Gibbons, Ph.D., et al., published in the September 2007 issue of the *Journal*, incorrectly analyzed the relationship between U.S. selective serotonin reuptake inhibitor (SSRI) prescription rates and suicide rates among children (1). Dr. Gibbons et al. indicated that there is a correspondence between a 22% decrease in prescriptions after warnings were issued by the Food and Drug Administration (FDA) and the 14% increase in youth suicide rates between 2003 and 2004. They concluded that decreases in prescriptions "were associated with increases in suicide rates in children and adolescents" (1, p. 1357). Unless carefully examined, Figure 1 and Figure 2 in their article create the same impression. However, the data show no such association. In the year in which suicide rates rose sharply, there was no significant drop in SSRI prescribing. This fact is only acknowledged in the Discussion section, where an attempt is made to explain away the inconvenient truth: "While only a small decrease in the SSRI prescription rate for U.S. children and adolescents occurred from 2003 to 2004, the public health warnings may have left some of the most vulnerable youths untreated" (1, p. 1359). The discussion then continues at length as though a clear association (if not causal relationship) has been established, with alarmist predictions regarding the consequences of decreased prescribing. As it turns out, preliminary figures are now available from the Centers for Disease Control (CDC), which show that fewer people under age 25 committed suicide in 2005 (when prescribing did decrease) than in 2004 (2).

In the editorial accompanying the article, James F. Leckman, M.D., and Robert A. King, M.D., noted that the authors cited several studies that agreed with their position, but no studies that reported neutral or opposite findings (3). There is no mention of the fact that the suicide rate was already declining before SSRIs were introduced. The 2004 suicide figures were compared simplistically with the previous year, rather than examining the change in trends over several years. The y axes were contracted to make trends appear more impressive and no data tables were provided, and thus it is difficult for readers to make their own calculations.

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SSRI Prescriptions and the Rate of Suicide

To the Editor: Dr. Gibbons et al. pointed to recent trends in SSRI prescriptions and the rate of suicide in young people to suggest that the FDA warnings have contributed to the increase in the number of youth suicides from 2003 to 2004. On the basis of their analyses, the authors predicted that if the recent expansion of the FDA black box warning to young adults decreases overall SSRI prescriptions by 20%, there would be an additional 3,040 suicides in the United States over a 1-year period.

The authors reported that the national SSRI antidepressant prescription rates declined between 2004 and 2005 for all age groups, except those ≥60 years. In light of these declines, it is instructive to compare the national number of suicides in 2004 (1) with recently available preliminary figures for 2005 (2), overall and within the relevant age strata. Between 2004 and 2005, the total number of suicides declined from 32,439 (2004) to 31,769 (2005). More specifically, the number of suicides declined for persons ages 25 to 44 (11,712 to 11,262), ages 15 to 24 (4,316 to 4,139), and ages 5 to 14 (285 to 270) (1, 2). These declines occurred despite decreasing overall SSRI prescriptions among these age groups reported by Dr. Gibbons et al. In terms of rates per 100,000, the suicide rate for all ages declined from 11.0 (2004) to 10.7 (2005). For ages 25 to 44, the rate of suicide declined from 13.9 to 13.4, and it declined from 10.3 to 9.8 for ages 15 to 24. For ages 5 to 14, the rate of suicide remained constant at 0.7 (1, 2). The ratio of preliminary-to-final all-age suicides was 0.968 in 2002, 0.973 in 2003, and 0.976 in 2004 (2).

The focus of Dr. Gibbons et al. on SSRI prescriptions may not have captured the full range of effects of the warnings on clinical practice. For example, the warnings were associated with an increase in prescriptions of non-SSRI antidepressants to youth as physicians searched for alternative treatments (3). The effects of the warnings on the use of antipsychotic medications and other psychotropic medications remain poorly defined. Detailed longitudinal analyses of various classes of psychotropic medications and psychotherapy would enrich our understanding of the various effects of the warnings on clinical practice.

We feel that it is risky to draw conclusions from limited ecologic analyses of isolated year-to-year fluctuations in antidepressant prescriptions and suicides. One promising epidemiological approach involves examining the associations between trends in psychotropic medication use and suicide over time across a large number of small geographic regions. Until the results of more detailed analyses are known, prudence dictates deferring judgment concerning the public health effects of the FDA warnings.

