



HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2015 November 06.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2013 October ; 22(10): 1099–1106. doi:10.1002/pds.3499.

US-Based Emergency Department Visits for Fluoroquinolone-Associated Hypersensitivity Reactions

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Abstract

Purpose—To estimate the rate of hypersensitivity reactions per 100,000 prescription dispensings of fluoroquinolones based on care rendered in a nationally-representative sample of US hospital emergency departments (ED).

Methods—We analyzed the frequency of fluoroquinolone-associated hypersensitivity reactions using the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance system (2004–2010) in conjunction with US retail outpatient prescription data from IMS Health (2004–2010). We further categorized reaction severity into three subgroups (mild, moderate, severe).

Results—Based on 1,422 cases of fluoroquinolone-associated hypersensitivity reactions and national drug utilization projections, we estimated risk of hypersensitivity reactions for moxifloxacin, ciprofloxacin, and levofloxacin. The absolute risk of a fluoroquinolone-related hypersensitivity reaction of any severity was low (44.0 (95% CI 34.8–53.3) ED visits/100,000 prescriptions; however, we identified a statistically significant difference in the relative risk (rate ratios) of seeking care in an ED attributed to moxifloxacin hypersensitivity compared to either levofloxacin or ciprofloxacin. For all reaction severities, the estimated ED visits/100,000 prescriptions were 141.3 (95% CI 99.9–182.7) for moxifloxacin, 40.8 (95% CI 31.5–50.0) for levofloxacin, and 26.3 (95% CI 20.8–31.9) for ciprofloxacin. When the rates were stratified by reaction severity category (mild or moderate-severe), moxifloxacin continued to be implicated in more ED visits per 100,000 prescriptions dispensed than either levofloxacin or ciprofloxacin.

Conclusion—Fluoroquinolones may cause hypersensitivity reactions requiring care in an ED, and relative to use, the rate of moxifloxacin-related hypersensitivity reactions is higher than comparator fluoroquinolones.

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Sponsorship of this Work: None. All authors are employees of the US government.

Conflict of Interest Statement: All authors declare no financial conflicts of interest. The views expressed are those of the authors and do not necessarily represent the views of FDA or CDC.

Statement about Prior Postings and Presentations

This work has not been posted or presented in another forum.

Keywords

fluoroquinolone; hypersensitivity; allergy; moxifloxacin; ciprofloxacin; levofloxacin

Introduction

Fluoroquinolones are an important and widely used class of antimicrobials in contemporary medical practice in the United States (US). The US Food and Drug Administration has approved six currently marketed, oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, norfloxacin, ofloxacin). Although fluoroquinolones have a favorable safety profile relative to their effectiveness, tendinopathy, exacerbation of myasthenia gravis, central and peripheral nervous system toxicities, QT interval prolongation resulting in torsade de pointes, *Clostridium difficile*-associated colitis, and hypersensitivity reactions, including anaphylaxis, are important safety concerns.

Fluoroquinolones induce hypersensitivity reactions via IgE mediated pathways and delayed T-cell mediated responses.¹ Safety information in FDA approved fluoroquinolone labeling warns prescribers that serious and occasionally fatal hypersensitivity or anaphylactic reactions have been reported in patients receiving fluoroquinolone therapy. Among non-beta lactam antimicrobials, fluoroquinolones exhibited the highest frequency of hypersensitivity reactions during the past decade.² It is not clear whether expanded use of fluoroquinolones or increased immunogenicity to newer fluoroquinolones is responsible for this trend.

Published data suggests that the risk of a hypersensitivity reaction is not uniform across the fluoroquinolone class. An *in vitro* study,³ analyses of spontaneous reports^{4,5} and a recent retrospective analysis of patients attending an allergy clinic,⁶ implicate moxifloxacin frequently or more often compared to other fluoroquinolones in hypersensitivity reactions. Johannes et al, in contrast, expanded on these studies by estimating the incidence of serious allergic reactions to fluoroquinolones using administrative claims data and determined that allergic diagnoses rates were similar for moxifloxacin and comparator fluoroquinolones.⁷ Although most of the studies cited above implicate moxifloxacin more often than other fluoroquinolones, the data are largely based either on laboratory investigations, non-randomized samples of convenience, or voluntarily submitted adverse drug event reports. Spontaneous adverse event reporting is prone to selection bias and is not amenable to providing estimates of incidence or comparative risks within a drug class, because the numerator and denominator cannot be reliably estimated.

