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Signal Detection and Clarification of Peripheral Neuropathy and Guillain-Barré Syndrome Associated with Exposure to Systemic Fluoroquinolones

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Author's contribution

The entire work was conducted by the author AKA.

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ABSTRACT

Aims: Peripheral neuropathy (PN) is an identified risk of systemic antibacterial therapy with fluoroquinolones. The risk and its severity, including the development of Guillain-Barré syndrome (GBS) between individual agents is uncertain. This study examines the association between fluoroquinolones and PN and GBS in cases spontaneously reported to the FDA Adverse Event Reporting System (FAERS).
Study Design: Retrospective pharmacovigilance analysis.
Place and Duration of Study: Cases submitted to FAERS between 1997 and 2012.
Methodology: The MedDRA Preferred Term was used to define PN and GBS. Individual fluoroquinolones were identified by generic names and route of administration. Empirical Bayes Geometric Mean (EBGM) with 95% confidence interval (EB05-EB95) was calculated as disproportionality measure. Safety signals with EB05≥2 was considered a significant disproportional increase in event reporting of at least twice times higher than expected.
Results: There were 539 PN reports out of 46,257 adverse event reports submitted for fluoroquinolones. 9% of PN reports were for GBS. Significant disproportionality of PN (EBGM 2.70; EB05-EB95 2.51-2.90) and GBS (EBGM 3.22; EB05-EB95 2.55-4.02) was identified for fluoroquinolones. Signals of PN were detected for ciprofloxacin (EBGM 3.24; EB05-EB95 2.87-3.66) and levofloxacin (EBGM 3.36; EB05-EB95 3.02-3.72). A GBS signal was detected for ciprofloxacin (EBGM 4.15; EB05-EB95 2.94-5.74). GBS and PN respectively ranked 6th and 8th among reported neurological events.

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Conclusion: This study reemphasizes the link between fluoroquinolones and PN, and shows potential association with more severe forms of nerve damage, e.g. GBS. Unless the benefit of fluoroquinolone therapy outweighs PN risk, treatment with alternative antibacterial agents is recommended.

Keywords: Guillain-Barré syndrome; peripheral neuropathy; fluoroquinolones; FAERS.

1. INTRODUCTION

Fluoroquinolones are broad-spectrum antibacterial agents with wide prophylactic and therapeutic indications against respiratory, genito-urinary, gastrointestinal, bone, and ophthalmic infections. In 3Q 2004, peripheral neuropathy was added to product labels and medication guides as an identified risk of systemic treatment with fluoroquinolones [1-5].Despite these risk evaluation and mitigation strategies (REMS), reports of peripheral neuropathy continued to be submitted to the FDA Adverse Event Reporting System (FAERS). In August 2013, the FDA required manufacturers of systemic fluoroquinolones to revise product REMS for optimal characterization of the risk [6].

In US, approximately 27 million patients received systemic fluoroquinolones in 2011; 23.1 million received oral and 3.8 million received injectable formulations. About 70% of the pharmacy-dispensed oral and 63% of the hospital-administered injectable fluoroquinolones was for ciprofloxacin and levofloxacin, respectively [6].

Peripheral neuropathy is a rare degenerative disorder of the peripheral nervous system with an estimated annual incidence of 1.6 per 100,000 persons in the US [7], and a prevalence of 2.4% [8]. Among US individuals 40 years or older, the prevalence of insensate peripheral neuropathy was about two-folds among those with diabetes compared to those without diabetes (21.2% vs. 11.5%) [9].The symptoms, severity, and duration of peripheral neuropathy depend on the nerves affected. Sensory neuropathy is accompanied by burning sensation, numbness, pain, and loss of reflexes and sensation to touch. Motor neuropathy is associated with muscular weakness, and problems with mobility, coordination, and respiration [10].

