

InFocus



Adverse Reactions to Fluoroquinolones



By James R. Roberts, MD

Author Credentials and Financial Disclosure:

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Learning Objectives: After reading this article, the physician should be able to:

1. Discuss six important side effects of fluoroquinolone antibiotic therapy that may bring patients to the ED.
2. Identify how to diagnose conditions related to side effects of fluoroquinolone antibiotic therapy.
3. Describe the management of conditions related to side effects of fluoroquinolone antibiotic therapy.

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Emergency physicians prescribe antibiotics daily, and except for concerns about allergies and selecting the right antibiotic for the right infection, little thought is given to potential adverse effects. Little can be done to predict side effects, and we never get to appreciate them if the patient does not return on our subsequent ED shift. Although we occasionally see antibiotic-related side effects in the ED, such as drug-induced diarrhea and skin rashes, most adverse events are usually easily handled by simply stopping the antibiotic and choosing a different one. It's not rocket science by any means.

It's important, nonetheless, to be cognizant of additional unexpected antibiotic-related adverse effects and to recognize those that do not fit the common profiles or even make common sense to the intuitive mind. This month's column begins a series of discussions on important and universally underappreciated adverse drug reactions to fluoroquinolone antibiotics relevant to the EP. This column deals with some rather bizarre and totally unexpected complications to a class of antibiotics that has gained wide popularity. Many drugs of this class are prescribed with relative impunity, but a second cogitation is in order. While the majority of fluoroquinolones are well tolerated and have been proven to be excellent antimicro-



Fluoroquinolones, such as ciprofloxacin (Cipro), levofloxacin (Levaquin), and moxifloxacin (Avelox) are generally safe and effective broad-spectrum antibiotics. They do, however, have their peccadilloes, and can cause some unusual and bothersome side effects that might not be readily associated with an antibiotic. Some adverse effects, such as acute CNS dysfunction, are seen while the patient is still taking the antibiotic. Others, such as tendinopathy, can surface after the drugs are stopped, when prior use does not make it to the now-required medicine reconciliation list. One would not usually attribute a malignant ventricular dysrhythmia, such as torsades, to an antibiotic, but the QTc prolongation of quinolones has this remote connection.

bials, the adverse reactions noted in the next few columns should be viewed as essential knowledge for emergency physicians. I am sure we have all seen most of them but failed to relate the non-intuitive ones, quite common for us mere mortals.

Safety Concerns with Fluoroquinolones

Mehlhorn AJ, Brown DA
Ann Pharmacother
2007;41(11):1859

This is a recent, easy-to-read, concise review of some of the more common and clinically important side effects of quinolones that should be in your mental database when prescribing this class of antibiotics. It's also occasionally helpful in sorting out some ED patients who present clinical quandaries or voice inscrutable complaints. The authors begin by noting that quinolones have a broad spectrum of activity, many approved indications, high bioavailability, and comparable blood concentrations when given IV or orally. There are a number of brands on the market, but gatifloxacin (Tequin) is no longer available, withdrawn in 2006 because of problems with hyperglycemia and hypoglycemia.

The extant quinolones have a similar spectrum of adverse effects, although their clinical use differs depending on the infectious etiology. Often used as a sub-

stitute antibiotic in penicillin-allergic patients, the most common adverse effects associated with quinolones are nausea and vomiting. Many antibiotics share this propensity to insult the GI track, and often it's merely an annoyance. Not always true with quinolones, however, when loose stools may be a harbinger of future serious pathology. Although there are literally hundreds of possible side effects to any drug, the authors review six specific and important-to-recognize adverse reactions that may be encountered but may be missed by practicing clinicians of all ilk.

Alterations in glucose levels: All quinolones can produce either hypoglycemia or hyperglycemia. Risks for low blood sugar include the usual suspects: advanced age, renal failure, decreased albumin, liver disease, congestive heart failure, malignancy, sepsis, female sex, and concomitant treatment with a sulfonyleurea or insulin. Diabetics, those using steroids, or those with a variety of systemic infections are at risk for hyperglycemia. One need not be diabetic, however, to experience dysglycemia from quinolones. The exact cause for alterations in blood sugar is unknown, and the most serious cases were linked to the now unavailable gatifloxacin. Fortunately, ciprofloxacin (Cipro) and levofloxacin (Levaquin) do not appear to be independently associated with significant dysglycemia.