Considering the conflicting analyses described above, the objective of this work was to estimate the rate of hypersensitivity reactions attributed to fluoroquinolones based on national public health surveillance data. We analyzed the frequency of fluoroquinolone-related hypersensitivity reactions based on care rendered in a nationally-representative sample of US hospital emergency departments (ED) using dispensed prescriptions to estimate drug exposure.

Methods

National estimates of ED visits were made using the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) system from January 1, 2004 through December 31, 2010. NEISS-CADES is a national public health surveillance system and has been previously described.⁸ Briefly, NEISS-CADES collects data from a nationally representative, stratified probability sample of 63 participating hospitals located within the United States or its territories, which have a minimum of six beds and a 24 hour ED. Trained coders at each hospital review the clinical records of each ED visit to identify physician-diagnosed drug related adverse events, reporting up to two implicated medications, select patient demographics, physician clinical diagnoses, testing, treatments, and brief narratives describing the visit, which are coded at the Centers for Disease Control and Prevention (CDC) using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. NEISS-CADES entries are de-identified data used to conduct public health surveillance and, therefore, are exempt from investigational review board oversight.

We queried NEISS-CADES for cases in which any one of the current US marketed fluoroquinolones was implicated in a hypersensitivity reaction requiring evaluation in an ED. We defined a case as any ED encounter attributed to a hypersensitivity reaction from a single orally administered fluoroquinolone based on the reported physician diagnosis and narrative description without additional reviewer imputation. Cases reporting known exposure to an otic, ophthalmic or an intravenous dosage formulation were excluded from analysis.

The primary author (SCJ) conducted an unblinded review and categorized each ED visit report by severity of the adverse reaction (e.g. mild, moderate or severe). A mild hypersensitivity reaction was defined as any self-limiting, non-anaphylactic adverse event, most typically rash, which did not result in hospital admission and required only minimum medical intervention aimed to relieve temporary discomfort. Moderate reactions were defined as those with signs and symptoms consistent with anaphylaxis such as dyspnea, tachycardia or chest pain, or extensive or desquamating skin reactions, or facial or laryngeal edema that did not result in hospitalization. Severe reactions referred to anaphylaxis which required hospital admission or observation in the ED for an extended period of time before discharge. After reviewing each case, we chose to combine moderate and severe reactions into one category for analysis. We did this because there were few severe reactions which substantially reduced the statistical power to detect differences between the drugs studied for severe reactions alone and the only substantive difference between the categories was hospitalization.

National estimates of outpatient fluoroquinolone use were provided by IMS Health Vector One[®] National database. The Vector One[®] database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies to consumers via formal prescriptions from a sample of 59,000 retail pharmacies throughout the US. Using these data, we estimated the total number with 95% confidence intervals for

prescriptions dispensed throughout US outpatient retail pharmacies from January 1, 2004 through December 31, 2010 for US marketed fluoroquinolones.

We calculated national estimates (with corresponding 95% confidence intervals) for the frequency of ED visits from the NEISS-CADES sample, using the SURVEYMEANS procedure in SAS (Cary NC) version 9.2 to account for sample weights and complex sample designs in the stratified probability sample. National estimates using this procedure were considered reliable if there were ≥ 20 cases from the sample on which that estimate was based, the national estimate was $\geq 1,200$ cases and the coefficient of variation was <0.30 .

To estimate rates of ED visits for fluoroquinolone hypersensitivity reactions relative to outpatient medication use, we divided the estimated number of ED visits by the estimated number of outpatient prescriptions dispensed. Calculation of the 95% confidence interval for each rate incorporated variance estimates for both numerator and denominator components of the corresponding rate estimate^{9,10} Because these components were calculated from separate surveillance systems, they were treated as independent (and, thus, as having zero covariance).

Rate ratios (RRs) were used to compare rates of ED visits for fluoroquinolone hypersensitivity reactions relative to outpatient medication use for each drug within the fluoroquinolone drug class, using the fluoroquinolone with the lowest rate as the reference group. The estimates and variance for the RRs incorporated the estimated variance of the numerator and denominator components of the RR.⁹ The component rate estimates were again assumed to be independent across patient populations.

