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POLICY FORUM

Antidepressants and the FDA's Black-Box Warning: Determining a Rational Public Policy in the Absence of Sufficient Evidence

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In October of 2004, the Federal Drug Administration (FDA) issued a “black-box” label warning indicating that the use of certain antidepressants to treat major depressive disorder (MDD) in adolescents may increase the risk of suicidal ideations and behaviors. The warning came shortly after the FDA's British counterpart, the Medicines and Healthcare products Regulatory Agency (MHRA), concluded that selective serotonin reuptake inhibitors (SSRIs) with the exception of fluoxetine (Prozac) should not be used to treat adolescents with major depressive disorders.

The MHRA's 2003 recommendation, based on a report by the Committee on Safety of Medicines' Expert Working Group, states that, with the exception of fluoxetine, SSRIs have not been found efficacious in randomized clinical trials [1]. Moreover, the group also noticed an increased risk of suicidal behaviors among adolescent patients being treated with SSRIs and judged that the balance of risks and benefits did not favor the use of SSRIs for adolescents with MDD. Only fluoxetine showed significant therapeutic benefits; fluvoxamine (Luvox) lacked evidence to warrant any cost-benefit analysis.

The MHRA's investigation into the safety of SSRIs in treating adolescents with major depressive disorder came about serendipitously. In evaluating GlaxoSmithKline's application for approving the use of paroxetine (Paxil) to treat adolescents with obsessive compulsive disorder (OCD) and social anxiety disorder, the MHRA requested all data including unpublished trials from GlaxoSmithKline. An examination of the data showed that rate of suicide attempts was higher among adolescent patients taking paroxetine for MDD than among the placebo-controlled group [2]. The MHRA then launched a broader investigation into the safety of SSRIs and requested all data from pharmaceutical companies. It was this meta-analysis of the newly discovered evidence that led the Expert Working Group to its recommendation [3]. In response to the MHRA's recommendation, the FDA launched its own investigation to determine whether there was an increased risk for suicidality among pediatric patients with MDD being treated with SSRIs [4].

One significant difference between the FDA's study and that of the MHRA was that the FDA conducted an independent reclassification of suicidality. Since the original trials did not explicitly study the connection between SSRIs and suicidal behaviors, the FDA was concerned that the data did not use consistent measurements of suicidality across trials. A group of 10 pediatric suicidologists organized by

Columbia University led an independent and blind reclassification. The conclusion of this meta-analysis using the reclassified data was that the use of all antidepressants increased the risks of suicidality among pediatric patients with MDD [5]. As a result, the FDA issued a black-box warning for the nine antidepressants citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil), fluoxetine (Prozac), sertraline (Zoloft), venlafaxine (Effexor), mirtazapine (Remeron), nefazodone (Serzone), and bupropion (Wellbutrin).

The black box is the most severe warning the FDA can place on a drug short of an outright ban. The boldfaced text appears at the beginning of the package insert accompanying each prescription, warning that antidepressant usage for children and adolescents may increase the risk of suicidality. It also indicates that, with the exceptions of fluoxetine for MDD and OCD and sertraline and fluvoxamine for OCD, antidepressants are not approved for pediatric patients. Black-box warnings also prohibit the dissemination of “reminder ads” (i.e., advertisements that mention the drugs’ names but not their indications). Along with a black-box warning, a patient medication guide accompanies each prescription or refill for an antidepressant [6]. The guide warns that a child’s or adolescent’s suicide risk may increase as a result of taking antidepressants to treat MDD. In May 2006, the FDA expanded the warning to include 36 antidepressants and raised the age of potentially vulnerable patients from 18 to 24 [7].

Evidence

The primary difficulty the FDA confronted was determining what public health policy to adopt in the absence of robust evidence; reliable and consistent data on the effects of antidepressants, especially with regards to suicidality, on pediatric patients with MDD were and continue to be scarce.

Although the FDA’s meta-analysis of data supplied by pharmaceutical manufacturers indicates that suicidality risk for the 9 antidepressants in MDD trials were 1.37 (citalopram) to 8.84 (extended-release venlafaxine) times higher than for the placebo, a number of other studies show different results [8]. In an ecologic study comparing suicide rates against antidepressant prescription rates at the county level in the United States, investigators found that higher antidepressant prescription rates correlated with lower suicide rates among children [9]. Another population-based study of suicide risk during the initial phase of antidepressant treatment for 65,103 patients (not restricted to children) did not show an elevated risk of suicide or suicide attempts that led to hospitalization [10]. More recently, a meta-analysis found that the use of fluoxetine to treat pediatric patients with MDD neither increased nor significantly decreased the risk of suicidality [11].