The seriousness, onset, and reversibility of peripheral neuropathy and the development of acute nerve damage, including Guillain-Barré syndrome (GBS) between individual fluoroquinolones are uncertain, and there is no published review of peripheral neuropathy cases after fluoroquinolone REMS implementation in 2004. This study examines the association between fluoroquinolones and peripheral neuropathy and GBS in cases recorded in the FAERS.

2. METHODOLOGY

2.1 Data Source

Adverse event reports submitted to the FAERS between 3Q 1997 and 3Q 2012 were included in the analysis. The FAERS is a database of spontaneously submitted adverse event reports from healthcare professionals, consumers, caregivers, manufacturers, and other sources. The database is a crucial source of safety signal detection and risk management for marketed pharmaceutical products in the US, and has been extensively utilized for pharmacovigilance studies and disproportionality analyses [11-13].

2.2 Exposures

Fluoroquinolones are available in systemic and topical formulations (table 1). The following agents in oral and injectable formulations are included in the analysis: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. Exposures are identified by the generic name recorded within the 5th hierarchy of the World Health Organization's Anatomical Therapeutic Chemical (ATC, January 2012) classification system.

2.3 Outcomes

The Preferred Term (PT) hierarchy of the Medical Dictionary for Regulatory Activities (MedDRA 15.0, March 2012) is used to identify the events of interest. Events were retrieved by the following PTs: "neuropathy peripheral" and "Guillain-Barré syndrome". Serious events are defined as any peripheral neuropathy or GBS event that was associated with patient death, life-threatening outcome, initial or prolonged hospitalization, disability, congenital anomaly, or required intervention. The proportion of cases associated with death and disability are reported.

Table 1. Approved and discontinued fluoroquinolones in the US

Fluoroquinolone		FDA approval date by formulation[a]	
Generic name	**Brand name[b]**	**Systemic**	**Ophthalmic**
Besifloxacin	Besivance	n/a	May 28, 2009
Ciprofloxacin	Cipro; Cloxan	Oct. 22, 1987	Dec. 31, 1990
Gatifloxacin	Zymar	n/a	Mar. 28, 2003
Gemifloxacin	Factive	Apr. 4, 2003	n/a
Grepafloxacin[c]	Raxar	Nov. 6, 1997	n/a
Levofloxacin	Levaquin; Iquix	Dec. 20, 1996	Mar. 1, 2004
Lomefloxacin	Maxaquin	n/a	Feb. 21, 1992
Moxifloxacin	Avelox; Vigamox	Dec. 10, 1999	Apr. 15, 2003
Norfloxacin	Noroxin; Chibroxin	Oct. 31, 1986	Jun. 17, 1991
Ofloxacin	Floxin; Floxin Otic	Dec. 28, 1990	Dec. 16, 1997
Sparfloxacin[d]	Zagam	Dec. 19, 1996	n/a
Temafloxacin[e]	Omniflox	Jan. 1992	n/a
Trovafloxacin[f]	Trovan	Dec. 18, 1997	n/a

FDA=Food and Drug Administration.

[a]Source: www.fda.gov, [b]Brand names are the property of their respective manufacturers.

Discontinued from US market in: [c]1999 for cardiovascular toxicity, [d]2001 for cardiac arrhythmia risks, [e]1992 for allergic and hemolytic anemia risks, and [f] 2001 for hepatotoxicity.

2.4 Disproportionality Analysis

Statistical analyses are conducted in Empirica Signal 7.3 (November 2011, Oracle USA, Inc., Redwood City, CA). The Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm is applied to estimate disproportional reporting of peripheral neuropathy and GBS events in relation to exposure to systemic fluoroquinolones. The MGPS algorithm tests the null hypothesis of no association between the drug and adverse event of interest in the spontaneous reporting database. This algorithm estimates Empirical Bayes Geometric Mean (EBGM) values with corresponding 95% confidence intervals (EB05-EB95) as a measure of disproportionality. An EBGM estimate denotes to the ratio of the number of adverse event reports mentioned the drug of interest to the expected count of events for that drug, or a comparison [14,15]. Safety signals with EB05$\geq$2 was considered a significant disproportional increase in event reporting of at least twice times higher than expected.

