FDA Boxed Warnings: How to Prescribe Drugs Safely

NINA R. O'CONNOR, MD, *Chestnut Hill Family Practice Residency Program, Philadelphia, Pennsylvania*

Boxed warnings, commonly referred to as "black box" warnings, are issued by the U.S. Food and Drug Administration and featured in the labeling of drugs associated with serious adverse reactions. These safety concerns are typically identified through the Adverse Event Reporting System and the Office of Surveillance and Epidemiology, which evaluates postmarket safety findings. The most common type of warning is issued when there is a potentially serious adverse effect that must be carefully weighed against the potential benefit of the drug. Warnings are also issued to draw attention to dosing, monitoring requirements, and potential drug interactions. Boxed warnings have been issued recently for oral sodium phosphate bowel preparations, fluoroquinolone antibiotics, and salmeterol. Despite these highly publicized warnings, all of these medications remain viable treatment options with appropriate patient selection. Ultimately, physicians must decide whether to prescribe drugs with boxed warnings. (*Am Fam Physician.* 2010;81(3):298-303, 304. Copyright © 2010 American Academy of Family Physicians.)

▶ **See related editorial on page 259.**

▶ **Patient information:** A handout on boxed warnings, written by the author of this article, is provided on page 304.

A boxed warning, commonly referred to as a "black box" warning, is the most serious type of warning mandated by the U.S. Food and Drug Administration (FDA). They are prominently featured in the labeling of drugs to warn prescribers about serious adverse reactions or special problems. Boxed warnings are displayed on a drug's package insert, in the *Physicians' Desk Reference,* on the FDA's Web site, and on the Web sites of drug marketing companies. Physicians are required to provide patients with information about relevant risks, but they can use professional judgment to decide whether to prescribe a drug with a boxed warning. Thus, physicians should be familiar with the process by which these warnings are created. In this article, several recent warnings will be used to illustrate this process, and strategies for safe prescribing of drugs with boxed warnings will be discussed.

Drug Approval and Safety Monitoring

The process for the approval of new drugs involves three phases of testing and typically spans several years *(Figure 1)*.[1,2] After a drug has been approved by the FDA, the FDA's Office of Surveillance and Epidemiology (formerly known as the Office of Drug Safety) conducts postmarket safety evaluation, with a focus on medication error prevention and risk management.[1] This office monitors postmarketing safety findings for adverse drug events. In addition, reports of adverse drug reactions are submitted to the FDA by consumers, health care professionals, pharmacists, and drug manufacturers. Physicians can submit reports directly on a standardized MedWatch form (available at http://www.fda.gov/safety/medwatch/howtoreport/downloadforms). These reports are collected in the Adverse Event Reporting System (AERS; http://www.fda.gov/cder/aers). The AERS has received more than 4 million reports since its inception in 1969.[3]

If a safety concern emerges from clinical trial data or consistent reports to the AERS, an interdisciplinary FDA team convenes with representatives from the Office of Surveillance and Epidemiology and the Office of New Drugs. Using a collaborative approach, this team then decides whether to continue monitoring, require a boxed warning on product labeling, or withdraw a drug from the market *(Table 1)*.[4,5] Less serious safety concerns are simply added to the "Warnings and Precautions" section of the package insert.[6]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Physicians should report adverse drug reactions to the U.S. Food and Drug Administration through the Adverse Event Reporting System (http://www.fda.gov/cder/aers).	C	1, 3
The STEPS (safety, tolerability, effectiveness, price, simplicity) approach can help physicians decide whether to prescribe new drugs and drugs with boxed warnings.	C	28
Physicians can find independent reviews of drug effectiveness at the Drug Effectiveness Review Project Web site (http://www.ohsu.edu/drugeffectiveness; for specific drugs, go to http://derp.ohsu.edu/about/final-products.cfm).	C	29
Consumers can find information about drug effectiveness at the Consumer Reports Best Buy Drugs Web site (http://www.consumerreports.org/health/best-buy-drugs/index.htm).	C	29

