

reports about resistance of the balloon to withdrawal attempts after the stent is deployed — a problem sometimes described as “stickiness” of the balloon during withdrawal. This problem does not appear to be related to the mechanical defect observed in the investigation of the balloon-deflation failures; rather, it seems to result from a combination of patient-related and device-related factors. These factors are still under review but are currently presumed to include friction between the stent-delivery balloon and the drug-polymer coating on the stent, as well as certain characteristics of the coronary vessel. The association, if there is any, between these reports of resistance to withdrawal and adverse clinical events is currently being assessed.

The Boston Scientific case illustrates the dilemma we face in determining the appropriate threshold for product recall and notification when the risk is of a severe but rare adverse event. In these cases, the potential benefit to be accrued from recalling the product must be balanced against the possible negative effects this action might have on public health. Denying a potentially beneficial therapy to all patients, as in a complete recall of a product, might have greater adverse consequences than allowing the device to remain in use.

These cases exemplify the challenges that we face in regulating breakthrough technologies. In almost all instances, as in the Cypher case, we do not have a complete accounting of all cases or information on the number of devices actually in use, making it impossible to compare similar products in

terms of the rate of adverse events. Our responsibility to protect the public health, however, necessitates that we consider early notification about any legitimate risk, weighing the risk posed by neglecting to notify practitioners about a clinically significant problem against the consequences of “crying wolf” on the basis of inconclusive information. In attempting to strike the right balance, we may engage clinical and other stakeholders for review and comment on our draft notifications before we release them. Such a dialogue is particularly important in the case of breakthrough technologies, in which our decisions can have an immediate and profound effect on people’s lives.

From the Center for Devices and Radiological Health, Food and Drug Administration, Rockville, Md.

1. CYPHER sirolimus-eluting coronary stent on RAPTOR over-the-wire delivery system or RAPTORRAIL rapid exchange delivery system — P020026. Rockville, Md.: Food and Drug Administration, April 24, 2003. (Accessed September 29, 2004, at <http://www.fda.gov/cdrh/pdf2/p020026.html>.)
2. FDA public health Web notification: information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER coronary stent. October 29, 2003. (Accessed September 24, 2004, at <http://www.fda.gov/cdrh/safety/cypher.pdf>.)
3. FDA public health Web notification: updated information for physicians on sub-acute thromboses (SAT) and hypersensitivity reactions with use of the Cordis CYPHER sirolimus-eluting coronary stent. November 25, 2003. (Accessed September 28, 2004, at <http://www.fda.gov/cdrh/safety/cypher2.pdf>.)
4. TAXUS Express 2 paclitaxel-eluting coronary stent system (monorail and over-the-wire) — P030025. Rockville, Md.: Food and Drug Administration, March 4, 2004. (Accessed September 28, 2004, at <http://www.fda.gov/cdrh/pdf3/p030025.html>.)

TREATING DEPRESSION IN CHILDREN

The editors asked two members of the Psychopharmacologic Drugs and Pediatric Advisory Committees of the Food and Drug Administration to comment on the committees’ recent recommendations regarding the use of antidepressant medications in children and adolescents.

Their responses follow.

A Black-Box Warning for Antidepressants in Children?

Thomas B. Newman, M.D., M.P.H.

On September 14, 2004, a Food and Drug Administration (FDA) joint advisory committee voted 15 to 8 to recommend that a “black-box” warning label be required for antidepressant drugs, indicating that they increase the risk of suicidal thinking

and behavior (“suicidality”) in pediatric patients. Although, as an epidemiologist and general pediatrician, I do not have clinical experience caring for depressed patients, after reviewing the evidence, I strongly favored the black-box warning.

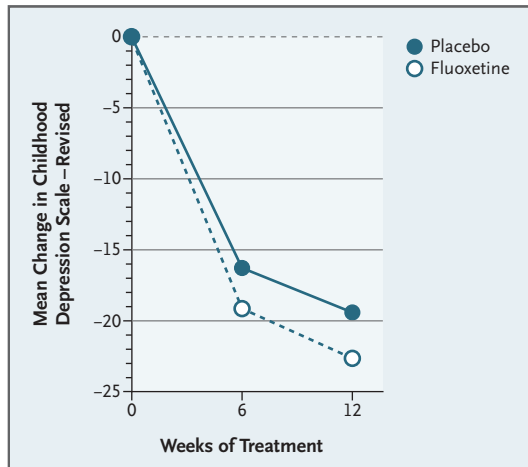


Figure. Mean Changes in Score on the Childhood Depression Scale—Revised in the Treatment for Adolescents with Depression Study.

