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GUEST EDITORIAL

Black-box warnings: Their consequences and how we should approach them

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The U.S. Food and Drug Administration (FDA) and other regulatory agencies issue warnings for specific drugs and medical devices. These warnings alert the public and medical community about newly identified and serious adverse effects and safety risk(s), including injury and death associated with the use of a certain medication or medication class and devices available in the United States.

The black-box warnings (named for the required black borders around the warning) are the most stringent of such warnings. Once a black-box warning is issued, the drug or device manufacturer must create a guide on how to safely use the medication. Information about FDA-issued warnings is available on the FDA website, www.fda.gov (not easy to navigate) or from pharmacies. The warnings are usually brief and outline the risk, how it was determined (eg, randomized placebo-controlled trials), and what should be done (eg, discontinue in certain conditions, balance risk and benefits, monitor and closely watch for worsening). They do not provide information beyond the warning. As Winterfield et al[1] wrote, "there is no clear metric to determine how and when the boxed warning is applied. Inconsistencies in the review process, language, timing, and dissemination of these warnings" impact physicians and their patients.

Unintended consequences of black-box warnings

These warnings, however, could have unintended consequences, as documented by several examples. For instance, in 1989, New York State introduced a regulation that required all prescriptions for benzodiazepines to be written in triplicate. The physician kept 1 paper copy, a pharmacist kept another, and a third was forwarded to the New York Department of Health. The intention was to "reduce diversion to illicit use, to reduce inappropriate prescribing, and to educate physician, pharmacist, and the public about benzodiazepines."[2 p 279]

While benzodiazepines prescribing significantly decreased, prescription rates for several sedative hypnotics (meprobamate, methyprylon,

ethchlorvynol, butabarbital, hydroxyzine, and chloral hydrate) increased in New York State, while rates decreased nationally.[3] These "replacement" medications were either less acceptable, less efficacious, or more dangerous. Interestingly, the reduction in benzodiazepine use in the elderly did not lead to a decreased incidence of hip fractures in New York or New Jersey.[4] Similar prescription monitoring programs were established elsewhere in the United States, some of which were eventually replaced by electronic prescription systems.

The most controversial and consequential black-box warning in psychiatry came in 2004. The FDA warned that antidepressants were associated with an increased risk of suicidal thinking and behavior (suicidality, not actual suicide) in children, adolescents, and young adults. This warning was based on a series of meta-analyses (conducted by the FDA) of 372 trials showing the rate of suicidality was 4% in patients receiving antidepressants and 2% in patients receiving placebo. There were no deaths by suicide in any of these studies. This warning was followed by a reduction in antidepressant prescriptions for youth. In 2007, Gibbons et al[5] found that while prescriptions for selective serotonin reuptake inhibitors (SSRIs) for youths decreased by approximately 22% in both the United States and the Netherlands, the youth suicide rate increased significantly in both countries and seemed to be associated with the decrease in SSRI prescribing. The methodology and findings of this study have been disputed.[6] However, another quasi-experimental study by Lu et al[7] using psychotropic drug poisoning as a validated proxy for suicide attempt reported data similar to Gibbons et al[5]—ie, that safety warnings and widespread media coverage decreased antidepressant use, and, as a likely consequence, suicide attempts among young people simultaneously increased.

This warning also had a spillover effect in the adult population. Valuck et al[8] found that following the warning about the use of antidepressants in youths, the rates of newly diagnosed episodes of depression in adults were lower than expected based on preadvisory historic trends, and the rates of adults with depression who did not receive an antidepressant increased. There were no compensatory increases in psychotherapy or prescription of second-generation antipsychotics or anxiolytics.[8] It is not clear whether these trends persist. A 2009 study by Libby et al[9] suggested that depression diagnoses decreased and the spillover effect persisted while compensatory treatments varied, while a later study by Kafali et al[10] covering the period from 2000 to 2011 suggested that the impact of the warning may have dissipated as the rates of prescribing antidepressants in youth had gradually increased over the years.

As a result of all findings about the consequences of this black-box warning, Friedman[11] suggested that the FDA consider removing the warning entirely, or at least that the medical community should discuss the possibility. He wrote that the FDA advisory "has unintentionally discouraged depressed patients from seeking treatment and doctors from prescribing antidepressants."[11]

The most recent example of a black-box warning's unintended consequences comes from Gerlach et al.[12] They studied the consequences of initiatives to reduce off-label use of antipsychotics in patients with dementia living in nursing homes from the Veterans Health Administration and Centers for Medicare and Medicaid Services. Antipsychotic and anxiolytic prescribing in this population decreased, though the prescribing of other psychotropic medications such as antiepileptics (namely gabapentin), antidepressants (sertraline, mirtazapine, and trazodone), and opioids increased. These alternative medications have even less evidence of benefits than antipsychotics for these patients, and also have risks.[12]

How to respond to warnings

In their 2014 review, Stevens et al[13] noted "Almost all psychotropics recommended by psychiatric consultants carry a BBW [black-box warning]." They added that despite these warnings, "all of these medications remain viable—and necessary—treatment options with appropriate patient selection. Ultimately, physicians must decide how (not if) to recommend and prescribe medications with BBWs." The question remains how physicians make this decision, and what information and on which clinical situations they base their decision(s). There has not been much clinical guidance regarding these decisions, especially in psychiatry, though other specialties have tried to address them.

Winterfield et al[1] found that dermatologists raised many valid questions regarding the reaction to these warnings. They asked multiple questions on how the system works; how dermatologists learn about the warnings; how the knowledge of boxed warnings changes dermatology practice; if dermatologists feel compelled to counsel patients more before prescribing medications with black-box warnings; if dermatologists avoid prescribing these medications and instead choose alternatives to avoid

extra counseling and/or monitoring, or even potential liability; the magnitude of some of these unintentional effects of these warnings; and what physicians should do if there are no alternatives. All these questions apply to psychiatrists as well.

In their editorial in an allergy and immunology journal, Szefler et al[14] made several recommendations. They recommend that physicians develop their own policy about informing and educating patients about the warnings and suggested the FDA provide an informative list of black-box warnings. They also recommend that pharmaceutical companies provide useful information to help physicians and their patients make informed decisions. The involvement of medical societies, they suggest, would be helpful in providing a balanced assessment of the medication and associated black-box warning. The medical society "should assume the role of adequately informing their physician constituency with available information that aids in safely prescribing these medications and educating patients."

Is that sufficient? Not necessarily. My own view is that we should certainly adopt and address all ideas and recommendations mentioned in these 2 articles,[1,14] but also understand that black-box and other warnings may have legal implications. We need to build trusting relationships with our patients to better convey and explain the information in these warnings. We should document our communication about warnings with patients. Yet these measures do not tell us what to do regarding prescribing medications with warnings. I believe that major psychiatric journal(s) should publish a series of articles addressing warnings and keep adding new articles as new warnings are disseminated. These articles should be clinically useful, addressing issues such as whether and how to continue prescribing a specific medication with a warning; what the specific patient monitoring should be; whether to avoid medications with warnings in certain patients/populations; how to discontinue these medications if discontinuation is indicated; and what to do when one has to stop a medication—the alternatives, and their advantages and disadvantages/risks, and how to weigh risks and benefits of prescribing these alternatives instead of the medication with a warning. The articles/materials should also consider consequences of warnings on individual and population levels.

Black-box warnings are here to stay and may have unexpected consequences. We have to figure out how to appropriately work with the warnings and how to avoid their possible unintended consequences. ■

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