Association between oral fluoroquinolones and seizures: a self-controlled case series study

Celine SL Chui MSc[1], Esther W Chan PhD[1], Angel YS Wong BSc[1], Adrian Root MSc[2], Ian J Douglas PhD[2], and Ian CK Wong PhD[1,3]

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 2/F, 21 Sassoon Road, Laboratory Block, Faculty of Medicine Building, Hong Kong

[2]Department of Non-communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom

[3]Research Department of Practice and Policy, UCL School of Pharmacy, 29-39 Brunswick Square, London, United Kingdom

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Corresponding author: Professor Ian CK Wong

Address: Research Department of Practice and Policy, UCL School of Pharmacy, 29-39 Brunswick Square, London, United Kingdom

Phone and Fax: (44) 20 7753 5966

E-mail: i.wong@ucl.ac.uk; wongick@hku.hk

Celine SL Chui: cceline@connect.hku.hk

Esther W Chan: ewchan@hku.hk

Angel YS Wong: aywong@connect.hku.hk

Adrian Root: adrian.root@lshtm.ac.uk

Ian J Douglas: ian.douglas@lshtm.ac.uk

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Abstract

Objectives: This study aimed to investigate the association and to estimate the crude absolute risk of seizure among patients exposed to fluoroquinolones (FQ) in Hong Kong and United Kingdom.

Methods: A self-controlled case series study (SCCS) was conducted. Data were collected from the Hong Kong Clinical Data Analysis and Reporting System database (CDARS) and the Clinical Practice Research Datalink (CPRD). Patients who were prescribed any oral FQ and had an incident seizure diagnosis from 2001-2013 were included. The risk windows were defined as pre-FQ start, FQ exposed and post-FQ completion. Incident rate ratios (IRR) were estimated in all risk windows and compared with baseline periods. A post-hoc subgroup analysis was conducted to examine the effect of patients with a history of seizure.

Results: Increased IRR was found in the pre-FQ start periods and no association was found in the post-FQ completion periods in both databases. The crude absolute risk of an incident seizure in 10,000 oral FQ prescriptions was 0.72 (95% CI 0.47-1.10) in CDARS and 0.40 (95% CI 0.30-0.54) in CPRD. The rate ratio during treatment was not higher than pre-FQ start periods among patients with a history of seizure, therefore, the results did not raise serious concerns.

Conclusions: This study does not support a causal association between the use of oral FQ and the subsequent occurrence of seizure. An increased risk prior to the FQ exposure period suggests that the clinical indication for which FQ was prescribed may have contributed to the development of seizure rather than the drug itself.

Introduction

Fluoroquinolones (FQ) are a class of broad-spectrum antibiotics. Convulsion is listed as one of the potential side effects of FQ[1]. Numerous case reports on the association between FQ and seizure has also been published[2-11]. Concerns were raised about the safety of FQ on the central nervous system. Although some studies have explored the potential mechanisms of FQ-induced seizure[12-15], comprehensive epidemiological data from population-based studies are needed. The primary objective of this study was to investigate the relationship between FQ and incident seizures using data from Hong Kong (HK) and the United Kingdom (UK). The objective of the post-hoc subgroup analysis was to investigate this relationship in patients with a history of seizure. Further, we aimed to estimate the crude absolute risk of incident seizure among patients prescribed oral FQ.

Methods

We conducted a self-controlled case series (SCCS) study with the data retrieved from the Clinical Data Analysis and Reporting System (CDARS) in HK and the Clinical Practice Research Datalink (CPRD) in the UK to investigate the association between the use of oral FQ and seizures.

Data sources

CDARS

CDARS is a computerised clinical management system developed by the HK Hospital Authority (HA) that contains electronic patient records. The health services

provided by HA (primary care, emergency room, hospital out-patient and in-patient) are available to all 7.2 million HK citizens. CDARS includes information on demographics, diagnoses, procedures, prescription details, laboratory tests and hospitalization details. Patient records in CDARS are de-identified i.e. name, identification card number and contact information are not available to ensure patient confidentiality. A unique reference key was generated and assigned to each patient to facilitate data retrieval and further analysis. CDARS has been used in previous epidemiological studies[16-21].

CPRD

The CPRD contains the anonymised electronic primary care records for approximately 8.5% of the UK population with more than 5 million currently active patients and more than 13 million records dating back to 1987. CPRD contains information on patient demographics, consultations, prescribed medication and diagnoses. The crude death rates in the CPRD population are representative of national rates[22]. Numerous high-quality studies have been published using data from CPRD which affirms the validity and credibility of this database[23, 24].

