Doing Nothing Is Doing Something: Primary Care Antidepressant Treatment in the Era of FDA Boxed Warnings

Benjamin W. Lacy, MD; David A. Baron, DO; Marcia K. Goin, MD; Lawrence S. Gross, MD; Andrew E. Slaby, MD; and Calvin R. Sumner, MD

From the psychiatry service program at the North Florida/South Georgia Veterans Health System in Gainesville, Florida (Dr Lacy); the Department of Psychiatry & Behavioral Sciences at the Keck School of Medicine of the University of Southern California in Los Angeles (Drs Baron, Goin, and Gross); the Department of Psychiatry at New York University in New York (Dr Slaby); and the BioBehavioral Diagnostics Company in Cambridge, Massachusetts, and the Department of Medicine and Psychiatry at the West Virginia University School of Medicine in Lewisburg (Dr Sumner).

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Address correspondence to David A. Baron, DO, Department of Psychiatry & Behavioral Sciences, Keck School of Medicine of the University of Southern California, 2250 Alcazar St, CSC 2203, Los Angeles, CA 90089-0107.

E-mail: dab.msed.do@gmail.com

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The boxed warning created by the US Food and Drug Administration (FDA) in 1979 has come to be known by the ominous term *black box warning*. The overall effectiveness of these warnings in reducing adverse drug events remains controversial.[1-3] Meanwhile, boxed warnings that are expanded to include entire drug classes may result in unintended consequences to the diagnostic and prescribing practices of physicians.[4] An example of this type of unintended consequence is the response to the class boxed warning of the increased risk of suicidality (ie, suicidal thinking or behavior) in children, adolescents, and young adults who are receiving antidepressants. The FDA boxed warning did not mandate prescribing restrictions but instead recommended appropriate patient selection and monitoring to ensure safe use. Physicians prescribed fewer antidepressants, however, rather than thoughtfully determining what was best for their patients.

The presence of the boxed warning is ordinarily based on concerns about clinical data, including postmarketing surveillance. Any warning elevated to the status of a black box warning must be bolded and "boxed" by a solid black line on all 4 sides. A boxed warning is indicated in the following 3 situations[5]:

- A potentially serious adverse reaction outweighs the benefit from the drug.
- A serious reaction from the drug can be prevented or reduced in frequency or severity by patient selection, monitoring, and avoiding certain concomitant therapy.
- A mandatory prescribing restriction on the drug is in place to ensure safe use.

Officials at the FDA became aware of data showing increased suicidality among children treated with antidepressants as early as 1996 (James Knudson, MD, PhD, written communication, March 1996). The association between suicidality and antidepressants remained unclear for several years, however, and the agency did not take substantial action until further reports accumulated in early 2003. The FDA issued an initial Public Health Advisory on antidepressants in late 2003, which reported clinical trial data that revealed increased suicidality among pediatric patients with depression who were receiving 1 of 8 selective serotonin reuptake inhibitors.[6] A subsequent boxed warning issued in late 2004 was based on a meta-analysis of 24 randomized, placebo-controlled medication trials involving approximately 4500 children and adolescents who showed an increase in suicidality when receiving medication compared with placebo (4% vs 2%). However, no suicides occurred in the study sample.[7]

In May 2007, after further compilation of evidence, the boxed warning was extended to include young adults aged 18 to 24 years. The boxed warning covers 36 drugs, including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors. The warning advises physicians of a potential increase of suicidality (but not suicide completion) for children and young adults.[8] It recommends close monitoring for clinical worsening, suicidal thinking, or unusual changes in behavior, especially during initiation or changes in antidepressant treatment.[9]

After the risk disclosure and boxed warning by the FDA were released in 2003 and 2004, there was substantial media coverage on the dangers of antidepressants in youth and anecdotal cases of antidepressant-related suicides in children.[9] Several studies found major reductions in the diagnosis of depression and prescription of antidepressants to children, adolescents, and adults.[11-14] Libby et al[14] reported that, among primary care providers, there

was a 44% decrease in the diagnosis rate of depression in children and adolescents younger than 18 years, a 37% decrease in young adults, and a 29% decrease in adults after the boxed warning was released. Prescription of antidepressants decreased, while the use of treatment alternatives such as anxiolytics, atypical antipsychotics, and child psychotherapy did not change considerably. According to Gibbons et al,[15] rates of antidepressant prescriptions for children decreased by 20% after the warnings were released in 2003 and 2004. These findings demonstrated the first major reduction in antidepressant prescription rates in 15 years.

Although the FDA advisory warnings recommended that physicians have weekly face-to-face contact with patients during the first month of antidepressant treatment, physician visits did not increase notably after the advisory. In a large retrospective cohort study, Morrato et al[16] found less than 5% of patients met FDA contact recommendations before the advisory, and this rate did not improve after the advisory. Another retrospective analysis of national claims data demonstrated a statistically significant decrease in the use of antidepressants after the FDA recommendation and no statisically significant change in the frequency of follow-up monitoring.[17]

The change in physician prescribing practices after the warnings inadvertently provided epidemiologists with a unique opportunity to observe the prevalence of suicide with and without antidepressant treatment. After the 2003 and 2004 advisories, the rates of completed suicide rose substantially in children, adolescents, and young adults in the United States, resulting in the largest year-to-year change previously observed in the population.[15] A 22% decrease in antidepressant prescriptions was correlated with a 14% increase in completed youth suicides in the United States and a 49% increase in youth suicides in the Netherlands.[15] Additionally, ecological studies[18,19] revealed that regions with higher antidepressant prescription rates had lower suicide rates than regions with lower antidepressant prescription rates.

The FDA's intention in 2004 was to launch "a multi-pronged strategy to strengthen safeguards for children treated with antidepressant medications."[20] Recommendations were made to balance medication risk with clinical need, provide information guides for parents and caregivers, and provide close monitoring of patients.[20] Instead of strengthening safeguards, the FDA advisory and boxed warnings led to reductions in rates of diagnosis and medication management of pediatric depression, with spillover effects into the diagnosis and management of adult depression.[21] Several studies later showed that the reduction in antidepressant prescription rates was associated with increased rates of completed suicide. However, population studies could not establish a definitive causal relationship between decreased prescribing of antidepressants and increased suicide rates.[22] Despite nearly a decade of FDA boxed warnings, controversy exists over whether antidepressant medication results in increased suicidality in children, adolescents, and young adults.

The unintended consequences of the FDA's boxed warning on antidepressants can serve as a reminder to physicians: a boxed warning on a medication does not mean "thou shall not use," but rather, "thou shall consider carefully and choose wisely." Far from being a directive to physicians, the boxed warning is an important advisory to prescribers. Primary care physicians must weigh the potential for increased suicidality from antidepressants in younger patients against the risk of suicidality in those with untreated depression. Continued vigilance in the recognition, diagnosis, and management of depression in children, adolescents, and young adults is essential in the primary care setting.

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