Bryan D. Hayes, PharmD, FAACT, FASHP
Massachusetts General Hospital/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

Black Box Drugs We Use: What's the Risk?

Session Overview

The black box drug list seems to be growing yet we are constantly faced with drug shortages limiting our choices when caring for patients in the ED. Many of us have used these drugs extensively in the past & feel quite comfortable with continuing this use on our patients. What is our risk when we do this? Is it a reasonable risk? The speaker will summarize black box warnings on drugs frequently used in the ED, assess the risk of this continued use, justify appropriate use in specific patients, & identify critical documentation needed when choosing to use these drugs.

Objectives

1) Summarize black box warnings on drugs frequently used when caring for patients in the ED
2) Assess the risk of continued use of these drugs despite these warnings
3) Justify appropriate continued use of black box drugs in the context of specific patients presented through a case-based approach

BACKGROUND

Boxed warning: This type of warning is also commonly referred to as a "black box warning." It appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks. Boxed warnings are issued by the FDA and are different than contraindications, which generally mean the drug should be avoided in that situation. It is the strongest form of warning required by the FDA for prescription drug labeling. The boxed warning is presented in a box surrounded by a black border and is placed on the drug label and any package inserts or promotional materials intended for the prescriber or patient.

Staying current with new literature is a challenge, particularly in emergency medicine where our purview covers all specialties. And, new and revised black box warnings for medications used in the ED are regularly added. In one study, only 37% of EM physicians reported that they consider BW when prescribing medications (Smollin 2016). Many of the survey respondents did not have a consistent method for staying current with boxed warnings.

FLUOROQUINOLONES

The Problem

Still among the most commonly prescribed antibiotics, fluoroquinolones top my least-favorite-antibiotic list. Two great summaries of the FQ adverse effects from EMPharmD blog and ALiEM blog. The risk rarely outweighs the benefit even in critically ill patients, as summarized on the EMCrit blog. Some of the major adverse effects include:

- Tendinitis/tendon rupture [boxed warning] (Corrao 2006)
    - General population - 1 in 6,000
    - Patients on concomitant steroids - 1 in 1,000
- Peripheral neuropathy [boxed warning] (Etiminan 2014, Francis 2014)

- CNS effects (seizures/psychiatric effects) [boxed warning]
- Exacerbation of myasthenia gravis [boxed warning]
- GI perforation
- Aortic aneurysm/dissection (Lee 2015, Singh 2017)
- Retinal detachment (Etminan 2012, Raguideau 2016)
- Hypo/hyperglycemia (Chou 2015)
- QT prolongation (Mehrzad 2015, Zeltser 2003)
- *C. Difficile* (Pepin 2005, Sarma 2015)

Patients taking FQs are at a high enough risk that the FDA published a 2018 safety alert recommending levofloxacin be reserved for use only in patients who have no alternative treatment options for the following indications: uncomplicated urinary tract infection, acute bacterial exacerbation of chronic bronchitis, and acute bacterial sinusitis. Unfortunately, safety alerts have not changed prescribing practices much (Cowart 2019).

Use in the ED
ED, ED Obs, Inpatient Boarders, Discharge Rx

Verdict
FQs should be avoided in favor of other antibiotics. Instead, they should be considered only if other options are contraindicated or if individual patient resistant patterns leave FQs as the best option.

TRAMADOL

Tramadol has a reputation for being a safe, non-opioid alternative to opioids. Nothing could be further from the truth. It is an opioid after all, and it comes with significant adverse effects (Young 2013, Thiels 2019).