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

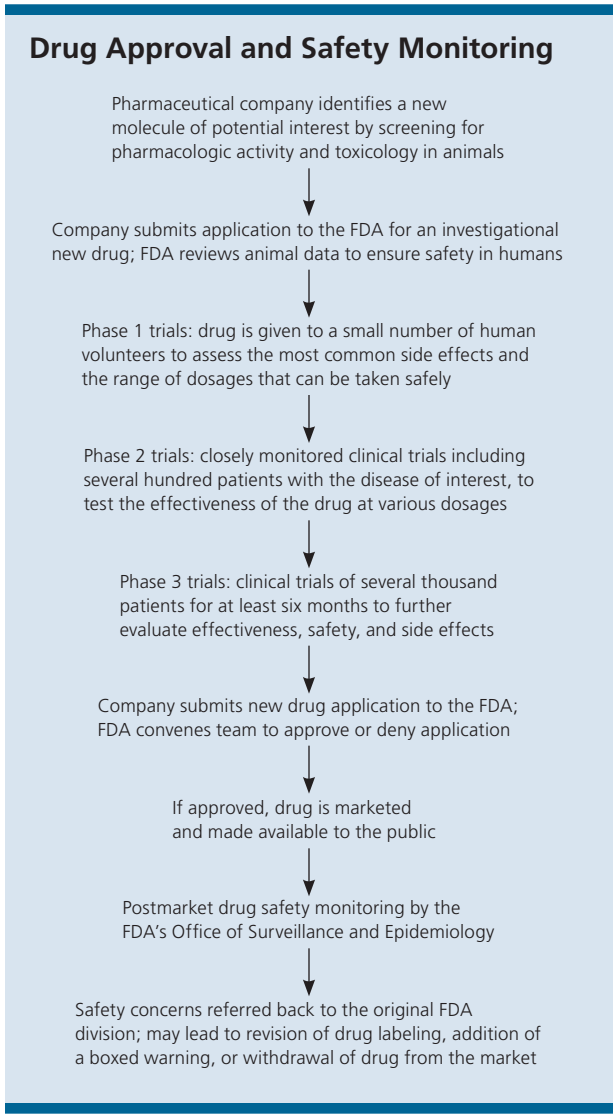

Figure 1. Drug approval and safety monitoring process. (FDA = U.S. Food and Drug Administration.)

Information from references 1 and 2.

Drug manufacturers may notify prescribers about new boxed warnings through "Dear Prescriber" letters.[2] Many drugs with boxed warnings also have FDA-mandated medication guides that must be given to patients at the pharmacy.[2] In recent years, the FDA has reached out to the general public. An advisory is now posted on the FDA Web site when a potential drug safety issue is identified, sometimes before the FDA determines whether any regulatory action will be taken.[2] These advisories are heavily publicized and may prompt questions to physicians before definitive information is available.

Frequency of Boxed Warnings

Between 1975 and 1999, the FDA approved 548 new drugs. By 2000, 45 (8.2 percent) of these drugs had at least one boxed warning, and 16 (2.9 percent) were withdrawn.[7] More recently, the incidence of boxed warnings has increased, while the number of drug withdrawals has remained relatively constant.[4,8,9] This may reflect an FDA initiative started in 2004 to strengthen postmarketing risk surveillance.[2]

Types of Boxed Warnings

Federal regulations specify three situations in which boxed warnings are appropriate. First, they are used when an adverse reaction is so serious in comparison to the drug's benefits that consideration is essential when assessing the risks versus benefits of the drug.[6] These warnings are typically used for potentially permanently disabling or fatal reactions. For example, the risk of anaphylaxis with iron dextran injection justifies its use only when anemia is severe and refractory to oral therapy.[10]

Second, boxed warnings are applied to drugs with the potential for serious adverse reactions that may be prevented or reduced in severity by appropriate prescribing.[6] This may include specific monitoring (e.g., liver function tests for valproic acid [Depakene]) or patient