Part 1 in a Series

QTc prolongation: Some quinolones were removed from the market because of excessive QTc prolongation, defined as a QTc interval greater than 500 msec. This condition can lead to torsades de pointes, a rare but potentially life-threatening ventricular tachycardia. Acquired QTc prolongation is common with many drugs. Often it is a mere curiosity but reported with such unlikely culprits as methadone, haloperidol, and cocaine. Other risk factors for this arrhythmia in quinolone-treated patients include hypokalemia, low magnesium levels, and the use of additional drugs that cause QTc prolongation, such as macrolides, amiodarone, and quinidine-like drugs. Ciprofloxacin and levofloxacin have the least QTc prolongation, but this EKG finding appears to be more common than QTc prolongation associated with macrolide antibiotics.

Central nervous system effects: Quinolones cause a variety of CNS-related adverse effects, including dizziness, insomnia, drowsiness, headache, bizarre dreams, confusion, tremors, and occasionally seizures. Quinolones may displace the neuroinhibitor, GABA, resulting in CNS stimulation. Quinolones may lower the seizure threshold, and are all best eschewed, when possible or clinically reasonable, in patients with seizure disorders. The more subtle CNS side effects are surprisingly common and likely often unrecognized.

Phototoxicity: While this risk is low, all quinolones have the potential to predispose to phototoxicity. This is a common side effect of many drugs, and one that is also frequently not appreciated. The most common manifestation is probably an exaggerated sunburn.

Tendinopathy: Although quinolones rarely produce serious tendinopathy, a recent black box warning has been added to fluoroquinolones. The clinical spectrum ranges from clinically mild tendinitis to overt tendon rupture. The Achilles tendon is the most affected site. Patients with renal failure, diabetes, degenerative diseases, and those taking steroids are at greater risk. This unusual side effect has been known for more than 20 years and is rather rare, but it was brought into the limelight in patients taking ciprofloxacin for the previous anthrax scare.

Clostridium difficile-associated diarrhea: Although any antibiotic can alter GI flora and allow for the overgrowth of *C. difficile*, quinolones have been incriminated in this increasingly more common entity. Theoretically, because these antibiotics have a good anaerobic spectrum, they inhibit growth of the more likable and normally protective anaerobic flora in the gut. Quinolones



kill those good guys with gusto, allowing for the increased replication of normally quiescent *C. difficile*. Quinolones are probably the most common cause of *C. difficile* of cases caused by antibiotics. Ciprofloxacin appears to be more of a culprit than levofloxacin, but this may be a spurious data issue. Overall, however, levofloxacin seems to have an edge of safety with regard to *C. difficile* susceptibility. The commonly used moxifloxacin (Avelox), an antibiotic with significant anaerobic activity, also has been thought to be more likely to cause the overgrowth of *C. difficile* than other antibiotics.

Comment: Emergency physicians see these six conditions and symptoms in many patients each day, and usually there is no quinolone in sight. I suspect that most of us do not ask about antibiotic use or posit that quinolones may be the actual offender. Because GI upset, dizziness, and an abnormal glucose are omnipresent ED issues and usually not quinolone-related, it would likely be very difficult to study these conditions, much less prevent them. Fluoroquinolones are still a workhorse antibiotic class that has an overall good safety rating.

Patients who receive quinolones in the ED range from those with mild cystitis to those with full blown sepsis. Respiratory quinolones are CMS-sanctioned for community-acquired pneumonia as monotherapy, vigorously targeting the atypicals. The Leva-Pak is almost as popular as the Z-Pak these days. Many patients also are concomitantly prescribed a variety of confounding medications, have risk factors that predispose to these conditions without the use of quinolones, and have a slew of medical problems that could be considered etiologic agents for a passel of vague effects. All in all, quinolones are pretty good drugs for a variety of conditions, but I personally have decreased my use of this class of antibiotics for such simple things as minor soft tissue infections, uncomplicated cystitis, and those questionable

cases of "bronchitis" that are likely viral anyway. (Just call bronchitis a "chest cold" to diffuse an argument for any antibiotic.)

The nursing home patients who present with hypoglycemia or hyperglycemia in the throws of sepsis may have been recently treated for a UTI with a quinolone. Many of their concomitant medications, underlying diseases, and newly acquired pathologies conjure up a plethora of reasons for dysglycemia. I suspect most cases will be unrelated to quinolones, or even if truly related, will be glossed over by even the sharpest diagnostician in the heat of battle. If a patient is taking a sulfonylurea or insulin in the nursing home and then becomes hypoglycemic, I don't think many physicians will search for quinolone use for a UTI a few days before, and simply implicate the diabetic drug and dietary issues.

