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Improving the Quality of Care: Risks Associated with Use of Fluoroquinolones

Learning Objectives:

- Review the United States Food and Drug Administration (FDA) labeling changes for fluoroquinolones, including the updated *Boxed Warning.*
- Describe potential adverse effects associated with use of fluoroquinolones.
- Summarize best practices for responsible prescribing of fluoroquinolones.

Key Points:

- Fluoroquinolones are broad-spectrum antibiotics that are FDA-approved to treat various bacterial infections, including infections caused by gram-negative bacilli.
- On July 26, 2016, the FDA approved safety labeling changes for fluoroquinolones, including an updated *Boxed Warning* regarding the association of fluoroquinolones with disabling and potentially permanent side effects involving tendons, muscles, joints, nerves, and the central nervous system.
- Fluoroquinolones should not be prescribed to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections (UTIs), as the risks outweigh the benefits.
- In a study of community-dwelling Medi-Cal fee-for-service beneficiaries, approximately 68% of fluoroquinolone use appeared to be for potentially inappropriate indications, based on the new FDA recommendations.

Background

Fluoroquinolones, including ciprofloxacin, ofloxacin, gemifloxacin, levofloxacin, and moxifloxacin, are broad-spectrum antibiotics that interfere with the growth of bacteria via inhibition of certain enzymes needed for bacterial replication.[1] Fluoroquinolones are FDA-approved to treat various bacterial infections and are the only oral antibiotics that can be reliably used to treat infections caused by gram-negative bacilli, including strains of antibiotic resistant bacteria.[1] As shown in Table 1, most fluoroquinolones appear on the Medi-Cal List of Contract Drugs, with some having restrictions to their use without an approved *Treatment Authorization Request* (TAR).

Table 1. Fluoroquinolones on the Medi-Cal List of Contract Drugs

Drug*	Formulation	Restrictions (indications, age and quantity)
Ciprofloxacin	Suspension	Treatment of 1) lower respiratory tract infections in persons 50 years of age or older; 2) osteomyelitis; and 3) pulmonary exacerbation of cystic fibrosis.
Ciprofloxacin	Tablets	Treatment of 1) lower respiratory tract infections in persons 50 years of age or older; 2) osteomyelitis; 3) pulmonary exacerbation of cystic fibrosis; 4) UTIs, including pyelonephritis; and 5) prophylaxis of meningococcal disease.
Levofloxacin	Tablets	Maximum quantity per dispensing of ten tablets and a maximum of two dispensings in any 30-day period.
Moxifloxacin	Tablets	Maximum quantity per dispensing of ten tablets and a maximum of two dispensings in any 30-day period.
Ofloxacin	Tablets	Treatment of sexually transmitted diseases.

* Some medications may have additional restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File Web page of the Department of Health Care Services (DHCS) website.

Despite the many FDA-approved indications for use, the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), and other professional organizations all recommend fluoroquinolones not be used as first-line therapy in community settings when other treatment options are available.[2-5] Fluoroquinolones should be initiated only after other antibiotic classes have been tried and failed, or in such cases with a demonstrated drug resistance.[2-5]

In addition, on May 12, 2016, the FDA issued a Drug Safety Communication regarding potential serious adverse effects related to use of fluoroquinolones, including tendinitis, tendon rupture, peripheral neuropathy, confusion, and hallucinations. In particular, the risk of Achilles tendon rupture related to fluoroquinolone use was found to be high in the adult population (prevalence rate 15 – 25 per 100,000), with even greater risk among older adults and those with a history of steroid therapy.

On July 26, 2016, the FDA approved safety labeling changes for fluoroquinolones.[6,7] The labeling changes include an updated *Boxed Warning* and revisions to the *Warnings and Precautions* section to enhance warnings about the association of fluoroquinolones with disabling and potentially permanent side effects, and to limit their use in patients with less serious bacterial infections.[7] The complete list of potential serious side effects provided by the FDA is shown in Table 2.