Results

NEISS-CADES includes 1,659 cases of ED visits for a hypersensitivity reaction attributed to any fluoroquinolone between the years 2004–2010. We excluded cases with more than one implicated drug ($n=187$) and cases involving a suspect non-oral formulation ($n=29$). We also excluded cases relevant to gemifloxacin ($n=12$) and ofloxacin ($n=9$), because these sample sizes were insufficient to reliably project national estimates. No cases of norfloxacin-associated hypersensitivity were retrieved from the database. After these exclusions, 1,422 cases remained, composed of three suspect fluoroquinolones; ciprofloxacin ($n=469$), levofloxacin ($n=505$), and moxifloxacin ($n=448$). Figure 1 is a flow diagram of the case selection criteria used in this analysis.

The demographic and clinical characteristics of the case patients were comparable across the three fluoroquinolones (Table 1). Reaction severities were also proportionate across the fluoroquinolone subgroups with mild reactions occurring most frequently (63%) followed by moderate (31%) and severe (6%) reactions. Likewise there were similar proportions of cases with comparable concomitant medications per case for each fluoroquinolone evaluated, with roughly half of all cases not reporting any concomitant drug. The hypersensitivity reactions experienced by these patients rarely resulted in hospitalization (6%). Mortality is not a measured outcome in NEISS-CADES, so we were unable to use fatality as a surrogate indicator of reaction severity. Additionally, the dose, duration and

indication of the fluoroquinolone, and clinical details of the hypersensitivity reactions in this NEISS-CASES sample were infrequently reported.

National estimates of prescriptions dispensed (with corresponding 95% confidence intervals) for fluoroquinolones are provided in Table 2. Between 2004 and 2010, there were an estimated 236.9 (95% CI 236,882,377 – 236,954,618) million prescriptions dispensed for fluoroquinolones in the United States. In that time period, the most frequently dispensed fluoroquinolone prescription was ciprofloxacin, followed by levofloxacin and moxifloxacin. Approximately one-tenth of all fluoroquinolone prescriptions dispensed (10.3%) were for moxifloxacin.

Between 2004–2010, we estimated 102,684 (95% CI 81,026–124,342) ED visits occurred because of a hypersensitivity reaction of any severity that was attributed to either ciprofloxacin, levofloxacin or moxifloxacin (Table 3). We observed no statistically significant differences in the number of ED visits across the three fluoroquinolones when the data were either combined or stratified by reaction severity. However, a higher proportion met criteria for moderate to severe reactions for moxifloxacin and levofloxacin versus ciprofloxacin, although this difference was not significant.

We combined national estimates of ED visits for hypersensitivity reactions and the estimated number of prescriptions dispensed to compute the overall rates and rate ratios for ED visits per 100,000 prescriptions (Table 4). In pooling all hypersensitivity reactions regardless of severity, moxifloxacin [141.3 visits/100,000 prescriptions (95% CI 99.9–182.7)] was associated with the highest rate of ED visits and this difference was statistically significant compared to both levofloxacin [40.8 visits/100,000 prescriptions (95% CI 31.5–50.0)] and ciprofloxacin [26.3 visits/100,000 prescriptions (95% CI 20.8–31.9)]. The difference between levofloxacin and ciprofloxacin was not significant. The absolute risk of a fluoroquinolone-related hypersensitivity reaction of any severity was 44.0 (95% CI 34.8–53.3) ED visits/100,000 prescriptions.

Across all severity categories, the rate ratios (relative risks) of hypersensitivity reaction requiring an ED visit for moxifloxacin was 3.5 (95% CI 2.2–4.7) and 5.4 (95% CI 3.4–7.3) times higher than with levofloxacin and ciprofloxacin, respectively (Table 4). When rates are stratified by reaction severity (mild or moderate-severe), the risk difference widens with moxifloxacin and levofloxacin approximately 7.4 (95% CI 4.4–10.4) and 2.0 (95% CI 1.3–2.7) times more likely than ciprofloxacin to be implicated in a moderate-severe hypersensitivity reaction requiring treatment in an ED. Among mild reactions, moxifloxacin was associated with 4.5-fold (95% CI 2.6–6.4) more hypersensitivity reactions than ciprofloxacin. The difference between ciprofloxacin and levofloxacin for mild reactions was not significant.

