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.

References

1. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings R, Mann JJ: Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007; 164:1356–1363
2. Kung HC, Hoyert DL, Xu J, Murphy SL: Deaths: Preliminary Data for 2005. Hyattsville, Md, National Center for Health Statistics, 2005. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/prelimdeaths05/prelimdeaths05.htm (accessed September 2007)
3. Leckman JF, King RA: A developmental perspective on the controversy surrounding the use of SSRIs to treat pediatric depression (editorial). Am J Psychiatry 2007; 164:1304–1306

JON JUREIDINI, M.B.B.S., F.R.A.N.Z.C.P., PH.D.
British Columbia, Canada

The author reports no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07091463) was accepted for publication in October 2007.

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.

References

1. Minino AM, Heron MP, Murphy SL, Kochanek KD; Division of Vital Statistics: Deaths: Final Data for 2004. Hyattsville, Md, National Center for Health Statistics, 2007

2. Kung HC, Hoyert DL, Xu J, Murphy SL: Deaths: Preliminary Data for 2005. Hyattsville, Md, National Center for Health Statistics, 2005
3. Nemeroff CB, Kalali A, Keller MB, Charney DS, Lenderts SE, Cascade EF, Stephenson H, Schatzberg AF: Impact of publicity concerning pediatric suicidality data on physician practice patterns in the United States. Arch Gen Psychiatry 2007; 64:466–472

MARK OLFSON, M.D., M.P.H.
DAVID SHAFFER, M.D.
New York, N.Y.

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.

This letter (doi: 10.1176/appi.ajp.2007.07091467) was accepted for publication in October 2007.

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.

References

1. Libby AM, Brent DA, Morrato EH, Orton HD, Allen R, Valuck RJ: Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am J Psychiatry 2007; 164:884–891
2. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ: Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry 2007; 164:1044–1049

TAMAR WOHLFARTH, PH.D.
FRITS BOER, M.D., PH.D.
WIM VAN DEN BRINK, M.D., PH.D.
Amsterdam, the Netherlands

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07091448) was accepted for publication in October 2007.

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-