Table 2. List of Serious Side Effects from Fluoroquinolones[7]

System	Side Effect
Musculoskeletal and Peripheral Nervous System	Tendinitis Tendon rupture Numbness or tingling or pricking sensation in arms or legs Muscle weakness Muscle pain Joint pain Joint swelling
Central Nervous System	Anxiety Depression Hallucinations Suicidal thoughts Confusion
Other Body Systems	Worsening of myasthenia gravis Skin rash Sunburn Abnormal, rapid, or strong heart beat Severe diarrhea

The labels also contain new limitation-of-use statements to reserve fluoroquinolones for patients who do not have other available treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated UTIs, as the risk of these serious side effects generally outweigh the benefits.[6,7] First-line therapies for these conditions are listed in Table 3.

Table 3. First-Line Alternatives to Fluoroquinolones on the Medi-Cal List of Contract Drugs[3-5,8-10]

Indication	Drug*	Usual adult dosage (may need adjustment for renal or hepatic impairment)
Acute sinusitis and acute exacerbation of chronic bronchitis due to a bacterial pathogen	Amoxicillin	500 mg PO TID for 5 – 7 days, with a higher dose of amoxicillin (2 g/d) considered for severe disease and those at risk of infection with *S pneumoniae* with reduced susceptibility to penicillin
	Amoxicillin/clavulanate	875 mg/125 mg PO BID for 5 – 7 days or 500 mg/125 mg PO BID for 5 – 7 days
	Doxycycline	100 mg PO BID for 5 – 7 days
Uncomplicated UTIs	Trimethoprim/sulfamethoxazole	160 mg/800 mg PO BID for 3 days
	Nitrofurantoin monohydrate/ macrocrystals	100 mg PO BID for 5 days

* First-line therapies were selected based on the highest ranking of A-I (where A represents the strength of recommendation, and I represents the quality of evidence) using the IDSA guidelines. Some medications may have additional restrictions on manufacturer codes. For current information, use the online Medi-Cal Formulary search tool available on the Formulary File Web page of the DHCS website.

For serious bacterial infections, including anthrax, plague, and bacterial pneumonia, and in cases where the infection is severe enough to necessitate hospitalization, the benefits of luoroquinolones outweigh the risks and it is appropriate for them to remain available as a therapeutic option.[2-5]

Fluoroquinolone Use in the Medi-Cal Fee-for-Service Population

A retrospective cohort study was conducted to assess the use of fluoroquinolone antibiotics in the Medi-Cal fee-for-service population using pharmacy and medical claims data. The initial study population included all Medi-Cal fee-for-service beneficiaries with at least one paid claim for a fluoroquinolone between December 1, 2015, and November 30, 2016.

For each individual beneficiary, the date of service of the fluoroquinolone paid claim was used as the index date and all paid medical claims within seven days prior to the index date were reviewed. In order to focus on beneficiaries living in the community setting, beneficiaries were excluded if one of these paid claims showed the place of service to be a long-term care facility, skilled nursing facility, or inpatient hospital.

In order to determine the appropriateness of prescribing fluoroquinolone, all available medical claims data were reviewed and beneficiaries with any indication of penicillin or other drug allergy that would impact the use of fluoroquinolones as a first-line therapy were excluded. Any beneficiary with one of the following primary or secondary ICD-9-CM diagnostic codes within the seven-day window of the index date was coded as a potentially inappropriate use of fluoroquinolone:

- Acute bacterial sinusitis (461)
- Acute bacterial exacerbation of chronic bronchitis (491.21)
- Uncomplicated UTIs (595.00, 595.89, 595.90, or 599)

Demographic characteristics, including gender, age, race/ethnicity, and geographic region of residence, were reviewed for all beneficiaries in the study population.

Results

A total of 50,843 community-dwelling Medi-Cal fee-for-service beneficiaries had at least one paid claim for a fluoroquinolone between December 1, 2015, and November 30, 2016, and at least one primary or secondary ICD-10-CM diagnosis code within the seven days prior. There were 1,567 beneficiaries excluded from the study population (3%) as they were identified as having a history of penicillin or other drug allergy that would impact the use of fluoroquinolones as a first-line therapy, leaving a total of 49,276 beneficiaries in the study population.

Approximately two-thirds (n = 33,483; 68%) of fluoroquinolone use during the measurement year appeared to be potentially inappropriate based on the new FDA recommendations, with 5,102 beneficiaries (10%) having a primary or secondary diagnosis of acute bacterial exacerbation of chronic bronchitis, a total of 9,165 beneficiaries (19%) with acute sinusitis, and 19,306 beneficiaries (39%) with an uncomplicated UTI. For reference, uncomplicated UTI was the most frequent diagnosis given preceding a paid claim for a fluoroquinolone, followed by septicemia.