Compared to other algorithms applied in pharmacovigilance, Bayesian-based MGPS algorithm improves signal interpretability by yielding more reliable association estimates and confidence intervals [16-18]. Additionally, signal sector mapping is applied to further describe the relative rank and importance of peripheral neuropathy in relation to other neurological events and all adverse events reported for systemic fluoroquinolones. Within each System Organ Class (SOC), events with the strongest signal (EB05) are reported for top 22 events; top 12 events for nervous system SOC are reported. The color and size of sector map tiles are controlled by signal strength and Public Health Impact (PHI) score within each SOC [19]. The PHI score takes into consideration the number of reports with serious outcomes for reported drug in relation to all serious events reported for all the drugs in the database [19].

Furthermore, disproportional reporting of peripheral neuropathy for individual fluoroquinolones was compared with selected antibacterial agents for which the event is an identified risk as positive controls (co-trimoxazole, linezolid, metronidazole and nitrofurantoin), and unidentified risk as negative controls (amoxicillin, azithromycin, clindamycin and erythromycin).

3. RESULTS AND DISCUSSION

3.1 Overview of Peripheral Neuropathy Reports

Between 3Q 1997 and 3Q 2012, the FAERS recorded 46,257 adverse event reports for treatment with systemic fluoroquinolones. Out of these, peripheral neuropathy was recorded in 539 reports (1% of all submitted events), and GBS was recorded in 48 reports (9% of peripheral neuropathy reports). Overall, the majority of patients experienced peripheral neuropathy after exposure to fluoroquinolones were females with median age of 48 years (range between 9 and 100). Most of the reports were directly submitted by healthcare professionals and consumers. About 78% of the reports indicated fluoroquinolones as the primary suspect in the occurrence of peripheral neuropathy, and about 52% of submitted reports didn't include a concomitant drug, and only 48% of peripheral neuropathy reports indicated $\geq$1 concurrent exposure to another drug. Co morbidity with diabetes mellitus was determined by concurrent exposure to anti-diabetes medications, including insulin therapy. Only 11 patients had diabetes mellitus at the time of exposure to fluoroquinolones and peripheral neuropathy experience (ciprofloxacin=4 and levofloxacin=7). None of the patients who experienced peripheral neuropathy or GBS was recovered from the event, and the vast majority of peripheral neuropathy events were serious outcomes (n=492, including all GBS reports). Among serious events, 6 (1.2%) contributed to patient death, and 137 (27.8%) lead to physical disability. The median onset of peripheral neuropathy after exposure to fluoroquinolones was 4 days, and the median duration of therapy was 6 days.

There was variable distribution of report characteristics between individual fluoroquinolones (Table 2). About 80% of the reported events were for ciprofloxacin and levofloxacin, which are the most frequently utilized fluoroquinolones in the US. Among reports with known reporting source, healthcare professionals contributed to the majority of reports; followed by consumers, including patients and caregivers (except for norfloxacin). Reports from the manufacturer of respective fluoroquinolones were submitted for ciprofloxacin, levofloxacin, and moxifloxacin (for GBS); and only two reports were submitted from a clinical study involving moxifloxacin (for GBS) and ofloxacin. Half of ciprofloxacin and levofloxacin reports were directly submitted by the reporting source; most of norfloxacin and ofloxacin reports

Table 2. Characteristics of peripheral neuropathy reports submitted for fluoroquinolones