Discussion

Using nationally representative samples of ED visits and outpatient prescriptions dispensing, we estimate the rate of ED visits for hypersensitivity attributed to ciprofloxacin, levofloxacin and moxifloxacin. Regardless of severity, the overall risk of hypersensitivity

reactions resulting in ED visits was low for all fluoroquinolones studied; however, moxifloxacin exhibited a significantly higher rate of hypersensitivity reactions per 100,000 prescriptions dispensed across all severity categories compared with levofloxacin or ciprofloxacin.

Shehab et al.¹¹ published a paper which provide context to the magnitude of fluoroquinolone-induced hypersensitivity compared to other antimicrobials. This group used NEISS-CADES data, and estimates of outpatient prescriptions using national medical surveys to compare the relative rates of mild or moderate-severe allergic reactions across various classes of antimicrobials. Based on these data, fluoroquinolones are less frequently implicated in ED visits for mild allergic reactions than penicillins, sulfonamides, or lincosamides. Although, the rate of moderate-severe allergic reactions for fluoroquinolones appears to be comparable to penicillin and cephalosporin beta-lactams, yet less than those attributed to sulfonamides.

Our findings are consistent with those of previously described published studies³⁻⁶ that have shown an enhanced risk of hypersensitivity associated with moxifloxacin use compared to other fluoroquinolones, but differ from the results of Johannes et al⁷ that indicated no difference across the fluoroquinolone class. While we observed a disproportionate number of ED visits for moxifloxacin-associated hypersensitivity reactions relative to dispensings, Johannes et al. observed no difference using administrative claims data. They determined that the incidence of any allergic diagnosis made in the hospital or ED was similar for moxifloxacin and comparators. While a strength of their study was its statistical power, enabled by a large sample size, limitations compared to the NEISS-CADES database may affect interpretability. First, Johannes et al. used administrative data (ICD-9 codes) to identify cases supported by medical record review of anaphylaxis cases only, which may not be sufficiently sensitive to identify true cases. All NEISS-CADES data is derived from chart review without reliance on administrative coding. Secondly, in the Johannes study, the source population was insured US residents concentrated in the Midwest and the Southeast, which may not adequately represent the entire US populace. Our sample is solely composed of persons who seek care in an US-based ED for hypersensitivity, which may represent a different demographic.

The methods employed in our analysis offer several additional strengths. First, NEISS-CADES data are actively collected and are a nationally representative sample of US-based EDs which permit inferences about drug related adverse events in the entire US population seeking care in an ED. This level of statistical inference is not possible with a spontaneous surveillance system, similar to that employed by Sachs⁴ to compute reporting rates of fluoroquinolone-induced allergic reactions, because there is uncertainty with respect to underreporting of adverse events. Second, each case was subjected to a detailed review to categorize the severity of the hypersensitivity reaction using our case definition. This categorization minimized potential misclassification of cases that may occur with automated methods, such as categorizing cases based on MedDRA coding alone. The most frequent MedDRA preferred terms reported for each severity category across the fluoroquinolones were consistent for mild reactions ('rash', 'drug hypersensitivity' and 'urticaria') and for moderate-severe reactions ('dyspnoea', 'drug hypersensitivity' and 'swelling face'). This

provides a level of reassurance that we categorized cases appropriately without systemic bias. Although attribution can be biased, we believe an additional strength of using NEISS-CADES as a data source is that each case includes physician attribution, which in this surveillance system, has been demonstrated to have a high positive predictive value (92%),⁸ based on a sample of 29 reports of all types (allergic reactions and others). Additionally, because the physicians who make diagnoses in NEISS-CADES data collection hospitals are not part of the data extraction process, they are acting as caregivers and not as researchers in a surveillance system and are therefore, less likely to bias the data toward any one drug.