Study design

The SCCS method conducts within-person comparisons of individuals who have both the exposure and outcome of interest[25]. An incidence rate ratio (IRR) is estimated by comparing the rate of events during the exposure period and non-exposure periods. This study method has been used frequently in pharmacoepidemiological studies[24, 26].

However, to apply SCCS correctly, several assumptions should be met. First, the occurrence of the event should not affect the occurrence of subsequent events. In this study, since patients who experienced the first seizure would have a higher chance of a recurrent event, only patients with their initial seizure recorded within the study period were considered in the analyses. A post-hoc subgroup analysis was also conducted to examine the effect of oral FQ on the risk of the subsequent seizure in patients with a history of seizure. Second, the occurrence of the event should not permanently influence the chance of exposure. In this case, seizure is not a contraindication for the use of FQ. Therefore, the occurrence of the seizure would not influence the exposure to FQ. Third, occurrence of the outcome should not censor the observation period, for example, in the event of death. Although we believe such censoring to be unlikely in this study, we conducted sensitivity analysis with an extended SCCS which is not vulnerable to this assumption[27].

The extended SCCS is applied if the censoring of the observation period is event-dependent. In this case, the event is seizure and the potentially seizure-related death may lead to censoring of the observation period. The extended SCCS was conditioned on the age at censoring and also involved weighting cases with the density of intervals from the event to censoring of observation periods. It corrects for event-dependent censoring which may otherwise result in bias if the standard SCCS method was used.

In addition to the SCCS analyses, we calculated the crude absolute risk of a seizure during current oral FQ use to estimate how often this event occurred in a general clinical setting.

Patient identification

CDARS

The study period was from 1st January 2001 to 31st December 2013. Patients of any age and gender who were prescribed oral FQ from an out-patient setting during the study period were identified from the CDARS database. Patients who had received at least one FQ prescription and also had a diagnosis of incident seizure [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)] (Table e-1) during the study period were defined as the cases. Date of the incident seizure recorded in the database was defined as the index date.

CPRD

Study period and patient identification criteria were similar to that in CDARS. All patients with at least one seizure (Read codes) (Table e-1) and at least one FQ prescription during the same period as defined in CDARS were included in the SCCS. The recorded seizure date was defined as the index date.

Exclusion criteria

In both databases, patients with unknown date of birth or gender were excluded. Those who had previous seizure(s) or history of post-traumatic seizure or febrile convulsion since the beginning of the database (CDARS: 1993, CPRD: 1987) were excluded (Table e-1). In CPRD, patients with less than 12 months of continuous registration or temporary registration were excluded. Patients with any FQ prescription or seizure diagnosis in the first 12 months of registration during the observation period were also excluded, to ensure only incident events were considered in the analysis.

Exposure definition

Prescriptions less than or equal to 7 days apart were combined as they were probably prescribed for the same indication. The prescription duration was calculated by using the quantity dispensed, frequency and dosage information in the database. Prescriptions with missing duration or insufficient information to estimate prescription duration were imputed with the median duration of the other prescriptions amongst the study population in each database.

Statistical analysis

The observation period for each patient was defined as follows: in CDARS, a patient's observation period began on 1st January 2001 or the first record in the database, whichever was latest. It was then censored at the end of the study period or registered date of death if this was earlier than the end of study period. In CPRD, the observation period began on 1st January 2001 or 12 months after the first record in the database, whichever was latest. It was censored on transfer out, death or last data collection date of practice, whichever came first. Risk periods were defined as: 8 to 14 days before FQ start (8-14 days pre-FQ), 1 to 7 days before FQ start (7 days pre-FQ), the FQ exposed period, 1 to 7 days after FQ completion (7 days post-FQ) and 8 to 28 days after FQ completion (8-28 days post-FQ) (Figure 1A). The pre-exposure period serves to measure whether the occurrence of incident seizure may itself be temporarily associated with the probability of being prescribed a FQ. The post-exposure period allowed us to determine whether any increased risk observed during FQ exposure would decline after FQ treatment is ceased. This approach would detect seizures potentially induced by the underlying disease that required a prescription of oral FQ, if an increased IRR was observed before the FQ prescription period. Any

delayed effect would also be captured in the post-FQ completion period. The IRRs estimated in CDARS and CPRD were meta-analyzed with random-effects model to obtain the summary measure of effect. I^2 statistics was used to test for heterogeneity. If no heterogeneity were found, then a fixed-effects model would be used.