Table 1. Selected Drug Withdrawals Since 2000

Drug	*Approved*	*Indication*	*Withdrawn*	*Reason for withdrawal*
Cerivastatin (Baycol)	1997	Hyperlipidemia	2001	Rhabdomyolysis
Cisapride (Propulsid)	1993	Gastroesophageal reflux disease	2000	QT prolongation
Hydromorphone, extended release (Palladone)	2004	Moderate to severe pain	2005	Potentially fatal interaction with alcohol
Pemoline (Cylert)	1975	Attention-deficit/hyperactivity disorder	2005	Hepatotoxicity
Pergolide (Permax)	1988	Parkinson disease	2007	Valvular disease
Rofecoxib (Vioxx)	1999	Inflammation, pain	2004	Cardiovascular events
Tegaserod (Zelnorm)	2004	Constipation-predominant irritable bowel syndrome	2007	Cardiovascular events
Troglitazone (Rezulin)	1999	Type 2 diabetes mellitus	2000	Hepatotoxicity
Valdecoxib (Bextra)	2004	Inflammation, pain	2005	Cardiovascular events

Information from references 4 and 5.

Table 2. Common Drug Classes with Boxed Warnings

Drug class	*Examples*	*Risks*
Aminoglycosides, injectable	Tobramycin, gentamicin	Ototoxicity, nephrotoxicity
Angiotensin-converting enzyme inhibitors	Enalapril (Vasotec), lisinopril (Zestril)	Injury or death to developing fetus
Angiotensin receptor blockers	Irbesartan (Avapro), valsartan (Diovan)	Injury or death to developing fetus
Beta blockers	Metoprolol, atenolol (Tenormin)	Exacerbation of angina and risk of MI with abrupt discontinuation
Calcineurin inhibitors, topical	Pimecrolimus cream (Elidel), tacrolimus ointment (Protopic)	Malignancy (causation not proven); avoid continuous long-term use; not indicated for use in patients younger than two years
Diuretics, loop	Furosemide (Lasix), bumetanide	Volume and electrolyte depletion
Estrogen	Estradiol in various preparations	MI, stroke, deep venous thrombosis, pulmonary embolism, and breast cancer in postmenopausal women
Iron supplements, oral	Ferrous sulfate, many vitamin supplements	Overdose may be fatal in children
Nonsteroidal anti-inflammatory drugs	Naproxen (Naprosyn), ibuprofen	Cardiovascular events, ulcers, and gastrointestinal bleeding
Oral contraceptives, combined	Various estrogens and progesterones	Increased cardiovascular risk in smokers, especially in those older than 35 years
Salicylates	Aspirin	Reye syndrome in children; potential for serious allergic reaction
Selective serotonin reuptake inhibitors	Fluoxetine (Prozac), duloxetine (Cymbalta)	Increased suicidality in children and adolescents

MI = myocardial infarction.

Information from reference 5.

selection (e.g., avoidance of angiotensin-converting enzyme [ACE] inhibitors in pregnant women).[10]

Third, the FDA issues boxed warnings for drugs with mandatory restrictions to ensure safe use.[6] For example, physicians must complete a certification program before prescribing isotretinoin (formerly Accutane). Other drugs, such as chemotherapeutic agents, may be administered only in supervised or inpatient settings.

Some boxed warnings apply to individual drugs, and others apply to entire classes *(Tables 2 and 3)*.[5] Physicians may be surprised to learn that many drugs they prescribe on a daily basis carry boxed warnings.

