HEALTH & MEDICINE

A Tragic Unintended Consequence

Did adding a "black box" warning to antidepressants lower their usage and increase youth suicides?

BY ARIF KHAN, ANSHU ARORA, AND AISHWARYA PRASAD

In October 2002, the British current-affairs program *Panorama* aired a 50-minute documentary titled "Secrets of Seroxat" about serious mood disorders and drug withdrawal symptoms linked to the antidepressant paroxetine, sold under the brand name Paxil in the United States and Seroxat in the United Kingdom. The documentary claimed that paroxetine could, in some individuals, trigger severe mood changes leading to self-harm or suicidal behavior, risks that *Panorama* claimed were not adequately disclosed to patients or clinicians. An estimated 4.5 million people watched the program. The following May, *Panorama* broadcast a follow-up, "Seroxat: E-mails from the Edge," that presented patient stories about their negative experiences with the drug.

The episodes caught the attention of the US Food and Drug Administration, which requested the randomized clinical trial data from GlaxoSmithKline, the manufacturer of paroxetine. Eventually, the FDA requested data from manufacturers of all antidepressants utilized for children, specifically Celexa, Luvox, Prozac, Zoloft, Effexor XR, Remeron, Serzone, and Wellbutrin.

This effort was driven by the Pediatric Exclusivity Provision established under the FDA Modernization Act of 1997, which incentivized pharmaceutical companies to study medications already approved for adults for use in children. The provision aimed to generate safety and efficacy data specific to children, leading to the development of several exploratory clinical trial models for pediatric depression.

After a series of internal deliberations, the FDA convened a two-day advisory committee meeting in September 2004, where attendees considered mixed and inconclusive data about suicidality (a term created by the FDA meaning "suicidal thinking and behavior") that failed to showcase statistical significance. Nonetheless, the committee decided that a permanent "black box" warning should appear on the drug's label—a high-visibility warning as opposed to a "Warnings and Precautions" note elsewhere on the label—when the medications are prescribed to young people, to highlight this concern. Committee members defended this decision

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Figure 1

Black Box Warnings for Wellbutrin

Original Label (2006)

Suicide in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. WELLBUTRIN is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

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by claiming it was pertinent to convey any sort of risk to clinicians, patients, and families about the medications to promote open conversation and discussion about benefits and potential risks of taking the medications. A subsequent advisory meeting in May 2006 likewise failed to adduce statistically significant data showing suicidality, yet the committee decided the black box warning should continue and extend to the antidepressants Lexapro and Cymbalta, and expanded it to include young adults up to 24 years of age.

However, as we will soon explain, instead of tamping down on the risk of youth suicide, the FDA decision appears to have increased it.

THE BLACK BOX WARNING

Figure 1 shows the three versions of the warning (implemented in 2006, 2013, and 2024) used over the past two decades for Wellbutrin, the branded version of bupropion. The original label followed the standardized wording used across most antidepressants, as determined by the Psychopharmacologic Drugs Advisory Committee in 2004. Similar boxed warnings appeared on Wellbutrin labels until 2013, when the FDA implemented the Physician Labeling Rule, which required boxed warnings to be more concise. In 2016, the FDA removed the neuropsychiatric events warning after a large trial showed that bupropion did not increase serious neuropsychiatric risks compared to placebo or nicotine replacement therapy, even in patients with psychiatric histories. As a result, the FDA concluded the boxed warning overstated the risk and moved that information to the "Warnings and Precautions" section of the label.

THE OPPOSITE OF THE INTENDED EFFECT

Two decades later, despite the FDA's well-intentioned efforts to promote patient safety, youth suicide has climbed rather than fallen. Figure 2 shows the suicide rate among 10–14 year-olds has tripled since the period 2001–2005, just prior to

Updated (2013)

WARNINGS: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**
- **Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.2)**

Updated (2024)

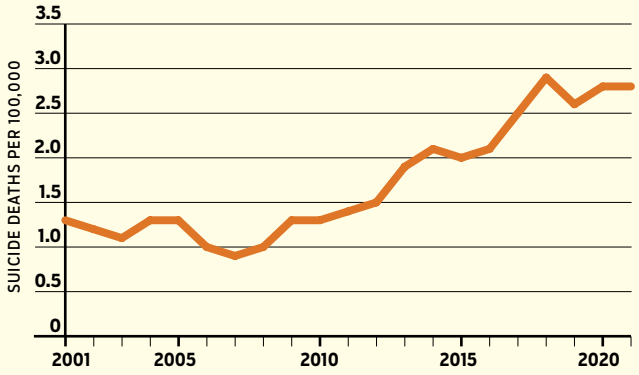
WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants. (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**

Figure 2

Suicide Rate Among People Ages 10–14



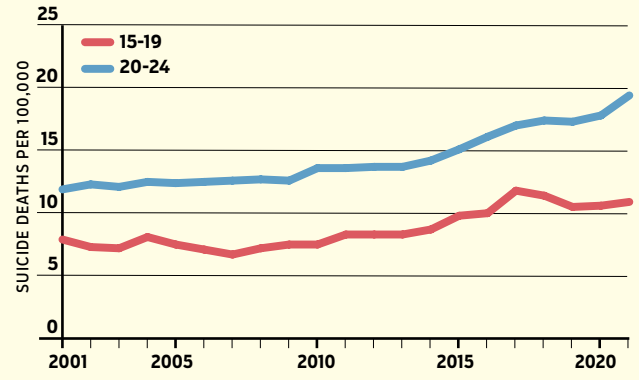
NOTE: Significant decreasing trend 2001–2007, then significant increasing trend 2007–2021 ($p < 0.05$).
SOURCE: National Center for Health Statistics, Data Brief no. 471, "Data tables for Figure 2."

the warning's introduction. This suggests the black box label is having the unintended consequence of discouraging the drugs' use when they would help young people, with tragic results. This should prompt reconsideration of the black box warning. These data are particularly important because they were independently generated and analyzed by the Centers for Disease Control and Prevention. This provides an external and unbiased perspective on outcomes observed since the warnings were implemented.