Characteristic[a]	Ciprofloxacin n=186	Levofloxacin n=244	Moxifloxacin n=75	Norfloxacin n=9	Ofloxacin n=25
Patient's age (years)[b]	44 (9, 90) n=141	48 (16, 84) n=191	48 (26, 100) n=48	45 (10, 69) n=8	52 (15, 89) n=24
Patient's sex					
Female	90 (48.4)	139 (57)	43 (57.3)	7 (77.8)	15 (60)
Male	87 (46.8)	94 (38.5)	29 (38.7)	1 (11.1)	10 (40)
Unknown	9 (4.8)	11 (4.5)	3 (4)	1 (11.1)	0
Report type					
Direct	93 (50)	123 (50.4)	19 (25.3)	2 (22.2)	3 (12)
Periodic	24 (13)	41 (16.8)	28 (37.3)	0	6 (24)
Expedited	69 (37)	80 (32.8)	28 (37.3)	7 (77.8)	16 (64)
Event outcome					
Death	2 (1)	3 (1.2)	0	1 (11.1)	0
Disability	54 (29)	58 (23.8)	15 (20)	2 (22.2)	8 (32)
Reporting source					
Healthcare professional	30 (16.1)	36 (14.8)	11 (14.7)	2 (22.2)	9 (36)
Consumer	17 (9.1)	24 (9.8)	5 (6.7)	0	7 (28)
Manufacturer	4 (2.1)	20 (8.2)	2 (2.6)	0	0
Clinical study	0	0	1 (1.3)	0	1 (4)
Other/unknown	135 (72.6)	164 (67.2)	56 (74.7)	7 (77.8)	8 (32)
Drug role in event occurrence					
Primary suspect	145 (78)	186 (76.2)	62 (82.7)	5 (55.5)	22 (88)
Secondary suspect	39 (21)	56 (23)	12 (16)	4 (44.4)	3 (12)
Concomitant	2 (1)	2 (0.8)	1 (1.3)	0	0
Onset of event (days)[b]	4 (0, 73) n=99	4 (0, 91) n=123	2 (0, 81) n=34	38 (14, 63) n=2	44 (n/a) n=1
Duration of therapy (days)[b]	7 (0, 83) n=100	6 (0, 72) n=143	4 (0, 38) n=39	1 (0, 18) n=7	12 (2, 69) n=12
Number of concomitant drugs					
0	95 (51.1)	130 (53.3)	45 (60)	2 (22.2)	6 (24)
1	36 (19.3)	42 (17.2)	9 (12)	1 (11.1)	4 (16)
≥2	55 (29.6)	72 (29.5)	21 (28)	6 (66.6)	15 (60)
Comorbidity with diabetes	4 (2.1)	7 (2.8)	0	0	0

[a] *Values reported as frequencies and percentages unless otherwise specified.*
[b] *Median (Min, Max) and number of reports with valid information.*

were reported within 15 days of event occurrence (expedite); and about 75% of moxifloxacin reports were expedite and quarterly submitted (periodic). Compared to norfloxacin and ofloxacin, peripheral neuropathy occurred sooner after treatment with ciprofloxacin, levofloxacin, and moxifloxacin.

Most of the reported events for ciprofloxacin, levofloxacin, and moxifloxacin did not state a concurrent exposure to another drug; in contrast, most of the reports for norfloxacin and ofloxacin stated concomitant treatment with ≥2 medications in addition to respective fluoroquinolones. However, all individual fluoroquinolones were reported as the primary suspect in the occurrence of peripheral neuropathy. Among serious events, patient death was reported for ciprofloxacin, levofloxacin, and norfloxacin; disability was reported for all fluoroquinolones with the following reducing order of frequency: ofloxacin > ciprofloxacin > levofloxacin > norfloxacin > moxifloxacin.

Table 3 shows the characteristics of GBS reports for individual fluoroquinolones. GBS was reported for ciprofloxacin (n=24), levofloxacin (n=13), and moxifloxacin (n=11). Most of the patients who experienced GBS after exposure were males with a median age of 49 years. Most of GBS reports were directly submitted by healthcare professionals, with fluoroquinolones being the primary suspect in GBS occurrence.

