

## Proceed with Caution: **BLACK BOX WARNING** and **High Risk** drugs



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## Background

- Healthcare provider's role in medication safety
  - Stay updated and informed
- What's the difference between a **warning**, **precaution**, **contraindication**, and a BBW?
  - **Warning**: Serious adverse events that have been observed and potential safety hazards
  - **Precaution**: Consideration must be taken in special situations/patient groups
  - **Contraindication**: Drug should not be used due to risk of use >> possible benefit

## Black Box Warning

- **Definition**: Black Box warnings are the strongest warning the FDA requires and typically details safety data (eg, adverse events, drug interactions) but may also include information regarding restrictions for use or distribution.
  - Constant updates and revisions

## Did you know...

- Currently 400+ drugs on market with FDA-mandated BBW
- Affects almost any medication class you can think of
  - Antidepressants
  - Contrast agents
  - Asthma inhalers
  - Acne medication
  - Many more

## Clinical Pharmacist Role

- FDA updates
- Monitor patients on target BBW and High Risk drugs
- Epoetin dosing per pharmacy
- Monitor "Trigger Drug" usage
  - Is it an Adverse Drug Event?
- Food-Drug interactions
- PCA monitoring
- Non-formulary requests
  - Pharmacotherapy education

## Target BBW drugs at RCRMC

- ACE/ARBs
  - Benazepril (LOTENSIN)
  - Captopril (CAPOTEN)
  - Enalaprilat (VASOTEC)
  - Ramipril (ALTACE)
  - Losartan (COZAAR)
- NSAIDs
  - Naproxen (ANAPROX, NAPROSYN)
  - Sulindac (CLINORIL)
  - Piroxicam (FELDENE)
  - Ibuprofen (MOTRIN, ADVIL)
  - Ketorolac (TORADOL)
- Fentanyl patch (DURAGESIC)
- Epoetin alfa (EPOGEN, PROCRIT)

## ACE/ARBs

- When used in pregnancy during the 2nd and 3rd trimesters, ACEs can cause injury and even death to the developing fetus.
- When pregnancy is detected, ACEs should be discontinued as soon as possible.

## Fentanyl patch (DURAGESIC)

- Indicated for management of persistent moderate to severe chronic pain in  $\geq 2$  y/o
- Indicated for opioid-tolerant: those who have been taking for  $\geq 1$  week:
  - $\geq 60$  mg of morphine daily
  - $\geq 30$  mg of PO oxycodone daily
  - $\geq 8$  mg of PO hydromorphone daily
  - an equianalgesic dose of another opioid
- Avoid concomitant liver enzyme CYP 3A4 inhibitors

## NSAIDs

### Cardiovascular Risk

- NSAIDs may cause an increased risk of serious CV thrombotic events, MI, and stroke, which can be fatal. This risk may increase with duration of use. Patients with CV or risk factors for CV disease may be at greater risk.
- NSAIDs are contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms.
- Elderly patients are at greater risk for serious GI events.

## Drug interactions

- Aspirin
- Anticoagulants/blood thinners/antiplatelets (i.e., warfarin, heparin)
- Celecoxib (CELEBREX)
- Vitamin E
- Certain antidepressants in elderly
- Anything that can increase bleeding

## Epoetin alfa (EPOGEN, PROCRIT)

### Renal failure

- Patients experienced greater risks for death and serious CV events when administered ESAs to target higher vs lower Hgb levels.
- Individualize dosing to achieve and maintain Hgb levels within the range of 10 to 12 g/dL.

### Perisurgery

- Epoetin increased the rate of DVTs in patients not receiving prophylactic anticoagulation. Consider DVT prophylaxis.

### Cancer

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical CAs when dosed to target a Hgb of  $\geq 12$  g/dL.
- Use only for treatment of anemia due to concomitant myelosuppressive chemotherapy.
- Discontinue following the completion of a chemotherapy course.
- Use the lowest dose needed to avoid RBCs transfusions.