There are also several limitations that should be considered when interpreting these data. The classification of hypersensitivity severity for each fluoroquinolone was assigned in an unblinded review, as the suspect drug was readily available in each report. However, to minimize this potential bias, we applied an *a priori* case definition to objectively categorize each case. Additionally, our rate estimates are crude measures that have not been statistically adjusted. Even though the baseline patient characteristics stratified by drug (Table 1) were comparable, because these data are not randomized, we cannot exclude the possibility of confounding. However, the sample of NEISS-CADES cases are prospectively collected, in the absence of a research hypothesis, which should reduce the chance of selection bias preferentially implicating a given fluoroquinolone. Information bias is also a potential concern because available drug information in the literature could influence the diagnosing physician to selectively attribute more hypersensitivity cases to moxifloxacin. We also used prescriptions dispensed as the basis of fluoroquinolone exposure, although, we have no means to ascertain whether prescriptions dispensed proportionately correspond to patient exposure. However, there is no reason to believe there is differential misclassification of these exposures across the fluoroquinolones. Although these data are derived from two nationally representative samples of ED visits and outpatient prescriptions dispensed, we cannot exclude the possibility of sampling error, whereby prescription patterns for moxifloxacin in the NEISS-CADES sample could be disproportionately higher than those of the IMS Health population. However, to minimize this chance of this error, we incorporated estimates of variability using 95% confidence intervals in our rate estimates that make this possibility unlikely.

The methods employed in this work do not fully capture all fluoroquinolone-induced hypersensitivity reactions. Although, this work likely accurately measures the most serious reactions attributed to fluoroquinolones requiring an evaluation by an emergency physician, it does not capture events that were not diagnosed by an ED physician or were managed in a setting outside of the ED (e.g. medical offices, clinics or self-treatment). Arguably, the morbidity attributed to hypersensitivity reactions is likely higher than what we estimate.

Differential risk of hypersensitivity reactions following fluoroquinolone exposure may be plausible based on laboratory investigations, published case reports and differences in the chemical structures of the fluoroquinolones. All fluoroquinolones exhibit some form of cross reactivity in hypersensitivity reactions owing to the 4-oxo-1,4,-dihydroquinoline ring common to these drugs,¹² but the degree of this cross reactivity is inconsistent across the drug class. Several case reports have shown that one patient may develop a hypersensitivity reaction to moxifloxacin, only to be re-challenged with a different fluoroquinolone without

sequelae,^{13,14,15} suggesting that substituents other than the fluoroquinolone ring nucleus are potential hypersensitivity determinants. Data reported in the literature support the importance of the moieties situated in positions N-1, 7 and 8 of the quinolone nucleus in immunogenicity.^{1,6,13} While speculative, select substituents could bind to protein with varying degrees of affinity, to elicit an immune response to a fluoroquinolone-protein complex at different rates.

Fluoroquinolones are implicated in ED visits for hypersensitivity in the United States, albeit the risk appears to be low. Even though the absolute risk of a hypersensitivity reaction (regardless of severity) requiring an ED visit was low, the relative differences in risk, implicating moxifloxacin more often in these reactions than levofloxacin or ciprofloxacin could be important. Considering the high volume of prescriptions dispensed for moxifloxacin, even small absolute risks could substantially contribute to ED visits, and switching large populations of patients to moxifloxacin-based regimens would be expected to increase hypersensitivity-associated ED visits.

Acknowledgments

The authors would like to thank Dr. Thamban Valappil for his assistance with SAS statistical programming, and Drs. Andy Mosholder and G. Caleb Alexander for their insightful review of early versions of this manuscript. We would also like to thank Kathleen Rose and Kelly Weidenbach of CDC and Joel Friedman of the US Consumer Product Safety Commission for assistance with data collection. No sources of funding were used to conduct this study or prepare the manuscript and the authors have no conflicts of interest that are directly relevant to the content of this study. The views expressed are those of the authors and do not necessarily represent the views of the FDA or CDC.

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Key Points

- Fluoroquinolone-associated hypersensitivity reactions requiring treatment in an emergency department are rare in the United States.
- The comparative rate of emergency department visits for moxifloxacin-associated hypersensitivity reactions was higher than that for ciprofloxacin and levofloxacin, and the difference was statistically significant.
- The risk of hypersensitivity reaction is comparable for ciprofloxacin and levofloxacin.