Table 3. Characteristics of Guillain-Barre syndrome submitted for fluoroquinolones

Characteristic[a]	**Ciprofloxacin n=24**	**Levofloxacin n=13**	**Moxifloxacin n=11**
Patient's age (years)[b]	62 (26, 90) n=22	49 (12, 83) n=11	52 (28, 68) n=11
Patient's sex			
Female	5 (20.8)	5 (38.5)	2 (18.2)
Male	17 (70.8)	7 (53.8)	9 (81.8)
Unknown	2 (8.3)	1 (7.7)	0
Report type			
Direct	2 (8.3)	2 (15.4)	1 (9)
Periodic	0	1 (7.7)	0
Expedited	22 (91.7)	10 (77)	10 (91)
Event outcome			
Death	2 (8.3)	0	1 (9)
Disability	3 (12.5)	2 (15.4)	0
Reporting source			
Healthcare professional	13 (54.2)	8 (61.5)	5 (45.4)
Consumer	0	1 (7.7)	0
Manufacturer	0	0	2 (18.2)
Clinical study	0	0	1 (9)
Other/unknown	11 (45.8)	4 (30.8)	3 (27.3)
Drug role in event occurrence			
Primary suspect	22 (91.7)	12 (92.3)	10 (91)
Secondary suspect	2 (8.3)	1 (7.7)	0
Concomitant	0	0	1 (1)
Onset of event (days)[b]	3 (0, 26) n=7	4 (0, 7) n=9	2 (0, 9) n=6
Duration of therapy (days)[b]	5 (1, 20) n=11	3 (0, 7) n=10	5 (0, 7) n=7
Number of concomitant drugs			
0	11 (45.8)	3 (23.1)	3 (27.3)
1	5 (20.8)	3 (23.1)	0
≥2	8 (33.3)	7 (53.8)	8 (72.7)
Comorbidity with diabetes	3 (12.5)	1 (7.7)	0

[a]*Values reported as frequencies and percentages unless otherwise specified.*
[b]*Median (Min, Max) and number of reports with valid information.*

Table 4. Experimental information recorded in peripheral neuropathy reports

Fluoroquinolone	Experimental information[a]					
	Dechallenge			Rechallenge		
	Positive	Negative	N	Positive	Negative	N
Ciprofloxacin[b]	18 (22.2)	63 (77.8)	81	10 (83.3)	2 (16.7)	12
Levofloxacin[b]	12 (11)	97 (89)	109	18 (72)	7 (28)	25
Moxifloxacin	3 (17.6)	14 (82.4)	17	2 (100)	0	2
Norfloxacin	1 (33.3)	2 (66.7)	3	0	1 (100)	1
Ofloxacin[c]	3 (27.3)	8 (72.7)	11	3 (100)	0	3

[a]Values reported as frequencies and percentages of total number of reports (N) with available/applicable information. Simultaneous positive dechallenge and positive rechallenge was observed in: [b]3 reports and [c]1 report.

3.2 Peripheral Neuropathy Signals

Disproportionality analysis results are depicted in Table 5. Significant disproportional reporting of peripheral neuropathy and GBS was identified for fluoroquinolones (EBGM 2.70; EB05-EB95 2.51-2.90 and EBGM 3.22; EB05-EB95 2.55-4.02 respectively). Signals of peripheral neuropathy were detected for ciprofloxacin (EBGM 3.24; EB05-EB95 2.87-3.66) and levofloxacin (EBGM 3.36; EB05-EB95 3.02-3.72); and a GBS signal was identified for ciprofloxacin (EBGM 4.15; EB05-EB95 2.94-5.74).

Reporting of peripheral neuropathy was more than expected for moxifloxacin (EBGM 1.34; EB05-EB95 1.10-1.61), norfloxacin (EBGM 2.18; EB05-EB95 1.23-3.63), and ofloxacin (EBGM 1.90; EB05-EB95 1.36-2.61); however, a signal threshold was not reached (EB05$\underline{>}$2). Likewise, disproportional reporting GBS was found for levofloxacin (EBGM 1.92; EB05-EB95 1.20-2.96) and moxifloxacin (EBGM 2.10; EB05-EB95 1.26-3.34).