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Dr. Olfson has received research support from NIH, Substance Abuse and Mental Health Administration, Agency for Healthcare Research and Quality, American Foundation for Suicide Prevention, National Association for Research on Schizophrenia and Affective Disorders, New York State Office of Mental Health, Bristol-Myers Squibb, Eli Lilly, and AstraZeneca; he has also worked as a consultant for McNeil Pharmaceuticals, Pfizer, Janssen, Bristol-Myers Squibb, and Eli Lilly. Dr. Shaffer reports no competing interests.

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Withdrawal of Attention Rather Than Pharmacological Treatment Affects Suicide Rates in Depressed Children and Adolescents

TO THE EDITOR: Dr. Gibbons et al. concluded that regulators' suicidality warning on SSRI prescriptions to children and adolescents has caused a decrease in the use of antidepressants and subsequent increase in suicide rates among this age group.

However, instead of being due to the withdrawal of medication (i.e., SSRIs), the increase in suicidality may result from the withdrawal of attention that was previously provided in the context of pharmacological treatment. With pharmacological possibilities being restricted, patients are not only getting fewer pills but are receiving altogether less professional attention and care, contributing in turn to an increased suicide rate.

The plausibility of this alternative explanation is supported by two pieces of evidence. First, a decline in attention to pediatric patients with depression was reported by Libby et al. (1). In addition to a decrease in the number of patients receiving the diagnosis of depression, those diagnosed with depression received pharmacological treatment less frequently, while no alternative treatments were offered. Second, a favorable effect of placebo (i.e., attention) on suicidality was suggested when attempted suicide rates among young adults in a Veterans Health Administration (VA) study (2) were compared with rates from the FDA meta-analysis. Suicide rates among treated patients in the FDA and VA studies were remarkably similar (551 and 447 per 100,000, respectively), while rates in the placebo-treated groups in the FDA analysis were considerably lower than those of the untreated group in the VA study (447 versus 1,368 per 100,000). Attributing this difference to the recruitment of nonsuicidal patients to clinical trials is not very likely, given the similar suicide rates of the treated groups. The difference is more likely the result of the favorable effect of placebo among patients in clinical trials, from which the untreated VA patients could not benefit.

The warning issued with respect to the use of SSRIs has apparently not only led to a more cautious and judicial use of medication (as was intended), but also to a reduction in attention that was previously provided in the context of pharmacological treatment. It is the latter effect that may be responsible for the increase in suicidality and should be ideally reversed. It seems therefore necessary to clarify to treatment providers and treatment seekers that caution in prescribing SSRIs does not imply withdrawal of other forms of providing attention to depressed patients.

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Dr. Gibbons Replies

TO THE EDITOR: We would like to thank our colleagues for their thoughtful comments on our recent article and furthering the discussion on this critically important issue.

Dr. Jureidini suggests that we incorrectly concluded that decreases in prescriptions were associated with increases in suicide rates in children and adolescents. He notes that for the U.S. data, there was no significant drop in prescriptions in 2004, the last year for which suicide data in the United States were available at the time our study was published. However, our data reveal substantial decreases that already existed in 2004, particularly for new antidepressant prescriptions. As seen in Table 1, among U.S. children and adolescents ages 0 to 19, total SSRI prescriptions decreased by 1.3%, but new prescriptions decreased by 4.0%. Similarly, total serotonin-norepinephrine reuptake inhibitor (SNRI) prescriptions decreased by 3.3%, and new SNRI prescriptions decreased by 5.7%. Total tricyclic antidepressant prescriptions decreased by 5.0%, and new total tricyclic antidepressant prescriptions decreased by 7.1%. Decreases in new antidepressant prescription rates for the younger children (under age 15) were even larger (6.2% for SSRIs, 12.4% for SNRIs, and 9.6% for total tricyclic antidepressants). These data are further detailed in an online data supplement that has been appended to the original article in the September issue (http://ajp.psychiatryonline.org/cgi/content/full/164/9/1356/DC1).