The gargantuan list of medications causing QTc prolongation fills an entire web site. Likewise, hypokalemia and low magnesium levels are omnipresent in patients on diuretics and those with heart failure or kidney disease, vomiting, and diarrhea. Even these electrolyte-challenged patients often tolerate quinolones quite well. But if a hypokalemic patient on amiodarone receives a quinolone for sepsis and then suffers ventricular tachycardia in the hospital, the sagacious clinician who relates it to quinolone use will be few and far between.

I am told by my general practice colleagues (and by my wife and daughter who both took levofloxacin last year) that many patients taking a quinolone suffer some type of vague CNS effect. Unless asked, many minor adverse reactions like insomnia will never surface. "I had a scary dream last night" is an unusual ED complaint, but they are all "dizzy" at one time or another. I have seen a few patients who downright hallucinate or become markedly confused and a few who have suffered grand mal seizures while taking oral quinolones.

COMMON ADVERSE REACTIONS TO FLUOROQUINOLONES (RARE, BUT THEY'RE OUT THERE)

General Risk Factors: Advanced age, a plethora of chronic medical conditions, metabolic disturbances, and numerous drug-drug interactions.

Dysglycemia: Most commonly hyperglycemia, but hypoglycemia also seen. More common in diabetics, but previous diabetes not necessary.

QTc Prolongation: May lead to torsades de pointes. More common with hypokalemia, hypomagnesemia, use of amiodarone and other QTc prolongation drugs.

Central Nervous System Effects: Very common, especially in the elderly. Includes insomnia, dizziness, hallucinations, confusion, delirium, and seizures.

Tendinopathy: May be prolonged and lead to tendon rupture. Achilles tendon most commonly affected. Risks include advanced age, degenerative diseases, and steroid use. Quinolone use may be weeks prior.

Clostridium difficile-Associated Diarrhea: Occurs from anaerobic activity of the antibiotics, allowing *C. difficile* overgrowth. Nonspecific nausea and diarrhea very common and not serious.

FDA BLACK BOX WARNING FOR FLUOROQUINOLONE TENDINOPATHY

FDA ALERT [7/8/2008]: FDA is notifying the makers of fluoroquinolone antimicrobial drugs for systemic use of the need to add a boxed warning to the prescribing information about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones and to develop a Medication Guide for patients. The addition of a boxed warning and a Medication Guide would strengthen the existing warning information already included in the prescribing information for fluoroquinolone drugs.

Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Physicians should advise patients at the first sign of tendon pain, swelling, or inflammation to stop taking the fluoroquinolone, to avoid exercise and use of the affected area, and to promptly contact their doctor about changing to a non-fluoroquinolone antimicrobial drug.

Just last month I saw a patient with a nasty dog bite worthy of antibiotics. Because he was penicillin-allergic, I opted for levofloxacin, and started with an IV dose followed by a generous PO dose. Three days later, this patient was brought back to the hospital markedly confused and acutely delirious for the first time, and everyone thought he was septic. He was admitted to the hospital, the antibiotics were changed, and he got better, likely on his own because the quinolone was stopped. Not a single clinician, not even the otherwise academic ID expert following this case, considered quinolone therapy a cause of the newly acquired yet transient and totally temporary acute dementia. No other cause was ever unearthed, and it took my brilliant toxicology fellow to come up with this diagnosis. I am sure many patients with a new onset seizure get a full neurological workup without someone ever investigating the recent use of a quinolone.

The next time you see a patient with a sore Achilles tendon or peri-joint pain and stiffness, ask him if he recently had a quinolone for bronchitis. Some may have taken the antibiotics many weeks before. Ask the question, and also stop the quinolone because the tendinopathy may go on to tendon rupture. Again, there are many reasons for patients to have sore or inflamed tendons, and few emergency physicians would take a detailed antibiotic history after seeing a straightforward case of tendonitis in the fast track. This problem did, however, grow into a cottage industry for malpractice lawyers; Google this subject and be prepared for an onslaught of legal remedies (AKA sue the doctor who prescribed that nasty antibiotic or did not identify the problem prior to tendon rupture). Some of the personal stories on the Internet are truly wacky, but this can be a real problem with significant morbidity. More on this topic next month.

The incidence of *C. difficile* diarrhea has markedly increased in this country. We see it almost everyday, and it can kill rather quickly. A little loose stool is an allowable side effect of many antibiotics, but if the patient is taking a quinolone, stop that drug immediately, and consider *C. difficile* as the culprit. In the septic patient with diarrhea who has taken a quinolone, *C. difficile* is high on the list, and it can produce an acute abdomen and unexpected mortality. Such patients require oral antibiotics (vancomycin or metronidazole [Flagyl]), so even three IV antimicrobials, including vancomycin, may not save the day.