Data are from March et al.¹ The average scores at baseline, out of a possible 113, were 58.9 in the fluoxetine group and 61.2 in the placebo group. Higher scores indicate more severe depression.

During consideration of the proposed labeling change, the committee heard a number of presentations summarizing evidence that suicidality in children and adolescents may be increased by the newer antidepressant drugs, primarily selective serotonin-reuptake inhibitors. The most convincing evidence came from an FDA analysis of randomized trials. Most of these trials had been conducted by the drug manufacturers under the Best Pharmaceuticals for Children Act, which provides companies an additional six months of patent protection for their product if they do pediatric studies. These studies need not be published and need not be of high quality. In fact, we heard that because these medications are already widely prescribed “off-label” and patents may be close to expiration, sponsors may have more incentive to do the studies quickly than to do them well. To facilitate analysis of the patchwork of pediatric studies, the FDA obtained narratives of adverse-event reports from the trials and contracted with experts on suicide at Columbia University to review them. The Columbia staff members, who were unaware of the treatment-group assignments, were asked to determine whether the adverse events represented suicidality. FDA staff members then combined the results into a meta-analysis.

The results were striking. When all the pediatric trials were pooled, the rate of definite or possible

suicidality among children assigned to receive antidepressants was twice that in the placebo group. (The summary risk ratio was 2.19; 95 percent confidence interval, 1.50 to 3.19.) Although the FDA staff did not provide this information to the committee, according to my own calculations, such a dramatic result would be expected to occur by chance only 1 time in 20,000 ($P=0.00005$).

Nonetheless, some FDA staff and committee members expressed reservations about the data used for this analysis. For example, there was a relatively small number of events, the trials had not been designed to evaluate suicidality, and the methods of ascertainment and classification of the events in the various trials were not uniform. To me, however, these concerns only made the results more compelling. Inadequate sample size and misclassification of outcomes make it more — not less — difficult to detect differences between groups in randomized, blinded trials. The fact that an association emerged from the meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing.

Inferences from the randomized trials were supported by public testimony from people who believed that antidepressant drugs had caused their loved ones to commit suicide (or, in some cases, homicide). Several of these cases involved patients who had shown no hint of suicidality before beginning treatment with the drugs and who had been given these drugs for indications other than depression, including migraine headaches, nail biting, anxiety, and insomnia.

Several committee members spoke in favor of the antidepressants, citing either their own clinical experience or the Treatment for Adolescents with Depression Study (TADS),¹ a recently published randomized, double-blind study of fluoxetine for major depression in adolescents, which the committee reviewed in detail. However, others and I found the evidence of efficacy much less convincing than the evidence of harm. In reviewing TADS, we were struck by the small size of the difference between fluoxetine and placebo as compared with the effect of placebo alone. For example, after 12 weeks, the average decrease in the Childhood Depression Scale—Revised (scores on which were around 60 of a possible 113 at baseline in both groups, with higher scores indicating more severe depression) was 19.4 points with placebo, as compared with 22.6 points with fluoxetine (see Figure).

FDA Statement on Recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees, September 16, 2004.*

The Food and Drug Administration (FDA) generally supports the recommendations that were recently made to the agency by the Psychopharmacologic Drugs and Pediatric Advisory Committees regarding reports of an increased risk of suicidality (suicidal thoughts and actions) associated with the use of certain antidepressants in pediatric patients. FDA has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of antidepressants and to bolster the information provided to patients when these drugs are dispensed.

In summary, the members of the advisory committees:

- endorsed FDA's approach to classifying and analyzing the suicidal events and behaviors observed in controlled clinical trials and ex-

pressed their view that the new analyses increased their confidence in the results

- concluded that the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (Prozac, Zoloft, Remeron, Paxil, Effexor, Celexa, Wellbutrin, Luvox and Serzone) in controlled clinical trials
- recommended that any warning related to an increased risk of suicidality in pediatric patients should be applied to all antidepressant drugs, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single medication from an increased risk
- reached a split decision (15-yes, 8-no) regarding rec-

ommending a "black-box" warning related to an increased risk for suicidality in pediatric patients for all antidepressant drugs

- endorsed a patient information sheet ("Medication Guide") for this class of drugs to be provided to the patient or their caregiver with every prescription
- recommended that the products not be contraindicated in this country because the Committees thought access to these therapies was important for those who could benefit
- recommended that the results of controlled pediatric trials of depression be included in the labeling for antidepressant drugs.

