A black box warning (BBW) is the highest level of warning issued by the U.S. Food and Drug Administration (FDA). It aims to inform the patient and the prescriber of the potential major risks or life-threatening adverse reactions associated with the use of a medication. The warning is usually placed on top of the drug information label and is highlighted with a black box that distinguishes it from the rest of the text. These warnings are required when there is reasonable evidence of association between the drug and a significant safety concern suggested by either human or animal studies (1).

Boxed warnings have been associated with changes in clinical practice. A survey conducted in 2009 to assess the effect of BBWs for long-acting β-agonists found that 42% of primary care physicians and 35% of specialists were likely to change their treatment regimen for asthma on the basis of the warning (2). In 2010, Dorsey and colleagues published a time-series study in which they examined the use of atypical antipsychotics before and after issuance of a BBW. They found a significant decrease in their use in the years after the BBW was issued (3).

Despite their potential importance, BBWs have been the subject of controversy, due in part to their opaque connection to the underlying body of evidence. In 2004, Stades and colleagues called for easing of the restrictions on metformin use after demonstrating the low-quality evidence supporting its association with lactic acidosis. They also argued that the metformin BBW predisposed scientists to find a link when none existed (4). In 2006, researchers questioned the BBWs for different contraceptive medications that warned against several surrogate risk factors, including low bone calcium, hyperkalemia, and high levels of ethinyl estradiol (5). The researchers’ concern was partly due to what they judged to be outdated or recycled warnings from earlier package inserts and warnings that were not linked to trustworthy evidence. In 2011, Kaunitz and Grimes doubted the BBW against possible fracture risk for depot medroxyprogesterone acetate because of its reliance on a surrogate outcome (bone mineral density) (6).

Black box warnings have also been questioned because of the opaque nature of the risk–benefit judgments leading to their formulation. In 2014, dueling articles attacked and defended the BBW of the risk for suicide with antidepressants. The authors were concerned about the safety of depressed patients, who would be threatened either by the medication or by its avoidance (and resulting lack of treatment) (7, 8).

A clinician–patient dyad engaged in shared decision making and acting on the BBW requires 3 elements: an estimate of effect that allows tradeoffs; a level of certainty in the evidence; and guidance on how to implement or act on the BBW in a way consistent with the patient’s clinical context, values, and preferences.

The Current Study
Two of us independently evaluated 70 BBWs that were identified from the top 200 drugs (by prescription volume) dispensed in retail settings in the United States in 2012 (Table). We found that only 19 (27%) provided an estimate of the likelihood of harm, and only 8 (11%) reported a CI for that estimate. All of the BBWs described the population at risk, with nearly half (47%) specifying a subpopulation. Fewer than half (43%) presented the source of the evidence. None described the quality (certainty) of the evidence, and none provided guidance on how to communicate or act on the evidence. In the Appendix Table (available at www.annals.org), we provide examples of BBWs with varying levels of utility to practitioners.

In summary, although BBWs often affect the most commonly prescribed drugs in the United States, they infrequently contain 3 elements required for evidence-based practice (estimate of effect, source and trustworthiness of evidence, and guidance on implementation).

Proposal
We propose improving BBWs by adding an evidence profile and an implementation guide. The evidence profile should inform clinicians about the quality of the evidence and provide an absolute and relative effect estimate with uncertainty intervals. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group has developed a robust framework to create such profiles (9). Guidance on implementation should include risk stratification and communication tools to promote collaborative deliberation, an essential component of providing patient-centered care. As an example (10), the BBW on teriparatide-induced osteosarcoma should include an evidence profile highlighting the very-low-quality evidence supporting the association (demonstrated in animal studies); a risk calculator (such as the World Health Organization Fracture Risk Assessment Tool [www.shef.ac.uk/FRAX]) to assess the absolute risk for a fragility fracture; and a decision aid, when available (such as the Mayo Clinic Osteoporosis Decision Aid [http://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/other-decision-aids]).
The proposed approach is clearly not the only one, and perhaps various strategies can be prospectively tested to improve the utility of BBWs. Any future approach will require stakeholder engagement (patients, caregivers, physicians, the FDA, and manufacturers) to aid in its development, testing, and implementation.

In summary, although BBWs have a significant effect on health care practice, they do not present adequate information on the estimates of effect, the quality of evidence, or guidance on implementation. Evidence-based practice requires all of these elements. We propose a new structure for presenting BBWs that takes into consideration the fundamental principles of evidence-based medicine.

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## Appendix Table. Examples of Black Box Warnings With Varying Degrees of Rigor

<table>
<thead>
<tr>
<th>Quality</th>
<th>URL</th>
<th>Warning*</th>
<th>Comment</th>
</tr>
</thead>
</table>
See full prescribing information for complete boxed warning.  
• Long-acting beta2-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. A US trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.  
When treating patients with asthma, only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. | This warning presents an estimate of effect in both relative and absolute terms. It also indicates the source of the evidence, limitations of the available evidence, and guidance for implementation into practice. This example indicates that our standards are not unreasonably high. |
| Satisfactorily presented | www.accessdata.fda.gov/drugsatfda_docs/label/2013/018533s040lbl.pdf | WARNING: NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.  
Hepatotoxicity  
Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation, has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS section.  
QT Prolongation and Drug Interactions Leading to QT Prolongation  
Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, cisapride. Ketoconazole can cause elevated plasma concentrations of these drugs and may prolong QT intervals, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions sections. | Although this warning does not present estimates or sources of evidence, it is still informative because it provides general guidance for practice and refers to the appropriate sections in the package insert for more information. |
| Poorly presented | www.accessdata.fda.gov/drugsatfda_docs/lable/2012/202231s003lbl.pdf | WARNING: NOT FOR TREATMENT OF OBESITY OR FOR WEIGHT LOSS  
Thyroid hormones, including Levothyroxine Sodium for Injection, should not be used for the treatment of obesity or for weight loss. Larger doses may produce serious or even life threatening manifestations of toxicity. | This warning does not present any information on the source or quality of the evidence and does not refer to pertinent sections in the drug label. |

* Presented exactly as it appears on drug label.