Conditional Poisson regression was used to estimate the IRR and 95% confidence interval (CI). Age effect was adjusted in a one-year band. A significance level of 5% was used in all statistical analyses.

Sample size calculation

A total of approximately 3,224 cases are needed to detect an IRR of 2.0 with 95% confidence and 90% power[28].

Post-hoc subgroup analysis

The risk of a seizure subsequent to oral FQ exposure among patients with history of seizure is a clinically important question to be addressed. Therefore, a post-hoc subgroup analysis was conducted to investigate this further. Patients with prior history of seizure were defined as those with at least two seizure events with the initial seizure recorded after the beginning of the study period. The follow-up period began on the day after their first incident seizure event to ensure the baseline risk of recurrent seizure among the cases was standardized (Figure 1B). The rate ratios for each risk period in the two databases were meta-analyzed as for the primary analysis.

Crude absolute risk

The crude absolute risk for incident seizure was estimated using the method in the previous study[16], presented as per 10,000 oral FQ prescriptions.

Sensitivity analysis

In SCCS extension sensitivity analysis, the distribution of time from event to the censoring of observation periods was estimated for each patient in both CDARS and CPRD. To determine whether the extension is needed, we plotted the interval from event to censor of the observation period in a bar chart with a bin-width of 1 year. If clustering had been observed shortly after the seizure (less than or equal to 1 year), this would suggest the event might cause censoring of the observation period. This would violate a key assumption of the standard SCCS design, that event timing is independent of the observation period. Therefore, we applied the SCCS extension to account for event-dependent censoring.

As infection can lead to seizure and is subsequently treated with antibiotics, another sensitivity analysis was conducted by comparing seizure rates in the 7 days before the FQ prescription start date and the first 7 days of the FQ exposed period. The purpose of this comparison was to determine whether increased risk of incident seizure was associated with the FQ prescription or the infection. The 7 days before the FQ prescription start date is assumed to be the period when manifestation of infection began but before FQ were commenced. This served as a baseline and was compared with the period after FQ was prescribed (Figure 1C).

Microsoft Excel, RevMan 5.3 (Cochrane Collaboration, 2012), R 3.1.2 (R Development Core Team, 2008) and SAS 9.3 (SAS Inc, United States) were used for data manipulation and analyses.

Ethics approval

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB reference number: UW 13-458) and the Independent Scientific Advisory Committees for Medicines and Healthcare products Regulatory Agency database research and the London School of Hygiene and Tropical Medicine ethics committee.

Results

There were 2,208 patients from CDARS and 4,177 patients from CPRD who had both oral FQ and incident seizure during the study period and were included in the primary analysis (Table 1). The inclusion and exclusion criteria are illustrated (Figure 2).

A total of 21 cases were found during the FQ exposed period with an IRR of 1.38 (95% CI 0.88-2.17) in CDARS. Increased IRR was found in all pre-FQ start periods: 8-14 days pre-FQ [2.08 (95% CI 1.31-3.32)] and 7 days pre-FQ [1.81 (95% CI 1.10-2.97)]. No association was observed in the time periods post-FQ. In CPRD, 47 cases were observed during the FQ exposed period with an IRR of 1.66 (95% CI 1.23-2.24). An increased IRR was also found during the 7 days pre-FQ [1.79 (95% CI 95% CI 1.27-2.52)]. No association was observed 8-14 days pre-FQ, or during the post-FQ periods. Meta-analyses of the IRRs for the 7 days pre-FQ and FQ exposed periods also gave similar results (Table 2). Overall, similar trends were observed in both databases (Figure 3).

Post-hoc subgroup analysis

A total of 702 and 696 patients from CDARS and CPRD, who had at least two seizure events and with the first seizure recorded after the beginning of the observation period, were included in the analysis respectively (Table 1). A slightly increased IRR was observed during 7 days pre-FQ in CDARS only [2.08 (95% CI 1.17-3.67)]. The rate ratios of the two databases are presented in Table 2. The meta-analyzed rate ratios for all risk periods were not statistically significant (Table 2).