*From the Food and Drug Administration, www.fda.gov/bbs/topics/news/2004/new01116.html.

It is easy to see why the personal experience of clinicians and patients would lead them to believe the drug to be effective, since they would have no way of knowing that more than 85 percent of the benefit they observed would also have occurred with placebo.

Randomized trials other than TADS have had less favorable results. The FDA indicated that only 3 of 15 trials of antidepressant use in children with depression had found a statistically significant benefit. The agency also provided us with a meta-analysis² that showed that the estimated effi-

cacy of antidepressants in children was minimal and likely to have been overestimated, because published studies have much more favorable results than unpublished studies. Thus, both clinical experience and published trials are likely to lead to inflated estimates of the efficacy of these drugs.

The committee members agreed that there are wide gaps in our knowledge about antidepressants. Perhaps the most important relate to their medium-term and long-term safety and efficacy. The FDA's meta-analysis suggested that the new antidepressants double the risk of suicidality, from

about 2.5 percent to 5 percent, in trials lasting two or three months. But what happens if you take them for a year? Does a 5 percent risk over the course of three months become a 20 percent risk over the course of a year, or does the benefit–risk balance improve over time? Does the increase in the rate of suicidality translate into an increase in the rate of completed suicide? Do additional adverse effects occur after treatment with the medications is stopped? Are there important differences among the drugs in this class? What age groups are at risk? It seems unlikely that the drugs suddenly become safe after the patient's 18th birthday. Currently, no one knows the answer to any of these questions.

There was also agreement that the experience with antidepressants illustrates serious deficiencies in the implementation of the Best Pharmaceuticals for Children Act U.S. consumers, through higher drug prices buoyed by extended market exclusivity, are paying a high price for pediatric studies that may be poorly conducted and selectively disseminated. The public is the loser, both because the availability of generic versions of the drugs is then delayed and because poor science and selective publication can lead to false conclusions about pediatric safety and efficacy. If these studies are to provide value, the requirement to do them must be changed to a requirement to do them well. Extend-

ed exclusivity should be granted only if the studies conducted in order to receive it are judged to be of high quality by independent peer review and if their results are disseminated in a timely manner.

Finally, this controversy over the use of antidepressants in children illustrates the need for a more sophisticated approach to evaluating harms and efficacy than simply seeing whether they are statistically significant at a P value of less than 0.05. Regardless of the P value, no psychotropic drug is free of potential negative effects. The best available estimates of the magnitude and nature of the effects of the drugs must be discussed with patients and families, so that they can make an informed decision about treatment. My hope is that the FDA will follow the recommendation of the advisory committee and require a black-box warning—and that doing so will make these discussions more likely to take place.

From the Departments of Epidemiology and Biostatistics and Pediatrics, University of California San Francisco, San Francisco.

1. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004;292:807-20.
2. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341-5.

Antidepressants and Pediatric Depression — The Risk of Doing Nothing

David A. Brent, M.D.

There is great concern that antidepressants used in children and adolescents may paradoxically increase their risk of suicidal thoughts and behavior. Is this concern valid, and if so, how should it modify our clinical approach to pediatric depression?

Twenty-five years ago, long before the introduction of selective serotonin-reuptake inhibitors (SSRIs), the adolescent suicide rate was increasing rapidly, having tripled over the previous two decades, but the risk factors involved were unknown. Adolescents who committed suicide were regarded as misunderstood teenagers who had been under

too much stress. There was debate about whether depression could occur in children, and the prevailing view was that moodiness was normal in adolescents. Furthermore, even if we could have diagnosed depression and recognized young people who were at risk for suicide, there were no empirically validated treatments to offer.

Eventually, we learned that depression did indeed affect children and adolescents. Through retrospective interviews with family members and friends, this disorder emerged as the single most important risk factor for adolescent suicide,¹ al-