Polypharmacy Network Newsletter for Professionals

Welcome to the Polypharmacy Network's inaugural newsletter! Our newsletter is dedicated to highlighting a medication use topic and share Polypharmacy Network style analysis and perspective.

The information provided in our newsletter is not meant to provide official guidance; but our purpose is to help encourage robust discussion and analysis, informed choices and informed conversations about medication use.

FDA Label Change for Fluoroquinolones

Fluoroquinolones are a class of antibiotics typically reserved for serious bacterial infections. This class of medication cannot treat viral infections because it is an antibiotic. Sometimes these medications are used for upper respiratory infections, urinary tract infections, bone and joint infections, intestinal infections, and many others.

Fluoroquinolones were discovered and licensed in the 1970s and 1980s, and new generations of fluoroquinolones continue to evolve.

In 2008 the FDA send out a warning that fluoroquinolones can cause **tendon injuries**, such as ruptured Achilles heels. In 2016 the FDA sent out an advisory that due to serious side effects associated with fluoroquinolones, patients with sinus infections, bronchitis, and uncomplicated urinary tract infections, should use other treatments if possible, and fluoroquinolones should be reserved for those who do not have alternative treatment options. In other words, for most cases, fluoroquinolones would not be a first line choice for the treatment of bacterial infections. Also, these risks highlight the fact that taking an antibiotic "just in case" you have an infection, not only creates more resistant bacteria (or "bugs), but also places people at unnecessary risk. It is important to have your healthcare provider confirm the diagnosis that you have a bacterial infection before taking any sort of antibiotic.

The FDA warning labels for fluoroquinolones include boxed warnings for tendinitis, tendon rupture, and worsening of myasthenia gravis. Warnings also include risk of peripheral neuropathy and potentially permanent central nervous system effects (such as confusion, gait disturbance or difficulty walking, delirium), as well as cardiac, dermatologic, and strong allergic reactions.

If fluoroquinolones have been on the market since the 1980s, then why didn't these warnings come out earlier?

FDA requires labeling changes for fluoroquinolones (a class of antibiotics)

On 7/10/2018 the FDA announced that it is strengthening the current warnings in the prescribing information for fluoroquinolones.

The most recent warning: Fluoroquinolones can cause **significant decreases in blood sugar and certain mental health side effects.**

Fluoroquinolones include antibiotics such as:

Cipro®(ciprofloxacin)

Levaquin® (levofloxacin)

Tequin® (gatifloxacin)

Avelox® (moxifloxacin)

Ocuflox®/Floxin®/Floxacin® (ofloxacin)

Noroxin® (norfloxacin)

The new FDA safety announcement requires label changes; which means that updated information must be included in the official "drug labels", or drug information provided for patients and prescribers, as well as patient "Medication Guides".

Medication Guides are an FDA required paper handout that comes with prescription medications to help avoid serious adverse events.

The answer to that question is a complicated one. However, a starting place is to understand how medications are tested as new drugs and brought to market. You may have heard of investigational new drug (IND) studies. IND studies take a new drug compound (*which has been modeled and tested first in laboratory animals*), and tests in healthy volunteers, then people who have the condition which the drug treats. Sometimes these are called safety and efficacy studies. Once the FDA is sufficiently convinced that a medication is effective and relatively safe, the drug can be marketed to the public.

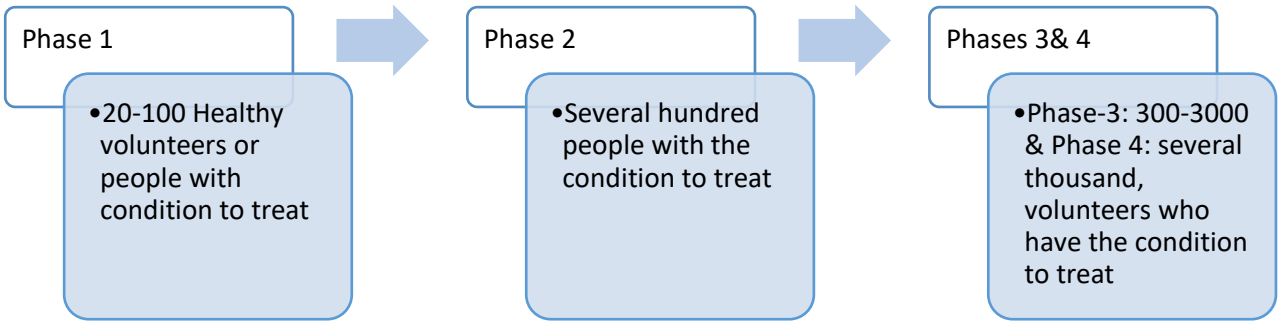

Figure 1: Investigational New Drug (IND) Process- How new drugs get to market.

From the IND studies, we can identify trends in adverse side effects. Consider that drugs are tested in thousands of people who are carefully selected (inclusion criteria) to participate in IND studies. Most IND study subjects are not representative of medically complex or frail persons.

Often, we don't discover the true nature of drug side effects, drug interactions, and drug-disease interactions, until a drug is released for use in the public at large, where the new drug can interact with an infinite number of combinations of prescription drugs, over the counter drugs, herbals and supplements. When released for public use, the drug is then used in people with an infinite variety of disease state mixes as well as physiological, genetic and environmental influences. The drug then interacts with these complexities to reveal unwanted side effects.

The data from IND studies involving several thousand carefully selected study participants is not the same as post marketing data. Post marketing surveillance is called "Phase 5" or FDA Post-Market Drug Safety Monitoring. You can sign up for "MedWatch" safety alerts from the FDA. MedWatch is a gateway for reporting problems with medical products.