Crude absolute risk

A total of 291,751 and 1,166,213 oral FQ prescriptions were identified from CDARS and CPRD respectively. The absolute risk of developing incident seizure during FQ exposed period in 10,000 oral FQ prescriptions was 0.72 (95% CI 0.47-1.10) in CDARS and 0.40 (95% CI 0.30-0.54) in CPRD.

Sensitivity analysis

Data from both databases were tested for the need for SCCS extension. Figure e-1 showed the time from event to censoring of observation period with each bin representing 1-year interval. In the CDARS data, a clustering of observation period censoring can be seen shortly after incident seizure, leading to the potential violation of a SCCS assumption similar to the example demonstrated in previous study[27]. The analysis was then repeated with the use of SCCS extension. The estimated IRRs of all risk windows were similar to those in the primary analysis (Table 2), suggesting the results of the primary analysis were not biased by this censoring. Clustering of observation period censoring was not observed in the CPRD dataset; therefore, analysis with the SCCS extension was not used.

In the sensitivity analysis comparing the first 7 days of FQ exposure against the 7 days before FQ initiation, 27 patients were included from CDARS and 45 were included from CPRD. Comparing the first 7 days of FQ exposure with the 7 days before FQ exposure, the IRR estimated in CDARS was 0.91 (95% CI 0.43-1.95) and 1.23 (95% CI 0.70-2.27) in CPRD (Table 2).

Discussion

This study shows an association between the use of oral FQ and the development of incident seizure. However, an increased risk of incident seizure is seen shortly before starting FQ treatment in both databases. If an association between the use of oral FQ and seizure exists, the seizure would be captured subsequent to the beginning of FQ prescription, thus an increased IRR in the FQ exposed or post-FQ periods would be expected. An increased IRR observed in the pre-FQ periods and no further increased risk after the start of FQ treatment suggests that it is not a causal effect of FQ. The increased IRR in the sensitivity analysis also suggested no causal effect but the clinical indication for which FQ was prescribed may have contributed to the development of incident seizure. Such a phenomenon is consistently seen in both CDARS and CPRD.

A possible reason for the increased risk of seizure before starting FQ treatment is the occurrence of infection induced seizure. Patients may have presented with signs of infection such as fever or febrile infection-related seizures[29] before they were prescribed oral FQ. Therefore, an increased risk of seizure was found before the FQ exposure. Although patients with febrile convulsion were excluded in the analysis, we cannot rule out the fact that the increased risk was associated with infection-related complications due to the limitations of data recorded in CDARS and CPRD.

Although several case reports described a potential association between FQ and the occurrence of seizure[3, 10, 30], most reported seizure as a subsequent event to FQ prescription. The result of this study contradicts speculation from the case reports. The findings of this study will not be detected in a classic cohort study where incident events before the exposure will not be typically considered. In addition, such a study design may exclude patients with pre-FQ seizure. The risk prior to the FQ exposure would not be observed and an association between the use of FQ and subsequent seizure may be concluded depending on the comparator chosen. A similar phenomenon had also been reported in previous literature[24].

The findings of this study do not support a causal relationship between the use of oral FQ and the development of seizure. In addition, the crude absolute risk estimated in this study was very low in both databases. Seizure is a rare adverse event of FQ if there was an association. Clinicians should weigh the risk and benefit of FQ and its use should not be precluded in patients with the appropriate indication.

The SCCS study design enabled within person comparison of the FQs exposed and non-exposed periods. Therefore, it controlled for time-invariant factors including genetic factors that could not be completely accounted for in classical epidemiological study designs.

The result of the SCCS extension is similar to that of the primary analysis in this study. This suggests that the occurrence of the event is independent of the censoring of the observation period. Hence, we are confident that SCCS is an appropriate study design.

The meta-analyzed findings of the two databases did not show any statistically significant increased risk of seizure before, during nor after the use of oral FQ among

patients with history of seizure. The observed differences between the primary and post-hoc subgroup analysis may be due to the small sample size of the post-hoc subgroup analysis; hence reduced power in detecting small increases in seizure risk. It is worth noting that the rate ratio during treatment is not higher than pre-FQ start periods, thus the results do not support FQ induce seizure in patients with a previous history of seizure.

This study does not support a causal relationship between the use of oral FQ and the development of incident seizure. The consistent results found in the two databases further enhance the credibility of the findings. We believe that the clinical indication for which oral FQ was prescribed may have contributed to the development of incident seizure rather than the drug itself. In patients with history of seizure, we did not find evidence of higher risk of seizure during FQ treatment than pre-FQ treatment; however we cannot exclude the possibility of Type 2 errors due to limited sample size. Therefore, further investigation with a larger sample size is warranted to confirm the findings of our post-hoc subgroup analysis.

