FDA Post-Marketing Safety Decisions

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The U.S. Food and Drug Administration (FDA) black box warning that antidepressants increase the risk of suicidal thinking and behavior in children was followed by a sharp fall in antidepressant prescriptions. No procedure for estimating the net public health impact exists.[1] No suicide occurred in clinical trials of approximately 4400 children, but the term *suicidality* clearly implies a high degree of lethal risk. The press unequivocally viewed probable lethal outcomes as requiring this nominally protective action.

The invalidating problems with the FDA analysis[2] and regulatory action are documented elsewhere.[3] However, 2 issues have not received adequate public and professional attention: (1) the predictive uselessness of the surrogate term *suicidality* and (2) the FDA's inability to estimate the risk of postmarketing harms because of late, rare, or off-label use from clinical trials or its inadequate spontaneous adverse event reporting system. As discussed in this column, proper prospective postmarketing surveillance by linked computerized medical records is a crucial issue deserving major public and political attention and prompt action.

What is the implication of a patient's report of suicidal thinking or any behavior considered to reflect possible suicidal intent (defined as *suicidality*)? Does it substantially increase the risk of completed suicides or call for extraordinary clinical precautions? The classification of adverse events by the group at Columbia University, New York, N.Y.,* necessarily relied on inferences, because the available evidence was not prospectively collected. Thus, it does not fulfill requirements, such as inquiry concerning intent to die, definite plan, concealment of injury, lethality of attempt, and suicide note. However, it is essential to realize that, even if prospective and well done, predictive attempts derived from ideation or inferences about behaviors will grossly overestimate the risk for the rare event of completed suicide.

A surrogate[4] is a more accessible variable on the direct causal pathway to a bad outcome. If the surrogate can be diminished, then the clinical end point of interest is thought likely to benefit.

Does suicidal thinking or behavior place one squarely on the road to suicide? Since those who complete suicide frequently made prior suicide attempts, whereas those who do not commit suicide rarely do so, it seems obvious that such an attempt predicts a very likely bad outcome. A conservative estimate of the U.S. teenage population is 12.5 million, of whom 2.5 million consider suicide annually; 5% to 8% of adolescents attempt suicide; approximately 1600 teenagers die by suicide.[5] A history of a prior suicide attempt is one of the strongest predictors of completed suicide, confirming a particularly higher risk for boys (30-fold increase) and a less elevated risk for girls (3-fold increase).[5]

A little arithmetic yields a counterintuitive conclusion. Predictions incur 2 types of error: false negatives and false positives.[6] Assuming 12.5 million adolescents in the U.S. population, the suicide rate is 0.0128%. In boys, approximately 0.5 million attempted suicide and 5.75 million did not. To allow maximum predictability, we assume that all 1600 completed suicides occurred in boys. Calculation indicates that among those who attempt suicide, completing suicide occurs in 0.232%. Among those who did not previously attempt suicide, the suicide rate is 0.008%. Therefore, the rate of completed suicide is 30 times greater in attempters than in nonattempters. Also, 72.5% of completed suicides had an antecedent attempt.

Nonetheless, although attempts are clearly a risk factor for completed suicides, 99.77% of attempters will not commit suicide (false positives). The large risk ratio, 30, is taken to show that suicide attempts are directly on the causal path to completed suicide. However, since less than 0.25% of attempts proceed to completed suicide, attempts must be extraordinarily heterogeneous. Few are on the direct path to completed suicide. For the much more common suicidal ideation, predictability is, of course, far worse. Therefore, only very few, perhaps none, of the "suicidal attempts" in the FDA-reviewed studies are actually on a suicide path.

