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Drugs with FDA Boxed Warnings: What's the Risk in the ED?

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 package insert (in a black box) 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.

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 boxed warnings 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. The ALiEM blog has a great summary of FQ adverse effects. The risk rarely outweighs the benefit even in critically ill patients, as summarized on the EMCrit blog. Major adverse effects include:

- Tendinitis/tendon rupture [boxed warning] (Corrao 2006, Morales 2019, Alves 2019, Arabyat 2015, Shu 2022)
    - Importantly, some have not found an association (Baik 2020, Ross 2021)
- Peripheral neuropathy [boxed warning] (Etiminan 2014, Francis 2014, Ali 2014)
- CNS effects (seizures/psychiatric effects) [boxed warning]
- Exacerbation of myasthenia gravis [boxed warning]
- GI perforation
- Aortic aneurysm/dissection (Lee 2015, Meng 2019, Rawla 2019)
- 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. Safety alerts have a variable effect on prescribing practices (Cowart 2019, Sankar 2021, Bratsman 2020). The FDA boxed warning for FQ's is here.

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 resistance 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). Here are some great, in-depth reviews of its safety profile.

- Tramadont from EMCrit
- Tramadol: When to Avoid It from Academic Life in EM

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's got 'messy' pharmacology and erratic metabolism (Young 2013, Leppert 2011)
- 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 (Babahajian 2019)
    - Previous studies were unable to confirm an increased seizure risk with therapeutic doses of tramadol. 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, de Canecaude 2021)
- Hyponatremia? (Fournier 2015, Falhammar 2019, de Canecaude 2021)
- Abuse/dependence/withdrawal risk (Senay 2003)
- Mortality? (Xie 2021, Zeng 2019)

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 black box 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, 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 boxed warning? Here is one approach (Mattson 2020).

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, Taylor 2017, Lee 2019, Klein 2019, Gaw 2020, Cole 2020).

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)

Bonus pearl: What about the other antiemetics?

Metoclopramide: Minimal risk of QT prolongation (Gaffigan 2015)

Prochlorperazine: Minimal risk of QT prolongation

Ondansetron: 4 mg IV prolongs QTc by a mean of ~20 msec in adult ED patients (Moffett 2016, Li 2018). It is similar in patients with cardiovascular disease (Hafermann 2011). Children seem less affected (Hoffman 2018, Assaad 2023).

MIDAZOLAM + OLANZAPINE (parenteral)

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).

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 separation of the 2 medications, but warns against coadministration. However, when these cases are thoroughly investigated, it seems like more of a polypharmacy problem than an olanzapine/benzodiazepine problem. Here’s a summary from the FOAMcast podcast.

Use in the ED

ED, ED Obs, Inpatient Boarders

Verdict

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

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, Hunt 2021). Separation by 60 minutes seems like a good middle ground to limit safety concerns.