The Revised Black Box Warning for Antidepressants Sets a Public Health Experiment in Motion

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On May 2, 2007, the U.S. Food and Drug Administration (FDA) issued the revised black box warning for all antidepressants that will now apply to patients under 25 years of age:

> Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. . . .[1]

This revision broadens the coverage of the 2004 black box warning for antidepressants that applied to children and adolescents.[2] The new, carefully worded warning conveys the risks of both antidepressants and depression. In so doing, the FDA has engaged in a difficult challenge to balance the risks of mandating a black box warning for antidepressants with the benefits of such a requirement. The importance of careful monitoring of patients who commence antidepressant treatment has been well known for years, but until recently, not explicitly stated on the antidepressant label. Nonetheless, there is a great fear echoing loudly in the clinical community. Many believe that an unintended consequence of this policy will be the restricted use of antidepressants among those who might benefit the most and, paradoxically, an increase in the very suicidality that the policy seeks to prevent. Yet, it is unclear whether that apprehension is based on relevant data, clinical intuition, or speculation. Here, I consider some of the issues faced by the FDA and possible consequences of their decision.

I am a member of the Psychopharmacologic Drugs Advisory Committee (PDAC) of the FDA that was called on to interpret the data that served as the basis for the black box warning. This issue is undoubtedly the most contentious that the PDAC has examined in recent years. Why so? Most stakeholders (patients, family members, physicians, and industry) held intractable positions on this topic long before the data were presented at the PDAC meeting on December 13, 2006. Few, if any, of those preconceptions were swayed by the results that were presented at the meeting.

Why such contention in our empirically guided field? It is not simply a debate between clinical intuition and unambiguous empirical results. Contrary to popular sentiment, there is no perfect dataset to examine this question. However, the FDA has attempted to predict the impact of policy change, or lack thereof, based on what are arguably the best available data. Their presentation focused primarily on the meta-analyses of 295 industry-sponsored, randomized, controlled, clinical trials (RCTs) of antidepressants that included 77,382 adults with MDD and other psychiatric disorders.[3] The trials showed that the risk of suicidality (i.e., suicidal ideation or behavior) on antidepressant treatment, relative to placebo, decreased and that the benefits increased with age. The readily apparent trend (Figure 1) across the ages is convincing, with a statistically significant 2-fold risk of suicidality among children and adolescents taking antidepressants and a significant protective effect of antidepressants among those

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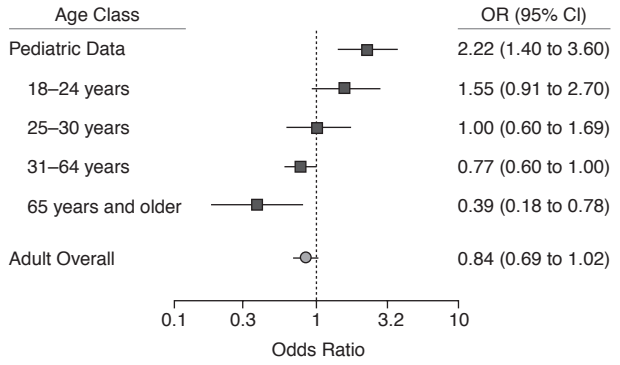
Figure 1. Odds Ratios (ORs) by Age Group for Suicidal Ideation and Behavior[a,b]



[a]Data from the U.S. Food and Drug Administration.[3]
[b]Values > 1.0 represent an elevated risk of suicidality for those randomly assigned to an antidepressant relative to those randomly assigned to placebo. Values < 1.0 represent a protective effect for those randomly assigned to an antidepressant. Values of 1.0 indicate that there is neither an elevation in risk nor a protective effect for those randomly assigned to an antidepressant.

aged 65 years and older (i.e., the risk of suicidality was reduced by about 60%).[3] Do the data provide evidence of a clear risk of suicidality for young adults aged 18 to 24? No, the results are equivocal. Do the data provide evidence that risk of suicidality can absolutely be ruled out? Clearly not. The nonsignificant elevation in risk for those aged 18 to 24 cannot be ignored in light of the trend across ages (Figure 1). The FDA chose to err on the side of caution. Let the *informed* prescriber and patient beware.

