Black Box Warnings

This guide outlines Black Box Warnings by drug class, indications, and management strategies, as well as the reasoning by the FDA and ramifications, geared to geriatric care

Black Box Warnings are issued by the Food and Drug Administration (FDA) to alert medical professionals of potentially serious adverse reactions a drug has demonstrated. The term "Black Box" refers to the fact that at the beginning of the package insert (PI) of the drug there is literally a black box encircling the written warning to capture the reader's attention. The FDA recently began a concerted effort to include more black box warnings on more products to increase public safety. Drugs may carry black box warnings for many reasons and the attached table contains specific examples of them pertinent to the geriatric population.

The FDA issues a black box warning to a drug's PI when "there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it (the black box warning) be considered in assessing the risks and benefits of using the drug." A warning is also issued if "there is a serious adverse reaction that can be prevented or reduced in frequency or severity *by appropriate use of the drug*" or "FDA approved the drug *with restrictions* to ensure safe use, because FDA concluded that the drug can be safely used only if distribution or use is restricted," such as through Risk Evaluation and Mitigation Strategy (REMS) programs (1). FDA continually monitors drugs after they have been approved to market for safety issues and will often issue a black box warning in response to post marketing surveillance observations where a significant safety issue has emerged.

One of the more talked about black box warning drugs in Long-Term Care is the one pertaining to the antipsychotic class of medications. This was issued to let medical practitioners know that when used inappropriately with a resident with dementia, the drug is being used off label, and the patient runs an increased risk of death. The legal ramifications of prescribing black box warning drugs draw scrutiny from practitioners, because using a black box medication in spite of a contraindication can be considered off label use. This could increase the liability of a practitioner, if in fact an adverse event related to the black box warning occurs. Important to note is that prescribers, Consultant Pharmacists, and facilities can fall under additional scrutiny from surveyors and ultimately incur citations as a result of inappropriate use of a medication, based on FDA warnings. For these reasons, prescribers, pharmacists, nursing facilities and most importantly patients benefit from being cognizant of FDA black box warnings. For more information on black box warnings, please contact your Remedi SeniorCare Consultant Pharmacist or Nurse.

Drug/Drug Class	Examples	Indication	Black Box Warning	Management Strategy
Antipsychotics	Quetiapine, Risperidone, Haloperidol, Olanzapine	Schizophrenia	Increased mortality in elderly patients with dementia-related psychosis	Monitor patients for improvement of dementia-related target symptoms. Antipsychotics are to be used for the shortest duration at the lowest dose possible in older adults with dementia. The need for a gradual dose reduction should be re-assessed periodically.
		Psychosis		
		Bipolar Disorder		
		Depression (adjunct)		
SSRIs/SNRIs	Sertraline, Trazodone, Escitalopram, Citalopram, Paroxetine, Duloxetine, Venlafaxine	Depression	Increased risk of suicidal thinking in children, adolescents, and young adults with major depressive disorder	Monitor patients *of all ages* who are started on antidepressant therapy and observe them closely for clinical worsening, suicidality, or unusual changes in behavior.
Opioids	Oxycodone IR/CR, Morphine, Hydrocodone, Fentanyl	Pain, acute and chronic	Increased risk of opioid addiction, abuse, and misuse	Monitor for the development of drug-seeking behaviors.
			Life-threatening respiratory depression	Do not crush, chew, or dissolve oxycodone CR tablets.
			Appropriate use of oral concentrate	Use 20mg/mL oral concentrate in opioid-tolerant patients only, with careful attention to volume measurements.
Fluoroquinolones	Ciprofloxacin, Levofloxacin, Moxifloxacin	Infection	Tendonitis and tendon rupture	Risk in increased in older adults (>60 years of age), kidney, heart, or lung transplant patient, and patients taking corticosteroids. Use carefully in this population.
Voltage-sensitive sodium channel blockers	Lamotrigine, Carbamazepine	Seizure Disorder	Serious dermatologic reactions (i.e. SJS, TEN) and HLA-B*1502 allele	Presence of the HLA-B*1502 allele is much higher in an Asian population; genetic testing is recommended. Discontinue drug if having a serious dermatologic reaction.
Long-Acting Beta Agonists (LABA)	Formoterol, Salmeterol	Asthma	Increased risk of asthma-related death	In those with asthma, LABAs should be used in combination with inhaled corticosteroids (i.e. fluticasone, budesonide).
		COPD		
Valproic acid derivatives	Valproic acid, Divalproex	Seizure Disorder	Hepatotoxicity	Usually occurs in first 6 months of use; perform LFTs at baseline and at frequent intervals thereafter.
		Bipolar Disease (mood stabilizer)	Pancreatitis	Can occur shortly after imitation or after several years of use; if pancreatitis is diagnosed, discontinue valproic acid.
Amiodarone	Amiodarone	Arrhythmias	Potentially fatal toxicities, particularly pulmonary/hepato- toxicity and heart block	Monitor PFTs and/or CXR if lung function declines, monitor LFTs yearly, and monitor blood pressure and heart rate regularly. Thyroid function should also be monitored.
Second generation anticoagulants	Pradaxa (dabigatran), Xarelto (rivaroxaban), Eliquis (apixaban)	Varies by agent; Nonvalvular atrial fibrillation; prevention and/or treatment of VTE	Thrombotic events upon premature discontinuation	Consider the risks and benefits of anticoagulation discontinuation; may consider switching to another anticoagulant prior to discontinuation.
			Spinal/Epidural hematoma	
Erythropoiesis-Stimulating Agents (ESAs)	Procrit, Epogen, Aranesp	Anemia due to CKD, Chemotherapy, HIV treatment	Increased risk of death, MI, thrombotic events, and stroke and venous thromboembolism	Weekly monitoring of Hemoglobin (Hgb) until stable then at least monthly with the target goal no greater than 11.0 g/dL

Abbreviations: CXR = chest x-ray, COPD = chronic obstructive pulmonary disease, MI = myocardial infarction, PFTs = pulmonary function tests, SJS = Stevens-Johnson Syndrome, SNRI = serotonin norepinephrine re-uptake inhibitor, SSRI = selective serotonin re-uptake inhibitor, TEN = Toxic Epidermal Necrolysis, VTE = venous thromboembolism

Lexi-Comp Online™ , Hudson, Ohio: Lexi-Comp, Inc.; October 09, 2014.