Black Boxes, Babies, and Bathwater

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> *"Our current state of knowledge suggests that safe and effective utilization of the black boxed antidepressant medications remains important to the treatment of pediatric mental illness."*

It has been a year since the final advisory committee meetings at the Food and Drug Administration (FDA) that ultimately led to the inclusion of a "black box" warning on the labeling of every class of antidepressant available in the United States.[1] This warning, and the accompanying package insert, specifically inform prescribing clinicians and consumers about findings of an increased risk of suicidal thinking or suicidal behavior in pediatric patients who take these medications. I believe the current black box warning is inaccurate and probably not justified.

The September 2004 advisory committee meetings followed a yearlong investigation by scientists at the FDA to address the suggestions of mostly industry-sponsored, placebo-controlled clinical trials that antidepressants caused children and adolescents to become suicidal.

By the time of the meetings considerable public controversy already had swelled about the use of antidepressants in children and adolescents. The idea that the antidepressant fluoxetine could actually be causing patients to become suicidal had been investigated a decade earlier in studies of adults, and had been refuted.[2] However, some level of public concern remained. In addition, pharmacologic research into pediatric illness increased, stimulated by FDA policies that offered marketing exclusivity to companies that completed pediatric studies with on-patent products. In their investigation, the FDA employed meta-analytic techniques to systematically collect data indicating "treatment-emergent" suicidality in randomized clinical trials, and the risks of these events occurring in youth taking active medication vs placebo were compared to obtain estimates of relative risk.[3]

It had seemed to me at the time that retrospectively studying the association between antidepressants and suicidality was going to be a challenge. Using what (in my mind) amounted to novel, untested chart review methods to address a research question that had never been anticipated in the original study planning was perilous. The search strategy for pertinent events, the method of developing vignettes from the adverse events, and the suicidality classification system employed in the project had never been used before. Most often these kinds of secondary analyses of data are performed as pilot projects and used to generate hypotheses rather than to make evidenced-based treatment decisions. The level of scientific evidence this type of approach generates is never that strong, and unless the findings are really convincing, it generally is unwise to make decisions based on findings from this level of evidence.

Two research approaches using different data sets were used by the FDA to address the treatment-emergent suicidality issue, and they came to conflicting conclusions.[3] The first employed adverse events data collected via spontaneous reporting or ascertainment; the second employed data from clinician-rated depression scales. In the first method, despite all the "noise" that was present due to method variance across trials, a weak, inconsistent "suicide signal" emerged. The second analysis, examining variables addressing suicidality in systematically collected rating scales used in some of the clinical trials (most likely the depression trials), found no evidence of an association between treatment-emergent suicidality and antidepressant treatment in children and adolescents.

In the context of a regular research project, one would imagine that significant discussion and consideration were given to these conflicting results. However, this was no ordinary research project. It was monitored closely by the public, by various stakeholder groups (healthcare professionals, concerned parents, antipsychiatry groups, personal injury lawyers, individuals with pending lawsuits against the drug companies, etc), and by the legislative branch of the federal government. Their regulatory recommendations and actions suggest that the FDA and its advisors based their conclusions on the adverse events data analysis, but in my

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opinion the fact that the 2 strategies produced conflicting results remains interesting and unexplained.

I would assert that 1 of the 2 analytic strategies employed in this project supports a weak association between antidepressants and treatment-emergent suicidality, but the other does not. No evidence suggesting that antidepressants lead to completed suicide was generated, because no child in these trials actually committed suicide. In fact, other evidence suggests that during a time of increasingly widespread use of antidepressant medications in pediatric patients, national suicide rates in this age group have fallen continuously—suggesting that, at the very least, antidepressant treatment has not set off a suicide epidemic in young people, even if one does not accept the idea that medication use was causally related to the decrease in suicide.[4]

These and other factors, in hindsight, lead to my conclusion that the current black box warning is not justified. However, I would raise no objection if the following modifications to the current warning were made:

(1) The FDA could acknowledge in the warning that the adverse events data and the systematic rating scale data do not agree and that no one is quite sure how to explain the discrepancy. The black box could reasonably be removed and a warning could remain that suggests a "possible association" between antidepressants and treatment-emergent suicidality.

(2) Because the methodology employed with the pediatric data during this investigation has never been used before, the warning's specification for youth seems a bit misleading. Recently published studies or meta-analyses of adult antidepressant trials suggest the possibility of a similarly weak treatment-emergent suicidality signal in this age group.[5,6] The FDA reportedly is planning to review the adult trials, but this will take time. So, in the interim a formal acknowledgment in the current warning regarding the limits of our knowledge regarding nonpediatric patients may be in order.

(3) I think the FDA took a very unusual step in requiring the pediatric black box warning on medications that were never even under investigation during this controversial period. All antidepressants have had the black box warning added to their labeling, even though data from studies of some of these agents (eg, tricyclics, monoamine oxidase inhibitors, duloxetine) were not under evaluation or even available during the FDA's investigation. I can see no reason why the black box warnings on these medications could not be modified to accurately acknowledge that some medications were branded because of class inclusion rather than actual data.

(4) The current warning suggests the FDA review of data was comprehensive, but for unexplained reasons, important and available studies with relevant data were not reviewed, including 3 large, rigorous, federally supported studies that found significant positive effects of various selective serotonin reuptake inhibitors in pediatric mental illness and no increased risk of suicidality.[7-9]

At the end of the day, clinicians trying to practice evidence-based medicine in pediatric mental health may be left feeling confused and fed up. On the one hand there is increasing evidence that antidepressants, alone or in combination with psychotherapy, may be highly effective for treating pediatric mood and anxiety disorders. On the other hand, there now exists a universal precaution that any child or adolescent taking these medications is vulnerable to the full range of treatment-emergent suicidality.

My sense is that it is unwise to throw the baby out with the bathwater. Our current state of knowledge suggests that safe and effective utilization of the black boxed antidepressant medications remains important to the treatment of pediatric mental illness. From a public health perspective, if the end result of the FDA proceedings is that clinicians utilize increased education, informed consent, and monitoring with families of pediatric patients treated with psychotropic medications, then this is probably not a bad thing. However, if the public becomes so alarmed, and clinicians so nervous, as to substantially reduce the utilization of effective evidence-based treatments for pediatric illness, I am not so convinced the FDA's decision is a beneficial one—even if it does appeal to the appetites of some stakeholders.

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