Table 5. Signals of peripheral neuropathy and GBS detected for fluoroquinolones

Fluoroquinolone	Event MedDRA preferred term No. of reports, EBGM (EB05-EB95)[a]			
	Peripheral neuropathy		Guillain-Barré syndrome	
Ciprofloxacin	186	3.24 (2.87-3.66)	24	4.15 (2.94-5.74)
Levofloxacin	244	3.36 (3.02-3.72)	13	1.92 (1.20-2.96)
Moxifloxacin	75	1.34 (1.10-1.61)	11	2.10 (1.26-3.34)
Norfloxacin	9	2.18 (1.23-3.63)	0	n/a
Ofloxacin	25	1.90 (1.36-2.61)	0	n/a
All fluoroquinolones	539	2.70 (2.51-2.90)	48	3.22 (2.55-4.02)

MedDRA=Medical Dictionary for Regulatory Activities, EBGM=Empirical Bayes Geometric Mean.
[a]Number of reports are mutually not exclusive between events, Guillain-Barré syndrome reports are included in peripheral neuropathy reports.

Furthermore, the risk profile of peripheral neuropathy for individual fluoroquinolones (e.g. ciprofloxacin and levofloxacin) was consistent with that for antibacterial agents for which the event is an identified risk (e.g. metronidazole and nitrofurantoin); and no disproportional reporting was identified for antibacterial agents for which peripheral neuropathy is not a labeled risk (e.g. amoxicillin and erythromycin) (Fig. 1). Compared to other adverse events reported for fluoroquinolones, events affecting the nervous system ranked 18th in signal sector mapping; and peripheral neuropathy ranked 8th within reported neurological events

(Fig. 2). Although events within the neurological SOC had an average PHI scores (tile sizes consistent with other SOC tiles), there was a considerable number of significant signals (EB≥2) almost similar to the distribution observed in other SOC events, e.g. muscular, skin, liver, and immune system.

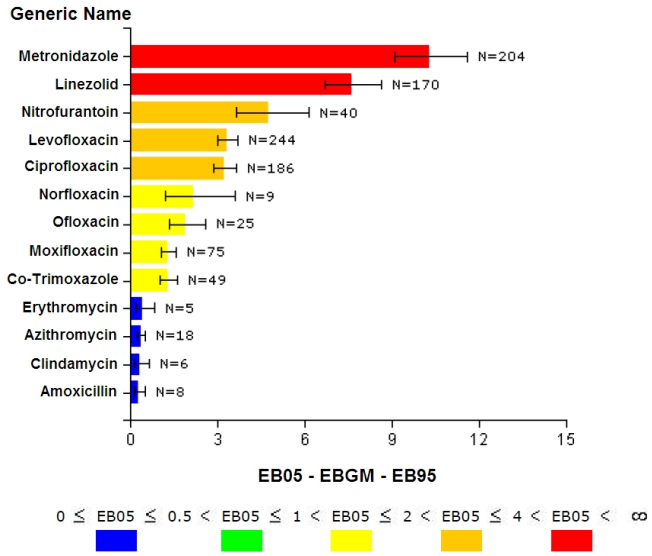
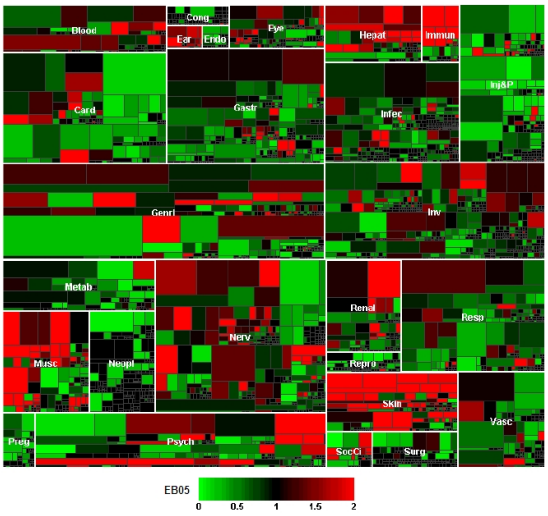