- Tramadont from EMCrit
- Tramadol: When to Avoid It from Academic Life in EM
- Three Reasons Not to Prescribe Tramadol from EM PharmD

Tramadol is an opioid, a synthetic one that is now schedule IV according to the DEA. It has no less than 8 parts to its boxed warning including: 1) Addiction, abuse, and misuse; 2) Opioid analgesic Risk Evaluation and Mitigation Strategy (REMS); 3) Life-threatening respiratory depression; 4) Accidental ingestion; 5) Ultra-rapid metabolism of tramadol and other risk factors for life-threatening respiratory depression in children; 6) Neonatal opioid withdrawal syndrome; 7) Interactions with drugs affecting cytochrome P450 isoenzymes; 8) Risks from concomitant use with benzodiazepines or other CNS depressants.

The Problem

- It may not work very well (Sachs 2005)
    - Osteoarthritis-related pain: modestly effective in placebo-controlled trials (Cepeda 2006)

    - Neuropathic pain: efficacy comparable to gabapentin, TCAs, & carbamazepine (Hollingshead 2006)
    - Emergency Department
        - Musculoskeletal: Inferior to hydrocodone/APAP (Turturro 1998)
        - Ankle sprain: tramadol/APAP equivalent to hydrocodone/APAP (Hewitt 2007)
- Seizure risk
    - Previous studies have been unable to confirm an increased seizure risk with therapeutic doses of tramadol (Seizure Risk Associated with Tramadol Use from EM PharmD blog). However, a newer study refutes that premise reporting up to 22% of first-seizure patients had recent tramadol use (Asadi 2015)
- Serotonin syndrome risk (Sansone 2009)
- Hypoglycemic risk (Fournier 2015, Juba 2020)
- Erratic metabolism (Leppert 2011)
- Abuse/dependence/withdrawal risk (Senay 2003)

Use in the ED
ED Obs, Inpatient Boarders, Discharge Rx

Verdict
Tramadol should be avoided in most patients in favor of acetaminophen, short courses of NSAIDs, topical analgesia (eg, lidocaine), or, if an opioid is indicated, use oxycodone or hydromorphone (for short courses).

DROPERIDOL

Droperidol has a well-known boxed warning for dysrhythmias (namely QT prolongation and torsade de pointes) (Habib 2008, Ludwin 2008, Rappaport 2008). It's also been MIA for many EDs in the past decade due to a prolonged shortage. However, it's back in 2019! Droperidol is effective for nausea and vomiting including cannabinoid hyperemesis syndrome, benign headache and migraine, and for the control of acute agitation in the ED.

The Problem
The history of droperidol is well-described and summarized succinctly in two open-access blog posts:

1. The Return of Droperidol from Taming the SRU
2. Droperidol Use in the ED from emDOCs.net

The question now is should we be adding this back to our hospital formularies despite its cousin, haloperidol, having similar efficacy for some of these indications. What is our liability if a patient has a bad outcome when using a drug with a black box warning?

Use in the ED
ED

Verdict

Droperidol should be added back to the ED armamentarium. The QT/torsades risk is overblown and based on old, largely unsubstantiated reports (Jackson 2007, Habib 2003). The QT prolongation is not clinically significant (Calver 2015, Gaw 2019, Lee 2019).

A 2015 American Academy of Emergency Medicine (AAEM) Position statement: *"Droperidol is an **effective and safe medication** in the treatment of nausea, headache, and agitation. The literature search **did not support mandating an electrocardiogram or telemetry monitoring for doses < 2.5 mg given either IM or IV**. IM doses of up to 10 mg of droperidol seem to be as safe and as effective as other medications used for sedation of agitated patients."* (Perkins 2015)

OTHER ANTIEMETICS

Background

We use a lot of QT-prolonging medications in the ED. (Tay 2014) One of the places I like to start is Credible Meds, which maintains a list of drugs categorized by their potential to cause QT prolongation and/or torsades de pointes (TdP). You need a free registration to view the QT med list, but it is worth it.