Decreases in antidepressant prescriptions following the FDA's strong warning in March 2004 were reported throughout the remainder of 2004 (1, 2) using two different prescrip-

TABLE 1. U.S. Antidepressant Prescriptions for Children[a]

Medication Class and Subjects' Age Group	Prescriptions					
	Total			New		
	2003	2004	2005	2003	2004	2005
Selective-serotonin reuptake inhibitors						
0–10 years	1,348,763	1,291,558	1,073,617	701,146	639,752	540,159
11–14 years	1,993,159	1,972,751	1,709,407	1,086,382	1,037,757	910,602
15–19 years	4,104,780	4,084,250	3,696,134	2,203,322	2,153,836	1,989,946
Selective-norepinephrine reuptake inhibitor						
0–10 years	322,905	302,092	258,264	177,817	158,299	130,417
11–14 years	587,755	524,694	446,706	336,648	292,526	246,157
15–19 years	1,306,976	1,318,723	1,232,135	745,826	737,637	683,050
Tricyclic antidepressants						
0–10 years	656,035	600,956	511,876	345,548	307,910	261,098
11–14 years	543,925	510,733	450,406	277,669	255,677	222,791
15–19 years	576,192	575,658	533,555	303,302	297,433	274,134

[a] Annual U.S. antidepressant prescription rate data for 2003–2005, by zip code, were drawn from a random sample of 20,000 pharmacies (stratified by type, size, and region) from the 36,000 pharmacies in the IMS Health database (IMS Health, Plymouth Meeting, Plymouth, Pa.), which represents more than one-half of all retail pharmacies in the continental United States.

tion databases that provided monthly prescription-rate data. In the first prescription database (2), antidepressant prescription rates peaked in March 2004 and then dropped precipitously by 12.6%, in just one month after FDA's Public Health Advisory on March 22nd, and continued to decrease gradually throughout the remainder of the year. In the second prescription database (1), 20% decreases in antidepressant prescriptions from March 2004 to December 2004 were observed for children under age 18. In light of these findings, our overall comparisons between 2003 and 2004 underestimated the true effect of the FDA warning because they represent a combination of early increases in antidepressant prescriptions in the first 3 months of 2004 and decreases in the following 9 months of 2004. Furthermore, our analysis of the data from the Netherlands, where age-stratified data were available from 1998 to 2005 for both antidepressant prescription rates and suicide rates, identified a statistically significant inverse association between antidepressant prescription rates and suicide rates.

Dr. Jureidini also suggests that we neglected evidence that supports an iatrogenic or neutral effect of antidepressants on suicide. Our approach examined the potential net effect of antidepressants, the same standard that guides a risk-benefit analysis by physicians prescribing medication. Medications for cancer, diabetes, and heart disease may carry a risk of serious side effects and even death, but they may also save a lot more lives than they cost and are thus widely used. Moreover, we make no claim that antidepressant use is the only factor affecting youth suicide. Drug and alcohol use are well known risk factors, and their changing prevalence could partially explain some of the dramatic reductions in youth suicide rates that have occurred over the last decade; the limited changes in drug and alcohol use in recent years do not provide an explanation of the elevated youth suicide rates in 2004 (3). In addition, our own data as well as that of others have indicated that there is still some elevated risk for suicide attempts during the first month after SSRI treatment is started (4), and we agree with the FDA that this period is important for clinical monitoring.

Drs. Olfson and Shaffer consider it risky to draw conclusions from yearly changes in the suicide and antidepressant use data of two countries. We found the 14% increase in youth suicides from 2003 to 2004, along with sizable decreases in all antidepressant prescriptions, to be too large to ignore without commenting on the potential for early evidence of the effects of the FDA and European warnings. Drs. Olfson and Shaffer suggest that the FDA warnings could be associated with increases in non-SSRI antidepressant prescriptions. However, as described in our article as well as above, our data through 2004 do not support this contention. Indeed, the decreases that we observed for SSRIs are equal to or greater for SNRIs and total tricyclic antidepressants and even larger for new prescriptions than for total prescriptions. Decreases in SNRI and total tricyclic antidepressant prescription rates continue to parallel decreases found for SSRIs in 2005. Furthermore, in their study of one-half million adult depressive episodes, Valuck et al. (5) showed that primary care physicians were less likely to make diagnoses of depression when the warnings began, and those individuals who were diagnosed were less likely to receive antidepressant prescriptions. These changes were not associated with compensatory increases in psychotherapy or prescription of atypical antipsychotics; anxiolytics did increase slightly, but not sufficient to compensate for the decreases in antidepressants.