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References

1. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary, 70th ed. UK: British Medical Journal Publishing Group, 2015.
2. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. Ann Pharmacother 2001;35:1194-1198.
3. Darwish T. Ciprofloxacin-induced seizures in a healthy patient. N Z Med J 2008;121:104-105.
4. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. Ann Pharmacother 2004;38:235-237.
5. Traeger SM, Bonfiglio MF, Wilson JA, Martin BR, Nackes NA. Seizures associated with ofloxacin therapy. Clin Infect Dis 1995;21:1504-1506.
6. Tattevin P, Messiaen T, Pras V, Ronco P, Biour M. Confusion and general seizures following ciprofloxacin administration. Nephrol Dial Transplant 1998;13:2712-2713.
7. Marinella MA. Myoclonus and generalized seizures associated with gatifloxacin treatment. Arch Intern Med 2001;161:2261-2262.
8. Bird SB, Orr PG, Mazzola JL, Brush DE, Boyer EW. Levofloxacin-related seizure activity in a patient with Alzheimer's disease: assessment of potential risk factors. J Clin Psychopharmacol 2005;25:287-288.
9. Koussa SF, Chahine SL, Samaha EI, Riachi MA. Generalized status epilepticus possibly induced by gatifloxacin. Eur J Neurol 2006;13:671-672.
10. Lahmek P, Michel L, Meunier N, Aubin HJ. A seizure attributed to ofloxacine in a woman undergoing detoxification for alcohol dependence. Case Rep Med 2009;2009:705635.
11. Famularo G, Pizzicannella M, Gasbarrone L. Levofloxacin and seizures: what risk for elderly adults? J Am Geriatr Soc 2014;62:2018-2019.
12. Gervasoni C, Cattaneo D, Falvella FS, et al. Levofloxacin-induced seizures in a patient without predisposing risk factors: the impact of pharmacogenetics. Eur J Clin Pharmacol 2013;69:1611-1613.
13. Schmuck G, Schurmann A, Schluter G. Determination of the excitatory potencies of fluoroquinolones in the central nervous system by an in vitro model. Antimicrob Agents Chemother 1998;42:1831-1836.
14. Akahane K, Sekiguchi M, Une T, Osada Y. Structure-epileptogenicity relationship of quinolones with special reference to their interaction with gamma-aminobutyric acid receptor sites. Antimicrob Agents Chemother 1989;33:1704-1708.
15. Christ W. Central nervous system toxicity of quinolones: human and animal findings. J Antimicrob Chemother 1990;26 Suppl B:219-225.
16. Chui CS, Man KK, Cheng CL, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. J Antimicrob Chemother 2014;69:2563-2567.
17. Man KK, Ip P, Hsia Y, et al. ADHD Drug Prescribing Trend Is Increasing Among Children and Adolescents in Hong Kong. J Atten Disord 2014 Epub 3rd July, 2014.
18. He Y, Chan EW, Man KK, et al. Dosage effects of histamine-2 receptor antagonist on the primary prophylaxis of non-steroidal anti-inflammatory drug (NSAID)-associated peptic ulcers: a retrospective cohort study. Drug Saf 2014;37:711-721.
19. Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology 2015;149:586-595 e583.
20. Man KK, Chan EW, Coghill D, et al. Methylphenidate and the risk of trauma. Pediatrics 2015;135:40-48.
21. Wong AYS, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ;(Accepted).

22. Campbell J, Dedman DJ, Eaton SC, Gallagher AM, Williams TJ. Is the CPRD GOLD Population Comparable to the UK Population? Pharmacoepidemiol Drug Saf 2013;22:280-281.
23. Rodriguez LAG, Gutthann SP. Use of the UK General Practice Research Database for pharmacoepidemiology. Brit J Clin Pharmaco 1998;45:419-425.
24. Douglas IJ, Langham J, Bhaskaran K, Brauer R, Smeeth L. Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink. BMJ 2013;346:f1936.
25. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;25:1768-1797.
26. Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med 2009;6:e1000154.
27. Farrington CP, Anaya K, Whitaker H, Hocine MN, Douglas IJ, Smeeth L. Self-Controlled Case Series Analysis with Event-Dependent Observation Periods. J Am Stat Assoc 2010;106:417-426.
28. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med 2006;25:2618-2631 Epub 2005/12/24.
29. Serrano-Castro PJ, Quiroga-Subirana P, Payan-Ortiz M, Fernandez-Perez J. The expanding spectrum of febrile infection-related epilepsy syndrome (FIRES). Seizure 2013;22:153-155.
30. Bellon A, Perez-Garcia G, Coverdale JH, Chacko RC. Seizures associated with levofloxacin: case presentation and literature review. Eur J Clin Pharmacol 2009;65:959-962.