Fig. 1. Disproportional reporting of peripheral neuropathy for fluoroquinolones compared with selected antibacterial agents



Signal Rank by System Organ Class (SOC):

Rank	SOC	Preferred Term	EB05
1	Musc	Tendon Pain	59.8
2	Injury	Tendon Rupture	46.7
3	Genrl	Infusion Site Rash	14.3
4	Infec	Clostridium Colitis	10.2
5	Eye	Corneal Deposits	10.0
6	Card	Torsade de Pointes	8.0
7	Ear	Deafness Permanent	7.7
8	Skin	Vascular Purpura	7.6
9	Immun	Anaphylactic Reaction	7.5
10	Hepat	Vanishing Bile Duct Syndrome	7.0
11	Renal	Tubulointerstitial Nephritis	5.1
12	Other	Impaired Work Ability	4.0
13	Gastr	Enterocolitis Hemorrhagic	3.7
14	Repro	Prostatitis	3.7
15	Vasc	Vein Discoloration	3.6
16	Blood	Agranulocytosis	3.4
17	Psych	Depersonalization	3.3
18	Nerv	Burning Sensation	3.2
19	Inv	Prothrombin Time Ratio Decreased	3.1
20	Resp	Pharyngeal Edema	3.0
21	Metab	Food Intolerance	2.6
22	Cong	Epidermolysis Bullosa	2.2

Signal Rank by Nervous System SOC:

Rank	SOC	Preferred Term	EB05
1	Nerv	Burning Sensation	59.8
2	Nerv	Muscle Contractions Involuntary	46.7
3	Nerv	Dysstasia	14.3
4	Nerv	Neuralgia	10.2
5	Nerv	Parasthesia	10.0
6	Nerv	Guillain-Barré Syndrome	8.0
7	Nerv	Myasthenia Gravis	7.7
8	Nerv	Neuropathy Peripheral	7.6
9	Nerv	Polyneuropathy	7.5
10	Nerv	Parosmia	7.0
11	Nerv	Hypoesthesia	5.1
12	Nerv	Carpal Tunnel Syndrome	4.0

Fig. 2. Sector map of selected signals detected for fluoroquinolones

This pharmacovigilance analysis of FAERS data underscores the link between systemic exposure to fluoroquinolones and peripheral neuropathy, and shows potential association

with more severe forms of nerve damage, including GBS. There was within-class variation in association magnitude and signal significance. The analysis yielded signals of peripheral neuropathy and GBS for systemic fluoroquinolones as an antibacterial class; however, there were noticeable differences in the number of events and degree of association reported for each agent. Peripheral neuropathy signals were detected for ciprofloxacin and levofloxacin, and signal of GBS was found for ciprofloxacin only. Highest reporting frequencies were found for ciprofloxacin and levofloxacin, partly because these agents were the most frequently used formulations in the US [6].