The strength of the extensive database compiled by the FDA, and the meta-analyses that they conducted, is that with randomized treatment assignment, causal statements can be made. Yet, that internal validity comes at the expense of generalizability, which is limited by the characteristics of the participants, settings, and treatment durations of those RCTs. More specifically, the trials tended to exclude those who were suicidal, those requiring polypharmacy, those with subsyndromal depressive symptoms, and those with comorbid psychiatric and other medical disorders. Thus, the FDA attempted to infer from the very large set of rarefied, homogeneous patients who participated in brief clinical trials for antidepressants (ranging from 4 to 12 weeks) to the highly varied, potential antidepressant consumers throughout the general population. The implications of the black box warning are unknown for that diverse group, who would possibly benefit from months or years of antidepressant treatment, if it were to be provided.

The FDA interpretation of the RCT results[3] has been criticized for a variety of methodological reasons. There is a risk of ascertainment bias; that is, the source of suicidality was not from prospectively collected, weekly ratings of suicidality, but instead was based on the somewhat voluntary adverse event reports. The younger participants who reported what they assumed were medication side effects may have been more likely to report suicidality. Furthermore, the outcome in the meta-analyses was primarily suicidal thoughts, not attempts or deaths. In fact, there were 8 suicide deaths in the adult trials (5 among those taking the investigational agent, 1 among those taking an active comparator, and 2 among those taking placebo) and none in the child and adolescent trials. Perhaps the most difficult challenge in interpreting the results is what is referred to as "confounding by indication." That is, because suicidality is a symptom of depression, it is difficult to disentangle the symptom from the side effect. However, the data from those patients randomly assigned to placebo, for the most part, controlled for this problem. Furthermore, no efficacy results were presented in the December 2006 PDAC meeting; thus, the risk-benefit of antidepressant use was not quantified. (We do know from other reports that about half of the RCTs for antidepressants approved in the United States from 1985 to 1997 failed to show efficacy of the investigational agent.[4]) Finally, the issues of attrition and differential exposure time were ignored.

The relationship between suicidality and antidepressants is a very complex phenomenon. Many in the field would prefer that other information had greater influence on the FDA decision. There are the postmortem toxicology studies of suicides that detected antidepressants in very few youth suicides.[5,6] Ecological studies have shown that as antidepressants became more widely distributed, there was a corresponding decrease in suicides.[7–11] Perhaps the most prevailing sentiment among readers of the *Journal* comes from the personal experience of clinicians who have seen remarkable success with the medications. Yet, the most vivid accounts at the PDAC meeting were conveyed by those who tragically lost a loved one to suicide shortly after antidepressant treatment had been initiated. However, each of these sources has its own limitations: an unknown age-specific denominator of those exposed to antidepressants in the postmortem studies, no tightly linked numerator and denominator in the ecological studies, and no randomly assigned comparator to allow interpretation of risk in the vignettes from clinicians and family members alike.

At this point, none of us can be certain of the ultimate impact of the black box warning. The FDA conducted extensive data analyses, sought guidance from experts, and in its wisdom, presented a very carefully worded warning that advocates careful monitoring of patients who commence psychopharmacologic antidepressant treatment. Astutely, the black box warning not only mentions the small risk of the medication, but implicitly refers to the risk of untreated depression. Nonetheless, this acknowledgment has not allayed fears of those who believe that

the warning will restrict access to psychopharmacologic interventions for depression. The guidance for monitoring is not news to those trained in psychiatry, but apparently careful monitoring has not been universally practiced by clinicians who write antidepressant prescriptions.

There is no dispute about the need for monitoring; instead, the dispute centers on the method of promoting monitoring. In absence of the ideal data, that is, data that could be used to accurately predict the consequences of the black box warning, the FDA has based their warning on the best available data. In so doing, they have initiated a large de facto public health experiment. In 5 years or so, the consequences of policy change will become the very data we lack today to guide policy development. Will those in need be restricted access to antidepressants and will the rates of suicidality increase? This quasi-experimental public health study will be used to evaluate the impact of the black box warning and will reveal whether the black box cost more lives than it saved.

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