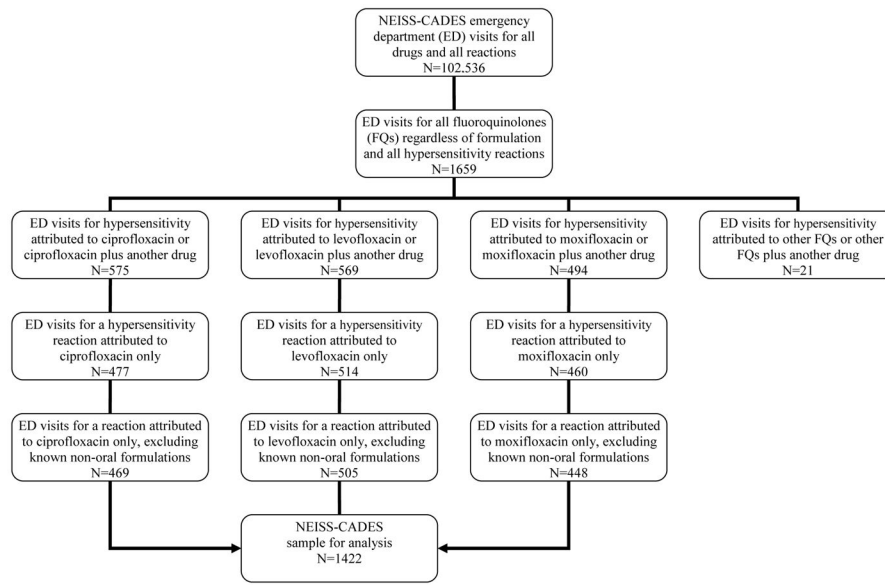


Figure 1.
Flow Diagram of NEISS-CADES Case Selection

Table 1

Cases of Emergency Department Visits for Hypersensitivity Reactions to Fluroquinolones, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance, 2004–2010

Demographic or Clinical Characteristic	Ciprofloxacin N=469	Levofloxacin N=505	Moxifloxacin N=448	Other FQs ^a N=18
Age				
Mean (years) ±SD	47±19.5	49±18.4	49±15.8	39±19.6
(Range) ^b	(1–98)	(13–93)	(12–90)	(7–80)
Gender				
Male	112 (24%)	154 (30%)	104 (23%)	8 (44%)
Female	357 (76%)	351 (70%)	344 (77%)	10 (56%)
Race				
White	242 (52%)	309 (61%)	274 (61%)	10 (56%)
Black	59 (13%)	49 (10%)	21 (5%)	2 (11%)
Asian	5 (1%)	0 (0%)	2 (<1%)	0 (0%)
Not Stated	125 (27%)	115 (23%)	135 (30%)	5 (28%)
Other	38 (8%)	32 (6%)	16 (4%)	1 (6%)
Allergic Reaction Category				
Mild	321 (68%)	311 (62%)	265 (59%)	14 (78%)
Moderate	123 (26%)	158 (31%)	155 (35%)	4 (22%)
Severe	25 (5%)	36 (7%)	28 (6%)	0 (0%)
Concomitant Medications per Case				
None Listed	241 (51%)	261 (52%)	218 (49%)	9 (50%)
1–3 medications	133 (28%)	153 (30%)	140 (31%)	7 (39%)
4–6 medications	64 (14%)	57 (11%)	60 (13%)	2 (11%)
7 medications	31 (7%)	34 (7%)	30 (7%)	0 (%)
Disposition				
Treated and Released	429 (91%)	459 (91%)	411 (92%)	17 (94%)
Admitted	24 (5%)	32 (6%)	24 (5%)	0 (0%)
LAMA ^c	12 (3%)	5 (1%)	6 (1%)	1 (6%)
Observation in ED	4 (1%)	6 (1%)	6 (1%)	0 (0%)
Transferred	0 (0%)	3 (1%)	1 (<1%)	0 (0%)

^aGemifloxacin (n=12) and Ofloxacin (n=6).

^bThere were a total of nine pediatric (<16 years) cases in the dataset distributed as ciprofloxacin (n=5), levofloxacin (n=1), moxifloxacin (n=1), gemifloxacin (n=1), and ofloxacin (n=1).