The demographic characteristics of the study population are shown in Table 4, stratified by appropriate or inappropriate use of fluoroquinolones. Beneficiaries with a paid claim for potentially inappropriate fluoroquinolone use were more likely to be female, 49 years of age and younger, white/Caucasian, non-Hispanic, and live outside of Los Angeles County.

Table 4. Demographic Characteristics of the Medi-Cal Fee-for-Service Study Population (n=49,276).

	Appropriate Fluoroquinolone Use n (%)	**Potentially Inappropriate Fluoroquinolone Use n (%)**
Overall population (n = 49,276)	***15,793 (32%)***	***33,438 (68%)***
Gender		
• Male (n = 15,779)	6,135 (39%)	9,644 (61%)
• Female (n = 33,452)	9,658 (29%)	23,794 (71%)
Age		
• 49 years of age and younger (n = 34,687)	10,817 (31%)	23,870 (69%)
• 50 years of age and older (n = 14,589)	4,976 (34%)	9,613 (66%)
Race/Ethnicity		
• White/Caucasian, non-Hispanic (n = 8,736)	2,446 (28%)	6,290 (72%)
• All other races/ethnicities (n = 40,540)	13,347 (33%)	27,193 (67%)
California Region of Residence		
• Los Angeles County (n = 20,377)	8,899 (44%)	11,478 (56%)
• All other regions/counties (n = 28,899)	6,939 (24%)	21,960 (76%)

The increased inappropriate use among females may be partially explained by the overall increased incidence of uncomplicated UTIs in this population, as 82% of the population with this indication was female. While the study population had only a relatively small population that was 17 years of age or younger (less than 1,000 beneficiaries), the rate of potential inappropriate use of fluoroquinolones was highest in this group at 78%. While claims data cannot explain the lower rate of inappropriate use among residents of Los Angeles County, the difference in the rate is significant enough to merit further evaluation in the future. Primarily, it will be important to determine if this lower rate is specific only to fluoroquinolones, or if these data are representative of an effective, comprehensive antimicrobial stewardship program within Los Angeles County that could be studied and replicated statewide.

Conclusion/Discussion

Fluoroquinolone use contributes to the proliferation of antibiotic-resistant bacteria and may result in disabling and potentially permanent side effects. Community-based treatment with fluoroquinolones should be initiated only after other antibiotic classes have been tried and failed, or in such cases with a demonstrated drug-resistance. Limiting the use of fluoroquinolones to those patients where the benefits clearly outweigh the potential risks can lead to improved patient outcomes and a reduction in adverse events.

Clinical Recommendations

General Antimicrobial Stewardship

- Incorporate allergy assessment into routine physical examination and evaluate patients for true penicillin allergy by conducting a history, physical, and (where appropriate) a skin test and challenge dose.
- Prescribe antibiotics carefully and correctly.
  - Avoid treating viral syndromes with antibiotics, even when patients ask for them
  - Obtain microbiology cultures, when possible, before starting antibiotics
  - Be aware of antibiotic-resistance patterns
  - Ensure all orders for antibiotics have the dose, duration, and indications
  - Take an “antibiotic timeout” reassessing antibiotics after 48-72 hours
- Work with pharmacists to ensure appropriate antibiotic use, prevent resistance, and early detection of adverse events.
- Educate patients and their families on appropriate indications for antimicrobials using patient-directed resources and materials, for example those offered on the Get Smart Programs & Observances Web page of the CDC website.

Use of Fluoroquinolones

- Providers should not prescribe systemic fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated UTIs because the risks outweigh the benefits in these patients.
- Pharmacists should discuss the signs and symptoms of adverse events associated with fluoroquinolones with patients, including the following serious side effects requiring immediate action:
  - Unusual joint or tendon pain
  - Muscle weakness
  - A “pins and needles” tingling or pricking sensation in the arms or legs
  - Numbness in the arms or legs
  - Confusion
  - Hallucinations
- Providers should discontinue fluoroquinolone treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient’s treatment course.
- Avoid fluoroquinolones in patients who have previously experienced serious adverse reactions associated with fluoroquinolones.

References:

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