Table 3. Selected Drugs with Boxed Warnings

Drug	*Risks*
Amiodarone (Cordarone)	Pulmonotoxicity, hepatotoxicity
Atomoxetine (Strattera)	Increased suicidality in children and adolescents
Clozapine (Clozaril)	Agranulocytosis, seizures, myocarditis, and orthostatic hypotension; mortality in older patients
Fentanyl, transdermal (Duragesic)	Respiratory depression; contraindicated in patients with mild, acute, or postoperative pain
Ketoconazole	Hepatotoxicity
Methadone	Respiratory depression, especially with initiation or conversion from a different opioid; QT prolongation
Metronidazole (Flagyl)	Carcinogenic in mice and rats
Pioglitazone (Actos)	May cause or exacerbate heart failure; contraindicated in patients with NYHA class III or IV heart failure
Raloxifene (Evista)	Deep venous thrombosis and pulmonary embolism; stroke in patients with cardiovascular risk factors
Rosiglitazone (Avandia)	May cause or exacerbate heart failure; contraindicated in patients with NYHA class III or IV heart failure; one meta-analysis showed increased risk of myocardial infarction, but three other studies did not confirm
Telithromycin (Ketek)	Respiratory failure in persons with myasthenia gravis; contraindicated in these patients

NYHA = New York Heart Association.

Information from reference 5.

Recent Boxed Warnings

ORAL SODIUM PHOSPHATE

In December 2008, the FDA issued a boxed warning for prescription oral sodium phosphate about the potential for acute phosphate nephropathy. Sodium phosphate is commonly used for bowel cleansing before colonoscopy and leads to better bowel preparation than polyethylene glycol (Golytely) in outpatient settings.[11] Acute phosphate nephropathy causes acute and chronic renal insufficiency and was first linked to bowel preparation products through case reports in 2000.[12] Risk factors include chronic kidney disease, bowel obstruction, and active colitis. The use of certain medications (e.g., diuretics, ACE inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs) increases risk, as does hypovolemia.[5] Older patients may also be at increased risk; a recent study showed a decrease in glomerular filtration rate for six months after oral sodium phosphate intake in older patients with normal baseline creatinine levels.[13]

Despite the boxed warning, studies suggest that oral sodium phosphate is a safe choice in properly screened patients.[14] A 2007 cohort study of 7,897 patients with normal renal function compared oral sodium phosphate and polyethylene glycol before colonoscopy. The risk of renal dysfunction was the same in both groups (relative risk = 1.13; 95% confidence interval [CI], 0.58 to 2.23).[15]

FLUOROQUINOLONES

In July 2008, the FDA issued a boxed warning describing an increased risk of tendinopathy and tendon rupture in patients taking fluoroquinolone antibiotics. The risk is greatest in adults older than 60 years, in patients taking corticosteroids, and in transplant recipients.[5] The accompanying product information counsels prescribers to consider alternatives in patients with multiple risk factors for tendon rupture and to discontinue use in patients who develop tendon pain or inflammation during treatment.

Fluoroquinolone-associated tendinopathy has been described in multiple case reports and seems to be a real but rare risk of treatment.[16] One population-based case-control study found that 5,958 patients need to be treated with fluoroquinolones to cause one case of Achilles tendon rupture.[17] The number needed to harm (NNH) decreases with concomitant corticosteroid use (NNH = 979; 95% CI, 122 to 9,172) and age greater than 60 years (NNH = 1,638; 95% CI, 351 to 8,843).[17] Tendon injury can occur as early as two hours after the first dose and as late as six months after treatment ends.[18]

SALMETEROL

In 2005, the FDA issued a boxed warning for all products containing salmeterol (Serevent) because of the possibility of increased asthma-related mortality. This warning was based on preliminary results from the Salmeterol Multicenter Asthma Research Trial (SMART), which showed a small but statistically significant increase in asthma-related deaths in patients taking salmeterol (13 in the salmeterol group versus three in the placebo group).[19] The risk of death was greatest in black participants and in those not receiving inhaled

corticosteroids. This study supported concerns that tolerance to beta-agonist effects could make treatment of exacerbations more difficult.