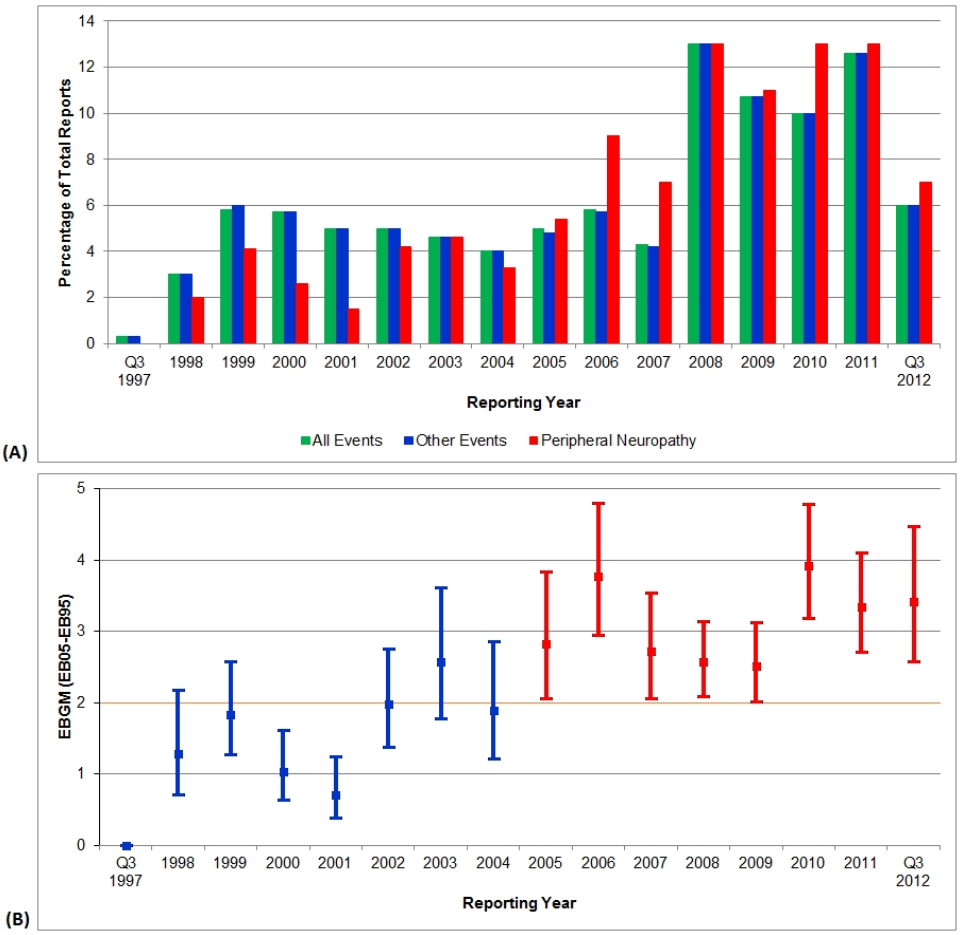


Fig. 3. Peripheral neuropathy (A) reporting and (B) signal trends for fluoroquinolones
Numbers are percentages of total reports for corresponding event category.

Notably, reports of peripheral neuropathy increased sharply after 2004 (Fig. 3-A), following warnings issued by the FDA. Likewise, signals (EB≥2) were only detected after 2004 (Fig. 3-B). Awareness of events contributes to over-reporting due to encouraged monitoring and management of patients with peripheral neuropathy following exposure to fluoroquinolones. Although there was an increase in reporting peripheral neuropathy relative to other events reported for fluoroquinolones after 2004, the potential for under-reporting in spontaneous reporting systems is always present for multiple reasons [20]. In addition, report quality in

terms of missing or inconsistent information is also an issue that should always be considered in such analyses, e.g. potential confounders. Consequently, these findings should be interpreted with caution given the inherent limitations of spontaneously submitted adverse events and analysis of such data, e.g. reporting bias.

Peripheral neuropathy is multifactorial in etiology and variable in presentation and severity [21]. The outcome of interest in this analysis was based on a MedDRA preferred term which was abstracted by case managers at the FDA based on the signs and symptoms of possible peripheral neuropathy that were reported by the source, e.g. healthcare professional or consumer. Therefore, reanalysis of the data by creating a custom term encompassing signs and symptoms of peripheral neuropathy might improve signal detection, although the detected signals might be over-estimated.

4. CONCLUSION

In tandem with the FDA recommendations, and unless the benefit of fluoroquinolone therapy outweighs the risk, e.g. overwhelming infection and development of bacterial resistance, prescribers should consider antibacterial therapy with alternative agents for which peripheral neuropathy is not an identified or potential risk. Nonetheless, pharmacoepidemiologic studies are suggested to test the generated hypothesis and to further characterize the safety profile of fluoroquinolones regarding peripheral neuropathy risk.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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