## Epoetin dosing

- Epoetin is a dangerous drug no matter what.
- Goal to *customize* dosing for each individual patient.
  - Verify indication
  - Labs
  - Avoid 40,000 weekly dosing
  - Appropriate dosage adjustments
  - Appropriate iron supplementation
  - Make sure Hgb stays within target range

## High Risk Drugs

- What is a High Risk drug?
  - Not necessarily BBW, but must be cautious
    - Narrow therapeutic index (i.e., phenytoin)
    - Potential serious adverse effects (i.e., amiodarone) if not monitored closely
- Target High Risk drugs at RCRM
  - Amiodarone (CORDARONE, PACERONE)
  - Phenytoin (DILANTIN)
  - INJ Haloperidol (HALDOL)
  - Fentanyl patch (DURAGESIC)

## Amiodarone (CORDARONE, PACERONE)

- Potentially fatal toxicities
  - Pulmonary, liver
  - Exacerbate arrhythmia
- Variable absorption, elimination → determining maintenance dose is difficult
- Arrhythmia may recur after discontinuing drug or adjusting dose → keep watch
- Other adverse effects:
  - Hyper/hypothyroidism
  - Vision loss
  - Photosensitivity
    - Blue-grey skin
  - Peripheral neuropathy
  - Many drug interactions
    - Metabolized by liver enzyme 3A4

## Injectable Haloperidol (HALDOL)

- Higher risk of QT prolongation and Torsades de Point
  - Avoid with other drugs that prolong QT
- Tardive dyskinesia
  - Irreversible involuntary movements
- Neuroleptic Malignant Syndrome
  - Potentially fatal
  - Increased body temperature, muscle rigidity, altered mental status, irregular pulse/BP
- Oversedation
- Duration of therapy
  - Use in acute situations, replace with oral ASAP

## Phenytoin (DILANTIN)

- Narrow therapeutic index
- Target serum level: 10-20 mcg/ml
- Albumin levels may affect serum levels
  - Corrected phenytoin level
- Many drug interactions
  - Liver enzyme CYP 3A4 substrate and inducer
- Liver impairment can cause toxicity
- Overdose can lead to delirium/psychotic symptoms, oscillation ...even fatality

## “Trigger Drugs”

- |   |   |
|---|---|
| ■ Sodium Polystyrene Sulfonate (SPS, KAYEXALATE) <ul style="list-style-type: none"> <li>■ Increased K+</li> <li>■ ACE, spironolactone, amiloride, triamterene, Klorcon/K-dur</li> </ul> | ■ Methylprednisolone sodium succinate (SOLU-MEDROL) <ul style="list-style-type: none"> <li>■ Allergic reaction</li> </ul>                       |
| ■ Diphenhydramine (BENADRYL) <ul style="list-style-type: none"> <li>■ Allergic reaction</li> </ul>  | ■ Protamine <ul style="list-style-type: none"> <li>■ Anticoagulants-heparin, enoxaparin (LOVENOX)</li> </ul>                                    |
| ■ Flumazenil (ROMAZICON) <ul style="list-style-type: none"> <li>■ Benzodiazepine toxicity-alprazolam, chlordiazepoxide, lorazepam, diazepam, clonazepam, midazolam</li> </ul>           | ■ Naloxone (NARCAN) <ul style="list-style-type: none"> <li>■ Opioid toxicity</li> <li>■ Morphine, fentanyl, oxycodone, codeine, etc.</li> </ul> |
|   | ■ Phytonadione / vitamin K <ul style="list-style-type: none"> <li>■ Increased INR</li> <li>■ Warfarin (COUMADIN)</li> </ul>                     |

## Resources

- Formulary Productions
  - <http://www.formularyproductions.com/blackbox/>
- FDA MedWatch
  - <http://www.fda.gov/medwatch/safety.htm>
- BBW binder at nursing stations
- Pyxis-Lexi-comp, Micromedex
- *Physician's Desk Reference* (PDR)
- Pharmacy services

## The End

Questions?

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**Thanks for your participation!**

## References

- Benazepril Package Insert
- Ibuprofen Package Insert
- Fentanyl Package Insert
- Epogen Package Insert
- Amiodarone Package Insert
- Phenytoin Package Insert
- Haloperidol Package Insert
- Metformin Package Insert
- Formulary Productions  
<http://www.formularyproductions.com/blackbox/>
- FDA MedWatch  
<<http://www.fda.gov/medwatch/safety.htm>>