Table 1. Patient characteristics

	Primary analysis		Post-hoc subgroup analysis	
	CDARS (n=2,208)	**CPRD (n=4,177)**	**CDARS (n=702)**	**CPRD (n=696)**
Sex (%)				
Male	1,112 (50.36%)	2,054 (49.17%)	378 (53.85%)	345 (49.57%)
Female	1,096 (49.64%)	2,123 (50.83%)	324 (46.15%)	351 (50.43%)
Age at baseline (year)				
Mean	61.85	52.44	66.17	53.57
S.D.*	17.38	21.52	18.12	22.07
Mean of follow-up (days)				
8-14 days pre-FQ† start	6.85	6.82	6.86	6.84
1-7 days pre-FQ start	6.87	6.81	6.84	6.82
FQ exposed	11.13	10.01	10.54	8.79
1-7 days post-FQ completion	6.88	6.87	6.86	6.83
8-28 days post-FQ completion	19.17	18.83	18.95	19.10
Baseline	308.76	296.65	268.90	269.20

*Standard deviation
†Fluoroquinolones

Table 2. Model details of self-controlled case series of the association between oral fluoroquinolones and seizure

	Primary analysis				Post-hoc subgroup analysis			
	CDARS (n=2,208)		CPRD (n=4,177)		CDARS (n=702)		CPRD (n=696)	
	No. of events	IRR* (95%CI†)	No. of events	IRR (95% CI)	No. of events	IRR (95% CI)	No. of events	IRR (95% CI)
8-14 days pre-FQ‡ start	18	2.08 (1.31-3.32)	24	1.33 (0.89-1.99)	7	1.16 (0.54-2.48)	5	1.07 (0.44-2.63)
1-7 days pre-FQ start	16	1.81 (1.10-2.97)	33	1.79 (1.27-2.52)	13	2.08 (1.17-3.67)	4	0.84 (0.31-2.28)
FQ exposed	21	1.38 (0.88-2.17)	47	1.66 (1.23-2.24)	6	0.66 (0.29-1.50)	8	1.38 (0.67-2.87)
1-7 days post-FQ completion	11	1.17 (0.64-2.11)	22	1.07 (0.70-1.63)	4	0.65 (0.24-1.75)	3	0.63 (0.20-1.99)
8-28 days post-FQ completion	33	1.23 (0.87-1.75)	68	1.18 (0.93-1.51)	10	0.54 (0.28-1.07)	11	0.86 (0.46-1.59)
Baseline	2 109	-	3 983	-	662	-	665	-
Meta-analysis (CDARS and CPRD)								
8-14 days pre-FQ start	1.64 (1.06-2.54); I^2=51%				1.12 (0.63-2.00); I^2=0%			
1-7 days pre-FQ start	1.80 (1.35-2.38); I^2=0%				1.46 (0.61-3.45); I^2=58%			
FQ exposed	1.57 (1.22-2.01); I^2=0%				0.98 (0.47-2.03); I^2=43%			
1-7 days post-FQ completion	1.10 (0.78-1.55); I^2=0%				0.64 (0.30-1.36); I^2=0%			
8-28 days post-FQ completion	1.20 (0.98-1.46); I^2=0%				0.70 (0.44-1.10); I^2=0%			
Sensitivity analysis								
Direct comparison of 7 days pre-FQ (baseline) and first 7 days of FQ exposed period	13	0.91 (0.43-1.95)	25	1.23 (0.70-2.27)			-	
SCCS extension								
8-14 days pre-FQ start	18	1.96 (1.23-3.12)	-	-			-	
1-7 days pre-FQ start	16	1.70 (1.04-2.79)	-	-			-	
FQ exposed	21	1.28 (0.81-2.01)	-	-			-	
1-7 days post-FQ completion	11	1.09 (0.60-1.98)	-	-			-	
8-28 days post-FQ completion	33	1.15 (0.82-1.63)	-	-			-	
Baseline	2,109	-	-	-			-	

*Incidence rate ratio
†Confidence Interval
‡Fluoroquinolones

Figure 1. Typical observation period of a patient

Legend: (A) In the primary analysis; (B) in the post-hoc subgroup analysis; and (C) in the sensitivity analysis comparing the 7 days pre-FQ (baseline) and first 7 days of FQ exposed period.