Ondansetron

- Mean QTc interval increase after ondansetron 4 mg IV in ED patients = 16-20 msec (Moffett 2016, Li 2018)
- Mean QTc interval increase after ondansetron 4 mg IV in patients with cardiovascular disease and additional risk factors for torsades = 19 msec (Hafermann 2011)
- No increase in QTc interval after ondansetron 0.15 mg/kg IV in children with gastroenteritis (Hoffman 2018)

Metoclopramide: ED studies have not found QT prolongation with 10 mg IV (Gaffigan 2015)
Prochlorperazine: Prochlorperazine has not been shown to cause QT prolongation, but it's guilty by association because other phenothiazines have shown QT prolongation.

Use in ED

ED, ED Obs, Inpatient Boarders, Discharge Rx

Verdict

Ondansetron: A systematic review concluded, "Current evidence does not support routine ECG and electrolyte screening before single oral ondansetron dose administration to individuals without known risk factors." (Freedman 2014) Consider obtaining ECG if a repeat dose is given within 1-2 hours.

Metoclopramide and prochlorperazine have the lowest risk of QT prolongation among the antiemetics commonly administered in the ED.

MIDAZOLAM

The Problem
Midazolam has 4 parts to its boxed warning: 1) Respiratory depression and personnel/equipment for monitoring and resuscitation; 2) Risks from concomitant use with opioids; 3) Individualization of dosage (injection); 4) Neonates (injection).

Use in the ED
ED

Verdict
Continue using midazolam in the ED with proper monitoring for respiratory depression.

OLANZAPINE (parenteral)

The Problem
Olanzapine has 2 boxed warnings, though mostly associated with long-term management of dementia-related psychosis in older adults. In the ED, there exists a potential risk of excess sedation and respiratory depression when IM/IV olanzapine administered with parenteral benzodiazepines. Currently, IM olanzapine is the only second-generation antipsychotic with a warning listed in its FDA prescribing information stating, "concomitant administration of intramuscular olanzapine along with benzodiazepines is not recommended due to the potential for excessive sedation and cardiorespiratory depression." This advisory is the result of 160 post-marketing adverse events, including 29 fatalities, associated with IM olanzapine (Marder 2010). The European Medicines Agency recommends separating the administration of IM olanzapine and IM benzodiazepines by at least 60 minutes. The FDA does not have a specific recommendation regarding the separation of the 2 medications but warns against coadministration.

Use in the ED
ED, ED Obs, Inpatient Boarders

Verdict
While caution is advised, several ED studies have used IV/IM olanzapine with parenteral benzodiazepines in agitated patients (Chan 2013, Cole 2017, Martel 2016, Wilson 2012, Williams 2018, Wilson 2012, Khorassani 2019).

NSAIDs

The Problem
NSAIDS have black box warnings linked to serious cardiovascular thrombotic events and gastrointestinal bleeding, ulceration, and perforation. Ketorolac, ibuprofen, and naproxen are the most common ones used in the ED.

Cardiovascular (Lancet 2013)

- Patient factors affecting risk: Presence of prior cardiovascular disease, history of systemic inflammatory disorder, older age, male gender, hypertension, hyperlipidemia, diabetes, and smoking
- NSAID factors affecting risk: Duration, frequency, dose of therapy, and maybe the degree of selectivity for inhibition of cyclooxygenase (COX)-2 relative to COX-1

GI Bleeding (Laine 2010) - Up to 5 X higher risk than controls (Savage 1993)

- Patient risk factors: Prior history of a GI ulcer/hemorrhage; age >60; high NSAID dose; concurrent use of glucocorticoids (Piper 1991), antiplatelet agents, or anticoagulants

Use in the ED

ED, ED Obs, Inpatient Boarders, Discharge Rx

Verdict

NSAIDs should be prescribed at the lowest effective dose for the shortest duration possible for the given indication (more on NSAID dosing from my ASHP 2017 lecture handout) and these recent ED studies (Motov 2017, Motov 2019). Naproxen or ibuprofen may be the best oral option. In patients with cardiovascular disease, alternatives to NSAIDs should be considered.