The excess deaths of 2,365 children and 3,593 young adults is nothing but a national tragedy. Moreover, other countries have adopted similar warnings, suggesting they too could be experiencing an increase in suicides by young people (Fornaro et al. 2019).

Figure 3

Suicide Rates Among People Ages 15–19 and 20-24



NOTE: For ages 15–19, no significant trend 2001–2009, then significance increasing trend 2009–2017, then no significant trend 2017–2021 ($p < 0.05$). For ages 20–24, signficantly increasing trend 2001–2021 with different rates of change over time ($p < 0.05$).
SOURCE: National Center for Health Statistics, Data Brief no. 471, "Data tables for Figure 3," "Data Tables for Figure 4."

Why did this happen? Simply put, the FDA physicians and scientists were not practicing as clinicians. Rather, their decisions reflect how they view medical practices in local communities in the United States: that the FDA is simply providing information to wise health care providers instead of contributing to risk-misperception.

This thinking is displayed in a response we received when we submitted our concerns and data on the black box warning to the FDA. It read in part:

> The purpose of the boxed warning is frequently misunderstood.... Its intent is not to stigmatize antidepressants or to imply that they are categorically harmful. Rather, it serves to alert clinicians to a counterintuitive and clinically dangerous possibility: that new or worsening suicidality shortly after treatment initiation may represent an adverse drug reaction rather than inadequate treatment response. Without this awareness, clinicians may respond by increasing the dose or persisting with treatment under the assumption that symptoms will improve with time, thereby potentially exacerbating harm. This risk of mismanagement justifies the prominence of a boxed warning.

The warnings appear to have led to significant shifts in the evaluation and management of pediatric and young adult patients. The reality is that almost every suicide or self-induced harm reaction leads to a medical malpractice lawsuit in the United States. The warnings thus put physicians—including primary care specialists, pediatricians, nurse practitioners, and psychiatrists—in a difficult position. The federal government's actions exposed them to litigation without any specific guidance they could use in their defense, while not prescribing the medication could be defended by citing the warning.

So, what happened? The diagnosis of *major depression*—which would have led the health care provider to consider prescribing an antidepressant—dropped dramatically, thereby preventing legal exposure for clinicians. Since medical guidelines did not have any specific strategies—like using antidepressants—for managing *mood disorder*, the legal exposure to clinicians was minimal, unlike the diagnosis of major depression.

Multiple sources provide abundant evidence that this occurred. Figure 3 likewise shows an increase in suicides when the warning was extended to older youths and young adults. Meanwhile, as shown in Figure 4, though the suicide rates for people age 55 and older—who are not subject to the black box warning—increased, the increase was much smaller than for youth.

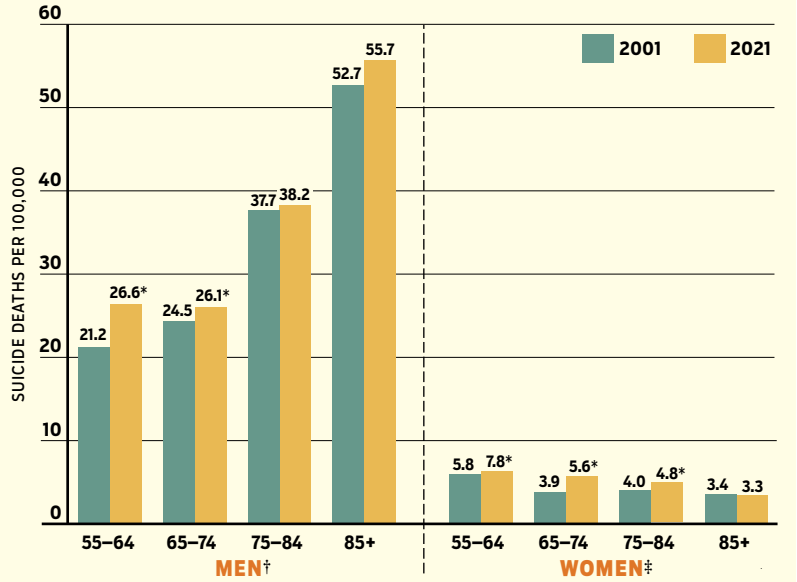
CALL FOR ACTION

We propose the FDA recall/remove the black box warning for all antidepressants to prevent further unnecessary deaths among young people who suffer various mood disorders. There is a long history of correcting such errors in the United States,

Figure 4

Suicide Rates Among People Age 55 and Older

Increase was much smaller than for youth.



*Rate in 2021 was significantly higher than in 2001, p < 0.05.
† Significant linear trend by age group in 2001, p < 0.05
‡ Significant linear trend by age group in 2021, p < 0.05

NOTES: Suicide deaths are identified using International Classification of Diseases, 10th Revision underlying cause-of-death codes U03, X60–X84, and Y87.0.
Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db483-tables.pdf#2.

SOURCE: US Centers for Disease Control, Data Brief no. 483.

as was seen with hormone replacement therapy (Howard and Goodman 2025) and antiepileptics (Yan 2008). If the FDA maintains that health care providers need information about this possible risk, it can be addressed in the "Warnings and Precautions" section of the label rather than a boxed warning. R

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