In addition to the unknown cost of increased suicidality risk, there is conflicting evidence about the efficacy of antidepressants in treating pediatric patients with major depressive disorder. The FDA approved fluoxetine for pediatric MDD treatment, and a number of studies offer supporting evidence [12, 13]. Nevertheless, a study on sertraline—a drug not approved by the FDA to treat pediatric

depression—demonstrated that it outperformed placebos in a randomized clinical trial [14].

With limited evidence, the FDA must determine if the therapeutic benefits of antidepressants for treating pediatric MDD outweigh the cost of an apparent elevated risk of suicidality. The dilemma is sharp: doing nothing could expose adolescents and children who are taking antidepressants to a heightened risk of suicidality for possibly meager therapeutic benefits, but premature warning on the danger of antidepressants could also discourage much needed treatment for patients with pediatric major depressive disorder.

Indeed, two recent studies identify some concerns with the FDA's black-box warning on antidepressants. A main goal of instituting the label warning was to ensure greater supervision for pediatric patients during the initial stages of antidepressant treatment. In a postwarning study, investigators discovered that the frequency of contact between patients and clinicians did not increase [15].

More worrisome still is the possibility that the FDA's warning might have led to an unforeseen decline in both depression diagnoses and treatments. In a 2009 study, investigators reported that between 2004 (the year of the emergence of the black-box warning) and 2007, there was a substantial decline in the number of MDD cases diagnosed nationwide, contrary to projections based on historic data [16]. The warning not only possibly affected pediatric cases but had a spillover effect on adult and geriatric cases as well.

The same study also noted that, while the use of antidepressants to treat major depressive disorder had decreased, there had been no corresponding increase in substitute treatments. Patients of all ages with MDD, it appears, are less likely to be diagnosed with the disease and are less likely to receive adequate treatments since the introduction of the black-box warning. Furthermore, a recent examination of teen suicide data from the National Center for Injury and Prevention and Control shows that, contrary to the downward trend prior to 2003, there was a significant increase in mortality due to teen suicide between 2003 and 2005 [17]. Although one cannot confidently draw a causal connection between the introduction of the black-box warning and the increase in teen suicides, the data raise serious concerns about unintended consequences of the FDA warning.

Analysis

One can question the wisdom of the FDA's decision to issue a black-box warning on the basis of limited evidence about both the risk of suicidality and the efficacy of antidepressants in treating MDD. The more substantive policy question is what a regulatory agency ought to do when a pressing policy decision must be made in the absence of quality evidence [18].

In his defense of theism, American philosopher William James argues in *The Will to Believe* that decisions do not always have to be made on the basis of evidence [19].

Indeed, under some circumstances, one would not be irrational to make decisions in the absence of supporting evidence. For James, the circumstances that justify making decisions not based on evidence must satisfy three conditions: they must be living, forced, and momentous. A living decision is one in which either choice or hypothesis contains some appeal, however small. A forced decision is a decision that cannot be avoided. James suggests that the imperative to “choose between going out with your umbrella or without it” is not a forced decision; one can simply avoid making a decision by not going out. A logically exhaustive disjunction such as “either be a theist or not” forces a decision. Finally, a momentous decision is one that entails a significant stake.

The dilemma confronting the FDA satisfied all three conditions. It was living in the sense that a wide range of cost-benefit results of prescribing antidepressants to pediatric patients with MDD were all plausible in light of a near-vacuum of evidence. According to James’s view of pragmatic reasoning, the lack of evidential support would mean that the belief for and the belief against the use of antidepressants to safely treat pediatric MDD patients were both equally rational. To warn or not to warn constitutes a logically exhaustive dilemma. Neither could the FDA have avoided the decision. Finally, the stakes riding on the decision were obviously high.

The FDA faced a dilemma in which it was epistemically defensible to make a nonevidence-based decision. But was its decision morally defensible? By making a public recommendation, the FDA undermined the evidential-neutrality in the advisability of treating pediatric MDD with antidepressants. The warning now becomes, in itself, “evidence” even though the FDA’s decision was not evidence-based.

A morally preferable route might have been to present the lack of evidence plainly and to reiterate the rationality of either choice. Allowing individuals to make their own decisions demonstrates a respect for multiple rational options in a context of evidential scarcity.

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