^cLAMA=left against medical advice

Table 2
 Estimated Number of Prescriptions Dispensed for Oral Fluoroquinolones in US Outpatient Retail Pharmacies, 2004–2010

	National Prescription Estimate	95% Confidence Interval
Ciprofloxacin	122,466,455	122,440,577 – 122,492,333
Levofloxacin	88,144,080	88,122,164 – 88,165,995
Moxifloxacin	24,395,259	24,383,808 – 24,406,709
Gemifloxacin	1,108,168	1,105,768 – 1,110,568
Ofloxacin	541,164	539,493 – 542,835
Norfloxacin	263,373	262,211 – 264,534
All Fluoroquinolones	236,918,498	236,882,377 – 236,954,618

Source data: IMS Health, Vector One®; National (VONA). Extracted March 8, 2013.

Table 3

Count of NEISS-CADES Cases and Projected National Estimates of US Emergency Department Visits Stratified by Fluoroquinolone and Hypersensitivity Reaction Severity Category, 2004–2010

Fluoroquinolone	All Reaction Severity Categories		Mild Reactions		Moderate to Severe ^c Reactions	
	Number of NEISS-CADES Cases	Estimated Number of ED Visits (95% CI)	Number of NEISS-CADES Cases	Estimated Number of ED Visits (95% CI)	Number of NEISS-CADES Cases	Estimated Number of ED Visits (95% CI)
Ciprofloxacin	469	32,269 (25,271–39,265)	321	22,523 (16,906–28,138)	148	9,746 (7,247–12,244)
Levofloxacin	505	35,947 (27,617–44,276)	311	22,028 (16,499–27,556)	194	13,918 (10,164–17,672)
Moxifloxacin	448	34,469 (24,148–44,789)	265	20,104 (12,966–27,212)	183	14,365 (9,781–18,948)
All Analyzable^a Fluoroquinolones	1422	102,684 (81,026–124,342)	897	64,655 (50,819–78,490)	525	38,029 (28,539–47,518)
All Fluoroquinolones^b	1440	104,338 (82,047–126,628)	910	65,901 (51,750–80,051)	530	38,437 (28,680–48,194)

Source data: NEISS-CADES database 2004–2010 Extracted November 9, 2012

^aIncludes cases attributed to ciprofloxacin, levofloxacin and moxifloxacin only.

^bIncludes cases attributed to ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin and ofloxacin. There were no cases of norfloxacin attributed hypersensitivity in the NEISS-CADES system.

^cModerate to severe reactions are pooled cases of moderate and severe reactions from the NEISS-CADES system.

Table 4

Rate of US Emergency Department Visits per 100,000 US Outpatient Prescriptions Dispensed, Stratified by Hypersensitivity Reaction Severity Category and Fluoroquinolone, 2004–2010

Hypersensitivity Reaction Severity Category	Fluoroquinolone	Estimated Number of ED Visits per 100,000 Prescriptions (95% CI)	Rate Ratio ^a (95% CI)	Rate Ratio ^b (95% CI)
Mild	Ciprofloxacin	18.4 (13.9–22.9)	Referent	-----
	Levofloxacin	25.0 (18.8–31.1)	1.4 (0.9–1.8)	Referent
	Moxifloxacin	82.4 (53.9–110.9)	4.5 (2.6–6.4)	3.3 (1.9–4.7)
Moderate to Severe^c	Ciprofloxacin	8.0 (6.0–10.0)	Referent	-----
	Levofloxacin	15.8 (11.6–20.0)	2.0 (1.3–2.7)	Referent
	Moxifloxacin	58.9 (40.5–77.3)	7.4 (4.4–10.4)	3.7 (2.2–5.3)
All Hypersensitivity Reaction Categories	Ciprofloxacin	26.3 (20.8–31.9)	Referent	-----
	Levofloxacin	40.8 (31.5–50.0)	1.5 (1.1–2.0)	Referent
	Moxifloxacin	141.3 (99.9–182.7)	5.4 (3.4–7.3)	3.5 (2.2–4.7)

^a Each rate ratio was calculated by dividing the rate of ED visits per 100,000 prescriptions for moxifloxacin and levofloxacin by the rate estimated for ciprofloxacin (referent-lowest incidence across categories).

^b Each rate ratio was calculated by dividing the rate of ED visits per 100,000 prescriptions for moxifloxacin by the rate estimated for levofloxacin.

^c Moderate to severe reactions are pooled cases of moderate and severe reactions from the NEISS-CADES system.