A subsequent meta-analysis was published in 2006 that pooled data from 19 randomized controlled trials comparing long-acting bronchodilators and placebo.[20] In this analysis, long-acting beta agonists increased the risk of exacerbations requiring hospitalization (odds ratio [OR] = 2.6; 95% CI, 1.6 to 4.3) and life-threatening exacerbations (OR = 1.8; 95% CI, 1.1 to 2.9). More recently, a second meta-analysis combined data from 62 studies and 30,000 patients.[21] This analysis found comparable hospitalization rates in patients taking long-acting bronchodilators versus placebo (OR = 1.06; 95% CI, 0.91 to 1.24). The total number of asthma-related deaths was too small to perform a statistical comparison.

The boxed warning for salmeterol has been controversial given the widespread use of the drug and the small number of absolute events in the SMART trial. Although long-acting beta agonists increase the risk of serious asthma exacerbations, and possibly asthma-related death, the effect size is small and must be weighed against evidence that the drug increases symptom-free days.[22-24]

Boxed Warnings and Physician Practice

Physician adherence to boxed warnings is voluntary; no formal system exists to document appropriate patient selection, risk counseling, or drug monitoring. A large observational study of 51 outpatient practices in Boston, Mass., accessed electronic medical records to evaluate physician prescribing of drugs with boxed warnings.[25] Of 324,548 prescriptions issued, 2,354 (0.7 percent) violated some aspect of a boxed warning (e.g., inappropriate patient selection, failure to monitor appropriately, potentially serious drug interaction). Nonadherence was more likely when prescribing for patients older than 75 years and for those taking multiple prescriptions. In this study, less than 1 percent of instances resulted in an adverse drug event.

Recommendations for Safe Prescribing

One qualitative study in England found that family physicians prescribe new drugs more often than subspecialists, and obtain more information about new drugs from pharmaceutical representatives.[26] Although it is unclear whether these trends are occurring in the United States, physicians must realize that all newly approved drugs pose a risk of unsuspected adverse events.[27]

The scope of family medicine makes it difficult for physicians to remain current with emerging information on all relevant drugs. As illustrated by the examples in this article, boxed warnings may be issued before definitive evidence substantiates a safety concern. In addition, boxed warnings alone cannot provide the context needed to individualize risks and benefits to each patient's circumstances.

Table 4. STEPS Approach to Prescribing Medications

Safety: Risk of long-term or serious side effects compared with other drugs with the same indication; may be unknown for the first few years of a new drug
Tolerability: Less serious but still bothersome side effects
Effectiveness: Compared with other drugs with the same indication; direct comparisons may not be available for new drugs
Price: Must include cost of any monitoring
Simplicity: Includes route of administration, frequency of dosing, number of potential drug interactions, and monitoring required

Information from reference 28.

The STEPS model was originally developed as a tool to evaluate new drugs *(Table 4)*.[28] Consideration of the five STEPS criteria (safety, tolerability, effectiveness, price, simplicity) helps physicians decide whether to prescribe a new medication or choose an older (and usually cheaper) alternative. The STEPS model can also be used when deciding whether to prescribe a medication with a boxed warning. Do equally effective and safer alternatives exist? Does the potential benefit of the drug outweigh the safety concern?

There is growing interest in making evidence-based information about drugs available to prescribers, patients, and policy makers. One such initiative, the Drug Effectiveness Review Project (DERP), is a collaboration between several states, the Oregon Evidence-Based Practice Center, and the Center for Evidence-Based Policy.[29] DERP issues systematic reviews of drug effectiveness and safety (http://www.ohsu.edu/drugeffectiveness). These reviews are used by the Consumers Union to produce Consumer Reports Best Buy Drugs for patients (http://www.consumerreports.org/health/best-buy-drugs/index.htm). Resources such as DERP can provide physicians with the evidence and context needed to confidently evaluate new drugs, drugs with boxed warnings, and their alternatives.

This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

The Author

NINA R. O'CONNOR, MD, is a faculty physician at Chestnut Hill Family Practice Residency Program in Philadelphia, Pa.

Address correspondence to Nina R. O'Connor, MD, Chestnut Hill Hospital, 8815 Germantown Ave., Fifth Floor, Philadelphia, PA 19118 (e-mail: nina_o'connor@chs.net). Reprints are not available from the author.

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