Black Box Warnings

Blair Wilbert Pharm. D.
Assistant Professor
College of Pharmacy
University of Louisiana at Monroe

Many misconceptions exist in the medical community as to what a black box warning on a medication actually means. Some prescribers are unable to differentiate between a warning and a contraindication of a medication. The Food and Drug Administration (FDA) defines a contraindication as a clinical situation where the risk from the drug's use clearly outweighs any possible therapeutic benefit.[1] This is different from a black box warning, which is usually reserved for medications with potentially serious, life-threatening risks that may be minimized by detailing specific information to the physician. Medications with black box warnings require more patient-specific evaluation prior to use and intense monitoring from the physician after prescribing.[3] These warnings are bolded and outlined in a "black box" and can usually be found in the first section of the prescribing information (package insert). There are currently over 500 medications in the United States that carry black box warnings. Table 1 gives examples of several medications (and classes) that carry a black box warning.

There are multiple criteria the Food and Drug Administration uses to determine whether a particular medication (or class) should be assigned a black box warning. These criteria may include:[1]

1. There is an adverse reaction so serious in proportion to the potential benefit of the drug that it is essential that it be considered in assessing the risks and benefits of using a drug,
2. There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug, or
3. FDA approved the drug with restrictions to assure safe use because the FDA concluded that the drug can be safely used only if distribution or use is restricted.

The FDA uses various types of evidence when deciding if a black box warning should be assigned to a medication.[3] Evidence supporting the use of this warning can be obtained directly from randomized-controlled trials during the medication's approval process. Information received after the medication has already been approved and a particular adverse event is discovered during post-marketing reporting can also be used.[3] If a new or more frequent adverse event appears after a drug is already on the market, the FDA may decide to review the data and will then determine if a new boxed warning is merited.[4]

Pharmaceutical companies are required by law to update the product's prescribing information once a new boxed warning has been issued. This action may have severe detrimental effects on the medication's place in the market, as physicians are less likely to prescribe a medication with a new, serious warning.[3] A good example of this occurred in the 1990s with the drug Seldane® (terfenadine). After the FDA placed a black box warning on the drug, sales decreased from $700 million to $450 million in one year.[3]

Additionally, the FDA may decide that a *Medication Guide* be included with any medication that receives a black box warning. This guide is different from the prescribing information, which is usually the official drug monograph. The prescribing information contains all of the product's labeling information and may have specific instructions for the patient, such as the directions that are dispensed with packs of oral contraceptives. The *Medication Guide* contains important information directed mainly toward the patient. The guide usually includes monitoring parameters, signs and symptoms of particular adverse reactions (usually the one responsible for the warning), and various other types of pertinent information.

The FDA uses multiple criteria to determine whether a drug needs a *Medication Guide*. If it is determined that increased labeling could prevent an adverse event, or strict adherence to the directions are vital for the drug's safety and effectiveness, a guide may be issued.[4] These guides should be dispensed with the medication upon each new prescription and refill. It is the responsibility of the pharmacist to ensure that each patient who is prescribed a medication that has an accompanying guide not only receive the guide, but also receive the appropriate counseling when they pick up their prescription. The only exception to this rule is if the prescribing practitioner decides that receiving the *Medication Guide* is not in the best interest of the patient.[4] A list of *Medication Guides* can be found on the FDA website (www.fda.gov/Drugs/DrugSafety/ucm085729.htm).

It is important for prescribers to be aware of a medication's (or class') boxed warnings and determine if the benefit of that particular therapy outweighs the potential adverse effect of the drug. The prescriber should adhere to any FDA-recommended monitoring parameters for the specific medication.

Table 1. Common Medications with Black Box Warnings[2]

Medication or Class	Summary of Boxed Warning
ACE-inhibitors/Angiotensin-Receptor blockers (examples: enalapril, lisinopril, olmesartan, valsartan)	Should not be used in pregnancy, especially in second and third trimester due to risk of fetal injury or death
Amiodarone	Several potentially fatal toxicities, most commonly pulmonary (as high as 17%), and hepatotoxicity
Amphetamines (examples: dextroamphetamine/amphetamine, methylphenidate)	High potential for abuse, long-term use should be avoided
Antidepressants (examples: citalopram, fluoxetine, venlafaxine)	Increased risk of suicidality, especially in children, adolescents, and young adults
Antipsychotics (examples: olanzapine, risperidone)	Increased mortality in elderly patients with dementia-related psychosis, most due to cardiovascular causes
Beta blockers (examples: atenolol, metoprolol)	Abrupt discontinuation may exacerbate angina, myocardial infarction, and arrhythmias
Estrogen replacement therapy (example: conjugated estrogens)	Increased risk of cardiovascular events, endometrial cancer, and dementia if age 65 or older
Fluoroquinolones (examples: ciprofloxacin, levofloxacin)	Increased risk of tendonitis and tendon rupture in all ages, but higher if age 60 or older, on corticosteroids, or in transplant patients
NSAIDs (including COX-2 inhibitors) (examples: celecoxib, ibuprofen, naproxen)	Increased risk of serious cardiovascular thrombotic events, especially with long-term use, also increased serious gastrointestinal events (ulceration and bleeding)
Oral contraceptives (examples: ethinyl estradiol/norethindrone, mestranol/norethindrone)	Smoking increases risk of cardiovascular events
Promethazine	Should not use in children under 2 years of age due to potentially fatal respiratory depression
Salmeterol	Long-acting beta-2 agonists may increase risk of asthma-related death
Thiazolidinediones (examples: pioglitazone, rosiglitazone)	Can cause or exacerbate heart failure
Valproic acid (and derivatives)	Can cause liver failure (fatal), life-threatening pancreatitis, can cause teratogenic effects
Warfarin	Bleeding risk, can cause major (fatal) hemorrhage

References:

1. Food and Drug Administration. "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format *Draft Guidance*" January 2006. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf Accessed December 8, 2009.

2. Facts & Comparisons 4.0. Available at www.factsandcomparisons.com Accessed December 9, 2009.

3. Beach, J, Faich, G, Bormel, FG, Sasinowski, FJ. Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs. *Food and Drug Law Journal*. 1998, issue 53: 403-412.

4. Products with a "Black Box" Warning. *Pharmacist Letter/Prescribers Letter*. 2006; 22 (3) 220332.