Could we have predicted this strong FDA warning about fluoroquinolones earlier?

When a potential problem with a drug exists, that problem can occur unexpectedly in any individual using any medication. However, as a society we look for **epidemiological "signals"** which identify potential associations between medical products and health outcomes.

For example: in the early days when Cipro® entered the market, and it was used to treat and older, frail adult for pneumonia, it would have been difficult to tell whether that person had confusion or delirium due to hospitalization, or the infection itself, or dementia, or the course of Cipro® they were given. It wasn't until enough people experienced confusion, gait disturbance, delirium, and other neurological effects when taking Cipro® that the epidemiological signal became significant enough for authorities to take note.

With fluoroquinolones as with most medications, the adverse effects are more noticeable in frail older adults who lack physiological reserve to survive insults such as infection, or strong medications. So, the adverse effects of fluoroquinolones would be more frequently observed in frail older adults, and in fact in the professional drug databases special consideration for geriatric patients is highlighted frequently. But, the central nervous system

affects described above may go unnoticed in an older patient yet may have been reported by a younger patient to the FDA.

Ultimately the risk versus benefit of using any medication is highly individual.

Can you take proactive steps to prevent adverse drug events, such as those linked to fluoroquinolones without waiting for the epidemiological signals to emerge?

The Polypharmacy Network encourages a proactive approach to safe medication use.

In the book "The Checklist Manifesto-How to Get Things Right" Dr. Atul Gawande describes the importance of avoiding mistakes because we don't make proper use of what we know. Dr. Gawande encourages us to apply a checklist approach to help avoid missteps. Obviously, medication misadventure is not a misstep of ignorance on the part of our physicians, and those who care for us. But, it is rather a problem of complexity: the healthcare system is so complex, there are so many medications, vitamins, supplements, as well as herbal products on the market (recall there were no pharmaceutical products before the late 1940s), and people are living longer with a higher number of chronic conditions than ever before in human history.

The Polypharmacy Network provides information, thoughtful discussion, and a forum to exchange perspectives about medication use to manage the complexity that leads to medication misadventure.

Below is the Polypharmacy Network's checklist approach to medication use. Although it is written for the medication user, the approach is the same for professionals and advisors regarding medication use.

- ☐ Know at least the 3 most common **adverse** effects of the medication
- ☐ Know how the medication can **interact** with your other **conditions**
- ☐ Know how the medication can **interact** with your other **medications**
- ☐ Have a **valid reason** to use the medication (avoid taking medications to treat side effects of other medications)
- ☐ Know **monitoring requirements** of the medication
  - Safety
  - Efficacy (know how to tell if the medication is effective, if not, why take it?)
- ☐ Know **when to stop** taking the medication if something goes wrong
- ☐ Know **how to stop** taking the medication (Discontinuation is usually impacted by withdrawal symptoms, or how severe the adverse effect is)
- ☐ Explore if a **lower dose would work just as well** with your healthcare provider or expert.

The item in blue is where the population data for most medications stop, and the rest are about individualization of medication use.

Now, let's apply this checklist to a fluoroquinolone (see next page).

SAMPLE ANALYSIS: *A **72-year-old female** who lives with cardiovascular disease, chronic kidney disease, arthritis pain, severe back pain and spasms, atrial fibrillation, mild cognitive impairment and depression. You are considering **Cipro® 500mg every 12 hours for 5 days, for a urinary tract infection (UTI).** This is the first UTI she's ever had, and when she started **feeling confused**, her daughter took her to the doctor. (Confusion can be a sign of infection in older people but can also be medication effects, pain. etc.)*

Current medications:

Lipitor®, lisinopril, ibuprofen, tizanidine, metoprolol, duloxetine, Aricept®

Sources of open access information:
FDA website, Drugs.com®, Epocrates®

- ☐ Know at least the 3 most common adverse effects of the medication

Cipro Warnings: not a first choice, and first time UTIs typically shouldn't be treated with fluoroquinolones, not to be used to treat "uncomplicated UTI"; Neurological or central nervous system effects (confused); Do not use with Tizanidine.

- ☐ Know how the medication can interact with your other conditions

She has baseline cognitive impairment and takes an Alzheimer's Dementia medication Aricept®; she has less physiological reserve and should avoid products that cause central nervous system effects like confusion or excessive sedation.

- ☐ Know how the medication can interact with your other medications

According to the drugs.com "interaction checker" there is a serious interaction with duloxetine. Serotonin syndrome is possible and life threatening if it occurs. Duloxetine levels can increase which can be dangerous for older adults especially.

- ☐ Have a valid reason to use the medication (avoid taking medications to treat side effects of other medications)

The UTI is not directly the side effect of other medications, however, duloxetine does encourage less complete bladder voiding which can lead to increased risk of UTI due to urinary retention. One purpose of venlafaxine (in addition to depression) is for stress incontinence.

- ☐ Know monitoring requirements of the medication
  - Safety: multiple adverse effect listed here (including tendon breaks)
  - Efficacy: if confusion lifted with subsequent doses, that's evidence its working, but follow up urinalysis for bacteria should be done. Any time you can measure numerical how effective a drug is (i.e. rate pain on 1-10 scale) that is ideal.
- ☐ Know when to stop taking the medication if something goes wrong: any serious side effect such as tendon rupture or confusion is a reason to stop.
- ☐ Know how to stop taking the medication (Discontinuation is usually impacted by withdrawal symptoms, or how severe the adverse effect is): Cipro® and most antibiotics can be abruptly stopped, but not psychoactive medications or many heart medications.
- ☐ Explore with your healthcare provider or expert, if a lower dose would work just as well: Cipro® collects in the urine a lower dose should be used, especially with her kidney disease.