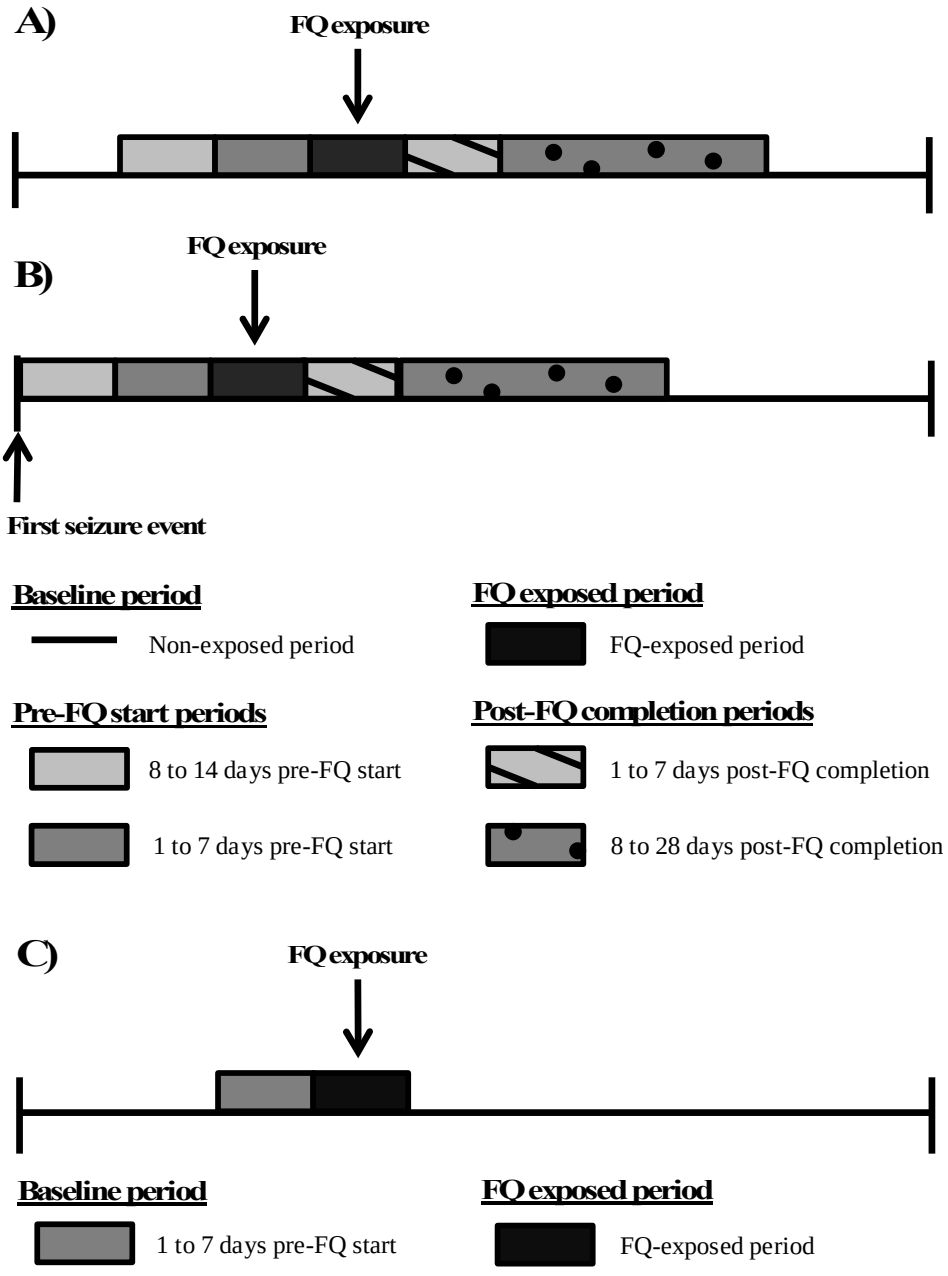
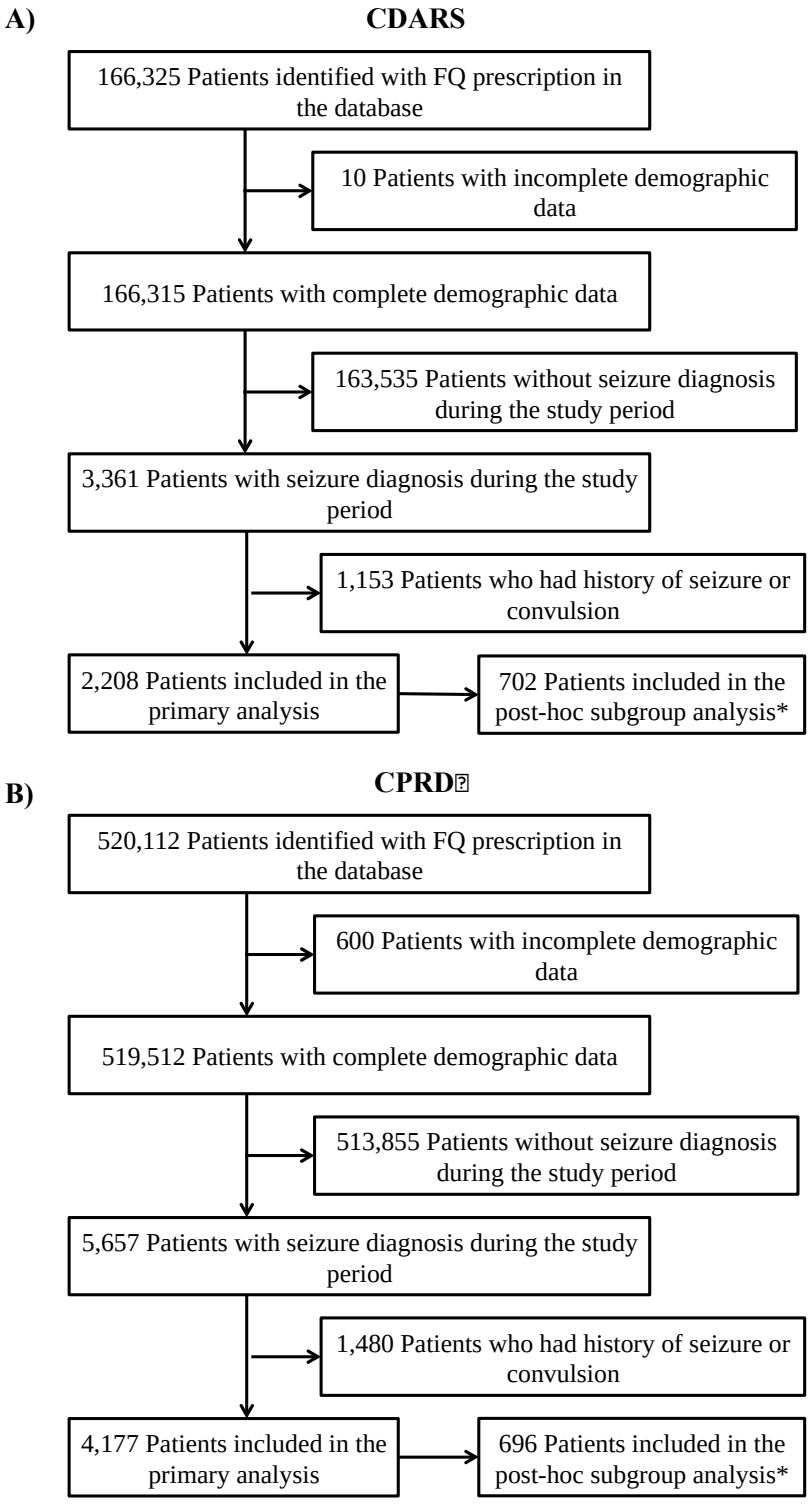


Figure 2. Flow chart of inclusion/exclusion of patients

Legend: Patient count for each stage of inclusion and exclusion in (A) CDARS and (B) CPRD.



*Post-hoc subgroup analysis: Patients with history of seizure

Figure 3. Incidence rate ratio trends of all risk periods

Legend: Incidence rate ratios and their corresponding confidence intervals from the primary analysis were used.