I wonder how many clinicians warn patients to stay out of the sun during the summer months or during the spring break in Mexico because of phototoxicity when they are taking ciprofloxacin for diarrhea. I'm going to take my fellows to Cancun next March just to study this issue personally. Certainly many of these cases go undiagnosed, or never make it to a doctor's attention to begin with.

So what is a clinician to do? After reading this article and having seen each and every side effect described in this article (and attributed it to something other than the quinolone patients were taking), I have become leery of prescribing this class of drug as often as before. As mentioned, I eschew their routine use for uncomplicated UTI, and if I am forced to give an antibiotic for "bronchitis," I now opt for ampicillin or tetracycline. Patients demand antibiotics for almost everything these days, and many look at you with a modicum of distrust and a lot of annoyance when you hedge on the easily written prescription and pontificate about side effects of antibiotics. Perhaps you should give them this article to ponder when they threaten to write a nasty note to the administrator or vow to see their doctor the next day. "Their doctor" is defined by the generally clueless public

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FLUOROQUINOLONES

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as a real physician who will give them a real antibiotic for a cold.

Neuropsychiatric Reactions to Drugs: An Analysis of Spontaneous Reports from General Practitioners in Italy

Galatti L, et al
Pharmacol Res
2005;51:211

If one needs yet another reason to regularly read this column in *EMN*, my review of this exotic journal and this likely overlooked article is that reason. It is a review of physicians in Italy who voluntarily reported a CNS reaction that they assessed to be attributed to a drug taken by their patient. It's not highbrow science, and there are reporting biases, underreporting, and overreporting, but it's worth the read. The complications fall under the heading of adverse drug reactions, commonly referred to as ADRs. I include it because quinolones are highlighted in a number of places, and they are common perpetrators of cerebral dysfunction.

Over a two-year period, 171 general practitioners reported almost 2000 ADRs to the database. Interestingly, 28 percent of them involved a CNS event, either neurological or psychiatric. CNS side effects were the leading ADR, but GI, skin, musculoskeletal, cardiovascular, and respiratory side effects occurred as well. Simply stated, neuropsychiatric complications were the most common ADR reported by these general practitioners. The CNS effects dwarfed even the expected gastrointestinal symptoms that everyone seems to get with almost any medication.

Neuropsychiatric ADRs included vertigo, confusion, headache, insomnia, hallucinations, agitation, dizziness, and anxiety, all everyday symptoms in the ED. It's almost impossible to ferret out the cause of many of these complaints. From now on, however, I will more readily consider an adverse drug reaction and specifically ask about quinolone use.

Of greatest importance to this discussion is the fact that fluoroquinolones were responsible for more adverse neuropsychiatric reactions than any other drug class. Who would have thought?

Quinolones accounted for about 10 percent of all neuropsychiatric ADRs! There were more patients with vertigo, confusion, and dizziness attributed to fluoroquinolones than to selective serotonin reuptake inhibitors, antidepressants, opiates, vascular medications, or anti-seizure medicines. And by the way, did you know that quinolones can cause ACE inhibitor-like acute angioedema?

It's unclear to me how far distant

quinolone use could be to be considered causal, but apparently the antibiotic use could have been days or weeks before some conditions. In my experience, the CNS effects are concomitant with drug use. Note to self: It may not be the fever that made grandpa goofy; maybe it was the quinolone.

I believe it is prudent to rethink the knee-jerk response of prescribing quinolones in bona fide infections, and in

those cases where it's easier to write a prescription than to spend time explaining the lack of antibiotic efficacy to your patient. Even more important, the next time you see a first-time seizure, an unexplained altered mental status, a case of tendinitis, a bad sunburn, or even tor-sades de pointes — difficult to find even in a patient with a known heart disease — ferret out the recent or perhaps surprisingly distant use of fluoroquinolones. 

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Questions:

- Quinolones can cause tendinopathy that can lead to inflammation and pain but not actual tendon rupture.
 True False
- The Achilles tendon is the tendon most often affected.
 True False
- Quinolones are essentially devoid of CNS or neuropsychiatric side effects.
 True False
- Quinolones are an antibiotic class associated with a high incidence of *C. difficile* diarrhea.
 True False
- Patients taking quinolones should be cautioned about the potential for photosensitivity and an exaggerated sunburn.
 True False

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