An opposing argument is that these estimates are based on annual rates, which may be substantially increased in depressed adolescents. There are limited prospective data incorporating both attempts and suicide rates. The Maudsley 20-year follow-up[7,8] of 245 depressed adolescents (36% with comorbid conduct disorders) found a 2.45% risk of completed suicide but a 44.3% lifetime risk of attempted suicides. Therefore the maximum true positive predictive rate is 0.056. This means that 94% of such patients who have attempted suicide are, over 20 years, not going to actually succeed in committing suicide.[7,8]

Even more to the point, 93% of 302 near fatal "attempters" treated for self-poisoning did not subsequently kill themselves during a 5-year follow-up. These findings indicate that, even among high-risk patients, completed suicide is too rare to identify those likely to die by suicide, which has important clinical implications. It indicates the need for high-quality follow-up, treatment, and surveillance of all those making serious suicide attempts rather than intensive care for all deemed at risk simply because of ideation or any behavior thought to suggest suicidal intent.[9] These practice recommendations run contrary to FDA recommendations.[10] That medication may cause behaviors that arouse clinical concern is common clinical experience, but that these behaviors predict completed suicide is quite unlikely, and, at best, false positives would swamp any predictive efforts.

A firm Advisory Committee conclusion could have been that concerns about lethality could not be adequately addressed by currently collected data. Firm conclusions about rare events cannot come from feasible, randomized, double-blind, placebo-controlled trials, even if relevant data were properly collected. Attaining adequate power in clinical trials to validly evaluate rare events is simply not realistic. Longer and larger premarketing trials incur major problems. Patients drop out, making studies progressively more difficult to evaluate. Large studies require multisite protocols, with attendant severe administrative and clinical problems. Longer studies delay the public's access to useful treatments. Further, since most prescriptions for drugs in the United States are "off-label," there are almost no relevant clinical trials.

Accusations of FDA corruption, bureaucracy, and pharmaceutical industry domination deflect the public's attention from the fact that the relevant representative data are not being collected. Horrifying public outcries (at times well orchestrated) cannot be effectively met by protesting the lack of meaningful data. The

*Available at: http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_07_FDA-Iyasu.ppt#353,12, Slide 12

current process leads to hasty worst-case restrictions that mimic effective protections. Blindly shooting from the hip may play politically but is unlikely to improve matters. Whether black boxes, increased monitoring (largely of false positives), or drug withdrawals improve the public health remains unknown.

While multiple replications of randomized controlled clinical trials provide the most secure basis for asserting specific benefits, their lack of feasibility for detecting rare events requires consideration of other methods. Attempts to derive causal risk estimates from naturalistic postmarketing epidemiologic data incite heated debates. Creating effective postmarketing surveillance must be brought to the forefront of public discussion to deal with the confusing barrage of horror stories that spark regulations, warnings, and changes in medical practice, with unclear net effects.

Rational attempts to develop systematic postmarketing surveillance do exist in Europe.[11] These may help guide such a program for the United States. Would it be too expensive? In the context of the many billions lost by industry because of the sudden withdrawal of popular products, as well as the blight on sales of related drugs, this investment is actually prudent. Industry would be wise to foster this development, since it is likely that such losses will increase catastrophically.

A complete system would require a radical revision of the private practice, disconnected, paper-based, medical information systems of the United States. However, such a program could be initiated in federally supported, supervised medical services. Extensive hospital, outpatient, and family services are provided by the armed services (Army, Navy, and Air Force), Veterans Administration (VA), and Public Health Service. Instituting a well-monitored mandatory system requires political awareness of the issues. The VA has already taken useful steps toward medical record computerization. Two other grave, mounting problems—the rising cost of medical care and the need for easily accessed, complex, longitudinal, medical records for individual patients—also support this necessary development.

A series of public meetings, including the range of stakeholders, should debate effective postmarketing surveillance, thus allowing public education, initiating relevant feasibility and cost/benefit studies, and gaining necessary legislative attention to this issue. The American College of Neuropsychopharmacology, with several cosponsors, plans such a meeting in Washington, D.C., for September 13, 2006, as an initial approach to a vital, complex issue.

This column can be summarized into 3 main points: (1) Meeting public concerns about drug safety has failed. (2) It is completely impractical to attempt to answer questions about rare, late, and off-label harms on the basis of clinical trials, even if the data were properly collected. (3) Computerized, cross-linked, population-based medical records should be mandated for federally supported medical facilities. Analyses should be carried out by an agency of independent experts, buffered from political and economic pressures.

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