Drs. Olfson and Shaffer also point out that one promising epidemiologic approach involves examining trends between psychotropic medication use and suicide over time across a large number of small geographic units. We agree that this is a very useful approach to the analysis of low-base rate events, and it is precisely the type of county-level analysis that we first used to examine the association between antidepressants and suicide (6, 7), and it is also the type of statistical methodology that we introduced in the 2002 Institute of Medicine report "Reducing Suicide: A National Imperative" (8). Finally, Drs. Olfson and Shaffer refer to recently released preliminary suicide-rate data for 2005, indicating that suicide rates have not increased further from 2004 to 2005, and suicide rates in some age groups have actually decreased (9). This is an important observation and, if verified in the final CDC data, deviates from our predictions. However, and perhaps most importantly, the 14% increase in the suicide rate among children ages 5 to 14

seen from 2003 to 2004 is not reversed in the preliminary 2005 data, and therefore remains a serious public health concern. This lack of decrease in suicide rates in younger age groups contrasts with a continuing decline in suicide rates among individuals over age 60, who experienced an ongoing increase in prescription rates during the same time period. These data continue to indicate that the FDA black box warning has not led to a reduction in youth suicide, which would be expected if the risk of antidepressant treatment outweighed the benefit. Although antidepressant prescriptions further decreased in this age cohort from 2004 to 2005, the real question is whether the most severely ill children who are at greatest risk of suicide are receiving treatment for their illness. It is possible that changes in the overall population-level antidepressant treatment rate may not accurately reflect the rate of antidepressant treatment among those children at greatest risk for suicide.

Drs. Wohlfarth, Boer, and van den Brink have done an excellent job synthesizing the results from our person-level findings from the VA study and our ecological studies and from those of Libby et al. Furthermore, they raise the important point of the limitations of randomized controlled trials that use placebo as a proxy for the absence of treatment. Our VA study (4) showed that estimates of suicide attempts based on patients in randomized controlled trials dramatically underestimate the rate of suicide attempts in untreated patients. However, Drs. Wohlfarth, Boer, and van den Brink suggest that instead of resulting from the withdrawal of medication, the increase in suicidality may be due to the withdrawal of continued attention and caring that was previously provided in the context of pharmacologic treatment. Depression does indeed lift for some individuals when they are enrolled in clinical trials but provided only placebo (so-called placebo responders [10, 11]), and the effectiveness of the supportive environment of psychotherapy suggests that a portion of the benefit of antidepressants could potentially be mediated by this continued attention. While we can think of no direct way to test this hypothesis using available data, the key issue remains that lack of attention to and/or denying treatment of children with clinical depression has serious public health consequences.

We thank our colleagues for continuing the dialogue and discussion of these important data and this important international issue. Families, clinicians, researchers, and suicide prevention advocates are all seeking to identify strategies to reduce the risk for suicide, and additional data are likely to provide a fuller understanding of this issue. We hope that the psychiatric research community will continue to work together to provide evidence-based answers to these important questions.

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Challenge to Atypical Antipsychotic Drug Effect on Cognition

TO THE EDITOR: In the July 2007 issue of the *Journal*, Richard S.E. Keefe, Ph.D., et al. (1) reported on the effects of olanzapine, quetiapine, and risperidone on neurocognitive function. Dr. Keefe et al. concluded that all three drugs produced significant improvements in neurocognition. The authors noted that cognitive improvement was modest, but they suggested clinical importance based on correlations of 0.14 and 0.18, with a component of the Quality of Life Scale, accounting for only 2%–3% of the variance. Even this small effect cannot be attributed to drug efficacy.

The study design did not include a comparison group. The drugs studied had a similar effect on cognition, but we do not know whether the effect was better, worse, or the same as placebo or treatment with a first-generation antipsychotic. In a study conducted by Keefe et al. (2), published in *Archives of General Psychiatry*, olanzapine, quetiapine, and risperidone failed to separate from perphenazine, a "typical" antipsychotic, using cognition data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

If the improvement observed is real, the following other causal explanations cannot be excluded:

1) The natural course of illness may lead to cognitive improvement when the baseline assessment is near the time of